

# Autism: The Eusocial Hominid Hypothesis

Updated 3:00 AM (EST), 1/15/2012

- “Eight autistic people have been associated with my group [...] They are there because of their intellectual and personal qualities. **I believe that they contribute to science because of their autism, not in spite of it.**  
**The hallmark of an enlightened society is its inclusion of non-dominant behaviours and phenotypes**, such as homosexuality, ethnic differences and disabilities.”  
- *Laurent Mottron, Ph.D., M.D.*  
[Changing perceptions: The power of autism](#)  
*Nature*, Nov 2011
- “...aspects of human uniqueness arose because of a primate evolutionary trend towards increasing and irreversible dependence on learned behaviours and culture — **perhaps relaxing allowable thresholds for large-scale genomic diversity.**”  
[Human uniqueness: genome interactions with environment, behaviour and culture](#)  
*Nature Reviews Genetics*, 2008
- “Interestingly, some of the deviations seen in the Neanderthal are present also in the modern human, whereas others are not. The latter group of sequences may indicate copy-number [variations] (**CNVs**) that are **unique to the Neanderthal relative to the modern human genome sequence.**”  
[Analysis of one million base pairs of Neanderthal DNA](#)  
*Nature*, 2006
- “Chromosomal regions that are hotspots for **primate-specific segmental dups** [...] frequently coincide with the breakpoints of **CNVs** found in **autism** and **schizophrenia**”  
[A genomic point-of-view on environmental factors influencing the human brain methylome](#)  
*Epigenetics*, July 2011
- “Introgression did take place between the ancestors of Europeans and the Neanderthals, and that introgression involved substantial parts of the Neanderthal genome that are scattered among modern humans. Will some of these Neanderthal fragments be found to be important in **cognition, language ability**, and other higher brain functions? To find out, **it will be necessary to understand the human epigenome and transcriptome in detail.**”  
[Genetic and Phenotypic Consequences of Introgression Between Humans and Neanderthals](#)  
*Advances in genetics*, Nov 2011
- “In most modern human populations, the majority of **MHC I** alleles have been acquired by introgression from archaic humans (Neanderthals and Denisovans)”  
[Origin and plasticity of MHC I-associated self-peptides](#)  
*Autoimmune Review*, Nov 2011
- “Accumulating evidence indicates that neuronal **MHC class I** does not simply function in an immune capacity, but **is also crucial for normal brain development, neuronal differentiation, synaptic plasticity and even behaviour.**”  
[Immune signalling in neural development, synaptic plasticity and disease](#)  
*Nature Reviews Neuroscience*, 2004

## Abstract:

ASDs (autism spectrum disorders) are hypothesized as one of many adaptive human cognitive variations that have been maintained in modern populations via multiple genetic and epigenetic mechanisms. Introgression from “archaic” hominids (adapted for **less demanding social environments**) is conjectured as the source of initial intraspecific heterogeneity because strict inclusive fitness does not adequately model the evolution of distinct, copy-number sensitive phenotypes within a freely reproducing population.

Evidence is given of divergent encephalization and brain organization in the Neanderthal (including a ~1520 cc cranial capacity, **larger** than that of modern humans) to explain the origin of the autism subgroup characterized by **abnormal brain growth**.

Autism and **immune dysfunction** are frequently comorbid. This supports an admixture model in light of the recent discovery that MHC alleles (genes linked to **immune function, mate selection, neuronal “pruning,”** etc.) found in most modern human populations come from “archaic” hominids.

**Mitochondrial dysfunction, differential fetal androgen exposure,** lung abnormalities, and **hypomethylation/CNV** due to hybridization are also presented as evidence.

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- Comments about a particular section of text are preceded by ↑↑
- General comments are preceded by ⇒
- Quotes are preceded by a bullet point •
- Permalinks: [goo.gl/aloZI](http://goo.gl/aloZI) (or [xg.us.to/eusocial](http://xg.us.to/eusocial))

## I. Background Info

### A. Some recent developments in autism

- i. [Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes \(5%, 2.5%, and 1%\).](#) (Oct 2011) [goo.gl/EYGna](http://goo.gl/EYGna)

- **Moderate to high heritability was found for autistic traits in the general population (53% for females and 72% for males).** High heritability was found in extreme-scoring groups. There were no differences in heritability among extreme groups or between the extreme groups and the general population. A continuous liability shift toward autistic trait affectedness was seen in the cotwins of individuals scoring in the top 1%, suggesting shared etiology between extreme scores and normal variation.

↑↑ *Autism is quite heritable.*

- This evidence of similar etiology across normal variation and the extremes has implications for molecular genetic models of autism spectrum disorders and for **conceptualizing autism spectrum disorders as the quantitative extreme of a neurodevelopmental continuum.**

↑↑ *Autism is a spectrum (or, more likely, a class of spectra) that begins at “normal” (neurotypical).*

- ii. [Autism, the Integrations of ‘Difference’ and the Origins of Modern Human Behaviour](#) (2009) [goo.gl/s8b7W](http://goo.gl/s8b7W)

- It is proposed here that the archaeological evidence for the emergence of ‘modern behaviour’ (160,000–40,000 bp) can best be explained as the rise of cognitive variation within populations through social mechanisms for integrating ‘different minds’, rather than by the development of a single ‘modern human mind.’ **Autism and the autistic spectrum within human populations are used as an example of ‘different minds’ which when integrated within society can confer various selective benefits.** It is proposed that social mechanisms for incorporating autistic difference are visible in the archaeological record and that these develop sporadically from 160,000 years bp in association with evidence for their consequences in terms of technological innovations, improved efficiency in technological and natural spheres and innovative thinking. Whilst other explanations for the emergence of modern human behavior may also contribute to observed changes, **it is argued that the incorporation of cognitive differences played a significant role in the technological, social and symbolic expression of ‘modern’ behavior.**

↑↑ *This article presents evidence to support the idea that the inclusion of autistic phenotypes can improve overall population fitness.*

- iii. [Facial phenotypes in subgroups of pre-pubertal boys with autism spectrum disorders are correlated with clinical phenotypes](#) (Oct 2011) [goo.gl/uGbli](http://goo.gl/uGbli)

- **BACKGROUND:** The brain develops in concert and in coordination with the developing facial tissues, with each influencing the development of the other and sharing genetic signaling pathways. Autism spectrum disorders (ASDs) result from alterations in the embryological brain, suggesting that

the development of the faces of children with ASD may result in subtle facial differences compared to typically developing children. In this study, **we tested two hypotheses. First, we asked whether children with ASD display a subtle but *distinct facial phenotype* compared to typically developing children. Second, we sought to determine whether there are subgroups of facial phenotypes within the population of children with ASD that denote biologically discrete subgroups.**

↑ *The discreteness might be an indicator of adaptive mosaicism early in development. This is addressed later.*

- First, **we found that there are significant differences in facial morphology in boys with ASD compared to typically developing boys.**

↑ *This was already somewhat known.*

- Second, **we also found two subgroups of boys with ASD with facial morphology that differed from the majority of the boys with ASD and the typically developing boys.**

↑ *This is new. Humans make extensive use of facial communication in social interaction. Distinct facial phenotypes that correspond to behavioral subgroups might increase population fitness by allowing another avenue to facilitate communal integration of polymorphic traits. [Facial structure is already known to be a good indicator of aggressive tendencies](#). [goo.gl/7gH0C](http://goo.gl/7gH0C)*

- Furthermore, **membership in each of these distinct subgroups was *correlated with particular clinical and behavioral traits*.**

## B. Evidence that ASD rates are rising

### i. [South Korean Autism Rates Head North](#) (May 2011) [goo.gl/HRs3j](http://goo.gl/HRs3j)

- South Korea just sent autism prevalence rates surging north. Autism-spectrum disorders affect an estimated 2.64 percent of the nation's schoolchildren, or **about 1 in 38 youngsters, a new study finds.**

### ii. [The prevalence puzzle: Autism counts](#) (Nov 2011) [goo.gl/6guU6](http://goo.gl/6guU6)

- If the rise in autism can be explained mainly by increased awareness, diagnosis and social factors, then the contributing environmental factors will always have been present — perhaps an ill-timed infection in pregnancy or some kind of nutritional deficit. **If the increase can't be explained away — and at least part of the rise is 'real' — then new factors must be causing it, and scientists urgently need to find them.**

↑ *The increase is no longer controversial.*

- Thomas Insel, director of the National Institute of Mental Health in Bethesda, Maryland, says ... **"This whole idea of whether the prevalence is increasing is so contentious for autism, but not for asthma, type 1 diabetes, food allergies — lots of other areas where people kind of accept the fact that there are more kids affected."** To him, it is clear that there is a real increase in autism, and researchers need more funding and encouragement to look at possible environmental causes. During the past decade, the US federal government has spent about US\$1 billion researching the genetics of autism and only about \$40 million on studies of possible environmental factors.

### iii. [Have Secular Changes in Perinatal Risk Factors Contributed to the Recent Autism Prevalence Increase? Development and Application of a Mathematical Assessment Model](#) (Oct 2011) [goo.gl/o82V0](http://goo.gl/o82V0)

- A 57% increase in the U.S. prevalence of autism spectrum disorders (ASD) for 8-year-old children born in 1994 versus 1998 was recently reported.
- [...]we formulated a mathematical model based on the baseline risk factor prevalence (RFP), the proportionate change in RFP (cRFP), and the magnitude of the association between the risk factor

and ASD [estimated relative risk (RR)]. We applied this model to several pregnancy-related factors (preterm, very preterm, low and very low birth weight, multiple birth, cesarean delivery, breech presentation, and assisted reproductive technology use).

- We estimate that each risk factor examined, alone or in various combinations, accounted for a very small proportion (<1%) of the ASD increase. Additionally, hypothetical scenarios indicate RFP, cRFP, and RR all need to be sizable for a risk factor to appreciably influence ASD prevalence.

- Thus, although various pregnancy factors have been found to be associated with ASDs, **the contribution of many of these factors to the recently observed ASD increase is likely minimal.**

iv. [Autism, Intellectual Disabilities Related to Parental Age, Education and Ethnicity, Not Income, Utah Study Finds](#) (Sept 16, 2011) [goo.gl/r7NkC](http://goo.gl/r7NkC)

- New research from the University of Utah in collaboration with the Utah Department of Health (UDOH) shows that the presence or absence of intellectual disability (ID) and **autism spectrum disorders (ASD) varies with risk factors such as gender, parental age, maternal ethnicity, and maternal level of education.** The study, published Sept. 15, 2011, in *Autism Research*, also shows that **household income level has no association with either ID or ASD**, in contrast to what other studies have suggested.

↑ The paper: [Sociodemographic risk factors associated with autism spectrum disorders and intellectual disability](#) [goo.gl/EtU7M](http://goo.gl/EtU7M)

C. Evidence that genes predisposing individuals to autism are not uniformly distributed

i. [Wired Magazine: The Geek Syndrome](#) (2001) [goo.gl/zecBL](http://goo.gl/zecBL)

- Autism - and its milder cousin Asperger's syndrome - **is surging among the children of Silicon Valley. Are math-and-tech genes to blame?**

↑ *That would indicate assortative mating.*

- At clinics and schools in the Valley, the observation that most parents of autistic kids are engineers and programmers who themselves display autistic behavior is not news. And it may not be news to other communities either. Last January, Microsoft became the first major US corporation to offer its employees insurance benefits to cover the cost of behavioral training for their autistic children. One Bay Area mother told me that when she was planning a move to Minnesota with her son, who has Asperger's syndrome, she asked the school district there if they could meet her son's needs. **"They told me that the northwest quadrant of Rochester, where the IBMers congregate, has a large number of Asperger kids," she recalls. "It was recommended I move to that part of town."**

ii. [Are autism spectrum conditions more prevalent in an information-technology region? A school-based study of three regions in the Netherlands](#) (2011) [goo.gl/79MBg](http://goo.gl/79MBg)

- The aim of this study was to test a prediction from the hyper-systemizing theory (Baron-Cohen 2006, 2008) that ASC are more common among children in areas where individuals who are **talented systemizers are attracted to work and raise a family.** Eindhoven is a candidate region of this kind, being the hub for IT and technology in the Netherlands. We examined the prevalence of ASC in the formal administrative records of school-aged children in the Eindhoven region, compared to two 'control' regions: the Haarlem and Utrecht regions. **As predicted, this estimate of the prevalence of school-aged children with a formal ASC diagnosis was significantly higher in the Eindhoven region, compared to the Haarlem and Utrecht region. This is consistent with the idea that strong systemizing in parents could be a risk factor for having a child with ASC**, although there are other factors that could relate to the increased prevalence in the Eindhoven region.

↑ *The distribution of autism is not geographically uniform.*

## II. The Evolution of Eusociality

*"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."*

– Darwin

### A. The definition of the word “Eusocial”

#### i. [A new eusocial vertebrate](http://goo.gl/IE4fU) (2005) [goo.gl/IE4fU](http://goo.gl/IE4fU)

- We go further and ask, **are humans eusocial**? Eusociality is usually defined by three criteria: (i) reproductive division of labour; (ii) overlap of generations; and (iii) cooperative brood care [6]. It is epitomized by the eusocial Hymenoptera (ants, some bees and wasps), which is unsurprising, given that it is based on them. But **humans also fit this definition**. That grandmothers are sterile and enhance the reproduction of close relatives is telling because reproductive division of labour is considered to be the most important definitional criterion of eusociality, and has been the focus of attempts to define it more clearly. Sherman et al. broadened the definition by introducing a eusociality continuum based on variation among society members in direct reproduction. **Here, species with temporary helpers, such as cooperatively breeding birds, are eusocial.**

↑ *This the definition I'm using.*

- Crespi and Yanega narrowed the definition by requiring irreversibly distinct groups or castes with respect to sterility and/or other features. Here, species that are traditionally considered to be eusocial, including some wasps and bees, and also the naked mole rat, are not eusocial.

↑ *This is **not** the definition I'm using.*

- **The newer definitions centre upon the reproductive division of labour, which occurs in humans.** Some aspects of human helping fit less well to the new definitions, but this is largely because **humans have intriguing idiosyncrasies**, which have not previously been considered. One is that reproducing individuals become permanently sterile later in life, which would not fit Crespi and Yanega's criterion of 'becoming irreversibly distinct at some point prior to reproductive maturity.' But it is not clear that helping after reproducing should be disallowed. Similarly, **both new definitions emphasize lifetime differences among individuals in reproductive success.**

↑ *From [Wired 9.12: The Geek Syndrome](http://Wired.9.12:TheGeekSyndrome): "In another age, [high functioning autistics] would have been monks, developing new ink for printing presses. Suddenly, they're reproducing at a much higher rate."*

- A third idiosyncrasy is that human parents help offspring rear grandchildren, rather than offspring helping parents rear siblings. **The former is less favourable from a relatedness perspective because relatedness to grand offspring is 0.25, whereas relatedness to full siblings is, on average, 0.5.**

↑ *Yes, because we evolved to fit into both a family **and** a tribe/society, which requires a certain decoupling from the physical limits of [Hamilton's rule](#). This is still apparently controversial in the academic community, but thankfully not in reality.*

- This suggests that the benefits of grandmothering must greatly outweigh the decreased personal reproduction costs.

↑ *Yes, by increasing the fitness of the whole tribe.*

- What could cause such a large benefit:cost ratio? **Older women have valuable experience that they can provide to many families headed by offspring.** Interestingly, an age benefit of experience is also known in elephants, where older matriarchs are better at leading troops between food and

water [9]. Grandmothers can also provide help at short-lived crucial points, such as at births. **Such helping is facilitated by our ability to recognize sons and daughters, which enables a grandmother to help all grandchildren living nearby, even if they are not living together.**

↑ *Recognizing faces (and underlying genetic similarity) is important in eusociality.*

## B. Inclusive fitness

### i. [Limitations of I.F.](#) (2010) [goo.gl/mKewo](http://goo.gl/mKewo)

- For the past four decades kin selection theory, based on the concept of inclusive fitness, has been the major theoretical attempt to explain the evolution of eusociality. Here we show the limitations of this approach. We argue that standard natural selection theory in the context of precise models of population structure represents a simpler and superior approach, allows the evaluation of multiple competing hypotheses, and provides an exact framework for interpreting empirical observations.

↑ *This is controversial. See the [top of the article's page in Nature](#) for the responses.*

- Many empiricists, who measure genetic relatedness and use inclusive fitness arguments, think that they are placing their considerations on a solid theoretical foundation. This is not the case. Inclusive fitness theory is a particular mathematical approach that has many limitations. It is not a general theory of evolution. **It does not describe evolutionary dynamics nor distributions of gene frequencies.**

↑ *This will be supported by later evidence.*

## C. EO Wilson's theory of eusocial evolution

### i. [Success and dominance in ecosystems: The case of the social insects](#) (Jan 2007) [goo.gl/vxYB6](http://goo.gl/vxYB6)

- Very conservatively, [social insects] compose more than half the insect biomass. It is clear that social life has been enormously successful in the evolution of insects. **When reef organisms and human beings are added, social life is ecologically preeminent among animals in general.** This disproportion seems even greater when it is considered that only 13,000 species of highly social insects are known, out of the 750,000 species of the described insect fauna of the world.

↑ *Call them what you will (social or eusocial), but the innate behaviors that facilitate cooperation between different minds are our greatest asset as a species (they let us collectively utilize all our other assets), and numerous analogues exist elsewhere in the animal kingdom.*

- In short, **2% of the known insect species of the world compose more than half the insect biomass.** It is my impression that in another, still unquantified sense these organisms, and particularly the ants and termites, also occupy center stage in the terrestrial environment. They have pushed out solitary insects from the generally most favorable nest sites. The solitary forms occupy the more distant twigs, the very moist or dry or excessively crumbling pieces of wood, the surface of leaves – in short, the more remote and transient resting places. They are also typically either very small, or fast moving, or cleverly camouflaged, or heavily armored. **At the risk of oversimplification, the picture I see is the following: social insects are at the ecological center, solitary insects at the periphery.**

↑ *Neanderthals are extinct. Among the various explanations proffered to explain this exist a few that directly implicate human expansion and replacement (presumably revised to include recent DNA evidence of admixture).*

- This then is the circumstance with which the social insects challenge our ingenuity: their attainment of a highly organized mode of colonial existence was rewarded by ecological dominance, leaving what must have been a deep imprint upon the evolution of the remainder of terrestrial life....Their impact is evident in the life cycles and behavior of many kinds of organisms. In a most general sense, ants and termites hold the central microhabitats where interference competition

allows the control of stable resources, while **solitary** insects ‘fill the cracks’ of less stable, accessible resources.

↑ *I’m pretty sure there’s a quote often attributed to Groucho Marx that’s applicable here.*

ii. [An alternative theory of eusocial evolution](#) (2010) [goo.gl/a6DBf](http://goo.gl/a6DBf) [same paper, different section]

- Eusociality, in which some individuals reduce their own lifetime reproductive potential to raise the offspring of others, underlies the most advanced forms of social organization and the ecologically dominant role of social insects **and humans**.

↑ *Here the author directly alludes to human eusociality (our persistent phenotypic diversity).*

- **The first step in the origin of animal eusociality is the formation of groups within a freely mixing population.** There are many ways in which this can occur. Groups can assemble when nest sites or food sources on which a species is specialized are local in distribution; or when parents and offspring stay together; or when migratory columns branch repeatedly before settling; or when flocks follow leaders to known feeding grounds; or even randomly by mutual local attraction. **A group can be pulled together when cooperation among unrelated members proves beneficial to them, whether by simple reciprocity or by mutualistic synergism or manipulation.**

↑ *His theory does away with kin selection as the major evolutionary pressure for eusociality, instead focusing on functional or geographic isolation (with adaptive divergence).*

- Inclusive fitness theorists have pointed to resulting close pedigree relatedness as evidence for the key role of kin selection in the origin of eusociality, but as argued here and elsewhere, **relatedness is better explained as the consequence rather than the cause of eusociality.**

↑ *The point made here is that relatedness is not the major force driving eusocial adaptation. Instead, it is a consequence of the species’ adaptive pursuit of eusociality.*

- **The second stage is the accumulation of other traits that make the change to eusociality more likely. All these pre-adaptations arise in the same manner as constructing a defensible nest by the solitary ancestor, by individual-level selection, with no anticipation of a potential future role in the origin of eusociality. They are products of adaptive radiation, in which species split and spread into different niches.** In the process some species are more likely than others to acquire potent pre-adaptations.

↑ *The Neanderthal and Denisova are niche hominids.*

- **It is evident that bees, and also wasps, are spring-loaded, that is, strongly predisposed with a trigger, for a rapid shift to eusociality, once natural selection favours the change.**

↑ *This is important, as it will be applied later to the genetic variation added to the sapiens line via archaic hominid introgression.*

- **We have not addressed the evolution of human social behaviour here, but parallels with the scenarios of animal eusocial evolution exist, and they are, we believe, well worth examining.**

↑ *That bit should speak for itself.*

iii. [Relaxed selection is a precursor to the evolution of phenotypic plasticity](#) (Sept 12, 2011) [goo.gl/L5V4c](http://goo.gl/L5V4c)

↑ *Note: This paper is not by EO Wilson, but it presents evidence that supports the parts of his theory that apply here.*

- **Phenotypic plasticity allows organisms to produce alternative phenotypes under different conditions and represents one of the most important ways by which organisms adaptively respond to the environment.** However, the relationship between phenotypic plasticity and molecular



↑↑ *There is no question that, in its most extreme forms, autism is a tragic, debilitating disorder. But, like sickle-cell anemia, the autism spectrum consists, **in part**, of phenotypes that are under positive selection because they have adaptive significance.*

- Populations can adapt to new environments in two distinct ways. They can either wait for the appearance of a novel mutation, which will sweep through the population if advantageous, or alternatively, **they can evolve immediately by using an allele from the standing (i.e. pre-existing) genetic variation**. Understanding which process more commonly underlies adaptation is important because much of the earliest and most influential theory on the genetics of adaptation was based on the mathematically enforced assumption that new mutations are the main source of genetic variation for adaptation. Furthermore, the evolutionary dynamics of ancient alleles will be different to that of new mutations. **Older alleles, that have been exposed to selection for generations and exist in the population at a higher frequency can reach fixation faster than young alleles, especially if their effects are recessive**, as they are more likely to appear in homozygous form if older.
- The age of adaptive loci can be estimated by sequencing adjacent regions of the genome and examining patterns of nucleotide variation in that region. If adaptation involves new mutations that were rapidly driven to high frequencies in a new environment, then those alleles will be found on genetically impoverished haplotypes, and they will not be observed in ancestral populations or environments. Strategies for inferring the age of adaptive alleles are based around the idea of genetic hitchhiking and are summarised elsewhere. **Among the adaptive loci that have been identified, most seem to have been present as part of the standing genetic variation, e.g. the favoured alleles are much older than the environmental change driving adaptation.**

↑↑ *In essence, old alleles that have persisted in a population are better (safer) for rapid adaptation.*

- **Another source of adaptive genetic variation is admixture between two divergent populations.** In the North American grey wolf (*Canis lupus*) an adaptively important coat colour polymorphism appears to have arisen through hybridisation between wild and domesticated species. Colour morph frequencies differ between forested and open habitats throughout the wolf's range. Melanism in grey wolves is caused by a mutation in the K locus, part of the melanin synthesis pathway; a three base-pair deletion (KB) causes the dominant inheritance of the black coat colour in grey wolves, coyotes and domestic dogs. It seems likely that the mutation arose shortly before the domestication of dogs and has reached high frequency in various dog breeds due to artificial selection. The black coat colour allele is thought to have been absent from North American and Italian grey wolf populations until relatively recently, when it was likely to have been introduced by hybridisation with domestic dogs. In North American grey wolves, black coats have reached highest frequencies in forest habitats, where it has been suggested that the melanic form has a selective advantage as it makes wolves less visible to their prey, although the latter point has not been convincingly demonstrated. In essence, the above is an example of a form of selection acting on standing genetic variation. **Clearly though, the possibility that adaptive genetic variation can arise in natural populations through introgression with domesticated relatives is an intriguing area worthy of further study.**

↑↑ *Indeed it is.*

ii. [Genetics: Seeking a gene genie](http://genetics.seekingagene.com) (Nov 23, 2011) [goo.gl/Crfe9](http://goo.gl/Crfe9)

- Go to a doctor with allergy-related symptoms and it's a safe bet you'll be asked about family history. Clearly there is a heritable component to allergies. The genetic elements, however, have proved fiendishly hard to pinpoint. Since a working draft of the human genome was published in 2001, **the focus of research has shifted from trying to link specific genes and allergies, to genome-**

wide association studies of increasing sensitivity. Evidence of ethnic propensity, and **an interplay between environmental factors and genetic predisposition**, are starting to acuminate this more subtle search for the heritability factors in allergy and asthma.

- The **epigenetics** approach, which seeks to understand how a phenotype may result from the interaction of genes and environmental factors, has been paired with ethnicity-based perspectives through research by Burchard's group. In a recent study they showed a correlation between a mutation in CD14, an immune system gene, and asthma severity in Mexican children who had been exposed to tobacco smoke.
- Providing more evidence of the relevance of epigenetics in understanding allergy, recent European studies suggest that microbes found on pets and farm animals can cause alterations in CD14 and in genes that control the Toll-like receptors, which are also involved with the immune response and confer a protective effect against asthma and allergies. **In order to translate these findings into treatments or preventive strategies, however, researchers need to figure out when and how these epigenetic interactions occur.**
- What's more, epigenetics allergy studies might do more than help scientists understand the development of allergies. **Their findings could also inform research into other disorders that involve gene-environment interactions such as autism and schizophrenia, which is a rich incentive indeed.**

## E. Evidence of recent human evolution

- [Cultural diversification promotes rapid phenotypic evolution in Xavánte Indians](http://goo.gl/10KXt) (Dec 19, 2011)  
[goo.gl/10KXt](http://goo.gl/10KXt)

• Because humans have lived in small aggregates in most of their evolutionary history, studying the influence of cultural practices on the demographic and genetic parameters of small groups can shed more light on modeling the effect of culture on biological evolution. These cultural practices act in combination with geographical and linguistic barriers and can promote faster evolutionary changes shaped by gene-culture interactions. In this context, Neel and Salzano, based on observations among South American native populations, postulated that bands of endogamous hunter-gatherers may split under social tensions, such as dictates of war, disease, and other autochthonous conditions. These fissions generally occur along kinship lines, leading to a highly nonrandom migration. Therefore, **social structure and cultural practices promote demographic isolation and periodic reshuffling of genetic variation, creating unusual combinations of allele frequencies that may play a role in promoting fast evolution.**

↑ *This is a direct indication of recent adaptive copy number changes in humans.*

• Our results support previous assertions that genes and culture plausibly coevolve, often revealing patterns and **rates of change that are uncharacteristic of more traditional population genetic theory**. Gene-culture dynamics are typically faster, stronger and operate over a broaderrange of conditions than conventional evolutionary dynamics, suggesting that **gene-culture coevolution could be the dominant mode of human evolution.**

↑ *Bingo*

• **The most remarkable result of our study is the Xavánte pace of morphological change; the mP on branch 11-XAV (56.5) is 3.8-times greater in relation to the average pace (14.89), which included the geographically and linguistically distant Otomí. The Xavánte pace is also distinct in relation to the morphological change of their sister group (mP 11-KAY = 14.8). This result suggests that the degree of phenotypic diversification of the Xavánte from the common ancestor with its genetic and linguistic sister group, the Kayapó, was accelerated by some mechanism** in comparison with the pattern observed in the remaining branches of the tree.

ii. [Evidence for evolution in response to natural selection in a contemporary human population](#) (Oct 3, 2011) [goo.gl/l6yX7](http://goo.gl/l6yX7)

• It is often claimed that modern humans have stopped evolving because cultural and technological advancements have annihilated natural selection. **In contrast, recent studies show that selection can be strong in contemporary populations.** However, detecting a response to selection is particularly challenging; previous evidence from wild animals has been criticized for both applying anticonservative statistical tests and failing to consider random genetic drift. Here we study life-history variation in an insular preindustrial French-Canadian population and apply a recently proposed conservative approach to testing microevolutionary responses to selection. As reported for other such societies, natural selection favored an earlier age at first reproduction (AFR) among women. AFR was also highly heritable and genetically correlated to fitness, predicting a microevolutionary change toward earlier reproduction. In agreement with this prediction, AFR declined from about 26–22 y over a 140-y period. Crucially, we uncovered a substantial change in the breeding values for this trait, indicating that **the change in AFR largely occurred at the genetic level.** Moreover, the genetic trend was **higher than expected under the effect of random genetic drift alone.** Our results show that **microevolution can be detectable over relatively few generations in humans** and underscore the need for studies of human demography and reproductive ecology to consider the role of evolutionary processes.

iii. [The sociobiology of molecular systems](#) (March 2011) [goo.gl/jFdPt](http://goo.gl/jFdPt)

• **The efficiency benefits of individual specialization and the division of labour apply to biological systems as they do to human society.** This section discusses how competition and cooperation affect the functional diversity that is seen among genes, cells and organisms and the impact of this diversity at the molecular level.

• One solution that is seen in bacteria is to make use of stochasticity, whereby **cells that happen to have a few more copies of a particular molecule have one phenotype, whereas other cells have another phenotype.** However, the most impressive system for generating diversity is that of eukaryotic development, in which stochasticity is used alongside positional signalling and cellular interactions to generate the sophistication that is seen in multicellular organisms.

↑ *Stochasticity ≈ randomness (antonymous with deterministic).*

• A full review of developmental biology is beyond the scope of this article, but **there are relevant parallels between the molecular interactions that take place during the development of a multicellular organism and the development of castes (for example, queen versus worker) in eusocial insects.** As for multicellular development, the field of sociogenomics is finding evidence that **DNA methylation and microRNA expression help insects to diversify into different castes.** There is also a potential role for the production of a range of transcripts from a single locus through alternative splicing of exons. Therefore, whereas intron evolution is often linked to the spread of selfish transposable elements, **the evolution of diversity in exons is more likely to be driven by selection for altruistic multicellular, and possibly societal, organization.**

• There are important differences in the way that cells of multicellular organisms generate functional diversity as compared to the individuals of insect societies. With the exception of cells of the immune system, the cells that make up multicellular organisms are basically clonal, whereas the individuals of most insect societies are not clonal. The existence of genetic differences among individuals opens up the possibility of using not only epigenetics but also genetics to generate functional diversity and determine caste fate. This has led to a wide variety of fascinating, and sometimes bizarre, caste-determination systems that use mixed sexual and asexual reproduction, **or the cross-hybridization of genetically distinct lineages.** The genetic diversity among individuals in social insect colonies also

generates reproductive competition that has strongly shaped their biology in ways not seen in multicellular organisms.

- the spectacular variability in MHC loci is thought to arise because parasites adapt to the most common MHC genotypes. The result is negative frequency-dependent selection, whereby the benefit of a particular MHC allele decreases as it becomes more frequent in a population. **This can drive the continual turnover of genotypes and maintain diversity, because no one genotype can dominate.**
- Another way to evaluate the effects of social evolution on rates of molecular change is to correlate sociality with changes in DNA sequence across genes and species. Recent natural selection for a new function is expected to cause more changes at sites that cause amino acid changes (non-synonymous changes) than at sites that do not (synonymous change). There is evidence that social evolution can affect this pattern. An excess of non-synonymous changes has been associated with social phenotypes in diverse systems, including selfish genetic elements and their repressors, sperm membrane genes and bacterial secretion.

↑↑ Relevant:

i. [A Draft Sequence of the Neandertal Genome](#) (May 2010)

- Features that occur in all present-day humans (i.e., have been fixed), although they were absent or variable in Neandertals, are of special interest. We found 78 nucleotide substitutions that change the protein-coding capacity of genes where modern humans are fixed for a derived state and where Neandertals carry the ancestral (chimpanzee-like) state. Thus, relatively few amino acid changes have become fixed in the last few hundred thousand years of human evolution; an observation consistent with a complementary study. We found only five genes with more than one fixed substitution changing the primary structure of the encoded proteins. **One of these is SPAG17, which encodes a protein important for the axoneme, a structure responsible for the beating of the sperm flagellum.**
- Evolutionary rates are also affected by fundamental factors such as protein abundance and localization, and **social phenotypes might generally experience weaker selection because they are often only expressed some of the time. When this weakens purifying selection, it will tend to increase the genetic diversity associated with social traits relative to the diversity associated with non-social traits.**

↑↑ The adage "If you've met one autistic person then you've met one autistic person" is applicable here.

### III. Epigenetics, Copy Number Variations, and Primate Eusociality

*"I'm interested in one thing, Neo, the future. And believe me, I know: The only way to get there is together."*

– The Oracle

#### A. How epigenetic changes accelerate "Red Queen" adaptations

i. [The Red Queen's Hypothesis](#):

- In reference to an evolutionary system, continuing adaptation is needed in order for a species to maintain its relative fitness amongst the systems being co-evolved with.

↑↑ From the Red Queen's line: **"It takes all the running you can do, to keep in the same place."**

⇒ *The human lineage has been under multiple, quasi-periodic evolutionary pressures (e.g. different ice ages, social group sizes, constitutional requirements, etc.) that we have not simply **adapted to**, but have **adapted to [more rapidly] adapt to**. Copy number variations allow information shared identically in a species' genome (although many CNVs are of rarer DNA) to provide a range of phenotypes that are not heritable in the strict Mendelian sense.*

ii. [Sociality and the Rate of Molecular Evolution](#) (2005) [goo.gl/9PBjp](http://goo.gl/9PBjp)

- The molecular clock does not tick at a uniform rate in all taxa but may be influenced by species characteristics. **Eusocial species (those with reproductive division of labor) have been predicted to have faster rates of molecular evolution** than their nonsocial relatives because of greatly reduced effective population size...

↑↑ *The hypothesis here is partly applicable to agrarian human populations, as they have many specialized social roles (with varying rates of reproduction).*

- ...if most individuals in a population are nonreproductive and only one or few queens produce all the offspring, then eusocial animals could have much lower effective population sizes than their solitary relatives, which should increase the rate of substitution of “nearly neutral” mutations. An earlier study reported faster rates in eusocial honeybees and vespine wasps but failed to correct for phylogenetic nonindependence or to distinguish between potential causes of rate variation. **Because sociality has evolved independently in many different lineages, it is possible to conduct a more wide-ranging study to test the generality of the relationship.** We have conducted a comparative analysis of 25 phylogenetically independent pairs of social lineages and their nonsocial relatives, including bees, wasps, ants, termites, shrimps, and **mole rats**...

↑↑ *Mole rats are notable here because **they are unquestionably eusocial, and are also mammals.***

- ...we show **that the most highly eusocial Hymenoptera do have faster rates than their nonsocial relatives. We also find that social parasites (that utilize the workers from related species to produce their own offspring) have faster rates than their social relatives**, which is consistent with an effect of lower effective population size on rate of molecular evolution.

↑↑ *It's unfortunate that the term “social parasite” was used here to describe a rapidly adapting subpopulation. The distinction between symbiote and parasite is ill-defined:*

From [Wikipedia](#):

**The definition of symbiosis is controversial among scientists.** Some believe symbiosis should only refer to persistent mutualisms, while others believe it should apply to all types of persistent biological interactions (i.e. mutualistic, commensalistic, or **parasitic**).

- The most widely discussed influence of sociality on molecular evolution is through the reduction in effective population size ( $N_e$ : the number of individuals that contribute alleles to each generation), which determines the relative strengths of selection and drift. In a large population with many reproductive individuals, the effect of random sampling on allele frequencies is minimal, so **selection can cause alleles with relatively small selective advantage to go to fixation.**

↑↑ *If I'm not mistaken, this means stronger selection for “babystep” mutations that might have cumulative effects.*

- ... **the fixation of advantageous mutations should be faster in large populations, but nearly neutral mutations will become fixed faster in small populations**—so the magnitude and direction of the population size effect is not clear.

↑↑ *The fact that larger social populations more rapidly affix advantageous mutations is significant to the human species, as we are now a single, global reproducing population. Rare variants that lead to specific phenotypes now have a much larger selection pool to find a compatible partner.*

## B. DNA modularity, copy number variation, and primate phenotypes

⇒ *Variations in copy number are frequent in primate DNA and may play an integral role in the evolution of eusocial (and “primitively eusocial”) organisms. Stably maintaining “intervals of variation” would appear to be any species’ optimal strategy for long-term survival (universal homogeneity has inherent weaknesses), but more so in social species.*

### i. [Hotspots for copy number variation in chimpanzees and humans](#) (2006) [goo.gl/kaOzl](#)

- Previous studies have shown that **human CNV loci** are enriched for genes involved in **immunity and environmental responses**. We performed an analysis based on Gene Ontology (GO) categories for genes that mapped to chimpanzee CNV loci and found a similar pattern for immunity and environmental response-related genes ( $P < 0.001$ ). Several other GO categories were also overrepresented. We then performed a similar analysis for the CNVs that are shared between humans and chimpanzees and found that these loci are enriched for genes in the GO categories of organismal physiological processes ( $P < 0.01$ ), defense response ( $P < 0.01$ ), receptor activity ( $P < 0.001$ ), non-membrane-bound organelles (e.g., cytoskeletal proteins with integral roles in cell structure and stability;  $P < 0.0001$ ), structural molecule activity ( $P < 0.0001$ ), and unknown biological processes ( $P < 0.01$ ). **It is possible that CNVs containing genes in these functional categories are favored and maintained by natural selection in both species.** Alternatively, the observed enrichment may reflect a relative relaxation of selective pressure on copy number for these genes (i.e., stronger purifying selection against copy number variation involving genes in nonenriched categories).

↑ *Human phenotypic variation (physical and cognitive) results from changes in copy number that can, in many cases, be seen as “adaptability intervals” that have been selected for.*

### ii. [A genomic point-of-view on environmental factors influencing the human brain methylome](#) (July 2011) [goo.gl/yOMaJ](#)

- While some common CNVs are polymorphic and often inherited in humans, a higher frequency of de novo rare CNVs are found in patients with autism and schizophrenia compared to unaffected controls.<sup>31-33</sup> In addition, individuals affected by neurodevelopmental disorders in general appear to have a greater overall burden of common polymorphic CNVs than unaffected controls. **Chromosomal regions that are hotspots for primate specific segmental dups and chimpanzee/human differences frequently coincide with the breakpoints of CNVs found in autism and schizophrenia, including 1q21.1, 15q11.2 and 15q13.3.<sup>31</sup>**

↑ *Regions of the genome that are involved in our recent divergence from other primate lineages are also involved in autism and other persistent neurological atypicalities.*

- The other major challenge to interpreting the genetic relevance of CNVs is understanding how the loss or gain of specific chromosomal loci may cause disease. Since the loss of a gene copy is generally expected to be more pathogenic than a gain, the goal of human CNV disease association studies is often to find genes within small rare CNV deletions. **However, this worthy approach may be unjustifiably ignoring the “elephant in the room” of rare CNV duplications associated with autism that are much larger than deletions (>500 kb) and contain more genes implicated in autism than the CNV deletions that are more intensely investigated.**

↑ *Many copy number variations are clearly adaptive. If genetic variation were selectively introduced (via evolved meiotic machinery or the like) to regions that are robust against recombination (i.e. that have minimal pathological recombination possibilities, perhaps as a result of their physical location on the chromosome molecule) at a rate mediated by external factors (e.g. fraternal birth order, perinatal environment, etc.), this could allow immune or sweat gland*

genes to adapt more rapidly in the progeny of a particularly disease-ridden or temperature varied generation. This process is akin to somatic hypermutation:

i. [Wikipedia: Somatic Hypermutation](#)

- When a B cell recognizes an antigen, it is stimulated to divide (or proliferate). During proliferation, the B cell receptor locus undergoes an extremely high rate of somatic mutation that is at least 10<sup>5</sup>-10<sup>6</sup> fold greater than the normal rate of mutation across the genome.

↑ *Adaptive, selective mutation in response to an environmental stimulus.*

- Variation is mainly in the form of single base substitutions, with insertions and deletions being less common.

↑ *The fact that intragenerational genetic changes to immune function rely on single base substitutions rather than CNVs might indicate selective pressure against the evolution of systems that directly alter genes in the germline. Immune adaptation would be exempt from this pressure because it is evidently not directly inherited. Phenotypic differences would arise mostly from copy number variable DNA that might be completely shared by the vast majority of humans (meaning most people would have at least one copy, and would hence be able to produce any of a number of phenotypes depending on how many deletions/duplications occur in their germ line).*

- These mutations occur mostly at “hotspots” in the DNA, known as hypervariable regions. These regions correspond to the complementarity determining regions; the sites involved in antigen recognition on the immunoglobulin. The exact nature of this targeting is poorly understood, although is thought to be controlled by a balance of error-prone and high fidelity repair.

↑ *CNVs also occur at “hot spots” that are primed for stable, advantageous adaptation. This priming could easily be part of an evolved mechanism to respond to **specific environmental stimuli**.*

- This directed hypermutation allows for the selection of B cells that express immunoglobulin receptors possessing an enhanced ability to recognize and bind a specific foreign antigen.

↑ *In the analogous CNV scenario, selection still plays a vital role. The introduced mutation might merely increase the total variation of a particular trait (like sweat production), but mate-selection and natural selection would ensure that the end result would be the same as in direction-specific models of epigenetic adaptation.*

## C. Hybridization and methylation

i. [Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain](#) (2011) [goo.gl/MXHMw](http://goo.gl/MXHMw)

- Global methylation profiling of [lymphoblastoid cell lines] from phenotypically discordant monozygotic twins and nonautistic siblings **highlights the role of epigenetic regulation in idiopathic autism and reveals DNA methylation as a mechanism** through which this regulation may occur. Two candidate genes, BCL-2 and RORA, which were identified from our coupling of methylation with gene expression data, exhibited increased methylation of specific CpG sites in respective upstream regulatory CpG islands that coincided with methylation-specific gene silencing. Translation of these findings from LCLs to the detection of decreased BCL-2 and RORA protein in post mortem brain tissues of autistic individuals further confirms the feasibility of using LCLs as a surrogate model for autism, particularly when investigating dysregulated genes with systemic functions, such as apoptosis

and circadian rhythm. In addition to identifying key autism candidate genes, these studies also yield further insight into the pathobiology of this complex disorder by elucidating **global epigenomic modifications relevant to the autistic phenotype**.

- Aside from shedding light on higher-order regulation of gene expression, another compelling reason to investigate epigenetic mechanisms in idiopathic autism is that such modifications can be influenced by exposure to biological modulators and environmental factors. **Epigenetics may thus mediate the interaction between genotype and intrinsic (biological) or extrinsic (environmental) factors contributing to ASDs.**

ii. [Evolutionary Breakpoints in the Gibbon Suggest Association between Cytosine Methylation and Karyotype Evolution](#) (2009) [goo.gl/5WHR5](http://goo.gl/5WHR5)

- This correlation suggests a common source of instability independent from genomic sequence and related to the epigenetic state of the DNA. O'Neill and colleagues showed that the genome of **a hybrid between two species of Australian wallaby (marsupials) was hypomethylated when compared to the parental species**. In these hybrids a hypomethylated retroviral element was abnormally replicated causing an evident centromeric expansion. The same group also reported double-minute chromosome formation in mouse interspecific hybrids (M. musculus×M. caroli) [30]. **Together with our findings this observation indicates that changes in methylation levels may explain perturbations of the uniform rate of genome evolution.**

↑ *This suggests that hybridization can disrupt methylation (epigenetic regulation of gene expression).*

## D. Neuronal differentiation

i. [blogs.nature.com | Brain cell genomes show their individuality](#) (Nov 14, 2011) [goo.gl/aFI6o](http://goo.gl/aFI6o)

- A study of the genomes of individual human neurons created from reprogrammed stem cells reveals huge variability between neurons from the same person. **Such variation could explain differences in behaviour and susceptibility to mental illness**, says Mike McConnell, a stem-cell biologist at the Salk Institute in La Jolla, California. He presented the work on 13 November at the Society for Neuroscience conference in Washington DC.
- **“Monozygotic twins can, from time to time, be discordant for things like schizophrenia, for things like autism. They grew up together. They have the same genome, why are they different,”** he says.

↑ *They're different because their individual brain epigenomes “unfolded” differently. Identical twins also don't share fingerprints and don't necessarily share sexual orientation. Many of the probabilistic, high-entropy functions that exist in biology are also adaptively chaotic (i.e. have unpredictable time evolutions and are sensitive to small changes in initial conditions) as part of a deterministically stable whole.*

- No brain cell's genome looked the same. They all contained numerous duplications and deletions, but never in the same pattern. The team also examined the genomes of the adult cells that were reprogrammed into iPS cells and then neurons, and these cells contained numerous insertions and deletions, but not the same ones as the neurons. McConnell says that this suggests that cells acquire their own genomes as they turn into neurons.

↑ [Neurons are epigenetically differentiated](#); this seems to occur mostly in utero. [goo.gl/BVLMG](http://goo.gl/BVLMG)

## E. Evidence that some primates have evolved eusocial capacities

i. [Routes to Eusociality in Primates and Other Species](#) (2005) [goo.gl/86pXX](http://goo.gl/86pXX)

- Jones (1996a) provided evidence suggesting that **female mantled howler monkeys (*Alouatta palliata*) demonstrate temporal division of labor (age-related polyethism) whereby apparently altruistic behavior ("social foraging") is increasingly likely to be exhibited with increasing age and decreased likelihood of selfish reproduction.**

- Studying meerkats (*Suricata suricatta*), Clutton-Brock et al. (2003) concluded that age-related polyethism in this species does not represent "incipient" division of labor in the sense of "functional specialization" found in eusocial taxa. The critical finding by these authors was that meerkats did not specialize in particular activities but that different activities were expressed as a function of age and that "individual differences in foraging success became the principal factor affecting contributions to cooperative behavior," as for female mantled howlers.

↑↑ *A few paragraphs later:*

**Further research is required to document this possibility and to test the claim by Clutton-Brock et al. (2003) that age (or size) polyethism is not "incipient" eusociality (functional specialization). Perhaps polyethisms are one route to eusociality (see, for example, Traniello and Rosengaus, 1997; Tofilski, 2002; Keller, 2003; "trajectories". Fig. 8.1).**

- The combined results from these studies suggest that factors, possibly energetic ones (Jones and Agoramoorthy, 2003, pp. 124-125; see Russell et al., 2003), related to foraging may be the initial route to advanced sociality in social mammals and, perhaps, other social species as well (Beshers et al., 2001; Wahl, 2002). **Crespi and Choe (1997a; also see Crespi and Yanega, 1995) point out the important relationship between eusociality and loss of the capacity to become a reproductive dominant.**

- Cases of incipient primate eusociality, then, should be sought in situations where individuals obtain a low likelihood of achieving reproductive dominance combined with high reproductive skew.

- Traniello and Rosengaus (1997, p. 209), for example, discuss the "dynamic nature and fluidity of task allocation" in social insects and quote Holldobler and Wilson (1990): "Each species has its own distinctive pattern of temporal polyethism." These authors point out that **the study of temporal (age-related) polyethism and related social features encompass the domains of behavioral flexibility, including development.**

- Consistent with the socioecological model advanced by Sterck et al. (1997) for primates. Traniello and Rosengaus (1997) emphasize the importance of historical and ecological factors, particularly "nutritional ecology," to explain interspecific variation in social structure.

- **Like primates, some social insects do not display irreversible nonreproductive roles** (see Traniello and Rosengaus, 1997, pp. 210-211), exhibiting what these authors term "reproductive plasticity."

ii. [Human uniqueness: genome interactions with environment, behaviour and culture](#) (2008) [goo.gl/VoKPs](http://goo.gl/VoKPs)

- Here we take a genomic and genetic perspective towards molecular variation, explore systems analysis of gene expression and discuss an organ-systems approach. Rejecting any 'genes versus environment' dichotomy, we then consider genome interactions with environment, behaviour and culture, finally speculating that **aspects of human uniqueness arose because of a primate evolutionary trend towards increasing and irreversible dependence on learned behaviours and culture — perhaps relaxing allowable thresholds for large-scale genomic diversity.**

↑↑ *Significant intraspecific variation has evolved in social primates, and is perhaps behind homo sapiens' recent evolutionary acceleration.*

iii. [Fission-fusion and the evolution of hominin social systems](#) (Dec 2011) [goo.gl/fVNGGq](http://goo.gl/fVNGGq)

• The model considered here suggests that **a trend towards larger group sizes in more recent populations combined with a trend towards lower population densities at higher latitudes** led to a dramatic increase in area requirements for hominin groups expanding from the tropics, and that those groups responded to this pressure by developing **fission-fusion social systems at varying levels**. This scenario is in accord with a number of studies examining patterns of fission and fusion in extant non-human primates, as well as with research examining **hierarchically nested grouping structures in modern hunter-gatherer and sedentary groups**. The Ecological Constraints Hypothesis (henceforth ECH) suggests that the area required to meet the energetic and nutritional requirements of a group of animals will increase with group size, resulting in a concomitant increase in travel costs as the group ranges further. Eventually, “some point will be reached at which energy spent in travel exceeds the energy obtained from the environment, and a smaller group size will become advantageous.” This premise has been tested extensively among primates, with the majority of studies reporting either positive correlations between group size, home range size, day range, or percentage time spent feeding or, primarily in fission-fusion societies, negative correlations between resource density and group size. **This latter result suggests that fission-fusion allows primate groups to achieve what is effectively a dynamic ideal free distribution**, adjusting group sizes at fine temporal scales to variations in resource abundance.

↑ *Humans have recently adapted to be able to fit into any one of a number of different social structures. Population-scale selection for different social-cognitive phenotypes is implied.*

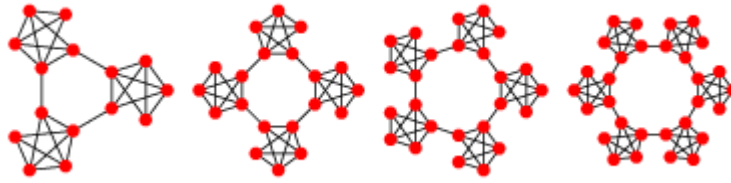
• A key component of the model presented here is that reductions in population density with group size held constant will necessitate larger areas per group. However, as pointed out by Chapman et al. (1995), density is one of three components that together characterize habitat structure. The size of individual patches and their distribution in space are variables that can change independently of patch density, and small foraging groups should be favoured primarily when patches are low in density, uniform in distribution, and small in size (Chapman et al., 1995). In all other situations, there is nothing to prevent the community foraging as a cohesive unit. The structure of the habitat is of equal importance to hunter-gatherers, although the scale at which it is perceived may be extended by the emphasis on equitable bonds with neighbouring groups (Grove, 2010b) and the function of those bonds as insurance mechanisms against potential subsistence failure (Whallon, 2006). Whallon (2006) has recently suggested that **the most important habitat variable among modern hunter-gatherers may be resource heterogeneity at the inter-community scale, since for the strategy of variance reduction through bonds with neighbouring groups to be effective those groups must inhabit areas that are non-synchronized in their resource potentials**. Only when this is true can extended networks avert risks created by unpredictable resource failures.

↑ *“No man is an island” is an understatement. Humans have to communicate and exchange to survive.*

• The research of Korstjens and colleagues suggests that, over evolutionary timescales, fission-fusion has arisen to facilitate the formation of larger communities via the elevated foraging efficiency achieved in small subgroups. This logic, combined with the scenario described by the results presented here, suggests that as community sizes increase, so the size of the foraging group should remain relatively constant, since this smaller group size should be optimized with respect to foraging efficiency in the context of additional constraints such as predation risk and other inherent benefits to grouping. In the hunter-gatherer sample utilised in the current paper, despite population size varying by over two orders of magnitude, and population home range by almost four orders of magnitude, the size of the foraging group is remarkably constant, with 91% of group sizes falling between five and 27 and a median of 16, mean of 17, and mode of 18. **This suggests that hunter-gatherers requiring larger areas to support their populations due to constraints on population**

density or other factors manage those areas by fissioning into ever-greater numbers of lower-level groups.

↑ Social networks can follow a similar pattern, known prophetically as a “*Caveman graph*”



From [Wolfram Mathworld](#):

The (connected) **caveman graph** is a graph arising in social network theory formed by modifying a set of isolated  $k$ -cliques (or "caves") by removing one edge from each clique and using it to connect to a neighboring clique along a central cycle such that all  $n$  cliques form a single unbroken loop (Watts 1999).

*On a circuitously related note, Mark Zuckerberg is probably somewhere on the spectrum.*

- That is, the size of the lower-level grouping remains approximately constant, but the number of groups of this size increases in linear fashion as the overall size of the area utilized increases. Regressing total area utilized against the ratio of foraging group to total population size (an index of the number of foraging groups that the population divides into), demonstrates that this is indeed the case ( $F_{1,187} = 94.57$ ,  $R^2 = 0.336$ ,  $p < 0.001$ ; see Fig. S3). **This suggests that the function of fission-fusion grouping patterns in humans may be the same as that among non-human primates and other animals, even though the former occurs over much larger spatio-temporal scales.**

↑ Yup.

iv. [Specialized Face Learning Is Associated with Individual Recognition in Paper Wasps](#) (Dec 2011)  
[goo.gl/eWgdU](http://goo.gl/eWgdU)

- We demonstrate that the evolution of facial recognition in wasps is associated with specialized face-learning abilities. **Polistes fuscatus can differentiate among normal wasp face images more rapidly and accurately than nonface images or manipulated faces. A close relative lacking facial recognition, Polistes metricus, however, lacks specialized face learning.**

↑ *Autism is associated with face-blindness and a good sense of folk physics. The following is from EO Wilson's [The Evolution of Eusociality](#) (2010):*

In a second example, discovered in the fire ant *Solenopsis invicta*, new variants of the major gene Gp-9 greatly reduce or remove the ability of workers to recognize aliens from other colonies, as well as the ability to discriminate among fertile queens. **The resulting ‘microgyne’ strain forms dense, continuous supercolonies that have spread over much of the species range in the southern United States.**

↑ *Presumably this rapid, eusocial colonization of North America didn't require the collective pursuit of “manifest destiny” or similarly nonsensical abstractions, but the parallels are still quite evident.*

- **Similar specializations for face learning are found in primates and other mammals, although *P. fuscatus* represents an independent evolution of specialization. Convergence toward face specialization in distant taxa as well as divergence among closely related taxa with different recognition behavior suggests that specialized cognition is surprisingly labile and may be adaptively shaped by species-specific selective pressures such as face recognition.**

↑ *This relates to primate eusociality via the following biological analog:*

v. [Identifying personality from the static, nonexpressive face in humans and chimpanzees: evidence of a shared system for signaling personality](#) (2010) [goo.gl/Ds25O](http://goo.gl/Ds25O)

- As expected from our previous studies, identification accuracy was again significantly above chance for chimpanzee dominance (accuracy=0.58;  $t_{35}=3.24$ ,  $p=.003$ ). Performance was also accurate on human Extraversion judgments (accuracy=0.77;  $t_{35}=10.34$ ,  $p<.001$ ). However, the within-rater correlation for accuracy on chimpanzee and human faces was not significant ( $r_{34}=-0.08$ ,  $p=.65$ ). We also saw some individual differences in performance on the tasks. **Participant scores on the “social skills” domain of the Autism Spectrum Quotient (AQ) were negatively correlated with accuracy on the human discrimination task ( $r_{34}=-0.37$ ,  $p=.025$ ) but not the chimpanzee task ( $r_{34}=-0.01$ ,  $p=.972$ ).** This negative relationship suggests that those with higher levels of **autistic-like traits** relating to social skills were **specifically** worse at reading the signs of extraversion in human faces.

↑↑ *Autistics can analyze chimp expressions as well as most people, but not always other human faces.*

vi. [Correlated evolution of brain regions involved in producing and processing facial expressions in anthropoid primates](#) (2010) [goo.gl/1DjtG](http://goo.gl/1DjtG)

- **The results of our study suggest a pattern of correlated evolution linking group size, facial motor control and cortical visual processing in catarrhine primates.** Species that live in relatively large social groups tended to have relatively large facial motor nuclei, and species with enlarged facial nuclei had relatively large primary visual cortices. **These results mirror previous findings that species characterized by relatively large social groups also have enhanced facial mobility** and relatively large V1 volume. Thus, our results support the view that the primary visual cortex is adapted for processing facial signals in certain anthropoids (Allman 1977). Alternative explanations for these patterns are possible however. Furthermore, additional factors may be responsible for V1 expansion in anthropoids, including diet (Barton 1998).

↑↑ *The hypothesis that facial mobility is correlated with social group size in primates is supported by experimental evidence.*

## F. Additional information regarding primates and CNVs

i. [Gene copy number variation spanning 60 million years of human and primate evolution](#) (2007) [goo.gl/e87aZ](http://goo.gl/e87aZ)

- Many of the genes identified here are likely to be important to lineage-specific traits including, for example, human-specific duplications of the AQP7 gene, which represent intriguing candidates to underlie the key physiological adaptations in thermoregulation and energy utilization that permitted human endurance running.

↑↑ *Perhaps only a subset of an organized, phenotypically heterogeneous tribe would be chasing caribou to death.*

ii. [Analysis of one million base pairs of Neanderthal DNA](#) (2006) [goo.gl/PKtld](http://goo.gl/PKtld)

- The data presented in Fig. 4 show that when the hit density for sequences that have a single best hit in the human genome is plotted along the chromosomes, several suggestive local deviations from the average hit density are seen, which may represent **copy-number differences** in the Neanderthal relative to the human reference genome. For comparison, we generated 454 sequence data from a DNA sample from a modern human. **Interestingly, some of the deviations seen in the Neanderthal are present also in the modern human**, whereas others are not. The latter group of sequences may indicate copy-number differences that are unique to the Neanderthal relative to the modern human genome sequence. Thus, when more Neanderthal sequence is generated in the future, it

may be possible to determine copy number differences between the Neanderthal, the chimpanzee and the human genomes.

↑ *Before the introgression Neanderthals had diverged from the homo sapiens line (~700 kya), in part through the “spring loaded” epigenetic mechanisms that our mutual ancestor had evolved.*

iii. [A Burst of Segmental Duplications in the African Great Ape Ancestor](#) (2009) [goo.gl/HtdeZ](http://goo.gl/HtdeZ)

- Wilson and King were among the first to recognize that **the extent of phenotypic change between humans and great apes was dissonant with the rate of molecular change**. Proteins are virtually identical; cytogenetically there are few rearrangements that distinguish ape-human chromosomes; rates of single-base pair change and retroposon activity have slowed particularly within hominid lineages when compared to rodents or monkeys.

↑ *This is because humans recently underwent **very rapid selection** for a specific phenotypic subset of our great ape ancestors’ more diverse genome. **In the space of all possible genomes, we used the additional volume offered by epigenetic changes and copy number variations** to quickly acquire big brains, physical endurance, sweat glands, long lifespans with distinct phases (including an incredibly long infancy and childhood), and a number of other uniquely human traits.*

- Here, we perform a systematic analysis of duplication content of four primate genomes (macaque, orangutan, chimpanzee and human) in an effort to understand the pattern and rates of genomic duplication during hominid evolution. We find that the ancestral branch leading to human and African great apes **shows the most significant increase in duplication activity both in terms of basepairs and in terms of events**. This duplication acceleration within the ancestral species is significant when compared to lineage-specific rate estimates even after accounting for copy-number polymorphism and homoplasy. We discover striking examples of recurrent and independent gene-containing duplications within the gorilla and chimpanzee that are absent in the human lineage.

↑ *In short: CNVs are relevant to recent human and primate evolution.*

- Our results suggest that the evolutionary properties of copy-number mutation differ significantly from other forms of genetic mutation and, in contrast to the hominid slowdown of single basepair mutations, **there has been a genomic burst of duplication activity at this period during human evolution.**

iv. [Human uniqueness: genome interactions with environment, behaviour and culture](#) (2008) [goo.gl/KtVcB](http://goo.gl/KtVcB)

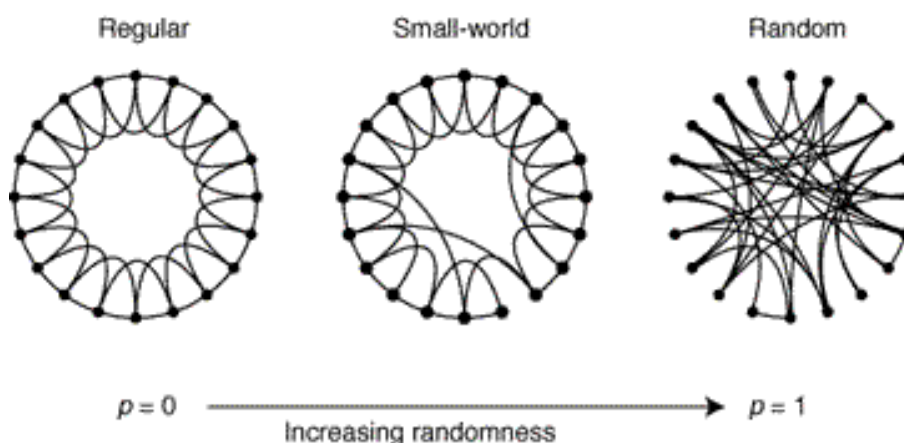
- CNV diversity might be higher in humans, despite the small effective population size. **There could also be fitness benefits associated with the propensity to generate and tolerate more CNVs, for example, the expansion of amylase gene copies in humans**. It is interesting that in this case **copy numbers progressively drop as we move from agricultural humans to non-agricultural humans to chimpanzee and bonobo.**

↑ *Agrarian societies tend to benefit more when their populations consist of individuals with variable physical makeups and behaviors. This is analogous to eusocial species structures that involve highly specialized phenotypes (queen, worker, etc.).*

- It is also interesting that CNVs are now being recognized as significant causes of neuropsychiatric conditions, and so the question is whether they are more common in more subtle forms of human-specific diseases related to brain function and social interaction.

↑ *Human social behavior is highly variable within populations. This relates to the ideal solution to the small world problem. If a subset of humans are “social butterflies,” maintaining distant connections, while others are introverts with a few close friends, the “degrees of separation”*

between any two people (and, hence, an “effective distance” involved in an exchange of information (like a method of stone knapping or a narrative)) are minimized on a bounded surface (e.g. a sphere). Analogously, a ring of points that are locally connected (linearly increasing distance between points requires a linearly increasing number of node jumps) is less ideal than a ring of points that are both locally **and** non-locally connected (assuming information is shared, implying [connectedness](#)):



↑ The small world phenomenon **is also evident at the genetic level**:

v. [Impact of epistasis and pleiotropy on evolutionary adaptation](#) (Jan 2012) [goo.gl/umBx7](http://goo.gl/umBx7)

- Evolutionary adaptation is often likened to climbing a hill or peak. **While this process is simple for fitness landscapes where mutations are independent, the interaction between mutations (epistasis) as well as mutations at loci that affect more than one trait (pleiotropy) are crucial in**

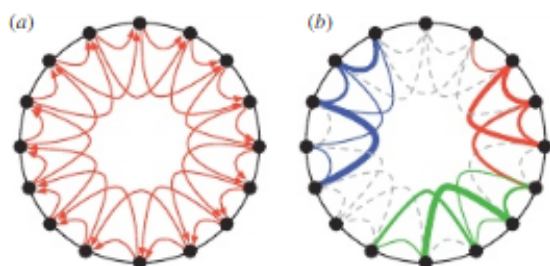


Figure 1. NK model haplotypes for  $N = 16$  and  $K = 2$ . For these parameters, the fitness contribution of each locus is determined by interacting with two loci (adjacent in the representation shown here), giving rise to blocks of  $2K + 1$  interacting genes. (a) Interactions between loci represented by lines, with arrows indicating which loci affect the fitness component of other loci. (b) Actual epistatic interactions on a particular high-fitness peak, where the width of the lines indicates the strength of epistatic interactions (thicker lines equal higher values of  $\epsilon$ , defined in the main text). Three modules of interacting loci are coloured. The remaining interactions (dashed grey lines) are weak (arrowheads omitted for clarity).

**complex and realistic fitness landscapes.** We investigate the impact of epistasis and pleiotropy on adaptive evolution by studying the evolution of a population of asexual haploid organisms (haplotypes) in a model of  $N$  interacting loci, where each locus interacts with  $K$  other loci. We use a quantitative measure of the magnitude of epistatic interactions between substitutions, and find that it is an increasing function of  $K$ . **When haplotypes adapt at high mutation rates, more epistatic pairs of substitutions are observed on the line of descent than expected. The highest fitness is attained in landscapes with an intermediate amount of ruggedness that balance the higher fitness potential of interacting genes with their concomitant decreased evolvability. Our findings imply that the synergism between loci that interact epistatically is crucial for evolving genetic modules with high fitness, while too much ruggedness stalls the adaptive process.**

↑ You'll notice that the rightmost graph approximates the connectedness of **a hybrid small-world/caveman graph** (discussed above). Community **and** individuality are fundamental parts of the human condition. Fancy that.

vi. [MicroRNA Expression and Regulation in Human, Chimpanzee, and Macaque Brains](#) (Oct 2011) [goo.gl/p8V4n](http://goo.gl/p8V4n)

- Enrichment in neural functions, as well as miRNA-driven regulation on the human evolutionary lineage, was further confirmed by experimental validation of predicted miRNA targets in two neuroblastoma cell lines. **Finally, we identified a signature of positive selection in the upstream**

region of one of the five miRNA with human-specific expression, miR-34c-5p. This suggests that miR-34c-5p expression change took place after the split of the human and the Neanderthal lineages and had adaptive significance. Taken together these results indicate that changes in miRNA expression might have contributed to evolution of human cognitive functions.

↑ *Human and Neanderthal brains differed in miRNA expression. This is relevant:*

[Copy number variation of microRNA genes in the human genome](https://doi.org/10.1016/j.cub.2011.05.001) (2011) [goo.gl/oS4s1](https://doi.org/10.1016/j.cub.2011.05.001)

- We postulate that CNV-miRNAs are potential functional variants **and should be considered high priority candidate variants in genotype-phenotype association studies.**

## G. Additional information regarding hybridization and adaptive social heterogeneity

### i. [Evolutionary genetics in wild primates: combining genetic approaches with field studies of natural populations](https://doi.org/10.1016/j.cub.2011.05.001) (June 2010) [goo.gl/0X40r](https://doi.org/10.1016/j.cub.2011.05.001)

- Similar kinds of data are available for many natural primate populations, making it possible to connect estimates of population genetic change with the underlying behavioral processes that generate it [36, 37]. Such studies can illustrate how **behavioral variation among individuals and behavioral plasticity within individuals—hallmarks of many primates—can influence the maintenance and distribution of genetic variation within populations (and also between populations and species in the more extreme case of hybridization: Box 2).**
- Genetic analyses and field observations can be merged to study an extreme case of gene flow, naturally occurring hybridization between primate species. **Hybridization is a common phenomenon among primates, and has been proposed to play an important role in the evolution of the primate lineage.** Studying hybridization in wild primates is therefore of great interest for investigating the emergence of genetic and phenotypic differences between divergent groups.

↑ *Our species has the capacity to organize culture around phenotypic diversity (e.g. the celebration of gigantism in Northern France, the recognition of third gender roles such as the Indian Hijra and Samoan Fa'afafine, etc.). This facet of the human condition is also a motif in many Wes Anderson movies:*

"When I look down this table, with the exquisite feast set before us, I see: two terrific lawyers, a skilled pediatrician, a wonderful chef, a savvy real estate agent, an excellent tailor, a crack accountant, a gifted musician, pretty good minnow fisherman, and possibly the best landscape painter working on the scene today. Maybe a few of you might even read my column from time to time, Who knows? I tend to doubt it.

I also see a room full of **wild animals.**

Wild animals, with true natures and pure talents. Wild animals with scientific-sounding Latin names that mean something about our DNA. Wild animals each with his own strengths and weaknesses due to his or her species.

Anyway, I think it may very well be all the beautiful differences among us that might just give us the tiniest glimmer of a chance of saving my nephew, and letting me make it up to you for getting us into this, this crazy... whatever it is. I don't know. It's just a thought. Thank you for listening. Cheers, everyone."

- Mr. Fox, (*The Fantastic Mr. Fox*, 2009)

- Phenotypic data and genetic estimates of admixture can be combined, for instance, to investigate how hybridization influences fitness-related traits. In baboons (genus *Papio*), naturally occurring hybridization occurs at the geographic boundaries between all five species. Long-term observations in a hybrid zone in Ethiopia between anubis baboons (*P. anubis*) and hamadryas baboons (*P. hamadryas*) suggest that **behavioral prezygotic isolation does not play a strong role in checking this**

process, despite markedly different social structures that characterize these two species. Although hybrid males suffer a disadvantage in gaining mates in some groups, they do equally as well as other males in groups that include many hybrids.

- In Kenya, where yellow baboons (*P. cynocephalus*) and anubis baboons sometimes hybridize, genetic and phenotypic data suggest that **hybrids might in fact enjoy a fitness advantage**. More anubis-like individuals mature earlier, especially males; anubis-like males also appear to be more successful in competing for mates (Tung, Alberts, and J. Altmann, unpublished data). **These data contrast sharply with work on hybridization in New World howler monkeys**. Although mantled howler monkeys (*Alouatta palliata*) and black howler monkeys (*A. pigra*) naturally hybridize where their ranges overlap in Mexico, observational and genetic evidence suggest that only female hybrids are viable and fertile. **This case represents perhaps the best evidence for the accumulation of intrinsic postzygotic isolation in naturally hybridizing primates, suggesting fertile ground for comparison between cases of hybridization across different primate taxa.**
- Future work on these systems will be able to both investigate how **genetic background correlates with interesting traits, and attempt to identify the loci responsible for phenotypic differences between hybridizing species**. Admixture mapping approaches, which investigate how ancestry-informative genetic markers and trait variation cosegregate among admixed individuals, will be particularly appropriate for this line of work. Additionally, increasing amounts of genetic data on hybridizing populations will enable investigators to complement data on hybridization in the present with estimates of the timing and rate of gene flow between species in the past.
- In nonhuman primates, sample sizes for genetic studies will generally be relatively small. Where possible, the existence of both captive and wild populations for a given species can be leveraged to test replication of apparent genetic effects (although some caveats attach to such comparisons: see Box 3). For example, **hybridization between yellow baboons and anubis baboons is known to influence morphological traits in the wild**. A QTL mapping study in captive baboons (a colony that also includes anubis-yellow hybrids) has identified candidate regions of the genome that influence morphological variation, providing insight into the possible basis for this effect. As the genetic basis for such traits becomes more clear, checking for consistency between multiple populations should therefore be of considerable interest.

ii. [A proper study for mankind: Analogies from the Papionin monkeys and their implications for human evolution](#). (2001) [goo.gl/Q1ThV](http://goo.gl/Q1ThV)

- **Another source of phylogenetic uncertainty is the possibility of gene-flow by occasional hybridization between hominins belonging to ecologically and adaptively distinct species or even genera**. Although the evidence is unsatisfactorily sparse...

↑ *Note: This was published almost 10 years before scientists confirmed admixture.*

- ...it suggests that among catarrhines generally, regardless of major chromosomal rearrangements, intersterility is roughly proportional to time since cladogenetic separation.

↑ *The more genetically divergent the two species, the harder it will be to produce a viable line. This may explain why there were, according to some models, very few (~500) successful Neanderthal admixtures.*

- On a papionin analogy, especially the crossability of *Papio hamadryas* with *Macaca mulatta* and *Theropithecus gelada*, crossing between extant hominine genera is unlikely to produce viable and fertile offspring, but **any hominine species whose ancestries diverged less than 4 ma previously may well have been able to produce hybrid offspring that could, by backcrossing, introduce alien genes with the potential of spreading if advantageous.**

↑ *Bingo*

- Selection against maladaptive traits would maintain adaptive complexes against occasional genetic infiltration, and **the latter does not justify reducing the hybridizing forms to a conspecific or congeneric rank.**

↑ *Which is why scientists haven't unanimously classified Neanderthals as "homo sapiens neanderthalensis."*

- **Whether reticulation could explain apparent parallels in hominin dentition and brain size is uncertain, pending genetic investigation of these apparently complex traits.**

↑ *They're working on it.*

- Neandertals and Afro-Arabian "premodern" populations may have been analogous to extant baboon (and macaque) allotaxa: "phylogenetic" species, but "biological" subspecies. "Replacement," in Europe, probably involved a rapidly sweeping hybrid zone, driven by differential population pressure from the "modern" side. **Since the genetic outcome of hybridization at allotaxon boundaries is so variable, the problem of whether any Neandertal genes survived the sweep, and subsequent genetic upheavals, is a purely empirical one; if any genes passed "upstream" across the moving zone, they are likely to be those conferring local adaptive advantage, and markers linked to these.**

↑ *Yup.*

### iii. [Molecular mechanisms of polyploidy and hybrid vigor](#) (2010) [goo.gl/3eU9y](http://goo.gl/3eU9y)

- By definition, **most heterozygous animals, including humans, are hybrids** that carry different alleles from female and male parents.

↑ *Evolving this form of hybridization helps to advantageously facilitate the more traditional kind by carefully divvying up genes amongst specific recombination zones on each chromosome. Genomic imprinting is an example of this lineage segregation:*

[Genomic imprinting](#) is a genetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner. It is an inheritance process independent of the classical Mendelian inheritance.

- In mammals, **hybrid incompatibilities** are related to abnormal expression patterns of imprinting genes in interspecific hybrids in *Peromyscus* or **epigenetic activation of retroelements** in marsupial hybrids. In plants, some imprinted genes were abnormally silenced in *Arabidopsis* interspecific hybrids, and many protein-coding genes are **epigenetically** regulated in allotetraploids.

↑ *Well that sure sounds relevant...*

- For the genetically viable hybrids, the degree of heterosis is proportional to the genic differences in two parental strains. In other words, **the levels of heterosis increase as the genetic distances between the parents increase.**

↑ *Inbreeding is widely understood to be a bad thing. What's slightly less well-known is the fact that the opposite, heterosis, is usually a good thing.*

- After evaluating the phenotypic data from 37 genera, including *Zea*, *Solanum*, and *Nicotiana*, E.M. East (1936) noted that interspecific hybrids generally show more heterosis than intraspecific hybrids, if the genetic difference between the species or genera does not prevent them from forming compatible hybrids. The hybrids formed between different subgenera show more heterosis than the hybrids formed between species within the same subgenera. **If the hybrids are incompatible, they are dwarf and stunted, probably because dramatic differences in growth and reproductive development inherited from the divergent parents fail to be reconciled.**

↑ *Certain human phenotypic outliers (dwarfism, gigantism, etc.) have both stable and unstable variants (Yao Ming's gigantism is seen as a beneficial extreme of the norm, but other cases (pituitary tumor-induced) shorten lifespan and are clearly deleterious). Perhaps the stable forms are, in part, from niche hominid introgression (perhaps this could be said of **all** consistent human phenotypes). Extreme human variation was viewed differently in the past:*

[Skeletal dysplasia in ancient Egypt](#) (2008) [goo.gl/HTCJN](http://goo.gl/HTCJN)

- Among the remains of dwarfs with achondroplasia from ancient Egypt (2686-2190 BCE), exists a skeleton of a pregnant female, believed to have died during delivery with a baby's remains in situ. British museums have partial skeletons of dwarfs with achondroplasia, humeri probably affected with mucopolysaccharidoses, and a skeleton of a child with osteogenesis imperfecta. **Skeletal dysplasia is also found among royal remains.** The mummy of the pharaoh Siptah (1342-1197 BCE) shows a deformity of the left leg and foot. A mummified fetus, believed to be the daughter of king Tutankhamun, has scoliosis, spina bifida, and Sprengel deformity. [...] **The artistic documentation of people with skeletal dysplasia from ancient Egypt is plentiful including hundreds of amulets, statues, and drawing on tomb and temple walls. Examination of artistic reliefs provides a glance of the role of people with skeletal dysplasia and the societal attitudes toward them. Both artistic evidence and moral teachings in ancient Egypt reveal wide integration of individuals with disabilities into the society.**
- Indeed, the hybrids formed between subgenera often have more heterosis as well as more dwarfs. For example, most intergeneric or interspecific hybrids are abnormal, and yet the greatest amount of heterosis is found in the hybrids derived from Raphanus and Brassica. In rice, the hybrids between two subspecies show more heterosis than the hybrids between varieties within a subspecies. However, the notion may not be generalized across all hybrids. In maize (*Z. mays*) and tobacco, although the varieties (inbred lines) are genetically similar, the hybrids formed between different combinations of varieties show dramatic levels of heterosis. **This suggests that the interaction between a few genes or the combination of a few genes in a genetic cross plays an important role in heterosis, as observed in tomato.** Alternatively, large-scale recombination suppression accompanied by a high level of residual heterozygosity could be associated with inbreeding depression and heterosis in maize. Notably, **genetic mechanisms responsible for heterosis may be different between the species that are naturally self-pollinating and out-crossing.** Heterosis is more predominant in outcrossing than inbreeding species, and the inbreeding populations do not have obvious heterosis of fitness.

↑ *Humans probably evolved to benefit from constant hybridization. We spread all over the place, used our culturally driven internal selection process to rapidly adapt to the local environment, then we swapped genes with our neighbors.*

iv. [Nature versus nurture in social insect caste differentiation](#) (2010) [goo.gl/xWgqR](http://goo.gl/xWgqR)

- Many southern US populations of *Pogonomyrmex* **contain differentiated genetic lineages, most or all of which derive from historical hybridization between the harvester ants *P. rugosus* and *P. barbatus*.** These lineages always occur in pairs and queens in each lineage-pair mate multiple times with males of their own as well as with males of the alternate lineage. Interlineage offspring develop into workers, whereas intralineage offspring develop into queens. **Crossing experiments revealed that intralineage individuals are developmentally constrained to become queens.**

↑ *Fancy that...*

- Interlineage individuals have partly retained plasticity and can develop into queens under some conditions, but the association of genotype and caste is very strong in natural populations, with only

0–7% of adult females (depending on the lineage and population) presenting a mismatch between the genotype and expected phenotype. Based on these data, a genetic model was proposed, in which two biallelic loci need to interact to trigger worker development. **Intralineage matings would result in allelic combinations that are incompatible with worker development, whereas compatible allelic combinations would be restored in interlineage matings and allow for worker and queen development.**

- A nuclear epistasis model was suggested to explain the loss of phenotypic plasticity in intralineage individuals of *Pogonomyrmex* lineages. In this model two biallelic loci (alleles a1 and a2 at locus A, and alleles b1 and b2 at locus B) need to interact to trigger worker development. Only interactions between the alleles a1 and b1, or between a2 and b2 can generate worker development. Intralineage matings would result in allelic combinations that are incompatible with worker development (genotypes a1a1/b2b2 or a2a2/b1b1), whereas compatible allelic combinations with correct interlocus communication would be restored in interlineage matings and allow for worker and queen development (genotype a1a2/b1b2). **This model could account for both the loss of phenotypic plasticity in intralineage individuals and the (partial) maintenance thereof in interlineage individuals.**

↑ *This is one molecular model of maintained, adaptive hybridization.*

- An alternative genetic model, based on cytonuclear epistasis, whereby only individuals with compatible cytonuclear combinations (i.e. intralineage individuals) can develop into queens would require additional elements for explaining the patterns of phenotypic plasticity. In addition, given the evidence for (nuclear) compatibility effects on caste in *P. rugosus*, a parsimonious assumption is that GCD in the lineages is based on the same or a similar genetic system; **this system might involve two loci as suggested in the original nuclear epistasis model or any larger number of loci.**

↑ *This is another model of hybridization. Both are potentially applicable to the human model of heritability (specifically, adaptive phenotypic discretization to maintain stable population heterogeneity).*

- Alternatively, genetic effects on caste development could also be maintained if there are no strictly queen-predisposing alleles. The crossing experiments in *P. rugosus* have shown that genetic variation for caste development in this species stems from epistasis rather than additive genetic effects. As a result, **selection might be relatively inefficient at removing genetic variation decreasing the plasticity range of an individual.**

↑ *Epistatic genetic information is preserved via redundancy (the effects of one gene are determined by several other genes).*

- It is well known from classical genetic models that the architecture of a trait influences the maintenance of genetic variation, with relatively more variance maintained if the trait depends on epistasis, heterozygote superiority, genotype-by-environment interactions, or indirect genetic effects.

↑ *Gene-environment interplay to determine phenotypes? Sounds familiar.*

- Interestingly, in addition to *P. rugosus*, such effects might also underlie the variation in caste predisposition observed in *A. mellifera*, the termites *R. speratus*, *Melipona* ssp. and the four groups with genetically hardwired caste determination. In *A. mellifera*, the propensity of particular subfamilies to develop as queens is context-dependent, indicating that either genotype-by-environment interactions or indirect genetic effects are involved. **In *R. speratus*, the maintenance of genetic variance for caste propensity might depend on the interactions between sex and caste-determining alleles (caste alleles have opposite effects in each sex).**

↑ There is limited evidence that certain cognitive disorders that tend to manifest more in women share susceptibility genes with autism (which is more common in men):

- i. [A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa](#) (Sept 2011) [goo.gl/RXv1p](#)

- we identified several regions with rare **copy number variations** that were only observed in anorexia cases, including a recurrent 13q12 deletion (1.5Mb) disrupting SCAS in two cases, and CNVs disrupting the CNTN6/CNTN4 region in several AN cases. In conclusion, our study suggests that both common SNPs and rare CNVs may confer genetic risk to AN. These results point to intriguing genes that await further validation in independent cohorts for confirmatory roles in AN.

- ii. [Gene Links to Anorexia Identified: Largest Genetic Study of the Eating Disorder Detects Common and Rare Variants](#) (Nov 2010) [goo.gl/dAKBx](#)

- "We confirmed results of previous studies of anorexia nervosa: SNPs in the gene OPRD1 and near the gene HTR1D confer risk for the disease," said Hakonarson. "We did not detect other obvious candidate genes, but we did generate a list of other genes that we are analyzing in follow-up studies." **One SNP is between the CHD10 and CHD9 genes, a region that Hakonarson associated with autism spectrum disorders in 2009.** Called cadherin genes, CHD10 and CHD9 code for neuronal cell-adhesion molecules -- proteins that influence how neurons communicate with each other in the brain.

- In the Pogonomyrmex lineages, the S. xyloni hybrid populations, W. auropunctata, and V. emeryi, caste is also determined by epistasis. In each system, **the same set of alleles trigger queen development if interacting with alleles of their own species or lineage, whereas they trigger worker development if interacting with alleles of a different species.** Finally, queen development in Melipona ssp. presumably requires heterozygosity (i.e. a case of "heterozygote superiority").

## IV. Ancestral Introgression/Admixture

*"I thought it was very cool. It means that they are not totally extinct—that they live on a little bit in us."*

— Svante Pääbo

### A. How introgression was first confirmed

⇒ In May of 2010, Neanderthal bones were successfully sequenced for nuclear DNA. Mitochondrial DNA had been previously acquired, and it did not indicate that there had been matrilineal introgression. The nuclear DNA, however, strongly indicates male Neanderthals successfully reproduced with humans ~30kya.

- i. The first paper: [A Draft Sequence of the Neandertal Genome](#) (May 2010) [goo.gl/Dsb6j](#)

- Neandertals, the closest evolutionary relatives of present-day humans, lived in large parts of Europe and western Asia before disappearing 30,000 years ago. We present a draft sequence of the Neandertal genome composed of more than 4 billion nucleotides from three individuals. **Comparisons of the Neandertal genome to the genomes of five present-day humans from different parts of the world identify a number of genomic regions that may have been affected by positive selection in ancestral modern humans, including genes involved in metabolism and in cognitive and skeletal development.** We show that Neandertals shared more genetic variants with present-day humans in Eurasia than with present-day humans in sub-Saharan Africa, suggesting that gene

flow from Neandertals into the ancestors of non-Africans occurred before the divergence of Eurasian groups from each other.

↑ *This indicates that the introgression was uneven and likely happened right as we left Africa.*

- We identified a total of 212 regions containing putative selective sweeps. **The region with the strongest statistical signal contained a stretch of 293 consecutive SNP positions in the first half of the gene *AUTS2* where only ancestral alleles are observed in the Neandertals.**
- The widest region is located on chromosome 2 and contains the gene *THADA*, where a region of 336 kb is depleted of derived alleles in Neandertals. **SNPs in the vicinity of *THADA* have been associated with type II diabetes, and *THADA* expression differs between individuals with diabetes and healthy controls.** Changes in *THADA* may thus have affected aspects of energy metabolism in early modern humans.

↑ *This is significant. Human chromosomes have a number of unique qualities that might be interpreted as adaptive mechanisms for facilitating successful hybridization with hominid relatives. Humans were apex predators for a while, which means we probably adapted to be able to out-adapt. Perhaps different local conditions required different blood sugar regulation mechanisms.*

- Mutations in several genes in Table 3 have been associated with diseases affecting cognitive capacities. *DYRK1A*, which lies in the Down syndrome critical region, is thought to underlie some of the cognitive impairment associated with having three copies of chromosome 21. **Mutations in *NRG3* have been associated with schizophrenia**, a condition that has been suggested to affect human-specific cognitive traits. **Mutations in *CADPS2* have been implicated in autism, as have mutations in *AUTS2*. Autism is a developmental disorder of brain function in which social interactions, communication, activity, and interest patterns are affected, as well as cognitive aspects crucial for human sociality and culture.** It may thus be that multiple genes involved in cognitive development were positively selected during the early history of modern humans.

↑ *Autism is characterized by impairments in speech and social cognition, atypical neuronal differentiation, and a number of other seemingly unrelated criteria. This lack of convergence supports the hypothesis that epigenetically maintained hybrid variability is behind autism, schizophrenia, bipolar disorder, and a number of other human-specific, heritable “diseases” of the mind. Analyzing these as population-scale adaptive variations is an approach that can be reasonably compared to EO Wilson’s theory of eusocial evolution.*

ii. [An X-linked haplotype of Neandertal origin is present among all non-African populations](http://goo.gl/or8cL) (July 2011) [goo.gl/or8cL](http://goo.gl/or8cL)

- Here we provide evidence of a notable presence (9% overall) of a Neandertal-derived X chromosome segment among all contemporary human populations outside Africa. Our analysis of 6092 X-chromosomes from all inhabited continents supports earlier contentions that **a mosaic of lineages of different time depths and different geographic provenance could have contributed to the genetic constitution of modern humans.**

iii. [Strong reproductive isolation between humans and Neanderthals inferred from observed patterns of introgression](http://goo.gl/6jDvo) (Sept 2011) [goo.gl/6jDvo](http://goo.gl/6jDvo)

- Recent studies have revealed that **2–3% of the genome of non-Africans might come from Neanderthals, suggesting a more complex scenario of modern human evolution than previously anticipated.** In this paper, we use a model of admixture during a spatial expansion to study the hybridization of Neanderthals with modern humans during their spread out of Africa. **We find that observed low levels of Neanderthal ancestry in Eurasians are compatible with a very low rate of**

**interbreeding (<2%), potentially attributable to a very strong avoidance of interspecific matings, a low fitness of hybrids, or both.**

↑ *They determine that the Neanderthal DNA in the genomes of most modern human populations may have come from a small sample of perhaps 500 introgressions from male Neanderthals. If homo sapiens was the most social hominid (200+ per tribe), we should tend to exhibit more molecular tolerance for intraspecific variation. This could also facilitate gene flow from more distant relatives, most of whom would have distinctly smaller social group sizes (and, hence, different adaptations for social cognition).*

• **These results suggesting the presence of very effective barriers to gene flow between the two species are robust to uncertainties about the exact demography of the Paleolithic populations, and they are also found to be compatible with the observed lack of mtDNA introgression.** Our model additionally suggests that similarly low levels of introgression in Europe and Asia may result from distinct admixture events having occurred beyond the Middle East, after the split of Europeans and Asians. This hypothesis could be tested because it predicts that different components of Neanderthal ancestry should be present in Europeans and in Asians.

↑ *The analysis is ongoing.*

iv. [Genetic and Phenotypic Consequences of Introgression Between Humans and Neanderthals](#) (Nov 2011) [goo.gl/TYU7U](http://goo.gl/TYU7U)

- ...the European-origin analysis leads to the conclusion that there are parts of the RCPI11 genome that have introgressed from Neanderthals into the RCPI11 genome but that are not represented in the Craig Venter genome. **Thus, introgression did take place between the ancestors of Europeans and the Neanderthals, and that introgression involved substantial parts of the Neanderthal genome that are scattered among modern humans.**
- **Will some of these Neanderthal fragments be found to be important in cognition, language ability, and other higher brain functions? To find out, it will be necessary to understand the human **epigenome** and transcriptome in detail**, so that we can determine the true impact of both structural and regulatory genes on the development and function of the brain.

## B. Neanderthals

i. [Neanderthals](#) (July 2010) [goo.gl/XJDQA](http://goo.gl/XJDQA)

- **Neanderthal average brain size is larger than that of modern humans, measuring approximately 1520 cubic centimeters**

↑ *There are ~~almost~~ more than 40,000 results for [Autism & Brain Overgrowth](#) on Google Scholar.*

ii. [Brain development after birth differs between Neanderthals and modern humans](#) (2010) [goo.gl/T0swS](http://goo.gl/T0swS)

- The development of cognitive abilities during individual growth is linked to the maturation of the underlying neural circuitry: in humans, major internal brain reorganization has been documented until adolescence, and even subtle alterations of pre- and perinatal brain development have been linked to changes of the neural wiring pattern that affect behavior and cognition. The uniquely modern human pattern of early brain development is particularly interesting in the light of the recent breakthroughs in the Neanderthal genome project, which identified genes relevant to cognition that are derived in living humans. **We speculate that a shift away from the ancestral pattern of brain development occurring in early Homo sapiens underlies brain reorganization and that the associated cognitive differences made this growth pattern a target for positive selection in modern humans.**

iii. [Aliens from Outer Time? Why the “Human Revolution” Is Wrong, and Where Do We Go from Here?](#)  
(2011) [goo.gl/vnzBA](http://goo.gl/vnzBA)

- For the better part of the last quarter of a century, the “Human Revolution” paradigm both framed and inspired most research on modern human origins. It brought together genetic, archaeological and paleontological data to form a coherent narrative of recent human evolution positing that all present-day populations derived from a speciation event in East Africa that, some 150,000 years ago, generated a small founder group of anatomically, cognitively and behaviorally fully modern people. The rest would have been history: subsequent Out-of-Africa dispersal of these early African moderns, entailing the inevitable replacement, without admixture, of the less advanced, outcompeted species of Eurasian archaics, namely the Neandertals. Recent empirical developments have falsified the basic tenets of these views. The archaeology and paleontology of the time of contact now show that **Neandertals and moderns featured similar levels of cultural achievement, that symbolic artifacts and personal ornaments had emerged in Neandertal Europe many millennia before the first in-dispersals of modern humans, and that significant admixture occurred as a result of such dispersals**, as evidenced by the presence in postcontact populations of diagnostically Neandertal anatomical and cultural traits. The fossil DNA evidence is consistent with these results. **Neandertals, therefore, can no longer be considered an evolutionary dead-end and productive explanations for their differentiation and eventual demise now must be sought in the realms of biogeography, demography and paleoethnography.**

↑ *This makes it clear that there is evidence that Neanderthals were highly intelligent. What is not clear, but can be inferred, is that they were cognitively different. There is no reason to assume that they co-evolved identical manifestations of sapiens’ communal behavior, lifespans, social cognition, memory, communication, etc.*

iv. [Paleoneurology of Two New Neandertal Occipitals from El Sidrón \(Asturias, Spain\) in the Context of Homo Endocranial Evolution](#) (2011) [goo.gl/aZBYI](http://goo.gl/aZBYI)

- The endocranial surface description and comparative analyses of two new neandertal occipital fragments from the El Sidrón site (Asturias, Spain) reveal new aspects of neandertal brain morphological asymmetries. The dural sinus drainage pattern, as observed on the sagittal-transverse system, as well as the cerebral occipito-petalias, point out a **slightly differential configuration of the neandertal brain when compared to other Homo species, especially H. sapiens.**

↑ *Neanderthal minds differed from homo sapiens’.*

- The neandertal dural sinus drainage pattern is organized in a **more asymmetric mode**, in such a way that the [superior sagittal sinus](#) (SSS) drains **either to the right or to the left transverse sinuses, but in no case in a confluent mode** (i.e. simultaneous continuation of SSS with both right (RTS) and left (LTS) transverse sinuses). Besides, the superior sagittal sinus shows an accentuated deviation from of the mid-sagittal plane in its way to the RTS in 35% of neandertals. This condition, which **increases the asymmetry of the system, is almost nonexistent neither in the analyzed Homo fossil species sample nor in that of anatomically modern humans.**

↑ *Eusocial species can take advantage of differentially asymmetrical neurological phenotypes. If hybrids exhibited more of this asymmetry in human groups, population-level selection might explain the persistence of Neanderthal genes.*

- Regarding the cerebral occipito-petalias, neandertals manifest one of the lowest percentages of left petalia of the Homo sample (including modern H. sapiens). As left occipito-petalia is the predominant pattern in hominins, **it seems as if neandertals would have developed a different pattern of brain hemispheres asymmetry.** Finally, the relief and position of the the cerebral sulci and

gyri impressions observed in the El Sidrón occipital specimens look **similar to those observed in modern *H. sapiens***.

↑ *The specimens in this study could be hybrids.*

v. [Mammoths used as food and building resources by Neanderthals: Zooarchaeological study applied to layer 4, Molodova I \(Ukraine\)](#) (Nov 2011) [goo.gl/l7o0u](http://goo.gl/l7o0u)

- Based on anthropogenic marks, mammoth meat has been eaten. **The presence of series of striations and ochre on mammoth bones are associated with a technical or symbolic use. Furthermore, mammoth bones have been deliberately selected (long and flat bones, tusks, connected vertebrae) and circularly arranged.** This mammoth bone structure could be described as the basement of a wooden cover or as a wind-screen. The inner presence of fifteen hearths, lithic artifacts and waste of mammal butchery and cooking is characteristic of a domestic area, which was probably the centre of a residential camp recurrently settled. **It appears that Neanderthals were the oldest known humans who used mammoth bones to build a dwelling structure.**

vi. [Last Neanderthals near the Arctic Circle?](#) (Dec 27, 2011) [goo.gl/PfcHR](http://goo.gl/PfcHR)

- The results intrigue scientists in more ways than one. They show that Mousterian culture may have lasted longer than scientists had originally thought. What's more, no Mousterian presence had ever been identified so close to the Arctic Circle. All other traces are at least 1000 km further south. Lastly, the Byzovaya site, in Eurasia, seems only to have been occupied once, approximately 28,500 years ago, **which is over 8,000 years after Neanderthals were thought to have disappeared.**
- So this discovery raises many questions, not least about how Mousterian society was organised. **Did Neanderthal Man live longer than thought?** Or could these last bearers of Mousterian culture in fact have been *Homo sapiens*? If so, the theories explaining that Neanderthals died out because their culture was archaic would be put into question. The studies open up new perspectives on this turning point in human history.

## C. Denisovans (a newly discovered hominid)

i. [From Wikipedia:](#)

- Tests comparing the Denisova hominin genome with those of six modern humans: a !Kung from South Africa, a Nigerian, a Frenchman, a Papua New Guinean, a Bougainville Islander and a Han Chinese showed that **between 4% and 6% of the genome of Melanesians (represented by the Papua New Guinean and Bougainville Islander) derives from a Denisovan population.** The genes were possibly introduced during the early migration of the ancestors of Melanesians into Southeast Asia. This history of interaction suggests that Denisovans once ranged widely over eastern Asia.

↑ *This supports significant genetic introgression from another ancient hominid.*

- Later research suggests that modern-day descendants of Denisovans range wider afield than Melanesia. Mark Stoneking, molecular anthropologist at the Max Planck Institute for Evolutionary Anthropology, led the research team which found **genetic evidence that, in addition to Melanesians, Australian Aborigines, and some small, scattered groups of people in Southeast Asia, such as the Negrito Mamanwa in the Philippines, share varying levels of Denisovan ancestry.** However, not all Negritos were found to possess Denisovan genes; Andaman Islanders and Malaysian Jehai, for example, were found to have no Denisovan inheritance. With their results, **they challenged the belief that the Denisovans interbred in mainland Asia before spreading to the island from southeast Asia, Melanesia, and Australia. They said that their data "can be most parsimoniously explained if the Denisova gene flow occurred in Southeast Asia itself."**

↑ *This might explain certain geographically specific human phenotypes.*

- In August 2011, Denisovan and Neandertal archaic HLA types were found to represent more than half the HLA alleles of modern Eurasians. The apparent over-representation of these alleles suggests a positive selective pressure for their retention in the human population.

ii. [Archaic human ancestry in East Asia](#) (Oct 2011) [goo.gl/Nzw4o](#)

- These results suggest admixture between Denisovans or a Denisova-related population and the ancestors of East Asians, and that the history of anatomically modern and archaic humans might be more complex than previously proposed.

↑ Recall that [autism diagnosis in South Korea are 1/38](#). [goo.gl/GbLf1](#)

## D. Links Between the Admixture and Immune Function

i. [The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans](#) (Aug 2011)

- These alleles, of which several encode unique or strong ligands for natural killer cell receptors, now represent more than half the HLA alleles of modern Eurasians and also appear to have been later introduced into Africans. Thus, adaptive introgression of archaic alleles has significantly shaped modern human immune systems.

↑ [The Guardian interviewed one of the paper's authors](#) [goo.gl/FVwjY](#), who more explicitly linked modern autoimmune disorders and ancient admixture:

- Paul Norman, a co-author on the paper, put it like this: "**There's enormous genetic variation in people's immune systems** and that can control how different people fight different diseases. This could go some way to explaining why some people are better at fighting some infections than others, **but we think it also goes some way to explaining why some people are susceptible to autoimmune diseases.**"

ii. [Virus-hunter gatherers](#) (Oct 2011) [goo.gl/cmJqi](#)

- And could this have been a dangerous liaison? **Human HLA alleles that are associated with autoimmune diseases were present in Denisovans.** Study co-author Paul Norman proposes that when we acquired those genes "we weren't kind of prepared for them, we hadn't grown up with them ... **they can start to attack us as well as the viruses**"

iii. [Origin and plasticity of MHC I-associated self peptides](#) (Nov 2011) [goo.gl/drOcB](#)

- The TCR of classic adaptive CD8 T cells recognizes MHC I-associated peptides (MIPs). MHC I genes are polygenic, extremely polymorphic and represent the most conserved MHC genes. **In most modern human populations, the majority of MHC I alleles have been acquired by introgression from archaic humans (Neanderthals and Denisovans)**

↑ This is a significant discovery for the following reasons:

- Evidence suggests that self MIPs excreted in body fluids act as chemosensory signals for neurons in the vomeronasal organs and may thereby influence mate selection and social behaviors in several vertebrates.

↑ The MHC might correspond to **social stuff**. This would be supported by evidence that it is polygenic in modern human populations. The overall behavior of the immune system has to shift when people live in cities. This is because a small increase in the daily transmission (through physical contact) of communicable pathogens (which is to be expected in a city), when combined with a significant increase in the number of potential hosts (city populations are dense), translates into an exponential increase in the number of opportunities each pathogen gets for adaptation (via horizontal genetic exchange or mutation).

iv. [Patchwork people: Our hybrid origins](#) (Aug 2, 2011) [goo.gl/MGMxg](#)

- The next step is to discover what these ancient genes do. **"It's possible that early modern humans could have used the Neanderthal or Denisovan genetic material to adapt to their environment,"** says David Reich from Harvard Medical School in Boston. **Indeed, the most recent studies indicate that interbreeding allowed early humans to acquire genes that helped protect them against local diseases as they migrated across the globe.**

## E. Evidence of a possible third archaic hominid introgression in Africa

### i. [Skull points to a more complex human evolution in Africa](#) (Sept 16, 2011) [goo.gl/ybkJZ](#)

- Scientists have collected more evidence to suggest that ancient and modern humans interbred in Africa. Reanalysis of the 13,000-year-old skull from a cave in West Africa reveals a skull more primitive-looking than its age suggests. **The result suggests that the ancestors of early humans did not die out quickly in Africa, but instead lived alongside their descendents and bred with them until comparatively recently.**

↑ *This strongly suggests that humans have maintained mosaic lineages.*

### ii. [Genetic evidence for archaic admixture in Africa](#) (2011) [goo.gl/bDNiD](#)

- Here we use DNA sequence data gathered from 61 noncoding autosomal regions in a sample of three sub-Saharan African populations (Mandenka, Biaka, and San) to test models of African archaic admixture.
- Extensive simulation results **reject the null model of no admixture and allow us to infer that contemporary African populations contain a small proportion of genetic material ( $\approx 2\%$ ) that introgressed  $\approx 35$  kya from an archaic population** that split from the ancestors of anatomically modern humans  $\approx 700$  kya.

↑ *Assuming that this ancestor evolved for social groups that were smaller than homo sapiens' 200+, introgression could have still provided genes corresponding to autism phenotypes.*

## V. How does all this relate to autism?

*"Just as a fish needs gills to survive in water, people need brains that make them able to deal with other people."*

— Richard Dawkins

## A. Autism and copy number variation (CNV)

### i. [NIGMS Human Genetic Variation Fact Sheet](#) [goo.gl/ACC5I](#)

- A key type of genetic variation is "copy number" variation, **which has been observed in identical twins that otherwise have identical DNA.** Typically, everyone has two copies of each gene, one inherited from each parent. But scientists are learning that these DNA regions can carry anywhere from zero to more than a dozen copies of a gene. In some cases, researchers have found, one twin's DNA differs from the other's by having different numbers of copies of the same gene. This can affect the gene's activity level, which can affect traits.

↑ *CNVs can differ between identical twins. This might indicate genetic mosaicism in utero. Fraternal birth order is linked to both [autism](#) [goo.gl/rQBBh](#) and [sexual orientation](#) [goo.gl/tyJUF](#) This might be explained by population-wide selection for non-reproductive phenotypes. The specific sensitivity to fraternal birth order could be the result of an evolved mechanism that selectively increases specialized phenotypic variation based on the number of males already in the family. This would make the ratio of variable, specialized phenotypes to neurotypicals partially dependent on population size.*

ii. [Genetics of autism spectrum disorders](#) (2011) [goo.gl/zURi2](http://goo.gl/zURi2)

- A series of important findings over the past four years clearly challenges the notion that autism is mainly caused by combinations of common variants by identifying a large number of rare, recurrent and nonrecurrent mutations that lead to ASD. At the same time, whole genome association studies with common variants, although identifying a few loci with very small effect sizes, have not yielded independently replicated results. These rare mutations, mostly in the form of submicroscopic chromosomal structural variation, called **copy number variants (CNV)**, are now known to account for up to 10% of cases of idiopathic autism (those with no obvious clinical syndrome). Because many of these CNV have large effect sizes and thus are thought sufficient to cause ASD, they are predicted to **significantly reduce reproductive fitness**. Consistent with this, these causal CNV are often not transmitted from the parent but **instead occur de novo in the germline**. However, in some cases, such as CNV at 16p11 and 15q11–13, the CNV are transmitted from an unaffected parent to cause the disorder in an offspring. The genetic or epigenetic mechanism of reduced penetrance for ASD in the mutation-carrying parent is not known. However, **it is also probable that the parent carriers of such CNV have more subtle neuropsychiatric or cognitive phenotypes that have not yet been systematically identified**.

iii. [Copy numbers count for autism](#) (Aug 9, 2011) [goo.gl/U4lah](http://goo.gl/U4lah)

- Autism, a neurodevelopmental disorder defined by the triad of impairments affecting social behaviour, communication, and imagination, has apparently become tenfold more prevalent in the last four decades. There is clear evidence for genetic causation but, of the around 80 genes that have been linked to autism or to the more widely defined autistic spectrum disorders (ASDs), **none accounts for a large proportion of cases, and none has a clearly established causation mechanism as yet**.
- Since 2007, **several studies have found evidence suggesting that rare copy number variations (CNVs) are linked to ASDs**. Genome sequencing has shown that CNVs, typically involving the duplication or deletion of more than 1,000 DNA nucleotides, are quite common in the human genome, and those that are widespread in the population are believed to be harmless, although genome studies of cancer cells have also detected CNVs that are under suspicion of causing or helping the cancer. Researchers have estimated that the genomes of any two unrelated people will differ with respect to copy number in around 0.4% of the total number of nucleotides. In 2010, the Autism Genome Project Consortium reported that **in a sample of nearly 1,000 people with ASDs, compared with a group of matched controls, there was a significantly higher burden of rare CNVs involving functional genes**. The researchers conclude that CNVs are likely to play a role in causing autism and other ASDs.
- While it has not yet been calibrated for comparison with inherited variations, the **surprisingly strong significance of de novo CNVs is compatible with a new genetic study that suggests the heritability of ASDs is much lower than presumed so far**. Joachim Hallmayer et al. give the heritability of autism as 37% (with a 95% confidence interval ranging from 8 to 84%), and for ASD 38% (14–67%).

↑ *Heritability does not mean what most people think it means. Heritability is the proportion of observable differences between individuals **that is due to genetic differences**. This means that molecular machinery that induces potentially adaptive mutations (duplications, deletions, etc.) in specific regions of the genome, despite being part of an almost exclusively genetic process, is still referred to as “environmental” because the mutations are “de novo” which is a fancy way of saying “not explicitly found in the parents’ genomes.”*

- Geneticist Richard Holt from the Wellcome Trust Centre for Human Genetics at Oxford comments on this finding: “This is an important study, especially given its size and the method of ascertainment of individuals with autism or ASD. While it should be viewed in the light of previous twin studies, if we accept the numbers from this study alone the significant decrease in the estimated genetic component may help explain the difficulties experienced in identifying the genes underlying autism.”

↑ *An increase in environmentally-induced mutations might still be adaptive (especially if physically localized and robustly heterogeneous).*

- However, **this still leaves space for genetic causes**, and even some of the non-inherited cases may arise from de novo change to genes, such as the CNVs. Holt concludes that “the study by Hallmayer et al. itself still points to a sizeable genetic contribution, and over the last decade the search for genetic factors for autism has met with significant success. Given their variance from previous studies, it will be interesting to see if these estimates are replicated in future work.”

↑ *This is likely the result of assortative mating.*

## B. Autism and Baron Coen’s “Extreme Male Brain Theory”

### i. [Empathizing, systemizing, and the extreme male brain theory of autism.](#) (2010) [goo.gl/jla0j](http://goo.gl/jla0j)

- Females in the general population on average have a stronger drive to empathize, and males in the general population on average have a stronger drive to systemize. Evidence related to these claims is reviewed. People with autism spectrum conditions have below average empathy alongside intact or even above average interest in systems. As such, they can be conceptualized as an extreme of the typical male brain.

↑ *Most introgressed DNA appears to be exclusively patrilineal. The greater susceptibility to mental illness in men might stem from this bias.*

*Autism’s characteristic “lack of empathy” is perhaps more accurately described as an inability to read and communicate emotion (technically, emotional communication is empathy, but “lack of empathy” is often misinterpreted as synonymous with “lack of emotion”).*

### ii. [Fetal androgen exposure and pragmatic language ability of girls in middle childhood: Implications for the extreme male-brain theory of autism](#) (2010) [goo.gl/CS4sO](http://goo.gl/CS4sO)

- Our findings are consistent with the extreme male-brain theory of autism. Baron-Cohen (2002) argued that the typically higher levels of prenatal exposure to testosterone for male compared to female fetuses contribute to sex-differences in brain morphology and to characteristic differences in development. **These characteristic differences include faster rates of development in social skills and in some aspects of communication in girls, and greater facility in developing specialized interests, especially in rule-governed systems, in boys.** In utero exposure to elevated levels of testosterone is argued to lead to an exaggeration of the pattern of male development which, in its most pronounced form, manifests as autism. **Studies investigating relationships between prenatal hormone levels and development in childhood provide direct tests of the extreme male-brain theory. We have shown a new association between higher levels of free testosterone in cord blood and pragmatic language difficulty at age 10, which complements existing findings.**

### iii. [Sexual dimorphism in environmental epigenetic programming](#) (2009) [goo.gl/jvEZK](http://goo.gl/jvEZK)

- The phenotype of an individual is the result of complex interactions between genotype and current, past and **ancestral** environment leading to a lifelong remodelling of our epigenomes. The vast majority of common diseases, including atherosclerosis, diabetes, osteoporosis, asthma, neuropsychological and autoimmune diseases, which often take root in early development, display some degree of **sex bias**, very marked in some cases. This bias could be explained by the role of sex chromosomes, the different regulatory pathways underlying sexual development of most organs and

finally, lifelong fluctuating impact of sex hormones. **A substantial proportion of dimorphic genes expression might be under the control of sex-specific epigenetic marks.** Environmental factors such as **social behaviour**, nutrition or chemical compounds can influence, in a gender-related manner, these flexible epigenetic marks during particular spatiotemporal windows of life. **Thus, finely tuned developmental program aspects, for each sex, may be more sensitive to specific environmental challenges, particularly during developmental programming and gametogenesis, but also throughout the individual's life under the influence of sex steroid hormones and/or sex chromosomes.** An unfavourable programming could thus lead to various defects and different susceptibility to diseases between males and females. **Recent studies suggest that this epigenetic programming could be sometimes transmitted to subsequent generations in a sex-specific manner and lead to transgenerational effects** (TGEs).

iv. [The 2nd to 4th digit ratio and autism](#) (2001) [goo.gl/6Mjbj](http://goo.gl/6Mjbj)

- There were positive associations between 2D:4D ratios of children with autism and the ratios of their relatives. **Children with autism had lower than expected 2D:4D ratios** and children with AS higher ratios than expected in relation to their fathers' 2D:4D ratio. It was concluded that 2D:4D ratio may be a possible marker for autism which could implicate prenatal testosterone in its aetiology.

↑ *Neanderthals have lower digit ratios than most contemporary human populations:*

v. [Digit ratios predict polygyny in early apes, Ardipithecus, Neanderthals and early modern humans but not in Australopithecus](#) (2010) [goo.gl/gCsWv](http://goo.gl/gCsWv)

- Social behaviour of fossil hominoid species is notoriously difficult to predict owing to difficulties in estimating body size dimorphism from fragmentary remains and, in hominins, low canine size dimorphism. **Recent studies have shown that the second-to-fourth digit ratio (2D : 4D), a putative biomarker for prenatal androgen effects (PAEs), covaries with intra-sexual competition and social systems across haplorrhines;** non-pair-bonded polygynous taxa have significantly lower 2D : 4D ratios (high PAE) than pair-bonded monogamous species. Here, we use proximal phalanx ratios of extant and fossil specimens to reconstruct the social systems of extinct hominoids. *Pierolapithecus catalaunicus*, *Hispanopithecus laietanus* and *Ardipithecus ramidus* have ratios consistent with polygynous extant species, whereas the ratio of *Australopithecus afarensis* is consistent with monogamous extant species. **The early anatomically modern human Qafzeh 9 and Neanderthals have lower digit ratios than most contemporary human populations, indicating increased androgenization and possibly higher incidence of polygyny.** Although speculative owing to small sample sizes, these results suggest that digit ratios represent a supplementary approach for elucidating the social systems of fossil hominins.

vi. [Genetic evidence for patrilocal mating behavior among Neandertal groups](#) (2010) [goo.gl/XkdFu](http://goo.gl/XkdFu)

- Our results show that the 12 individuals stem from three different maternal lineages, accounting for seven, four, and one individual(s), respectively. Using a Y-chromosome assay to confirm the morphological determination of sex for each individual, we found that, although the three adult males carried the same mtDNA lineage, each of the three adult females carried different mtDNA lineages. **These findings provide evidence to indicate that Neandertal groups not only were small and characterized by low genetic diversity but also were likely to have practiced patrilocal mating behavior.**

↑ *Patrilocal mating behavior supports polygyny and androgenization.*

## C. Nuclear DNA-mitochondrial DNA interplay

⇒ *The link between autism and mitochondrial dysfunction could be explained by the fact that DNA implicated in Autism has been delicately adapted to “fit” the behavior of mtDNA that we did not receive in the strictly patrilineal pattern of Neanderthal hybridization.*

i. [Environgenetic insights from the draft Neanderthal genome sequence](#) (June 2010) [goo.gl/Shr0F](http://goo.gl/Shr0F)

⇒ *Note: This paper vanished shortly after being published, but a copy remained in Google’s cache.*

- This finding raises intriguing questions about the basis of predominant selective advantage of the OOA genome, and the basis of persistence of small portions of Neanderthal DNA (1 – 4%) in the genomes of modern human descendants of the original interbreeding events.

↑ *This is a valid point.*

- Genes targeted to mitochondria constitute circa 5% of the nuclear gene repertoire of mammals including humans . Unlike **Ndtl ORs [olfactory receptors] which appear to be overrepresented, mitochondrially targeted nuclear genes of Ndtl origin appear to have been negatively selected (selectively depleted) in modern Eurasians.** Specifically, parsing the list of 78 genes, in which amino acid changes are fixed in humans but ancestral in Neanderthal, through a mitochondrial gene filter reveals that only NLRX1 is mitochondrial. NLRX1 is a modulator of innate immunity that is specifically implicated in mitochondrial innate antiviral response. Essentially, the current evidence shows that modern Eurasians have a dearth of Neanderthal mitochondrial genes (2.6x fewer fixed Ndtl mitochondrial gene alleles) than expected by chance, further **highlighting a contrast in selective sweep patterns of Ndtl OR and nuclear mitochondrial gene families within Eurasian gene pools.** We have previously highlighted **the likely profound impact of nuclear-mitochondrial compatibility/incompatibility on fitness and survival** (Box 1 - from Toye, unpublished). Further, that there exists marked selective pressure for compatibility of the two distinct component genomes of eukaryotes including humans

↑ *Mitochondrially targeted genes were selected against in Eurasians (after admixture), presumably because no Neanderthal mitochondrial DNA was acquired by introgression. This mismatch may be behind certain symptoms of autism. Neanderthal olfactory receptors have, however, undergone positive selection. Olfaction is an important part of social bonding (especially in infants).*

ii. [Reassessing the role of mitochondrial DNA mutations in autism spectrum disorder](#) (2011) [goo.gl/15aLA](http://goo.gl/15aLA)

- Our results are compatible with the idea that mtDNA mutations are not a relevant cause of ASD...

↑ *This supports admixture as an explanation for autism, as **any mitochondrial dysfunction that resulted from male-only archaic ancestry would come without discernible mtDNA difference.***

- ...and the frequent observation of concomitant mitochondrial dysfunction and ASD **could be due to nuclear factors influencing mitochondrion functions or to a more complex interplay between the nucleus and the mitochondrion/mtDNA.**

↑ *This is the most likely explanation.*

iii. [Mitochondrial Dysfunction Can Connect the Diverse Medical Symptoms Associated With Autism Spectrum Disorders](#) (May 2011) [goo.gl/h9VCP](http://goo.gl/h9VCP)

- Autism spectrum disorder (ASD) is a devastating neurodevelopmental disorder. Over the past decade, evidence has emerged that some children with ASD suffer from undiagnosed comorbid medical conditions. One of the medical disorders that has been consistently associated with ASD is mitochondrial dysfunction. **Individuals with mitochondrial disorders without concomitant ASD manifest dysfunction in multiple high-energy organ systems, such as the central nervous, muscular,**

and gastrointestinal (GI) systems. Interestingly, **these are the identical organ systems affected in a significant number of children with ASD**. This finding increases the possibility that mitochondrial dysfunction may be one of the keys that explains the many diverse symptoms observed in some children with ASD.

↑ *Many seemingly unrelated symptoms of autism can be explained as consequences the metabolic demands of ancestral nuclear DNA, acquired patrilineally from archaic hominids, on exclusively-homo sapiens mitochondrial DNA.*

iv. [Mitochondria and the great gender divide](#) (Dec 9, 2011) [goo.gl/dxFCF](http://goo.gl/dxFCF)

- Using a new mathematical model, the team led by Dr Nick Lane and colleagues from the UCL CoMPLEX, and the Research Department of Genetics, Evolution and Environment showed that inheriting mitochondria from only one parent – in effect, the ‘female’ – **improves fitness by optimizing the interactions between the two genomes**. [...] Dr. Lane said: “The difference between the sexes boils down to the need to keep fit when energy demands are high.”

↑ *This evolutionary restriction is significant because of its continuing capacity to facilitate cooperation between life with divergent DNA, starting with the first multicellular eukaryotes.*

- Descended from free-living bacteria, mitochondria were swallowed whole by another cell between one and a half to two billion years ago. But despite being engulfed, these tiny power packs have retained their own tiny genome, encoding just a handful of proteins, all of which are necessary for generating energy in the cell.

↑ *Matrilineal mitochondria control metabolism and the nucleus essentially runs the rest. Parallels can be drawn with topics as diverse as sexual dimorphism, bicameral legislatures, transient/dynamic stability, the politics of petroleum nationalization, the Y chromosome, the hydrogen atom, [the “duality” of stuff](#) etc. etc.*

- The strangest thing about this odd arrangement is that **cell respiration relies on proteins encoded by two genomes, the tiny mitochondrial genome and the nucleus**, where most DNA is stored. For respiration to work properly, the two genomes must work together to encode proteins that interact with nanoscopic precision.

## D. Encephalization and Olfaction

i. [Research Review: Constraining heterogeneity: the social brain and its development in autism spectrum disorder](#) (Jun 2011) [goo.gl/PMINW](http://goo.gl/PMINW)

- The expression of autism spectrum disorder (ASD) is highly heterogeneous, owing to the complex interactions between genes, the brain, and behavior throughout development. Here **we present a model of ASD that implicates an early and initial failure to develop the specialized functions of one or more of the set of neuroanatomical structures involved in social information processing** (i.e., the ‘social brain’). From this early and primary disruption, abnormal brain development is canalized because **the individual with an ASD must develop in a highly social world without the specialized neural systems that would ordinarily allow him or her to partake in the fabric of social life**, which is woven from the thread of opportunities for social reciprocity and the tools of social engagement. This brain canalization gives rise to other characteristic behavioral deficits in ASD including deficits in communication, restricted interests, and repetitive behaviors.

ii. [Evolution of the base of the brain in highly encephalized human species](#) (Dec 13, 2011) [goo.gl/nUIWJ](http://goo.gl/nUIWJ)

- Two genetically different evolutionary lineages, **Neanderthals and modern humans**, have produced similarly large-brained human species. [...] Three-dimensional geometric morphometric analyses of endobasicranial shape reveal previously undocumented details of **evolutionary changes in Homo sapiens. Larger olfactory bulbs, relatively wider orbitofrontal cortex, relatively increased and**

**forward projecting temporal lobe poles appear unique to modern humans.** Such brain reorganization, beside physical consequences for overall skull shape, **might have contributed to the evolution of H. sapiens' learning and social capacities**, in which higher olfactory functions and its cognitive, neurological behavioral implications could have been hitherto underestimated factors.

- Permutation tests of group membership (N=10.000) were used to statistically assess differences in Procrustes distance between non-allometric mean shapes of H. sapiens and other Homo species. **Neanderthals differed significantly from the early Homo average and modern humans were highly significantly different from all other Homo species.** Procrustes distance quantifies the overall difference between means of registered landmark configurations. **The average distance between means within modern human populations (d=0.037) was ~25% smaller than between modern humans and Neanderthals (d=0.049).**

↑ *Neanderthals' skull measurements are more physically divergent from our own than are the measurements of any population of humans from those of any other population of humans.*

- **The significantly different evolutionary patterns** in the modern human and Neanderthal lineages are shown in Figure 5. In H. sapiens cribriform expansion has occurred posteriorly. [...] Cribriform plate increase is well observed comparing mean shapes of modern humans with its putative ancestors (both early Homo in Figure 4, and Mid-Pleistocene humans in Supplementary Fig. S2) but also with Neanderthals. The size of the cribriform plate is driven by the **size of the olfactory bulbs** due to coordinated embryological development. Adult morphology of the cribriform plate is achieved early in ontogeny (4 years in humans and probably even earlier in Neanderthals due to faster maturation rates). However, due to this very early maturation ontogenetic changes of adjacent and surrounding facial structures, growing much longer than the cribriform plate, are very unlikely to influence cribriform morphology by craniofacial integration. **Moreover, the fact that large-faced Neanderthals showed smaller cribriform plates supports an interpretation in terms of neurological factors rather than by craniofacial integration.** Furthermore, its specific increase in H. sapiens implies a unique evolutionary condition of a large cribriform plate atop a nasal cavity within an extremely reduced face. After all, nasal cavity and facial sizes are more related to respiration and mastication than to olfaction.

↑ *The difference in brain structure between humans and neanderthals is likely due to different cognitive demands from their respective environments (presumably humans were more socially cognizant).*

- The coincident evolutionary changes of structures comprising **olfactory neuro-circuitry** could be a novel feature in the evolution of H. sapiens, and, if confirmed, **may have influenced some features of human behaviour.** The olfactory neurological circuitry is highly integrated in **cerebral, behavioural and immunological functions.** Following the initial sensory process, axons from thousands of cells expressing odour receptors in the mucosa of the nasal cavity converge via the cribriform plate in the olfactory bulb. From there, olfactory signals are transmitted to the olfactory cortex (rhinal, pyriform cortex, medioventral to temporal lobe poles) and **become relayed, on the one hand to higher cortical regions, where conscious thought processes are handled, and on the other hand to the limbic system, where emotional context is generated.** Olfactory information thus projects to regions critical for mating, emotions, and fear (amygdala) as well as for motivation, high-level cognitive and emotional processes (orbital prefrontal cortex). It, thus, serves a role in central nervous system function above and beyond smell. In that respect, olfaction differs from other sensory modalities. **Odour immediately triggers strong emotional evocations and provokes higher memory retention ('Marcel Proust Phenomenon')** due to anatomical overlap of structures involved in memory process and olfaction pathways. Such associations with cognitive processes have been termed by Savic 'higher olfactory functions'. **Smell, and linked higher olfactory functions, can thus be involved in**

modulating many different aspects of human behavior. **It has been reported that people who are congenitally deaf or blind have intact reproductive–social capacities, whereas individuals with congenital anosmia usually do not.**

↑ *Smell is fantastically important to human social interaction.*

- Moreover, **olfaction has been linked to the immunological system**. It is speculated that odour might be an important factor of attractiveness, that is, a mate selection criterion in human females, possibly selected for improving immunological fitness of the offspring, for example, in the case of the **major histocompatibility complex [MHC]**. Other recent research suggests that humans are also able to detect the 'scent of fear', potentially **important in human social interaction**.

↑ *Links between autism and the MHC are addressed in the “Immune and/or MHC – Autism link” section.*

- Different scaling also seems consistent with recent studies of endocranial development showing that **Neanderthal brains grew differently early in ontogeny, and probably prenatally, when compared with modern humans**. Evolutionary differences comprise the entire craniofacial system.

↑ *Autism involves divergent early brain development. The following is an example of another early cognitive specialization in a eusocial organism:*

i. [Socially induced brain development in a facultatively eusocial sweat bee \*Megalopta genalis\* \(Halictidae\)](#) (2010) [goo.gl/KHqpG](http://goo.gl/KHqpG)

- Changes in the relative size of brain regions are often dependent on experience and environmental stimulation, which includes an animal's social environment. Some studies suggest that social interactions are cognitively demanding, and have examined predictions that the evolution of sociality led to the evolution of larger brains. Previous studies have compared species with different social organizations or different groups within obligately social species. Here, we report **the first intraspecific study to examine how social experience shapes brain volume using a species with facultatively eusocial or solitary behaviour**, the sweat bee *Megalopta genalis*. Serial histological sections were used to reconstruct and measure the volume of brain areas of bees behaving as social reproductives, social workers, solitary reproductives or 1-day-old bees that are undifferentiated with respect to the social phenotype. **Social reproductives showed increased development of the mushroom body (an area of the insect brain associated with sensory integration and learning) relative to social workers and solitary reproductives.**

↑ *This indicates that genetic predispositions for social cognition exist in eusocial species (as is to be expected).*

- The gross neuroanatomy of young bees is developmentally similar to the advanced eusocial species previously studied, despite vast differences in colony size and social organization. Our results suggest that the transition from solitary to social behaviour is associated with modified brain development, and that **maintaining dominance, rather than sociality per se**, leads to increased mushroom body development, even in the smallest social groups possible (i.e. groups with two bees). **Such results suggest that capabilities to navigate the complexities of social life may be a factor shaping brain evolution in some social insects, as for some vertebrates.**

↑ *Social butterflies are evidently not the whole picture. Some folks are just good at manipulating people.*

- Our findings support previous hypotheses that **modern humans show a different evolutionary trajectory** because of the remaining significant shape differences between Neanderthals and *H. sapiens* after allometric size adjustment.
- Different evolutionary patterns likewise emerge from comparative genetic analyses, which—among other aspects—have shown **evidence for positive selection of genes related to cognitive development, that occurred after the split of *H. sapiens* and Neanderthals**. The same applies to roughly 4% of the 78 amino-acid configurations, which—ancestral in Neanderthals—are directly related to the olfactory system<sup>5</sup>. **Differences in the configuration of the olfactory sensory apparatus, and its previously discussed involvement into higher olfactory functions in social, and cognitive** (memory) aspects could be part of this evolutionary process.
- Although different regions of the prefrontal cortex (frontal lobes) have been associated with higher integrative and social functions, (for example, decision making), regions of the temporal lobes are traditionally related to **visual memory, language and to theory of mind**. All of them are compatible with higher olfactory functions.

↑ From Wikipedia:

In 1985 Simon Baron-Cohen, Alan M. Leslie and Uta Frith published research which **suggested that children with autism do not employ a theory of mind**, and suggested that children with autism have particular difficulties with tasks requiring the child to understand another person's beliefs. These difficulties persist when children are matched for verbal skills (Happé, 1995, Child Development) **and have been taken as a key feature of autism**.

It has been speculated that ToM exists on a continuum as opposed to the traditional view of a concrete presence or absence. While some research has suggested that some autistic populations are unable to attribute mental states to others, **recent evidence points to the possibility of coping mechanisms that facilitate a spectrum of mindful behavior**.

- 'Higher olfactory' functions relate odour reception with socially relevant cognitive processes, for example, **subliminally smell-mediated modulation of human-specific behavior**. Other possible factors may relate to the **immunological system, fear, kinship (or group recognition)** or food manipulation and could be among the implications of these new findings on the evolution of the basal areas of the human brain.

### iii. [Olfaction and Taste Processing in Autism](#) (2007) [goo.gl/Y8Qk9](http://goo.gl/Y8Qk9)

- **True differences exist in taste and olfactory identification in autism**. Impairment in taste identification with normal detection thresholds suggests cortical, rather than brainstem dysfunction. Further research is needed to determine the neurologic bases of olfactory and taste impairments, as well as the relationship of chemosensory dysfunction to other characteristics of autism.

### iv. [Impaired Olfactory Identification in Asperger's Syndrome](#) (2003) [goo.gl/jgn9C](http://goo.gl/jgn9C)

- **In nonhuman and human primates, damage to orbitofrontal cortex and medial temporal lobe, including amygdala, results in deficits in social behavior**. Medial temporal lobe lesions in infant monkeys produce social indifference and stereotypic behaviors analogous to those of autism. Moreover, in adult humans, **damage to orbitofrontal cortex may result in decreased empathy, inappropriate social interaction, and increased obsessionality**. Thus, selective dysfunction of medial temporal and orbitofrontal areas may be associated with features of autistic spectrum disorders. In human and nonhuman primates, medial temporal and orbitofrontal areas are also involved in processing of olfactory information. Lesions of medial temporal lobe structures impair odor detection, whereas orbitofrontal lesions impair olfactory identification. We therefore examined odor detection and identification to assess the functional integrity of brain areas **implicated in the control**

of social behavior and to determine whether specific neurobiological abnormalities are associated with AS.

## E. Immune and/or MHC – Autism link

### i. [Identification of autoimmune gene signatures in autism](http://goo.gl/OHLLV) (Dec 13, 2011) [goo.gl/OHLLV](http://goo.gl/OHLLV)

- Given that the magnitude of the association between ASD and the two autoimmune diseases, AS and MS, was either greater than or on par with the strength of association between what are considered now to be genetically similar autoimmune diseases, coupled with the lack of any other association of the same significance between ASD and the remaining autoimmune disorders examined, **our results clearly demonstrated that there are true genomic links between ASD and the two autoimmune diseases**, links that likely can inform our understanding of the genetics and treatments of ASD. However, further study and verification is required to characterize and explain these particular genomic associations. **An interesting, albeit anecdotal, similarity between ASD and AS is that they both have an appreciable male bias.**

### ii. [Origin and plasticity of MHC I-associated self peptides](http://goo.gl/ILdCX) (Nov 12, 2011) [goo.gl/ILdCX](http://goo.gl/ILdCX)

- In most modern human populations, the majority of MHC I alleles have been acquired by introgression from archaic humans (Neanderthals and Denisovans)**

### iii. [Boys With Regressive Autism, but Not Early Onset Autism, Have Larger Brains Than Age-Matched Healthy Counterparts, Study Finds](http://goo.gl/SYzJP) (Nov 28, 2011) [goo.gl/SYzJP](http://goo.gl/SYzJP)

- "The finding that boys with regressive autism show a different form of neuropathology than boys with early onset autism is novel," Nordahl said. "Moreover, when we evaluated girls with autism separately from boys, we found that no girls -- regardless of whether they had early onset or regressive autism -- had abnormal brain growth."

↑ *Neanderthal brain growth differs significantly from Homo sapiens.*

- "This adds to the growing evidence that **there are multiple biological subtypes of autism, with different neurobiological underpinnings**," Amaral said.

↑ *This has been repeatedly confirmed.*

- "It is not clear how many different types of autism will be identified," Amaral said. "The purpose of defining different types of autism is to more effectively study the cause of each type and eventually determine effective preventative measures and better, individualized treatments. This is a first step in defining autism subtypes based on the data from the Autism Phenome Project, but it certainly will not be the last. There are already indications that other subtypes of autism will be more closely associated with immunological differences or genetic alterations."

↑ Another article on the same study:

[US researchers' discovery promises answers on autism](http://goo.gl/aloZI) (Sept 2011)

Researchers from the University of California Davis's MIND Institute in Sacramento began the Autism Phenome Project in 2006. They have been studying the brain growth, environmental exposure and genetic make-up of 350 children aged between 2 and 3 1/2 years, and have so far found two biologically distinct subtypes of autistic brain development.

**One group of children - all boys - had enlarged brains** and most had regressed into autism after 18 months of age; **another group appeared to have immune systems that were not functioning properly.**

↑ *We know that the Denisova contributed DNA to modern immune systems and we know Neanderthals contributed cognitively-relevant DNA to modern genomes. Lex parsimoniae would seem to point to hominid introgression as a likely source of autism genes.*

iv. [Immune signalling in neural development, synaptic plasticity and disease](#) (2004) [goo.gl/t02MI](http://goo.gl/t02MI)

- Research has long supported the view that the brain is immunologically privileged, in part because normal, uninfected neurons were not thought to express major histocompatibility complex (MHC) class I molecules. Recently, however, it has been shown that **neurons normally express MHC class I molecules in vivo**. Furthermore, accumulating evidence indicates that neuronal MHC class I does not simply function in an immune capacity, but **is also crucial for normal brain development, neuronal differentiation, synaptic plasticity and even behaviour**. These findings point to new directions for research, and imply that immune proteins could be involved in the origin and expression of neurological disorders.

↑ *This would seem to link the MHC to many traits that characteristically vary in autism.*

- **over 60 studies to date have noted a genetic correlation between schizophrenia and MHC class I**, although these results remain controversial.

↑ [Schizophrenia and autism share many of the same genetic markers](#). [goo.gl/9MI4b](http://goo.gl/9MI4b)

- Environmental factors probably also have a crucial role, because identical twin concordance rates are only ~50%.

↑ *This is perhaps a misconception. The following comment is from the recently published Nature blog post "[Brain cell genomes show their individuality](#)"* [goo.gl/PECjQ](http://goo.gl/PECjQ)

"One of the conclusions of studies like this - and the Bruder et al study a few years ago on somatic copy number mosaicism - is that twin studies are not an accurate measure of the geneticness of any given disorder or trait. **Nature recently published a set of features on autism for example which repeated the well-known claim that twin studies show that autism has an environmental component. They don't. What they show is that there is a component that isn't inherited.** That component could be environmental but **as this result and others show it could also be genetic**. Indeed some studies have suggested that as much as 90% of autism may be genetic and yet, many years ago, Nature had a feature quoting Susan Folstein as claiming that roughly 10% of people with autism showed evidence for mosaicism, **which wouldn't be picked up in a twin study despite being genetic**. It's possible therefore that **autism may be much more strongly genetic than hinted at by twin studies.**" - Michael Chisnall (November 16, 2011 04:30 AM)

v. [Maternally Acting Alleles in Autism and Other Neurodevelopmental Disorders: The Role of HLA-DR4 Within the Major Histocompatibility Complex](#) (2010) [goo.gl/Ca0Mg](http://goo.gl/Ca0Mg)

- Maternally acting alleles are novel contributors to neurodevelopmental disorders, including autism, and with time, more are being reported in this rapidly moving field. As with autism, **neurodevelopmental disorders are considered to be complex disorders in which multiple genes contribute to the clinical phenotype and in which gene effects are modified by environmental factors**. Nearly all of the genes that have been reported as contributing to neurodevelopmental disorders act in the affected individual, i.e., the child or adult with the neurodevelopmental disorder. However, some of the genes that are now being identified for these disorders are maternal genes that act in the mothers to contribute to the phenotype of their affected offspring.

↑ *This paper establishes a link between MHC alleles and autism in the title.*

- At present, **at least 35 reports of these maternally acting gene alleles have been published**. Nearly all of these reports of maternally acting alleles involve neurodevelopmental disorders. Their number has more than doubled since the topic was first reviewed in 2003. It is possible that maternally acting alleles are a characteristic and even defining feature of neurodevelopmental disorders, but more work is needed to clarify their impact.

↑ This means it might involve a complex interplay between nuclear DNA and mtDNA. If the percentage of archaic DNA as well as the time since introgression are both factors, that might explain the following:

## F. Link between autism and maternal immigration status

### i. [Risk Factors for Autism and Asperger Syndrome: Perinatal Factors and Migration](#) (Oct 2010) [goo.gl/6Ax2O](http://goo.gl/6Ax2O)

- three parental characteristics and two obstetric conditions emerged as potential risk factors for autism; advanced paternal and maternal age, **maternal immigration**, growth restriction, and newborn hypoxia. One study found advanced maternal age to be specifically associated only with Asperger syndrome, but most studies did not report the risk factors for Asperger syndrome and autism separately. **Several investigators have reported an increased risk for autism in children whose mothers were born outside Europe or North America.** Lauritsen et al. (2005) found an association between immigration from outside Europe when investigating the whole group of ASD, and in a recent **Swedish study, Barnevik-Olsson et al. (2008) found a strong association between maternal immigration from Somalia and risk of autism or PDD-NOS.** Maternal immigration was not found to be a risk factor for autism in an American study, but maternal black ethnicity was.

↑ The most recent introgressions of archaic DNA have been outside Africa. There is evidence that autism rates are lower in certain populations.

- A strong positive association between autism and maternal birth outside Sweden was found; the magnitude of the association was similar across the time periods (p value for homogeneity = 0.44), and the association remained significant in the multivariate analysis. Quite contrary to this, a significant negative relationship between Asperger syndrome and maternal birth outside Sweden was detected (p value for homogeneity across time periods = 0.85).

↑ This is addressed in [this 6 minute video lecture](http://youtu.be/NCwq2_9iQAY).

### ii. [Risk factors for autism and Asperger syndrome: Perinatal factors and migration](#) (2011) [goo.gl/e8bai](http://goo.gl/e8bai)

- Using the Swedish Medical Birth Registry (MBR), obstetrical and demographic information was retrieved for 250 children with autism or Asperger syndrome who were born in Malmö, Sweden, and enrolled at the local Child and Youth Habilitation Center. The reference group consisted of all children born in Malmö during 1980—2005. **Obstetric sub-optimality (prematurity, low Apgar scores, growth restriction, or macrosomia) was positively associated with autism but not with Asperger syndrome. Maternal birth outside the Nordic countries was positively associated with autism (adjusted OR: 2.2; 95%CI: 1.6—3.1) and negatively associated with Asperger syndrome (OR: 0.6; 95%CI: 0.3—0.97). The highest risk estimate for autism was found among children to women who were born in sub-Saharan Africa (OR: 7.3), or in East Asia (OR: 3.4).**

↑ This might be explained by mitochondrial dysfunction/mismatch, vitamin D deficiency, an epigenetic mechanism triggered by maternal stress, etc.

## G. Lung abnormalities and divergent articulatory capacities

### i. Telegraph: [Neanderthals speak for first time in 50,000 years](#) (2008) [goo.gl/U3qaM](http://goo.gl/U3qaM)

- The linguist teamed with Prof McCarthy to simulate Neanderthal speech based on new reconstructions of the Neanderthal vocal tract, based on three 60,000-year old fossils from France.

"We are really saying that Neanderthals spoke, just a bit differently than we do," he says.

But they conclude that the ancient human's speech lacked the "quantal vowel" sounds that underlie modern speech.

Quantal vowels provide cues that **help speakers with different size vocal tracts understand one another**, says Prof McCarthy, who presented this work a few days ago at the American Association of Physical Anthropologists in Columbus.

↑ *There is a great deal of evidence to indicate that Neanderthals could articulate speech in a manner similar to that of modern humans. Quantal vowels might be necessary for communication in a tribe with significant phenotypic variation.*

ii. [Loss of air sacs and hominin speech](#) (Nov 2011) [goo.gl/TAqLo](http://goo.gl/TAqLo)

- In this paper, the acoustic-perceptual effects of air sacs are investigated. **Using an adaptive hearing experiment, it is shown that air sacs reduce the perceptual effect of vowel-like articulations. Air sacs are a feature of the vocal tract of all great apes, except humans.** Because the presence or absence of air sacs is correlated with the anatomy of the hyoid bone, a probable minimum and maximum date of the loss of air sacs can be estimated from fossil hyoid bones. Australopithecus afarensis still had air sacs about 3.3 Ma, while Homo heidelbergensis, some 600 000 years ago and **Homo neandethalensis some 60 000 years ago, did no longer.** The reduced distinctiveness of articulations produced with an air sac is in line with the hypothesis that **air sacs were selected against because of the evolution of complex vocal communication.** This relation between complex vocal communication and fossil evidence may help to get a firmer estimate of when speech first evolved.

iii. [Speech-sound-selective auditory impairment in children with autism: They can perceive but do not attend](#) (2003) [goo.gl/Wrva4](http://goo.gl/Wrva4)

- In contrast, their involuntary orienting was affected by stimulus nature. **It was normal to both simple and complex-tone changes but was entirely abolished by vowel changes.** These results demonstrate that, first, auditory orienting deficits in autism cannot be explained by sensory deficits and, second, that **orienting deficit in autism might be speech-sound specific.**

↑ *Autistic auditory impairment may be limited to certain vocalizations.*

iv. [Language and auditory processing in autism](#) (2003) [goo.gl/h36Eo](http://goo.gl/h36Eo)

- The absence of 'theory of mind' (ToM) reasoning (which includes the ability to infer the beliefs of others) has often been proposed to characterize the nature of autistic spectrum disorders. However, it is now apparent that performance on ToM tasks will not lead to a full understanding of autism. **For one thing, some children diagnosed as autistic pass the tasks whereas others who are not autistic fail.** Furthermore, children often display the symptoms of autism before the age at which they can usually be tested for whether they show ToM understanding. **Because the ToM hypothesis falls short of a full account of autism, new research directions have emerged with results that might eventually be seen to complement the ToM account.** Here we describe a recent set of studies designed to enable the delineation of autistic phenotypes. These serve to draw together a number of recent findings, and **point to a connection between autism and auditory processing.**

- According to this analysis, children who have low verbal ability, especially when this is combined with relatively high non-verbal ability, present severe symptoms of autism. This view is supported by other observations that Tager-Flusberg and Joseph report in their article. **For example, the children with autism who exhibit disproportionately low verbal ability also possess a significantly larger head circumference than other children with autism.** Many children with autism also share the characteristics of children without autism who have a Specific Language Impairment (SLI), in that both groups exhibit similar patterns of grammatical errors. Magnetic resonance brain scans also reveal that **children with autism, like children with SLI, can show a difference in brain asymmetry.** In normal children, the left hemisphere language areas are enlarged relative to the size of the homologous regions in the right hemisphere. In both children with autism and children with SLI,

**this asymmetry can be reversed.** Finally, recent work has frequently implicated gene loci known to be associated with language impairment in autism, and Tager-Flusberg and Joseph note that studies on the genetics of language have yielded similarities in the linkage between language and autism, and language and SLI.

↑↑ *'Archaic' hominid introgression is not a popular hypothesis, but it is also not an exaggeration to say that **no** popular hypothesis explains the characteristic language, mitochondrial, social, and immune dysfunction found in autism.*

v. CBS News: WebMD - [Autism linked to unusual shapes in lungs](#) (Oct, 2011) [goo.gl/jrBVu](#)

- Children born with a certain shape in their airways -- the tubes that take air to the lungs -- all have autism or autism spectrum disorder, according to a new study.

The study is one of the few to show a strong link between anatomy and autism and may indicate a genetic cause for the syndrome, says Barbara Stewart, MD. She presented the study today at CHEST 2011, the Annual Meeting of the American College of Chest Physicians.

- Searching for the cause of their coughs, she examined the passages that take air to the lungs by placing a tiny camera down their windpipes, a procedure known as bronchoscopy. In looking at the lungs in this way, she noticed that several patients had divisions in some of their airways, creating double passages, which she calls "doublets."

- Then she noticed that these patients all had something else in common: "**Every single one has autism, or autism spectrum disorder**," she says.

↑↑ *An important note at the bottom of the article:*

These findings were presented at a medical conference. **They should be considered preliminary as they have not yet undergone the "peer review" process**, in which outside experts scrutinize the data prior to publication in a medical journal.

## H. Autistic laughter as a population-wide adaptive trait

i. [Laughter differs in children with autism: an acoustic analysis of laughs produced by children with and without the disorder](#) (2009) [goo.gl/pueA9](#)

- Few studies have examined vocal expressions of emotion in children with autism. We tested the hypothesis that during social interactions, children diagnosed with autism would exhibit less extreme laugh acoustics than their nonautistic peers. Laughter was recorded during a series of playful interactions with an examiner. Results showed that children with autism exhibited only one type of laughter, whereas comparison participants exhibited two types. No group differences were found for laugh duration, mean fundamental frequency (F(0)) values, change in F(0), or number of laughs per bout. **Findings are interpreted to suggest that children with autism express laughter primarily in response to positive internal states, rather than using laughter to negotiate social interactions.**

↑↑ *Laughter, not as a socially mediated communication, but as a near-involuntary audible response to the unexpected resolution of cognitive dissonance, might be collectively advantageous if maintained in a subpopulation of systemizers.*

- In fact, by using laughter in a less social manner it may be that this expressive pattern actually contributes to the social deficits exhibited by children with autism instead of serving to facilitate connections with others.

↑↑ *This might lower individual fitness, but if Germany or Italy had had Saturday Night Live when Hitler and Mussolini were emphatically gesticulating at crowds of star-struck neurotypicals, perhaps their respective campaigns might have been preemptively disarmed through satire*

(created and broadcast by members of neurologically atypical sub-populations). [SNL castmember Dan Aykroyd is diagnosed with Asperger syndrome](#). [goo.gl/jgwwN](http://goo.gl/jgwwN)

In logic, the term [common knowledge](#) is defined as follows:

Common knowledge is a special kind of knowledge for a group of agents. There is common knowledge of p in a group of agents G when all the agents in G know p, they all know that they know p, they all know that they all know that they know p, and so on ad infinitum.

[The Emperor's New Clothes](#) demonstrates how a lack of common knowledge (knowledge of the knowledge of others) can cause a large population to behave irrationally, in this case requiring intervention from a **socially decoupled individual**. The child in the story is not hindered by his ignorance of the customs that shame the adults into silence, and he is not aware of the damage that his observation might do to his reputation if impulsively vocalized.

It is reasonable to suggest that autistic phenotypes might be maintained in human populations as a check against social restrictions on common knowledge (e.g. taboo, mitigated speech, etc.).

- ii. [Listeners prefer the laughs of children with autism to those of typically developing children](#). (Aug 2011) [goo.gl/JuuKO](http://goo.gl/JuuKO)

- The purpose of this study was to investigate the impact of laugh sounds produced by 8- to 10-year-old children with and without autism on naïve listeners, and to evaluate if listeners could distinguish between the laughs of the two groups. **Results showed that listeners rated the laughs of children with autism more positively than the laughs of typically developing children**, and that they were slightly above chance levels at judging which group produced the laugh.

↑↑ *This would seem to strongly indicate population-scale selection pressure for phenotypes that produce "honest laughter," perhaps initially acquired through admixture.*

## I. Link between autism and ancestry/ethnicity

- i. NewScientist: [Mental problems gave early humans an edge](#) (Nov 2011) [goo.gl/RKAJm](http://goo.gl/RKAJm)

- Harpending and colleagues found that a particular variant of the gene that codes for the D4 dopamine receptor has increased very rapidly in frequency in humans. People with this variant, known as DRD4-7R, tend to have very high energy levels and an increased risk of attention-deficit hyperactivity disorder (ADHD). Yet **the prevalence of the variant among certain groups – it is found in 80% of lowland Amazonian Indians, for example – indicates that extra energy has advantages.** "Previously these traits have been highly regarded in some societies," says Lesch. **"We see a higher percentage of ADHD-associated traits in migratory people, for example."**

↑↑ *There is abundant overlap in CNVs linked to autism and ADHD:*

- [11p14.1 microdeletions associated with ADHD, autism, developmental delay, and obesity](#) (Jun 2011) [goo.gl/F6Jzz](http://goo.gl/F6Jzz)
- [Autism and ADHD: Overlapping and discriminating symptoms](#) (Jun 2011) [goo.gl/38HXg](http://goo.gl/38HXg)
- [Overlap between ADHD and autism spectrum disorder in adults](#) (2011) [goo.gl/dFqHr](http://goo.gl/dFqHr)

- Klaus-Peter Lesch at the University of Wurzburg, Germany, and colleagues looked at the gene responsible for the serotonin transporter protein SERT, which has been implicated in several inherited disorders. This gene comes in a "long" and a "short" form. Every human carries a combination of two of these. **People with the long/long combination appear to be protected from very low moods, whereas those with the short/long version are more susceptible to depression, and the short/short version with emotional dysregulation.** [...] But the gene can also confer advantages. **The short variant appears to be linked with depression in a stressful environment, but in a supportive environment people with this variant are often highly successful.** "One trait that

humans and rhesus monkeys share is an ability to live almost anywhere,” says Lesch. **Noting that other primates thrive only in very specific niches**, he speculates that behavioural traits connected with the short versions of the SERT gene may have helped both humans and rhesus monkeys **to adapt to new and challenging environments**.

ii. [A comparison of Autism Spectrum Disorder DSM-IV criteria and associated features among African American and white children in Philadelphia County](#) (Oct 2011) [goo.gl/KDq57](#)

- **This study suggests differences in the types of ASD symptoms and associated behavioral features exhibited by African American as compared to white children with ASD.** Further research is needed to determine if these differences contribute to disparities in the timing or type of ASD diagnosis.

↑ *In the US, class and race are often correlated. This could significantly affect the time that autism is first diagnosed and therapy is started. Racial disparities in intervention and diagnosis are therefore a possible explanation.*

iii. [The relationship between race and challenging behaviours in infants and toddlers with autistic disorder and pervasive developmental disorder-not otherwise specified](#). (2011) [goo.gl/p89zD](#)

- Significant differences between races were found on five out of 10 aggressive behaviours, while no significant differences were found on self-injurious or stereotypic behaviours. **Significant differences between diagnostic groups were found on all behaviours.**

iv. [Autism spectrum disorders \(ASD\) in Africa : a perspective : review](#) (2011) [goo.gl/Zc716](#)

- A higher proportion of non-verbal cases of ASD compared to verbal cases was documented in literature coming from Africa. Associated co-morbid disorders included intellectual disability, epilepsy and **oculocutaneous albinism**.

↑ *Neanderthals and Denisova lived at a different latitude, and probably had slightly different adaptations for optimal vitamin D production.*

- Based on the present state of knowledge, there is no element of doubt that ASD does occur among African children living both in Africa and abroad. However, **many questions still remain unanswered about the definitive prevalence, aetiology and characteristics of children affected by ASD in Africa, especially sub-Saharan Africa.**

↑ [Humans have been migrating everywhere for a lot longer than we've been writing stuff down](#) [goo.gl/1TzAB](#) *Every population has a little of every population. Our ability to successfully implement “[Kirby copy abilities](#)” ([goo.gl/uKxqW](#)) with local “archaic” hominids via admixture and multi-generational selection for locally specific traits (immune, physical phenotypes, etc.) might explain the significant stable variation in the densities and distributions of different human societies. Different social environments require different adaptations.*

v. [Childhood Autism in Africa \(1978\)](#) [goo.gl/R9NLZ](#)

- Our aim was to find autistic behaviour in indigenous African children. For our purposes this meant black African children raised by black African parents.

- This was not a study of prevalence. Yet **from indirect evidence the numbers of autistic children found was much smaller than expected.** For example, in Middlesex between 5 and 8 per cent of all severely subnormal children would be expected to show some marked autistic behaviour (Lotter, 1966). At least 400 of the 1312 children seen in Africa could be considered severely subnormal, and we were able to identify altogether only nine children as autistic, not all of whom were severely subnormal. If the incidence of childhood autism is assumed to be similar in Africa and Britain, there is no obvious reason why relatively fewer such children should be found amongst the known severely subnormal population in African countries. **A possibility therefore is that autistic symptoms generally are less common in the African countries we visited, than in Britain.**

↑ *If autism is the result of 'archaic' hominid DNA, it should be less frequent in populations with less hybrid ancestry. There is significant evidence that populations from every continent, [including Africa](#) [goo.gl/bDNiD](http://goo.gl/bDNiD), have admixed ancestry. Homo sapiens is the only remaining hominid, perhaps due in part to the adaptability of our large, phenotypically diverse social groups. **Any local hominid (besides homo sapiens) could provide variations for a "spectrum of introversion"** and other characteristics originally adapted for smaller social groups. [We nerds](#) come from [everywhere](#). [youtu.be/QgKCrGvShZs](http://youtu.be/QgKCrGvShZs), [youtu.be/wcXSpXyZVuY](http://youtu.be/wcXSpXyZVuY), [goo.gl/1jXUI](http://goo.gl/1jXUI)*

- **A further possibility is that certain specific aspects of the syndrome occur less frequently in the African populations.** In our comparison of symptoms there was for example some indication that certain repetitive movements (e.g. flapping, rocking, headbanging) as well as more elaborate ritualistic activities involving objects were uncommon.

↑ *This claim has not been definitively tested, mostly because of a lack of funding for autism research in African populations. As genome sequencing technology drops in price and rises in complexity (in a manner increasingly like Moore's law), we should see more gene-disease studies published on impoverished populations.*

vi. [Racial Disparities in Community Identification of Autism Spectrum Disorders Over Time; Metropolitan Atlanta, Georgia, 2000–2006](#) (2011) [goo.gl/QqyY4](http://goo.gl/QqyY4)

- Total ASD prevalence was higher for NHW (Non-Hispanic White) than NHB (Non-Hispanic Black) children, but NHB children were more likely than NHW children to have autistic disorder and autism eligibility at a public school documented in records. NHB children were less likely than NHW children to have pervasive developmental disorder-not otherwise specified and Asperger's disorder documented in records, even after controlling for socioeconomic status. NHB children were more likely than NHW children to have co-occurring intellectual disability.

## J. Heterochrony and hybridogenesis

i. [An Examination of Autism Spectrum Disorders in Relation to Human Evolution and Life History Theory](#) (2010) [goo.gl/qinis](http://goo.gl/qinis)

- **The evolution of the brain in relation to human neoteny is important for understanding and evaluating autism.** Many of the traits associated with childhood in humans, such as social dependence and curiosity, are lacking in ASD individuals (Brune 2000). It has been suggested that due to the extended juvenile period, as well as due to delayed maturation in humans, that our minds are much more vulnerable to social and environmental stress. Studies looking at monozygotic twins with autism found that the trait was strongly associated with these more closely related individuals than in fraternal twins. **Additionally, the Broad Autism Phenotype (BAP) of traits that seem to resemble very mild versions of ASDs are seen in higher frequency among related individuals, parents as well as siblings (Losh et al. 2009). Mothers, in particular, with [Broad Autism Phenotype] traits are most closely associated with having children who are autistic.**

ii. [Heterochrony in Hybrid Macaques](#) (2008) [goo.gl/Y2Rea](http://goo.gl/Y2Rea)

- In this report, **we examine the effects of hybridization on growth allometry and the heterochronic growth** process in a sample of hybrids of *Macaca mulatta*.

↑ *From Wikipedia:*

**Heterochrony** is defined as a developmental change in the timing of events, leading to changes in size and shape. There are two main components, namely (i) the onset and offset of a particular process, and (ii) the rate at which the process operates. A developmental process in one species can only be described as heterochronic in relation to the same

process in another species, considered the basal or ancestral state, which operates with different onset and/or offset times, and/or at different rates.

- Comparisons of regression parameters describing the linear relationships of age with body weight and body length, and the allometric relationship between body weight and body length indicate that hybridization may be associated with predisplacement (body weight and length to age) and hypermorphosis (length to weight) **in males**. **Only the comparison of the male weight-to-age regression was statistically significant. Female hybrids exhibited a visible pattern of acceleration (body weight and length to age), or slight acceleration coupled with slight hypermorphosis (length to weight).** None of the female patterns, however, were statistically significant. **The results of our study indicate hybridization can affect growth patterns, although the magnitude of the difference varies and may be sex specific.**

iii. [Heterochrony, maternal effects, and phenotypic variation among sympatric pupfishes](#) (2007) [goo.gl/iLfG2](http://goo.gl/iLfG2)

- Variation in ontogeny can produce phenotypic variation both within and among species. I investigated whether changes in timing and rate of growth were a source of phenotypic variation in a putative incipient species group of pupfish (*Cyprinodon* spp.). On San Salvador Island, Bahamas, sympatric forms of pupfish differ in morphology but show only partial reproductive isolation in the laboratory. **Offspring from two forms and two geographical areas and their hybrids were bred in the laboratory, and ontogenetic trajectories of their feeding morphology were followed until maturity.** In the Bahamian pupfish the two forms grow along similar size but not shape trajectories. Two heterochronic parameters, onset and rate of growth, alter shape trajectories in the Bahamian pupfish. Similar forms from different geographical areas (Florida and the Bahamas) grow along parallel shape trajectories, differing only in one heterochronic parameter, the onset shape. **Hybrids within and between the pupfish forms produced intermediate feeding morphologies that were influenced by their maternal phenotype, suggesting that maternal effects may be a source of phenotypic variation in shape that can persist to maturity.** In *Cyprinodon*, small changes in multiple heterochronic parameters translate into large phenotypic differences in feeding morphology.

iv. [Caterpillars evolved from onychophorans by hybridogenesis](#) (2009) [goo.gl/HHYP9](http://goo.gl/HHYP9)

*Note: This paper is apparently controversial. Hah.*

- I reject the Darwinian assumption that larvae and their adults evolved from a single common ancestor. Rather **I posit that, in animals that metamorphose, the basic types of larvae originated as adults of different lineages, i.e., larvae were transferred when, through hybridization, their genomes were acquired by distantly related animals.** “Caterpillars,” the name for eruciforms with thoracic and abdominal legs, are larvae of lepidopterans, hymenopterans, and mecopterans (scorpionflies). Grubs and maggots, including the larvae of beetles, bees, and flies, evolved from caterpillars by loss of legs. Caterpillar larval organs are dismantled and reconstructed in the pupal phase. Such indirect developmental patterns (metamorphoses) did not originate solely by accumulation of random mutations followed by natural selection; rather they are fully consistent with my concept of evolution by hybridogenesis. Members of the phylum Onychophora (velvet worms) are proposed as the evolutionary source of caterpillars and their grub or maggot descendants. I present a molecular biological research proposal to test my thesis. By my hypothesis 2 recognizable sets of genes are detectable in the genomes of all insects with caterpillar grub- or maggot-like larvae: (i) onychophoran genes that code for proteins determining larval morphology/physiology and (ii) sequentially expressed insect genes that code for adult proteins. The genomes of insects and other animals that, by contrast, entirely lack larvae comprise recognizable sets of genes from single animal common ancestors.

↑ This paper [was published, in spite of its controversial nature, due to support from Lynn Margulis](#), who is quite famous for correctly theorizing the “hybrid introgression” origin of mitochondria in eukaryotic cells. Her hypothesis was also “controversial” for decades. Fancy that.

## K. Gut microflora

- i. [Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children](#) (2005) [goo.gl/o6dCH](#)  
 ↑ Gut microbiomes are adapted to suit local environments.
- ii. [Gut bacteria may contribute to autism](#) (2010) [goo.gl/hGnvO](#)  
 ↑ This is an example of a correlation-causation fallacy.
- iii. [Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to neurotypical children and correlation with autism severity](#) (2011) [goo.gl/5Wvmo](#)
  - **The strong correlation of gastrointestinal symptoms with autism severity indicates that children with more severe autism are likely to have more severe gastrointestinal symptoms and vice versa.** It is possible that autism symptoms are exacerbated or even partially due to the underlying gastrointestinal problems.

## L. Support for this hypothesis in the autistic community

- i. [Congratulations, It's Aspergers Syndrome](#) [goo.gl/IvkIo](#)
  - **I, myself, would be delighted if anyone could prove that I am a throw-back to the Neandertals.** These people had the brains and brawn to survive the Ice Age - which included catching woolly mammoths for dinner, using only stone tools. How many of us "moderns" could achieve that level of skill? – Chapter 25 “[The Stone Age Connection](#)” [goo.gl/dpLNn](#)
- ii. Wrongplanet.net (an autism/aspergers community) has numerous forum threads devoted to the topic:
  - [Discussing “The Neanderthal Theory of Autism”](#) (Oct 2011) [goo.gl/qUsZC](#)
  - [The day it was announced that the neanderthal nuclear genome confirmed introgression](#) (May 2010) [goo.gl/tA8DR](#)
  - [A discussion from before admixture had been confirmed](#) (May 2009) [goo.gl/qcjiH](#)

## VI. Some of the More Interesting Theories Out There

*“Let us think the unthinkable, let us do the undoable, let us prepare to grapple with the ineffable itself, and see if we may not eff it after all.”*

– Douglas Adams

### A. Neanderthal-bipolar disorder link

- i. [Evolutionary origin of bipolar disorder-revised: EOBD-R](#) (Oct 2011) [goo.gl/CVj93](#)
  - Given evidence of Neandertal contributions to the human genome, **the hypothesis is extended (EOBD-R) to suggest Neandertal as the ancestral source for bipolar vulnerability genes** (susceptibility alleles). The EOBD-R hypothesis explains and integrates existing observations: bipolar disorder has the epidemiology of an adaptation; it is correlated with a cold-adapted build, and its moods vary according to light and season. Since the hypothesis was first published, data consistent with it have continued to appear.

ii. [Common polygenic variation contributes to risk of schizophrenia and bipolar disorder](#) (Aug 2009) [goo.gl/rPYhC](http://goo.gl/rPYhC)

- Here we show, using two analytic approaches, the extent to which common genetic variation underlies the risk of schizophrenia. First, we implicate the major histocompatibility complex. Second, **we provide molecular genetic evidence for a substantial polygenic component to the risk of schizophrenia involving thousands of common alleles of very small effect. We show that this component also contributes to the risk of bipolar disorder, but not to several non-psychiatric diseases.**

## B. Autism and hunter gatherer adaptations

i. [Autism May Have Had Advantages in Humans' Hunter-Gatherer Past, Researcher Believes](#) (June 2011) [goo.gl/MKEVI](http://goo.gl/MKEVI)

- Some of the genes that contribute to autism may have been selected and maintained because they created beneficial behaviors in a solitary environment, amounting to an autism advantage, Reser said.

ii. The paper: [Conceptualizing the autism spectrum in terms of natural selection and behavioral ecology: The solitary forager hypothesis](#) (2011) [goo.gl/W0KFd](http://goo.gl/W0KFd)

- People on the autism spectrum are conceptualized here as ecologically competent individuals that could have been adept at learning and implementing hunting and gathering skills in the ancestral environment.
- Many of the behavioral and cognitive tendencies that autistic individuals exhibit are viewed here as adaptations that would have complemented a solitary lifestyle.
- A portion of this complexity and uncertainty arises from **the relatively large number of distinct susceptibility genes that have been identified, many of which can be completely absent even in pronounced autism (Freitag, 2007). This genetic heterogeneity may be responsible for the clinical heterogeneity**, which ranges from debilitating social deficits to minor personality traits.
- **Geneticists report that although the clinical distinctions do not map neatly onto specific genes or patterns of genes, lower functioning individuals may have a higher total number of susceptibility alleles** (Abrahams and Geschwind, 2008). For this reason this article will not make evolutionary distinctions between individual autistic disorders but will focus on the autism spectrum and the range of related genes as a whole.
- Autism is now known to be a biological phenomenon in which a genetic diathesis or susceptibility may interact with early environmental circumstances to determine the severity of outcome (Kumar and Christian, 2009). However, ***why this genetic susceptibility to autism is so prevalent and how the genes persisted despite the perceived negative effects is unclear.*** It is the author's view that conceptualizing autism in terms of evolutionary biology will offer insight into the underlying factors, and help to **make sense out of its seemingly incongruous characteristics.**
- **...these individuals, unlike neurotypical humans, would not have been obligately social and may have been predisposed toward taking up a relatively solitary lifestyle. Certain psychological characteristics of autism are taken here as a suite of cognitive adaptations that would have facilitated lone foraging. Like other solitary mammals with similar cognitive adaptations, they were probably not completely solitary; rather, they may have done much of their foraging alone and reconvened intermittently with familiar individuals. The article will use the perspectives from evolutionary medicine and evolutionary psychopathology to expound upon this hypothesis in a conjectural and exploratory manner. Corroborating evidence is sought from evolutionary medicine, the systemizing theory of autism, anthropology, primatology and comparative neuroscience.**

↑↑ *The man makes some strong arguments.*

C. [The Way We Are](#) by Stan Gooch (2000) [goo.gl/w0hYF](http://goo.gl/w0hYF)

- When widely divergent species of animal are crossed and subsequently observed in the laboratory the offspring are frequently found to have inherited conflicting sets of instincts, evolved in their parents' separate evolutionary pasts.
- **That is the kind of psychological impasse which is often created when widely divergent animal species are crossed. It is also what occurred when Neanderthal and Cro-Magnon interbred.** Now we can understand why our culture has so many established and enduring metaphors, and so many enduring and central storylines, attesting to our 'double life': the divided self, the two souls within one breast, the left hand not knowing what the right hand is doing, Cain and Abel, Jekyll and Hyde, Faust...

↑↑ *He goes on like that for a while. It's fascinating.*

D. [The Neanderthal Theory of Autism](#) (2001) [goo.gl/npzRX](http://goo.gl/npzRX)

⇒ *This fellow has compiled a great deal of evidence over the past decade. He's still being ignored by the academic community, but people are no longer trying to tell him that introgression is a crazy impossibility. Some in the autistic community have taken a liking to his theory.*

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I don't have the knowledge or resources to test this hypothesis. If you do (or if you have any suggestions/questions) please contact me at [EusocialHominid@gmail.com](mailto:EusocialHominid@gmail.com)