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The origins and evolution of genetic disease risk in modern humans

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Patterns and risks of human disease have evolved. In this article, I review evidence regarding the importance of recent adaptive evolution, positive selection, and genomic conflicts in shaping the genetic and phenotypic architectures of polygenic human diseases. Strong recent selection in human populations can create and maintain genetically based disease risk primarily through three processes: increased scope for dysregulation from recent human adaptations, divergent optima generated by intraspecific genomic conflicts, and transient or stable deleterious by-products of positive selection caused by antagonistic pleiotropy, ultimately due to trade-offs at the levels of molecular genetics, development, and physiology. Human disease due to these processes appears to be concentrated in three sets of phenotypes: cognition and emotion, reproductive traits, and life-history traits related to long life-span. Diverse, convergent lines of evidence suggest that a small set of tissues whose pleiotropic patterns of gene function and expression are under especially strong selection—brain, placenta, testis, prostate, breast, and ovary—has mediated a considerable proportion of disease risk in modern humans.

Keywords: human evolution; polygenic disease; genetics

> "*Medicine is of all the Arts the most noble; but, owing to the ignorance of those who practice it, and of those who, inconsiderately, form a judgment of them, it is at present behind all the arts.*"
> Hippocrates, *The Law of Hippocrates*

Introduction

Two of the greatest challenges in modern biology are to understand how selection and other population-genetic forces have driven human evolution and to decipher how genetic variation mediates variation in phenotypes associated with disease. In this review, I integrate these two questions in focusing on a specific set of human phenotypes, diseases, and their risk, and asking how the selective pressures that have "made us human" have also made us vulnerable to a set of noninfectious, genetically based diseases notably distinct from those of other animals. My main goal is to provide a conceptual framework, grounded in evolutionary biology, for analyses of the proximate and ultimate causes of such "intrinsic" human disease, with emphasis on applications to medical research and practice. This framework builds upon previous work in the broader field of evolutionary medicine,[1] using the viewpoint that genetics will provide the clearest insights, and most strongly testable predictions, to bring evolutionary biology into the mainstream of the health sciences.

A primary thesis of this review is that strong selection, in the contexts of genetically based intraspecific conflicts (Fig. 1)[2–4] and rapid evolution from other causes, has mediated a substantial proportion of human intrinsic disease risk. Strong selection impacts the evolution of disease risk in three main ways: by generating human-specific or human-elaborated phenotypes that generate novel scope for human-concentrated disease; by creating disease vulnerability via side effects of intraspecific conflicts, analogously to conflicts between humans and agents of pathogenic disease; and by supporting substantial negative effects on health via antagonistic pleiotropy, whereby stronger positive selection necessarily involves larger, associated negative effects on health. To the extent that this thesis holds true, it can provide direct insights into the causes of

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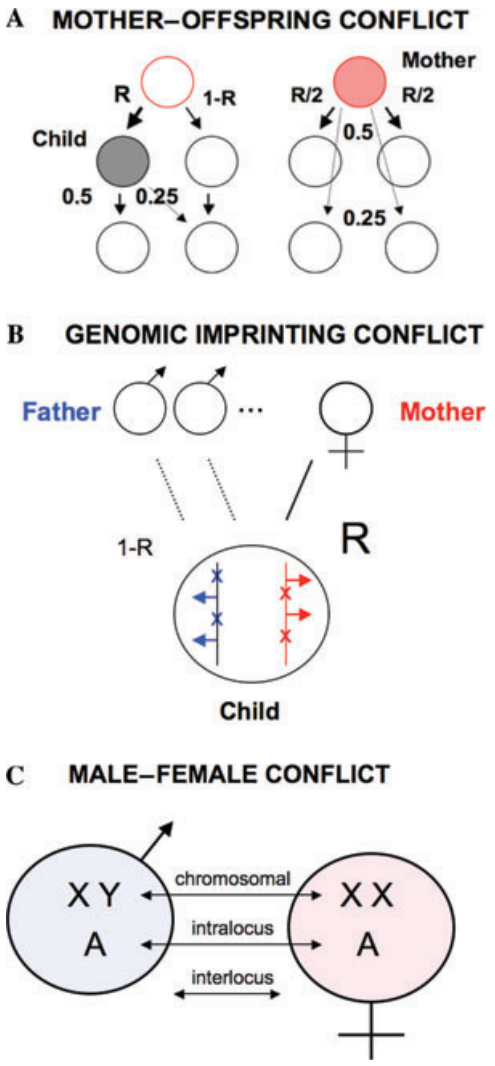

Figure 1. (A) Mother–offspring conflict is caused predominantly by twofold higher relatedness, for autosomal genes, from an offspring to its own children (1/2) than from an offspring to children of sibs (nieces and nephews, related by 1/4). Thus, whereas mothers are selected to invest equally in each offspring in a sibship (as a result of equal relatedness to each), each offspring is selected to solicit more from the mother than she is selected to provide. "R" refers to maternal investment. (B) Genomic imprinting conflict is caused by a combination of (i) lower average genetic relatedness of putative fathers to a female's offspring, compared to a female's relatedness to her offspring, due to an evolutionary history of multiple paternity, and (ii) higher maternal investment than paternal investment in child-rearing. Low paternal relatedness selects on males for germline silencing (imprinting, "X's" in the Figure, and arrows for expression) of genes that, when present in offspring, will reduce demands on the mother. Such silencing leads to maternal expression of demand-reducing genes in offspring. Increases in demand on mothers, mediated by paternal-gene silencing, engender selection on mothers to silence demand-increasing genes during oogenesis, leading to paternal expression of demand increasing in offspring. Demands may be behavioral as well as growth related. Mother–offspring conflict and genomic imprinting conflict interact in that outcomes of genomic imprinting conflict influence the setting of levels of demand imposed on mothers. "R" refers to parental investment. (C) Sexual conflict includes (i) intralocus conflict, due to selection for different patterns of gene expression or regulation between the sexes, for specific genes; (ii) interlocus conflict, over control of mating and other resources related to offspring production; and (iii) chromosomal conflict, due to differences between males and females in genetic relatedness to other individuals, for genes on the X and Y chromosomes.

human disease, and specific suggestions for disease prevention and therapy.

In this first section of this article, I present an overview of human-specific and human-elaborated adaptations and their effects on the scope of human disease, with emphasis on the lineage leading from our common ancestor with chimpanzees, but also considering the mammal and primate lineages more broadly, and the most recent several tens of thousands of years of human evolution more specifically. In doing so, I describe evidence of positive selection on human-elaborated and human-specific phenotypes, and explicate the primary arenas of human genetically based conflicts, pioneered by Haig[5] as mediators of disease risk in the context of maternal–fetal interactions, but yet to be fully appreciated as general causes of disease.

Second, I provide an overview of the evolutionary-genetic bases of disease risk, with a focus on polygenically based diseases, such as cancer and schizophrenia, that are especially prominent in humans and thus provide paradigmatic examples of how human evolutionary changes can potentiate and exacerbate risk of disease. A simple graphical model is developed that can help to explain core aspects of genetic disease risk, including the relative roles of *de novo* and segregating variation, highly variable penetrance of genetic risk factors, the causes and prevalence of sporadic compared to familial disease expression, and pleiotropic effects of strong recent or ongoing selection. I focus in particular on the separate and joint roles of mutation-selection balance, positive selection, and forms of antagonistic pleiotropy in generating and maintaining risk of disease.

Third, I apply the concepts and tools from the two sections described earlier to understanding human diseases associated with cognition and emotion, reproduction, and life span. In this context, I postulate a human "genetic axis of evil": a set of tissues—brain, testis, prostate, placenta, breast, and ovary—that appear especially vulnerable to disease due to their rapid evolution, tendencies to serve as selective arenas for genetic conflicts, and control by genes with strongly antagonistically pleiotropic effects in human physiology and development.

The traits, and disease, that have "made us human"

"*I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes deductions from what is observed.*"
Hippocrates, *Precepts*

How might the selective pressures, genes, and phenotypes that "made us human" also make us vulnerable to particular forms of disease? Of all the morphological, physiological, and life-historial traits that distinguish humans from other primates, none appears more obvious than the large human brain, which has increased threefold since our common ancestor with chimpanzees, especially from 2.5 to 0.5 mya[6,7] and developed specializations for general intelligence, language, complex social cognition, social emotionality, and causal thinking more generally.[8,9] Human reproduction has also evolved substantially, though less obviously: humans exhibit relatively low per-copula fertility in association with concealed ovulation, an especially invasive form of hemochorial placentation coupled with copious menstruation compared to other primates,[10,11] and remarkable fatness in babies, well beyond that of other mammals.[12,13] Finally, humans have evolved substantial alterations in life history, with neurologically precocial yet physically altricial infants, remarkably short interbirth intervals despite the high costs to mothers of fetal development, a relatively elongated childhood period and rapid growth transition to adulthood, a greatly extended adult stage, and a postreproductive period in females associated with alloparental care.[14–16] This set of changes appears to be functionally coupled, with a central role for increased brain size coevolving with a suite of physiological, anatomical, and life-historical mechanisms that support this organ, which is energetically highly expensive for its bearer and caregivers to grow and maintain, yet yields increasing, compensating returns on investment with age.[17–19]

Suites of evolutionary changes in the brain, reproduction, and life history have each potentiated specific sets of genetically based, human-concentrated, or human-specific diseases. Most generally, such disease vulnerability is a function of the potential for maladaptive alterations, mainly mutations, expression-pattern changes, or pleiotropic by-products, involving genes that have undergone adaptive change specific to the human lineage. This genetically based perspective contrasts with conceptualizations of human maladaptation based on recent, rapid environmental changes, although both processes are intimately associated with human disease risk and both underscore the importance of considering disease risk in the context of maladaptation or trade-off[20,21] rather than pathology disembodied from recent evolutionary history.

The primary forms of genomic conflict involved in the evolution of the human brain, reproduction, and life history are mother–offspring conflict, paternal–maternal conflict (genomic imprinting), and male–female conflict.[2] Each of these forms of conflict generates divergent optima for the parties involved, which manifests in forms of disease due to more or less novel physiological and developmental systems, evolved in the context of conflict, that potentiate increased disease risk; one party reaching its optimum, or being closer to its optimum, which by definition engenders maladaptation in the other party; and negative pleiotropic effects of selection, given that selective effects of conflict tend to be especially strong (such that larger negative by-products can be supported in all parties involved), and can involve antagonism expressed across levels of selection, such as benefits to meiotic drive elements that impose costs on individuals in terms of fertility or disease risk.

Unlike selection leading to adaptation with regard to abiotic or simple ecological situations, selection in situations of genomic conflict is expected to continue over evolutionary time owing to its intrinsically reciprocal, antagonistic, coevolutionary dynamics, much like those that underlie the evolution of hosts and pathogens.[22] The most important constraint on genomic conflicts is that they commonly involve interactions between genetically related individuals (such as mothers and offspring),

or between individuals with overlapping avenues of reproduction (such as male–female pairs). We thus expect complex mixtures of cooperative and conflictual phenotypes, which are difficult to disentange without detailed information on molecular-genetic, developmental, and physiological mechanisms of conflicts, and their effects on components of fitness. Such mechanisms are best revealed via experimentation or natural mutational variation but commonly will not be found unless hypotheses based on conflict are explicitly considered.

Brain

Compared to other primates, the human brain may be characterized most simply as larger, more intelligent, and more dedicated to social cognition in large groups.[23,24] In brain development, rare, recessive loss of function in any of a suite of "microcephaly genes" leads to development of a brain that is anatomically normal but about one third of average size—about the size of the brain of a chimpanzee or the inferred chimp-human ancestor, from fossil data.[6,7] The presence of mutational variants with such phylogenetically structured effects indicates that although enlarged brain size has evolved step by step via the effects of multiple substitutions in many genes over several million years, human-specific neurodevelopmental pathways can be "collapsed" by loss of function in specific single genes with key nonredundant functions. This scenario is supported by the notable patterns of positive selection, along the human lineage and in other great apes, in the best-studied "microcephaly genes," ASPM, CENPJ, CDK5RAP2, and MCPH1, and by patterns of positive selection on other genes whose deleterious-mutational effects include lesser degrees of reduced brain size, as well as diverse pleiotropic effects on development.[25–27]

Intellectual disability. Large brain size in humans, compared to other primates, is commonly associated with higher human intelligence, quantified in terms of cognitive skills such as problem solving. Brain size and "intelligence" are indeed positively correlated within humans,[28,29] but the low proportion of variance in "intelligence" explained by brain size or growth implies that the two traits are substantially dissociable. Are there positively selected genes that have mediated the evolution of human intelligence in the same ways that positively selected "microcephaly" genes have mediated the evolution of brain size? The clinical equivalent of microcephaly, for "intelligence," is referred to as intellectual disability, defined as IQ of 70 and below,[30,31] and this condition is known to be caused in many cases by rare, highly penetrant loss-of-function mutations affecting a set of identified genes.[32,33]

Lehrke[34] suggested that "intellectual disability genes," especially X-linked genes subject directly to selection in hemizygous males, might exhibit variants affecting "intelligence" in nonclinical populations. To evaluate this hypothesis, Crespi *et al.*[35] used the compilation of 264 intellectual disability genes from Inlow and Restifo[32] to test for a higher incidence of positive selection, using the human HapMap data[26] on such genes than on a set of brain-expressed control genes. They found no evidence for enrichment of positive selection on intellectual disability genes overall, or for the subset of such genes that are X-linked. These results are predicated on the assumption that genes subject to large-effect, loss of function mutations affecting "intelligence" also exhibit allelic variation of smaller effect that influences quantitative variation in phenotype among nonclinical populations. This assumption is met for genes affecting, for example, human lipid levels,[36] and for the SSADH gene,[37] and a handful of genes under apparent positive selection have been associated with variation in human intelligence,[38,39] but the issue of selection on genes related to human intelligence has yet to be addressed more generally.

A direct test of the general prevalence of positive selection on genes underlying intelligence can be conducted using data compiled by Deary *et al.*,[40] (Table 1 in Dreary *et al.*) on the genetics of intelligence. Of 23 genes associated with aspects of intelligence in one or more study, only one showed evidence of positive selection at 0.05 in the phase II HapMap;[26] by contrast, of the four well-characterized autosomal-recessive human microcephaly genes (MCPH1, ASPM, CENPJ, and CDKRAP2), two show evidence of positive selection in this database (Fisher's exact test, $P < 0.05$), and all four show such evidence from other studies. These results fit with the general lack of enriched positive-selection signal in brain-expressed genes, or neuronal-activities genes, within humans,[41–44] but more data are needed regarding the genetic and environmental factors that influence extant variation in human brain size and intelligence in its various forms.

The convergent findings regarding selection on brain size and intelligence genes described earlier suggest a contrast between frequent positive selection on a small set of human "brain-size" genes, and the lack of overall enriched selective signal across a large number of genes that mediate intelligence and intellectual disability. Such results may be explicable in part by three considerations: (1) a much larger number of genes, each of smaller, less-detectable effect, that influence intelligence compared to brain size; (2) the presence of purifying selection, rather than positive selection, on amino acid change in most brain-expressed genes;[42,43] and (3) the inference that much of increased human intelligence, compared to other primates, is mainly a simple function of increased brain size itself (which is correlated with measures of intelligence both across primates and within humans[28,29,45]) coupled with brain-specific elevated rates of overall gene expression.[44,46,47] Some such changes in gene expression rates may themselved have been driven by positive selection, given that genomic regions inferred to have undergone selective sweeps in humans show the greatest acceleration in brain-specific expression.[48] Indeed two categories of genes showing notably pronounced brain upregulation in humans are those involved in lipid metabolism,[46] and energetics;[46,48] both categories of gene are also known to have undergone accelerated adaptive evolution in humans and other primates, in both the nuclear and mitochondrial genomes.[26,49,50]

Autism and schizophrenia. The third brain-related phenotype that is especially highly developed in humans is social cognition: the perception, processing, and deployment of social information organizing complex and dynamic human interactions.[51] Evidence of a central role for enhanced social cognition in human evolution comes from diverse lines of inquiry, including comparative studies across primates that show positive associations between social group sizes and brain or neocortex size;[23] psychological research demonstrating relatively advanced social skills, but not physical-world skills, in young human children compared to chimpanzees;[52] and neurological studies of brain specializations of humans compared to other primates, most notably (a) Von Economo neurons in the anterior cingulate cortex[53] that mediate aspects of complex social interaction[54] and selectively degenerate in frontotemporal dementia;[55] (b) left-right asymmetries in Broca's area that underlie human-brain modifications for language;[56] and (c) the so-called mirror-neuron systems, that subserve perception and empathic understanding of the intentions and motivations of other humans.[57,58]

Given that loss of human-specific brain enlargement presents as microcephaly, and that reduced general intelligence manifests as "intellectual disability," selective reductions in social cognition are expected to generate a human-concentrated disorder: apparently, what we call "autism." Autism is defined formally by quantification of impairments in social reciprocity and language, and by the presence of restricted interests and repetitive behavior,[59] but it may also be described less arbitrarily as selectively reduced social-brain functions, encompassing effects on social emotionality, social-causal thinking, empathy, and sense of self as well as language and reciprocal social interactions.[60–62] Selective impairments in social cognition, with mechanistic language function and general intelligence largely unaffected, are specifically represented by the subset of autism spectrum conditions known as Asperger syndrome.[60]

An evolutionary-genetic framework for understanding autism implies that social–emotional–cognitive traits elaborated in the human lineage are selectively affected in this condition, which accords with studies positing and showing reduced function in autism of mirror neuron systems[63,64] and Von Economo neurons,[54] and altered asymmetry in brain regions subserving language.[65,66] From this perspective, the presence of restricted, nonsocial interests and repetitive behavior, as well as highly developed, mechanistic autistic savant skills such as calender calculating,[67] may represent secondary effects of reduced social cognition (or brain functions that trade off with social cognition), rather than primary "symptoms" of autism as a more or less coherent syndrome.[68] This perspective, and the cognitive profile of individuals with Asperger syndrome, underscore substantial partial dissociability of social intelligence from general intelligence,[69] and supports arguments from Skuse[70] that the apparent comorbidity of autism with intellectual disability is likely due to ascertainment bias (i.e., preferential recognition and diagnosis of individuals with intellectual disability as autistic), rather than shared genetic risk factors. Conflation

of autism with intellectual disability is especially important in the context of discerning the genetic bases of autism, and these considerations, as well as the high genetic and clinical heterogeneity of autism,[71] suggest that studies of nonclinical populations using dimensional, social-cognitive perspectives,[72,73] are likely to uncover common genetic variants that mediate the expression of autistic traits more effectively than are genome wide studies of autism per se.[74] The relevance of cognitive variation in nonclinical populations to individuals with autism remains uncertain, however, because it depends on the degree to which autism risk is due to inherited versus *de novo* genetic variation,[75] and how many alleles of what penetrance are involved.

Differential loss or reductions in traits that are highly derived among humans, such as brain size, intelligence, and social–emotional–cognitive abilities, indicate dimensions of specific, novel scope for human disease-related maladaptation. Such reductions should not be interpreted in terms of recapitulation of ancestral states because large sets of interrelated traits have coevolved unidirectionally and irreversibly in the human lineage, and suites of ancestral states of alleles that are derived in the human lineage cannot recur. One important implication of a temporal, evolutionary-genetic perspective on disease risk, however, is that derived, polygenetically mediated human traits are, like all traits, maintained under forces of developmental canalization and homeostasis that can vary, owing to inherited and *de novo* genetic variation, toward either reduced or increased expression; disease can thus be caused by Hippocratic "imbalances" with some degree of evolutionary dimensionality. In diametric contrast to microcephaly, a subset of humans exhibits genetically based macrocephaly—large brain size—which is commonly associated with disease.[76] Especially high general intelligence may be difficult for neurogenetic systems to achieve, as it presumably requires specific, rare constellations of myriad interacting alleles coupled with low levels of mutational load affecting brain-expressed genes. By contrast, maladaptive, dysregulated "overexpression" of human-specific traits related to language, causal thinking, and social-emotional cognition appear to underlie a range of phenotypes central to the psychotic-affective spectrum conditions of schizophrenia, bipolar disorder, and major depression. This perspective implies that autism-spectrum conditions and psychotic-affective spectrum conditions represent genomically, neurodevelopmentally, and psychologically diametric diseases,[61,77] due in part to diametric alterations, such as microdeletions versus microduplications, affecting genes involved in development of the human social brain.[77,78] At least in principle, the human genome should comprise large numbers of segregating and mutational variants for such social-brain genes, many of which are expected to retain signals of recent positive selection in extant human populations.[77,79]

Convergent evidence that selection has impacted the evolutionary-genetic underpinnings of schizophrenia in particular comes from four main sources. First, schizophrenia can be most broadly interpreted as a disorder of language, the neurocognitive trait most distinctly human.[80,81] Second, neurological studies have shown that brain areas differentially dysregulated in schizophrenia include the regions most notably subject to differential evolutionary elaboration along the human lineage, especially the prefrontal cortex and core social-brain areas such as the orbitofrontal cortex and anterior congulate cortex, and cerebral asymmetry underlying aspects of language, cognition, and emotion[82–85] Third, Wayland *et al.*[86] found that genes exhibiting positive selection for differential expression between humans and chimpanzees are differentially dysregulated in dorsolateral prefrontal and orbitofrontal cortices of individuals with schizophrenia. Finally, schizophrenia risk genes show enhanced signals of positive selection along the human lineage, compared to sets of control genes.[87]

These diverse findings link recent evolutionary changes in human cognition, neuroanatomy, gene expression, and allele and haplotype frequencies with alterations of these phenotypes in schizophrenia and demonstrate that the phenotypic substrates of this disorder, as well as its genetic basis, show evidence of effects from positive selection and adaptive evolution. Such findings imply not that schizophrenia or schizotypal cognition are adaptive compared to "normal" cognition, but that recent positive selection has generated the genetic and neurological substrates for schizophrenia-related dysregulation, and that some facets of psychotic-affective cognition and behavior, especially creativity and relatively enhanced verbal skills, reflect in part an ongoing history of human-specific selection and adaptation.[88–92] This hypothesis is also supported

by the extremely wide range of genetic and environmental factors that can convergently elicit psychosis[93] (manifest primarily as hallucinations and delusions), which suggest that the human mind and brain have evolved toward near to a cliff edge of schizophrenia,[94] whose phenotypic expression differentially represents dysfunction of human-specific adaptations. Conversely, the expression of autism has been described as a pleiotropic by-product of enhanced nonsocial skills at mechanistic and "systemizing" tasks,[62] as evidenced primarily by associations between autism and specific enhancement of such abilities, and a higher incidence of "systemizing" professions in parents of autistics.[95]

The degree to which positive selection has mediated the evolution of human brain-related traits remains largely unexplored, except in the case of the relatively simple phenotype of brain size itself. As a result, the hypothesis that specific, common human diseases, such as schizophrenia, are caused in part by collective, negative pleiotropic effects of strong selection for social–emotional–cognitive prowess remains difficult to evaluate at the level of evolutionary genetics. The primary indirect evidence consistent with such pleiotropic effects is positive associations of well-replicated schizophrenia risk alleles with enhanced performance in nonclinical populations, for tasks with high relevance to the evolution of human cognition. Such associations have been reported, for example, for NRG1 and creativity[96] and verbal fluency,[97] DAOA and enhanced semantic fluency,[97] G72 and verbal memory,[98] APOE and verbal skills,[99] and PPP1R1B and PRODH for frontostriatal connectivity.[100,101] In contrast to such reports, comparable studies of GRM3 and AKT1 have demonstrated poorer performance on several cognitive tests among nonclinical bearers of the risk alleles.[102,103] Additional studies of the cognitive effects of well-replicated, common-variant schizophrenia and autism risk loci are required, set in the context of which alleles are inferred as ancestral versus derived, or apparently subject to selection (positive, balancing, or purifying), along the human lineage.

Genomic conflicts in brain development. Genomic conflict in brain development has been studied almost exclusively in connection with genomic imprinting, because a considerable number of imprinted genes exert brain-specific effects or are imprinted primarily or entirely in this organ.[104–106] In theory, these patterns of differential expression fit with a role for genomic conflicts in imprinting, given that the brain, like the placenta (where imprinting effects are even more pervasive), plays a central role in the transfer of fitness-limiting resources between individuals that bear genes with partially divergent interests.[5,61,107–111]

Keverne *et al.*[112] conducted the first experiments to analyze imprinted gene effects in brain development, by creating chimeric mice with a mixture of androgenetic or parthenogenetic cells, to bypass the lethal effects of uniparental development. Initially, both types of cell were present in all neural tissues, but parthenogenetic cells differentially survived and proliferated in the forebrain (in particular, the neocortex, striatum and hippocampus), while androgenetic cells did so mainly in the hypothalamus. On the basis of these results, Keverne *et al.*[112,113] suggested that maternally expressed imprinted genes have driven the development and evolution of the "executive" or "maternal" brain, especially the neocortex, whereas paternally expressed imprinted genes mediate the development of the limbic, "paternal" brain, which subserves basic functions and drives, such as physiological regulation of activity and metabolism, as well as food intake and sex. Given that it is the neocortex that has expanded in mammalian evolution, especially among primates, he also suggested that "genomic imprinting may thus have facilitated a rapid, nonlinear expansion of the brain over an evolutionary time scale,"[112] in the context of matrilineal primate social systems that selected for social intelligence and "emancipation" of behavior from hormonal to neocortical control.[113]

The concept of the maternal and paternal brains is concordant with the conflict theory of imprinting, in that the primary motivated behaviors mediated by the hypothalamus can be seen as serving one's personal "selfish" agenda,[114] while neocortical functions subserve complex social interactions, including cooperation and altruism involving the mother and maternal kin. Badcock and Crespi[115] and Crespi and Badcock[61] describe genetic, physiological, neurological, psychological, and behavioral evidence relevant to the hypothesis that the development of autism is strongly affected by imbalances in brain development that lead to increased effects of paternally expressed genes at loci subject to imprinting, relative to maternally expressed ones. Such paternally expressed genes are

expected not just to enhance demands on the mother via fetal and childhood growth, but also to drive cognition and behavior toward more-demanding phenotypes.[5,109,115] Such demands are prominent in two conditions, Beckwith–Wiedemann syndrome and Angelman syndrome, which are caused by genetic biases toward increased relative effects of paternally expressed imprinted genes, and involve overgrowth, increased incidence of autism, and other phenotypes that appear adapted to elicit increased maternal attention and resources.[116–118]

In contrast to autism spectrum conditions, psychotic-affective spectrum conditions are mediated in part by genetic and epigenetic disruptions toward increased relative effects of maternally expressed imprinted genes.[61,119] Such maternal-gene effects are shown most clearly in Prader-Willi syndrome owing to maternal uniparental disomy of chromosome 15, which involves a 100% incidence of affective psychoses, with a neurodevelopmental substrate in dysfunction of the hypothalamus due to loss of one or more paternally expressed gene products.[106,120,121] The behavioral profile of children with Prader-Willi syndrome also involves pathological overexpression of traits that reduce demands on mothers, given that it is characterized by a complacent infancy with low demands on the mother, followed by a postweaning period of increased self-foraging for food.[15,122] Such traits may reflect, in part, disruptions to genes that underly a human evolutionary trajectory of earlier weaning,[5,16,123] a transition expected to impose strong selection in the context of maternal–offspring and imprinted-gene conflicts given high rates of early-childhood mortality. The generation of Prader-Willi-like phenotypes from a range of genetic and epigenetic disruptions, interpersed throughout the human genome,[119] suggests that human-evolutionary changes to mother–offspring interactions have involved a diversity of alterations to the neurodevelopmental pathways, centered in the interactions between the hypothalamus and maternal-brain neocortex, that underly childhood behavior toward one's mother. Most generally, psychological, neurological, hormonal, and genetic studies of variation in early-childhood attachment,[124,125] in relation to psychiatric conditions in later life, should provide useful insights into a range of questions regarding public health and psychological well being.[126]

Reproduction

Female reproduction in humans, compared to other primates, is characterized by concealment of ovulation, low rates of conception per coitus and births per conception, copious menstrual blood flow, more-invasive placentation, high production of chorionic gonadotropin by the fetal-placental unit, and the production of infants with extremely high levels of subcutaneous fat.[10–12,127–129] The evolution of this curious collection of phenotypes can be understood in the context of high energetic investment per offspring in humans due mainly to large brain size,[130,131] coupled with constrained maternal–fetal conflicts over maintenance of pregnancies and levels of maternal investment in the fetus,[5] both of which appear to potentiate a specific set of human-concentrated or human-specific disorders related to female reproduction. I will discuss the evidence relating human evolution to disease risk for three of the primary medical conditions affecting female reproduction: infertility, preeclampsia, and intrauterine growth restriction.

Infertility. The evolution of reduced fertility, especially in the context of fewer births eventuating from each coital event or reproductive cycle, appears paradoxical under evolutionary theory, yet it fits squarely in a life-history paradigm of maximizing female lifetime reproduction under a regime of high investment in each of relatively few offspring, which necessarily entails substantial reproductive losses to a female from investment in offspring of relatively low quality.[124] Humans represent the epitome of high, long-term maternal investment in slow-developing offspring, and as such, females are expected to benefit from systems of reproductive "quality control," whereby embryos are screened, as early as physiologically possible, for indicators of genetic and metabolic health and vigor.[5,107,110,132,133] So-called spontaneous early abortion of low-quality embryos imposes fitness costs on females, but a 1-month delay in starting one's next reproductive attempt represents a small cost compared to the energetics of gestation and lactation, followed by many years of rearing an offspring unlikely to yield grandchildren.

The primary physiological mechanism of early-pregnancy maintenance in humans is well understood: the preimplantation embryo produces high levels of human chorionic gonadotropins (hCG), which, in addition to serving as the

basis for detecting pregnancy via urine test kits, prevent the corpus luteum from undergoing apoptotic breakdown; the corpus luteum thus produces progesterone to maintain the pregnancy until the placenta takes over this role during midgestation.[134,135] Relatively low levels of hCGs have indeed been associated with increased risk of first-trimester miscarriage across many studies,[134,136] and genetic variants at hCG gene-family loci have been demonstrated to strongly modulate risk of recurrent miscarriage.[137] The primary evidence of a "screening" role for hCG is high rates of aneuploidy (mainly monosomies and trisomies) in early miscarriages,[127] with the primary trisomy that is maintained through pregnancy, trisomy for chromosome 21 (which causes Down syndrome), being characterized by especially high levels of hCG.[138]

Aneuplodies represent major genomic defects; association of hCG levels with fetal "quality" in concepti of normal karyotype is suggested by association of reduced first-trimester hCG levels with low birth weight,[139] and indeed, relatively high hCG production is generally regarded by clinicians as a good indicator of early fetal vigor. For the mother, the ability of a conceptus to efficiently produce high levels of such a secreted protein is presumably a genome-scale, accurate indicator of a high-quality fetus, that has passed a metabolic "test" and is worthy of retention.[110] But as described by Haig,[5,107,110] the mother and conceptus are expected under basic evolutionary theory to exhibit divergent test criteria, with the conceptus under strong selection to be retained in some circumstances where the mother is under (generally weaker) selection for miscarriage. The result is maternal–fetal genomic conflict expressed in reproductive physiology, a pattern consistent with the origin and evolution of chorionic gonadotropins in primates. Thus, these genes arose via duplication of the luteinizing hormone gene in the ancestor of anthropoid primates (New World monkeys, Old World monkeys, apes, and humans) and have rapidly undergone multiple episodes of gene duplication and divergence driven by positive selection, notaby in the human and chimp lineages,[140,141] with humans maintaining high levels of within-population genetic variation.[137] Conflicts between males and females may also be involved in the evolution of female fertility levels, given that forms of hCG are produced at high levels in the male prostate and testis and transferred to females in seminal fluid,[142] and that males should be under strong selection for the retention of embryos that they have sired.

Genomic conflicts involving human chorionic gonadotropins generate a range of implications for human reproductive health. For example, recurrent miscarriage has been associated with genetically based disruptions to the pathways involved in hCG function for maintaining pregnancy,[137] perhaps in part because different selective thresholds for pregnancy maintenance between mother and conceptus tend to maintain genetic variation underlying this system; one form of hCG mediates the expression of hyperemesis gravidum (nausea and vomiting of pregnancy) via its effects on maternal thyroid metabolism; this condition appears to benefit fetuses, at costs to mothers, by adjusting maternal metabolism toward anabolism and enhanced placental growth;[143] as noted earlier, Down syndrome appears to be due in part to the high hCG produced by fetuses with trisomy 21; and hCG is strongly overexpressed in many forms of cancer (including cancers of placental tissue), apparently due to its effects in preventing apoptosis and promoting angiogenesis[144,145]—its origin and evolution has thus potentiated novel molecular mechanisms of carcinogenesis.

The primary importance of analyzing the adaptive significance of hCG function, in the context of maternal–fetal conflicts, is that such a perspective provides direct insights into the genetic and physiological causes of maladaptations manifest as disease, makes clear that maternal and fetal optima for health need by no means always coincide, and directs research toward the analysis of otherwise-unexpected phenotypic mechanisms, such as maternal screening of peri-implantation embryos, that could be manipulated therapeutically. Such perspectives can also help to explain, for example, the presence of an increased incidence of miscarriage and cytogenetic abnormalities with maternal age[132,146,147] in terms of maternal life-history trade-offs. The example of hCG also illustrates the divergent maladaptive consequences that can stem from underexpression versus overexpression of a specific gene, here leading to miscarriage on one hand, and cancer cell phenotypes on the other.

Haig[148] describes evidence that the chorionic gonadotropin gene is imprinted in humans, with higher expression from the paternal chromosome (see also de Groot *et al.*[149]). Such a direction of

imprinting is expected under the conflict theory, and additional evidence of genomic imprinting affecting hCG comes from a bioinformatic prediction of monoallelic expression of the luteinizing hormone/chorionic gonadotropin receptor gene LHCGR,[150] suggesting the possible presence of reciprocal imprinting in fetal versus maternal tissues for this ligand/receptor system, as demonstrated for the IGF2/IGF2R system in mice (e.g., Ref. 109). Substantiation of imprinting effects for hCG and LHCGR is required to evaluate this hypothesis further. The primary additional evidence regarding aspects of selection on human hormonal systems regulating fertility comes from a study of the follicle-stimulating hormone beta-subunit gene FSHB, which indicates that this gene exhibits two main haplotypes in humans that are apparently under balancing selection, with the ancestral allele linked to more-rapid conception success,[151] as expected under a model of human evolution toward relatively low fertility. Additional molecular-evolutionary studies of the genes regulating female hormonal cycles, and implantation, might be expected to identify additional alleles, subject to positive or balancing selection, that modulate evolved human risk of infertility.

Preeclampsia. Hypertensive disorders of pregnancy, which include preeclampsia and eclampsia, affect up to 10% of human births, with over 40% of maternal pregnancy-related deaths in some developing countries attributed to this condition.[152] A primary cause of preeclampsia is incomplete invasion of the maternal uterine lining by developing placental tissue; in humans, this invasion is especially deep and extensive compared to other primates with hemochorial placentation, and it culminates with modification of the maternal spiral arteries, the source of maternal blood for the fetus, to preclude constriction.[5,107,110,153]

Given its apparent restriction to humans, and primary cause in underdevelopment of a human-specific phenotype, preeclampsia has been considered unique to the human lineage.[154] Robillard *et al.*[155–157] describe evidence from reproductive physiology that a long-term history of selection along the human lineage, in the context of high maternal mortality, child mortality, and fetal growth restriction from hypertensive disorders of pregnancy, can help to explain a suite of unique human reproductive phenotypes, including a low fertility rate, concealment of ovulation, and more or less continuous female sexual receptivity. This hypothesis is based on well-replicated findings that preeclampsia is predominantly a disorder of first pregnancies, and pregnancies following a change in sexual partner, whose expression is strongly reduced by an increased period of sexual contact with a partner prior to pregnancy; for example, one study showed that risk of preeclampsia is about 40% for new couples with fewer than 4 months of cohabitation before pregnancy.[157] The proximate mechanisms linking partner-specific sexual activity and preeclampsia risk are immunological, in that prepregnancy contact with paternal antigens modulates the maternal immune system to facilitate full, successful invasion of the placenta.[158,159] The molecular mechanisms underlying such interaction have yet to be deciphered in detail, and diverse genetic (e.g., Salonen *et al.*[160]) as well as environmental risk factors influence preeclampsia risk, but effects of parity and partner switching remain among the strongest causal factors. Preeclampsia risk may thus select for two unusual human phenotypes: (1) reduced female fertility, favoring longer cohabitation prior to pregnancy; (2) concealed ovulation and continuous sexual activity, favoring more frequent sexual contact. Robillard *et al.*[156,157] further suggest that deep placental invasion in humans was driven by selection for enhanced fetal nutrient acquisition, concomitant to enlarged human brain size; this hypothesis is broadly consistent with high relative brain to body size in hemochorial compared to epitheliochorial primates[161] but requires further tests based in placental physiology with regard to fetal brain growth.

The primary sequela to inadequate placental invasion is a fetus that is undernourished owing to inadequate maternal blood flow into placental tissues. One of few effective mechanisms to partially alleviate this deficit is hypertension in the mother; indeed, birth weights progressively increase with maternal blood pressure in normal pregnancies, below the threshold of preeclamptic symptoms such as proteinuria.[162] Yuan *et al.*[163] describe evidence that hypertension is induced in the mother via release of factors, by the placenta, that damage maternal endothelial tissue. This proximate mechanism indicates a central role for maternal–fetal conflicts in the evolution and etiology of preeclampsia risk,[5]

such that the effects of genetic and environmental risk factors depend critically upon evolved mechanisms of maternal and fetal manipulation and response.[163,164]

To the extent that reduced female fertility has evolved in humans, in the context of preeclampsia risk as well as embryo screening and FSHB haplotypes, the genetic architectures of infertility, recurrent miscarriage, and preeclampsia are expected to reflect allelic substitutions and segregating variation specific to the human lineage—rather than simple pathology induced by deleterious mutation. Patterns of molecular evolution in such genes are expected to reflect genomic conflicts, and the genetic architecture of preeclampsia in particular is mediated to a substantial degree by effects from genomic imprinting, including altered expression of the imprinted genes H19 and CDKN1C.[165–167] Directly analogous considerations apply to a third major cause of human infertility, polycystic ovary syndrome, which, like preeclampsia risk, appears to be potentiated by deep placental invasion coupled with increased endometrial tissue proliferation, and ultimately, by selection for rapid-trajectory growth of the human fetal brain.[153]

Intrauterine growth restriction and neonatal fat. Human neonates are unusual among primates in several respects, most notably in their physical altriciality (owing to a heterochronic life-history shift involving birth at a "fetal" stage),[168] neurological precociality (such that babies interact socially soon after birth), and extreme development of subcutaneous fat.[12] Compared to other mammals in general, and chimpanzee or gorilla babies in particular, human newborns exhibit an astonishing level of subcutaneous fat, the result of selective fat deposition during the final few weeks of pregnancy when development is otherwise essentially complete. The selective pressures underlying such a human-specific trait remain a matter of conjecture but center on the energetic costs of early neonatal brain growth,[12,13] risk of disrupted nutrient intake or early infection,[12] and selection for indicators of neonate health and vigor, given that historically, mothers may often benefit from termination of maternal investment at this stage, depending upon indicators of offspring condition.[124]

Whatever the ultimate causes of extreme fatness of human neonates, the evolution of this trait has generated increased scope for health-related maladaptation in the form of intrauterine growth restriction with specific effects on subcutaneous fat levels in neonates. Intrauterine growth restriction, defined in terms the failure of a fetus to achieve its growth potential in utero, exhibits a wide range of genetic and environmental causes, and its primary effect on fitness is perinatal mortality rates over 10 times higher than those of normal-weight infants,[169,170] followed in later life by greatly increased susceptibility to chronic diseases such as cardiovascular dysfunction and type 2 diabetes (e.g., Saenger *et al.*[171]). Intrauterine growth restriction involves overall growth as well as degree of fat deposition at birth; ponderal index (a measure of thinness) at birth has also been strongly associated with risk of neonatal mortality[172] and can exert effects on early mortality independent of other measures of size.[173] Similarly, ponderal index can also strongly predict late-life and cardiovascular and metabolic disease, in part because of negative effects from compensatory growth.[174,175]

Risk of intrauterine growth restriction is influenced by a wide variety of genetic and environmental causes,[169] including biases toward increased relative effects from maternally expressed imprinted genes (which tend to constrain growth), due to loss of imprinting and overexpression or maternal genes, or reduced paternal gene expression.[176,177] Such imprinted gene effects on fetal growth are largely a function of the central role of paternally expressed imprinted genes in driving placental growth and invasion.[111,178] In humans, the most common cause of intrauterine growth restriction involving imprinted genes is Silver–Russell syndrome, owing to loss of paternal-gene expression, or gain of maternal-gene expression, at loci on chromosomes 7 and 11. This syndrome, which represents the genomic opposite of Beckwith–Wiedemann overgrowth syndrome in being caused by reciprocal alterations to imprinted gene expression,[117] is characterized by a striking lack of subcutaneous fat at birth, in addition to overall small body size.[169] The presence of a much more general pattern of imprinted gene dysregulation being associated with the development of obesity in humans[179–184] suggests that genomic conflict plays a central role in lipid metabolism in the fetal stage, in childhood, and in later life, with paternally expressed genes favoring increased rates of acquisition and deposition of these energetically valuable

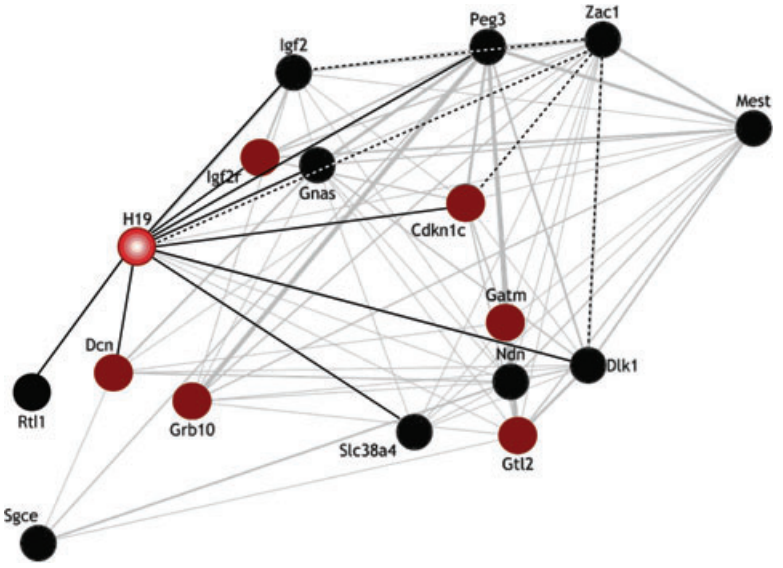

Figure 2. **An imprinted gene network whose patterns of coexpression orchestrate growth and deceleration of growth. Maternally expressed genes are in red, and paternally expressed genes in black. These patterns of coordinated imprinted gene coexpression apparently represent the outcome of genomic conflicts over demands imposed on mothers during development. From Gabory *et al.*,[186] with permission.**

resources in the context of physiological and behavioral interactions with mothers and other kin. Fetal and juvenile growth, and later deceleration of the growth stage, have recently been demonstrated to be under the control of a network of interacting imprinted genes[185,186] (Fig. 2), which appears to represent a complex, multilocus form of the simple tug-of-war genomic conflict manifested by the IGF2–IGF2R system.

All of the major disorders of human female reproduction, including infertility, preeclampsia, intrauterine growth restriction, and polycystic ovary syndrome, as well as gestational diabetes,[5,107,110,187] show evidence of strong effects from human-specific adaptation and genomic conflicts. The most immediate health implication of these considerations is that maternal or fetal phenotypes expressed in pregnancies subject to such disorders may be either conditionally adaptive responses of mothers or fetuses to developmental perturbations, or deleterious manifestations of pathology; in the former case, treatments to alleviate symptoms are expected to make matters worse for one or both parties.[110,164] Understanding the roles of selection in the genetic architectures of such conditions requires direct integration of genome-wide studies to identify risk haplotypes with analyses to identify signatures of positive, balancing, and purifying selection; thus far, such studies have been performed entirely in isolation from one another, making inferences regarding the evolutionary bases of disease risk unnecessarily indirect.

Human life history

The evolution of life history along the human lineage is characterized, relative to inferred primate ancestors, by extension of the childhood stage, followed by a relatively rapid transition to adulthood and an especially long adult stage, punctuated in females by a long postreproductive period after menopause.[188,189] Evidence from inferred ages of fossil humans suggests that elongated life span in humans evolved quite recently, in the Upper Paleolithic (around 50,000 years ago),[18] perhaps in association with enhanced cultural transmission of knowledge that led to increased survivorship and drove the increased human population sizes that started at about this time.[79] Long childhood on one hand, and menopause on the other, have compressed the primary period of female reproduction to ages 20–45, but with shorter interbirth intervals (3–4 years) than in ancestral great apes (5–7 years).[15,16] Alloparental care by grandmothers has been considered a primary selective force in human for the evolution of shorter interbirth intervals, menopause, and concomitant long female life span, with clear

evidence of fitness benefits to children, from the local presence of grandmothers, reported for some populations.[190]

Life histories evolve as suites of changes in patterns of survivorship, reproduction, and parental care, with a central role for trade-offs between aspects of growth, maintenance, and reproduction. Whatever its ultimate causes, the evolution of long life span in the human lineage potentiated greatly increased risks for both cancer,[191] whose incidence increases sharply with age, and age-related diseases associated with senescence. In principle, reproductive benefits from some combination of alloparental care and later-life fatherhood selected against alleles underlying risk of these age-related diseases as longer life span evolved, and signals of positive selection might be expected on genes associated with human life span, even if the fitness effects of late-life gene expression remain relatively low, compared to earlier. For example, one of the best-replicated genes affecting human longevity, FOXO3A, shows evidence of recent positive selection centered on the genetic polymorphism, rs2802292, that shows the strongest association with healthy aging[192] (T. Donlon, personal communication). Given strong trade-offs between cancer risk and tissue senescence following unrepaired DNA damage, ability to maintain and repair DNA integrity should represent primary foci of positive selection in the context of life span.[193] This hypothesis is consistent with a DNA-repair function for FOXO3A,[194] evidence of selection on cell cycle and tumor suppressor genes in general[41] and the PI3K pathway and BRCA-FANC DNA repair pathway in particular,[26,35] and a role for oxidative metabolism pathways in favoring physiological maintenance at the expense of reproduction under low nutrient conditions.[195,196]

Response to positive selection for longer life span in humans are expected, under life-history theory, to engender pleiotropic effects that reduce investment in growth and reproduction, as indicated, for example, by patterns of covariation between growth and longevity underlain by effects of genes in the insulin receptor-PI3K-FOXO signaling pathway.[197,198] Might trade-offs between growth and life span have mediated the evolution of reduced body size in humans, which began about 50,000 years ago,[199] more or less coincident with increases in longevity?[18]

The degree to which the expression and timing of menopause in humans is a by-product of selection for increased longevity, compared to a set of traits that has been driven directly by selection, is difficult to evaluate; however, the high heritability of age at menopause[200] suggests at least the potential for adaptive genetic change. To the extent that menopause has indeed evolved along the human lineage, its genetic basis may have generated human-specific liability, via segregation and mutation of alleles underlying age of menopause, to the disorder premature ovarian failure, defined more or less arbitrarily as loss of ovarian function prior to age 40. This hypothesis can be evaluated via evolutionary-genetic analyses of the genes that mediate risk of premature ovarian failure (or trade-offs between overactivation versus underactivation of ovarian functions),[201,202] and age at menopause more generally, with important implications for the evolution of age-specific fertility schedules along the human lineage. Moreover, if selection for extended life span in humans has centered on females more than males, then male–female genomic conflicts may extend to the architectures of human life-history trade-offs, at least to the extent that sex-specific life-history traits are difficult to jointly optimize under strong, recent selection.[3,203]

Genetic models of human disease risk

> "*Correct it is to recognize what diseases are and whence they come; which are long and which are short; which are mortal and which are not; which are in the process of changing into others; which are increasing and which are diminishing.*"
> *Hippocrates, Diseases*

Changes specific to the human lineage in phenotypes associated with brains, reproduction, and life history generate novel scope for maladaptation and polygenically based disease risk, but the actual expression of such disease is some function of how population-genetic forces, mainly mutation, selection, and drift, are involved in the generation, maintenance, and loss of disease-related alleles. Models based in population genetics must reconstruct the genomic architecture of human disease risk in terms of the degree to which disease-related variants are relatively common or rare in populations, their penetrance, and the degree to which positive selection, balancing selection, purifying selection, and other processes influence disease-allele frequencies.

I briefly review and evaluate models for human polygenic disease risk, and then expand the thesis that strong, recent positive selection, and rapid evolution in the human lineage, have mediated a considerably higher proportion of such risk than has yet been appreciated. Such strong selection is due to two main processes: (1) especially rapid directional evolutionary changes themselves along the human lineage, which potentiate and generate maladaptation[20,21,204] and (2) genetic conflicts within human populations, especially those that involve mothers versus offspring, maternal versus paternal genes (genomic imprinting), and males versus females (Fig. 1). Such conflicts generate and maintain genetically based disease risk through processes similar to those involved in human–pathogen interactions: divergent optima for perpetually competing parties, maladaptive pleiotropic by-products of intense positive selection, increased scope for large-scale mutational input, and continuously varying selective pressures as intrinsically antagonistic evolutionary changes proceed unrestrained by environmental context. Both processes are, to a considerable degree, functions of the extreme sociality of humans, and the degree to which social interactions from conception until late in life determine variation among individuals in fitness.

Segregating variation and mutation-selection balance

The genetic basis of disease risk is usually construed as evolving predominantly under regimes of mutation-selection balance.[205,206] Two main forms of population-genetic models have been developed in this context:

1. models based on a large number of slightly deleterious variants, most of small effect, subject to inputs via mutation across many loci, maintenance by drift under sufficiently weak selection or small population size, and removal via purifying selection,[207,208] and
2. models based on the effects of rare, more highly deleterious genetic or genomic variants, with common variants of small effect exerting a relatively small influence on overall disease risk.[75,208,209]

The first model corresponds to the common disease–common variants hypothesis,[210] whereby polygenic disease is due to cumulative and interactive combinations of many deleterious alleles, each of small effect, in the context of the myriad mutational targets provided by large numbers of genes, large mutation-prone genes and complex pathways.[211] By contrast, under the second model, segregating genetic variation in disease risk has minor effects compared to larger effect, mainly *de novo* deleterious variants that evolve under mutation-selection balance. These two models are by no means mutually exclusive, and they are expected to grade into one another given continuous distributions of frequencies for disease risk alleles across loci, variably deleterious effects,[212] and variation across alleles in levels of penetrance.[213] Moreover, genetic drift may interact with effects of purifying selection by generating increases in the frequencies of more-deleterious variants in relatively small groups, such as human founder populations as Europe and the rest of the world were colonized from modern human origins in Africa.[209,210,213]

For a threshold disease trait, dichotomously expressed but with continuous underlying liability,[214] a basic model of disease risk is illustrated in Figure 3A. The degree to which expression of a genetically based disease is due to effects from segregating variation, compared to *de novo* mutational input, increases with the width of the population-wide distribution of individual deviations from the average, and the relative contributions of *de novo* mutations of different effect sizes is shown by the lengths of the vectors representing mutation input into any given individual's genotype, from new mutations in the gametes that formed them as a zygote and somatic mutations early in development. This visualization of segregating and *de novo* disease risk helps to make clear the observed pattern that positive family history, but not negative family history, predicts disease risk[215,216] because families with negative history may center, in their distributions of alleles, either close or far from the disease threshold, but families with positive history are necessarily close and are expected to be segregating disease-risk alleles with moderate to large effect.[217,218] The degree to which segregating risk alleles of relatively small effect are relevant to disease risk (as compared to mainly mediating dimensional variation in underlying phenotypes, such as the broad autism phenotype or schizotypy, while disease is mainly caused by *de novo* variants) remains

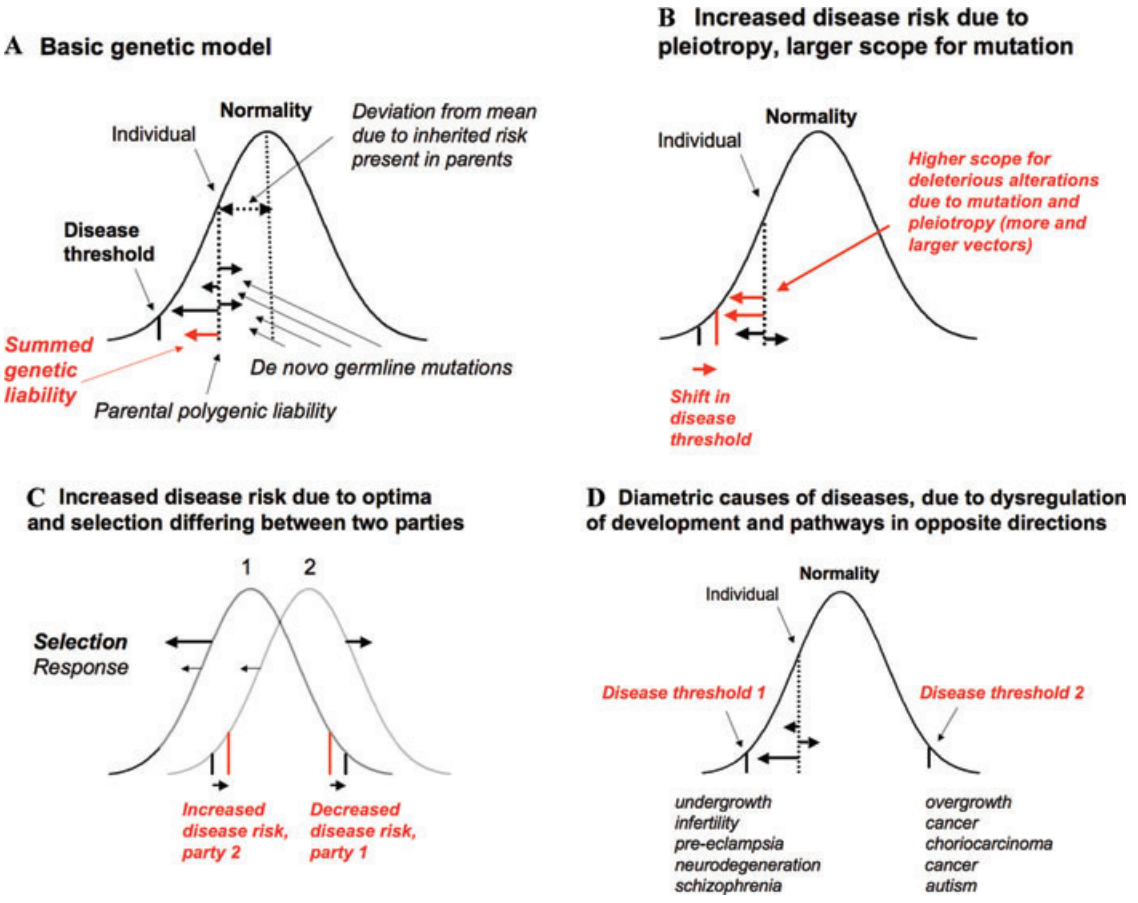

Figure 3. (A) Under the basic model, genetic disease risk is represented as the sum of segregating inherited risk (the distance from the mean phenotype) and risk generated *de novo* via germline and early somatic mutation. (B) Human-elaborated and uniquely human adaptations and selective pressures, and genomic conflicts, increase the scope for maladaptation in disease-related phenotypes. (C) Genomic conflicts between two parties can generate maladaptation via one party being displaced from its optimum as a result of selection on the other party, as in the example shown, and more generally. (D) Diametric patterns of disease are due to dysregulation of developmental, metabolic, or physiological systems in either of two directions.

to be determined for most polygenic diseases; in Figure 3A, this degree corresponds to the degree of kurtosis (flatness vs. peakedness) generated by segregating variation alone.

In the framework of Figure 3, human-specific adaptations and genomic conflicts generate novel scope for deleterious mutations (as represented by additional vectors) and an increased magnitude of mutational perturbation (larger size of vectors, with larger perturbations more likely to be negatively pleiotropic) (Fig. 3B), and conflicts can generate maladaptation by displacing one or both parties from their optimum for a given phenotype, thus moving them closer to disease thresholds (e.g., Fig. 3C). Representative situations illustrating such increased scope and magnitude for disease include microcephaly mediated by DUF1220 repeats,[219] genomically based cognitive-affective conditions such as Angelman, Prader-Willi, and Williams syndromes,[77] and adaptations followed by counter-adaptations in maternal–fetal conflict, especially with regard to highly invasive placentation.[5] For example, a novel, genetically based maternal adaptation to slightly restrict fetal growth generates a new target for mutational effects that can either overly or underly restrict growth, with maladaptive consequences for mother, fetus, or both.

One important aspect of this conceptualization of disease risk is that for some phenotypic axes, such as overall growth or social cognition, disease states

may manifest at both extremes of a distribution, ultimately as a result of diametric alterations to developmental or physiological pathways toward either underactivity or overactivity (Fig. 3D). Such sets of diametric conditions should exhibit interesting evolutionary dynamics, because increased genetically based risk for one of the diseases necessarily entails decreased risk of the other. Diametric diseases might be expected to be especially common in disorders caused by genomic copy-number variation or imprinted genes,[77,117] which naturally generate bidirectional variation in levels of gene expression,[220] and mouse models that involve both knockouts and knockins of the same gene or set of genes,[221] can be readily adapted to their analysis.

Positive selection and polygenic disease risk

A third general model for the generation and maintenance of genetic variation underlying disease risk, in addition to models based on segregating common variants of small effect, and models predicated on effects from rare deleterious mutations, is motivated by evidence regarding positive selection on disease-risk genes, and evolutionary advantages, now or in the past, of alleles that influence such risk.[205,207] Variation is maintained under this model by any of a number of selective processes, such as balancing selection or antagonistic pleiotropy, that can maintain risk alleles at nontrivial frequencies, either transiently as selection proceeds, or at stable equilibria. This form of model has a long history in population genetics, and several recent studies of positive selection in humans have demonstrated its relevance to genes mediating risk of polygenic disease. Thus, Thomas *et al.*[222] showed that genes involved in polygenic human disease risk exhibited some combination of weaker purifying selection and stronger positive selection than Mendelian disease genes. Three more recent analyses using different data sets have also shown enrichments of positive selection on polygenic disease genes, compared to other genes, in human populations,[206,223,224] and Amato *et al.*[225] demonstrated higher levels of among-population differentiation, which can be indicative of divergent positive selection, in complex-disease genes than in a set of control genes.

Several evolutionary-genetic models may plausibly explain enrichment of positive selection on polygenic disease genes. A primary such model is based on rapidly changing selection pressures, such that common alleles that were advantageous in ancestral environments (e.g., "thrifty" genes affecting regulation of metabolism) are deleterious in current environments, and derived, formerly maladapted alleles are now selected for.[226,227] This "ancestral-susceptibility" model has been supported by data from molecular-evolutionary, geographic, and physiological analyses of genes involved in risk of hypertension, type 2 diabetes, and several other common human diseases,[226–229] and it provides a strong predictive framework, based in processes driving evolutionary-genetic disequilibrium, for testing hypotheses on the dynamics of disease-related alleles.

Selective pressures underlying the ancestral-susceptibility model are generally conceived as ecological factors, such as climate and diet, that undergo rapid, large-scale unidirectional transitions. This model can, however, be generalized to other forms of selective pressure that generate evolutionary disequilibria, including genomic-conflict situations where antagonistic coevolution generates more or less constant states of disequilibrial change. For example, Crespi and Summers[230] describe evidence from genome-wide studies of selection, and case studies of specific genes, that positive selection has mediated the evolution of human cancer risk though the effects of strong antagonistic coevolution that generates maladaptation in the contexts of maternal–fetal, male–female, maternal–paternal, and host–parasite conflicts over cellular resources. More generally, genomic conflicts such as those described earlier that involve the evolution of brains and cognition, reproduction, and life history in humans are expected to potentiate, generate, and increase disease risk because of rapid, ongoing change in nonecological selective environments. Hypotheses based on such effects can be evaluated with fine-scale genetic association studies, combined with tests for positive or balancing selection, for diseases involving arenas of genomic conflicts. In our graphical model of disease risk, changing selective pressures and environments that increase disease risk can be represented by an increased area of the disease state of the distribution.

A second genetic process that may help to explain an enrichment of positive selection on polygenic disease genes is antagonistic pleiotropy.[204] A role for pleiotropy in patterns of positive selection and disease was first suggested by Nielsen

et al.[41] in the context of "selfish" mutations of tumor suppressor genes to increased rates of spermatogenesis that pleiotropically increase risks of cancer. Most generally, under antagonistic pleiotropy, selected alleles exert positive effects in one context, or early in the life span, that are stronger than, or balanced by, negative effects expressed in some other context or later in life. Stronger advantages in one selective situation, such as one tissue or one stage in life, can support stronger deleterious effects, manifest as risk of disease. The deleterious components of pleiotropic effects are, of course, expected to be selected against, to the extent that they are dissociable genetically via recombination, or can be alleviated by selection and response at interacting loci. Some antagonistically pleiotropic effects are thus expected to be evolutionarily transient, with the extent of deleterious effects in a given population being some increasing function of the number and strength of ongoing sweeps with negative by-products. In humans, deleterious pleiotropic effects from ongoing and recent selective sweeps may be substantial, given that the prevalence of positive selection shows evidence of having increased greatly over the past several tens of thousands of years.[79]

In contrast to transient antagonistic pleiotriopy due to selective sweeps, a second form of antagonistic pleiotropy is expected to be more or less stable because it is underlain by intrinsic trade-offs between opposing selective pressures, based ultimately on the necessity that energy or time devoted to one biological function, such as some aspects of growth, reproduction, or maintenance, must take away from others.[231] Trade-offs are fundamental to life-history theory and can maintain substantial levels of phenotypic variation in core life history traits.[232] Similarly, extensive pleiotropy is a virtually universal mode of gene action;[233,234] however, trade-offs at the levels of genes, proteins, and developmental–physiological pathways have yet to be systematically investigated except in a few cases,[231] such as the role of genetic variation in the TP53 gene in trade-offs between cancer risk and senescence,[235] and the trade-off between early-life verbal abilities and late-life disease mediated by variation in APOE.[99] Instead, pleiotropy in disease risk is usually analyzed at the level of comorbidities (epidemiological correlations among diseases; e.g., Rzhetsky *et al.*[236]) rather than the population-genetic processes and molecular-developmental mechanisms that provide direct insights into its ability to cause and maintain maladaptive phenotypes. Recognizing and characterizing transient and stable forms of antagonistic pleiotropy is especially important for managing disease risk because in these situations, expression of the disease is associated with benefits in other contexts (such as tissues, sexes, or life history stages) that represent its ultimate cause. As a result, preventatives or treatments that focus on just one end of a developmental or physiological trade-off run the risk of deleterious consequences from alterations to the other—and violating the dictum of Hippocrates to do no harm.

The genetic axis of evil

Human-specific and human-elaborated adaptation, positive selection, genetic conflicts, and antagonistic pleiotropy should exhibit concentrated effects in tissues whose functions have most directly mediated variation in reproductive success of the individual or units at other levels of selection, over recent evolutionary time.[237] The human tissues most directly subject to strong intraspecific selection should thus include the brain and two categories of reproductive tissue: those involved in mating—testis, prostate, and ovary—and those that nourish offspring—the placenta and breast (Fig. 4). This hypothesis can be evaluated using data on patterns of gene expression and coexpression, pleiotropy, positive selection, and genomic-conflict effects, for genes affecting risk of human disease. In particular, we predict pleiotropic effects of genes in brain and reproductive tissues with evidence of trade-offs, genomic conflicts, and positive selection impacting gene evolution, expression, and effects on disease-related phenotypes. Comprehensive evaluation of these ideas requires integrated analyses of evolutionary processes, genetic causes of disease, and data testing specifically for antagonistic pleiotropy. However, the broad outlines of a set of evolutionary-genetic axes for disease risk are beginning to emerge and can be sketched out with information available to date.

In the following sections, I describe evidence of impacts from pleiotropy and selection on disease risk with regard to three sets of phenotypes: neurodevelopment, neurodegeneration, and cancer risk; neurodevelopment, reproduction, and cancer risk; and reproductive tissues and cancer risk, that jointly define core components of a "genetic axis of evil."

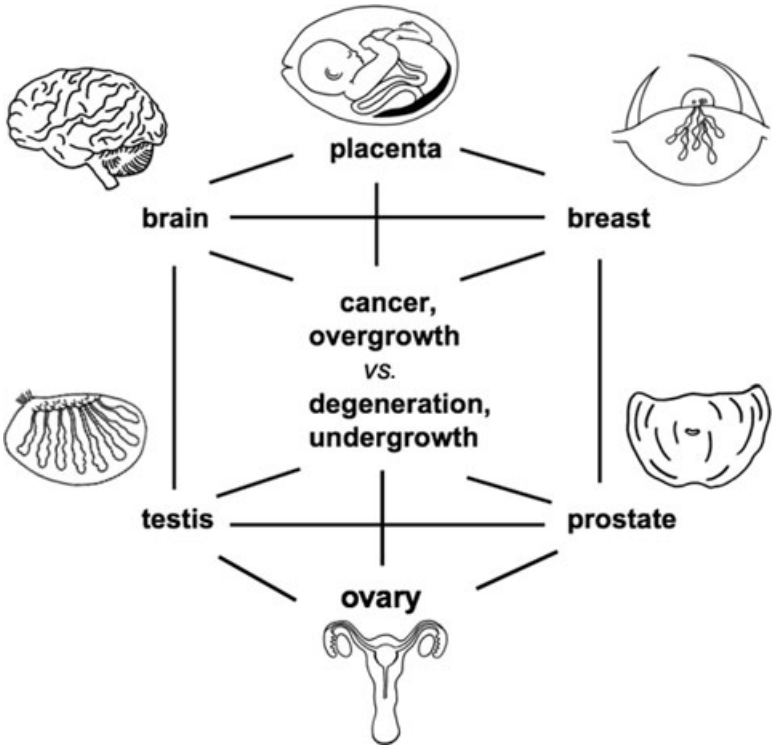

Figure 4. A "genetic axis of evil." Connecting lines represent patterns of gene co-expression, co-option of genetically based developmental, metabolic, and physiological pathways, and interactions between tissues that strongly mediate fitness and vulnerability to genetically based disease.

Neurodevelopment, neurodegeneration, and cancer risk

A history of strong selection on brain size and functions, and concomitant evolution of increased life span, typify human evolution,[17,238] and humans are likewise unusual among mammals in their high incidence of cancer[239] and broad suite of neurological and neurodegenerative conditions. Indeed, schizophrenia, Parkinson's, and Alzheimer's disease are all essentially human-specific conditions, with disease risk some function of human-elaborated brain phenotypes centered around the expanded social brain.[87,240,241] These three conditions also show striking negative epidemiological associations with incidence of cancer,[242–246] indicating strong pleiotropic effects of genes underlying neurodevelopment and neurodegeneration on risk of this disease; a simple explanation for these patterns is that less-activated growth-signaling pathways, and upregulated apoptosis, mediate both reduced cancer risk and higher risk of neuron loss and neurodegeneration. The genetic basis of some such manifestations of pleiotropy has been discerned in part via identification of genes, such as APC, NRG1, and TP53,[247] and pathways, such as PI3K-Akt[248–250] that strongly affect risk of both cancer and schizophrenia—and show evidence of population differentiation and positive selection.[26]

In contrast to the three conditions noted earlier, autism has been associated with increased risk of some cancers, due in part to loss of function mutations in tumor suppressor genes such as NF1, PTEN, TSC1, and TSC2, increased tissue exposure to growth factors[251] or testosterone,[252] and unspecified epidemiological factors that may include both genetic and environmental effects.[253] These data suggest that a disease-related axis of variation in general growth, cancer risk, and susceptibility to neurodegenerative disorders parallels an axis of social brain development, such that the genetic bases of schizophrenia, Parkinson's, and Alzheimer's involve antagonistically pleiotropic effects on patterns of growth, cancer risk, and neurodegeneration. In contrast to such effects, McAlonan *et al.*[254]

demonstrated a striking apparent lack of gray matter loss with age among individuals with Asperger syndrome compared to controls, which suggests lower rates of age-related neurodegenerative change in this psychiatric condition, as well as enhanced growth of brain and body early in life (reviewed in Crespi and Badcock[61]). Pleiotropic effects involving neurodevelopment, cancer risk and neurodegeneration define a diametric axis of disease risk (Fig. 3D) that appears to account for comorbidity between disorders that otherwise appear independent.

Neurodevelopment, reproduction, and cancer risk

A second axis of pleiotropy affecting human disease risk is indicated by associations between neurological and reproductive phenotypes, which provide evidence that variation in specific genes, or sets of genes, jointly affect brain development and reproductive functions. This axis is manifested by (1) joint alterations to cognitive-affective traits, and testicular or ovarian development, in a suite of neurogenetic conditions including Klinefelter syndrome, Turner syndrome, Prader-Willi syndrome, Fragile X syndrome, and other forms of monogenic intellectual disability;[201,255,256] (2) gene coexpression in brain and testis, within humans as well as mice;[257–259] (3) enrichment on the X chromosome of genes expressed in brain and reproductive organs, especially testis,[260] with strong enrichments of selection on testis-expressed genes;[26,41] (4) expression of a large suite of "neuronal" genes, such as CHRNA7, DRD2, and GABA receptors, in sperm development and function, due to shared molecular-physiological functions sufficiently pleiotropic to consider a sperm cell as "a neuron with a tail";[261–263] (5) positive correlations of measures of intelligence with sperm count and mobility;[264,265] and (6) similarities between brain and testis in rapidity of energy metabolism, as exemplified by the glutamate metabolism gene GLUD2, which evolved from a duplicated version of GLUD1 that underwent transposition to the X chromosome in hominoids, followed by an episode of strong positive selection and restriction of expression to the brain and testis.[266] A simple proximate explanation for pleiotropic genetic effects involving gonadal and reproductive functions is that reproduction-associated genes bear "tags" for sex-differential expression (such as protein domains for interaction with sex-determining or hormonal pathway genes), which can be exploited by evolution as mechanism for sexual differentiation in other tissues, such as the brain. SRY provides an example of this type of mechanism, in that it both initiates testicular development and mediates sex differentiation in the dopaminergic system of the brain.[267]

Joint expression in brain and testis also appears to be pleiotropically linked with cancer risk owing to effects on cell proliferation rates and DNA repair. For example, some of the well-known "microcephaly" genes whose evolution has driven human brain expansion, ASPM and MCPH1, are also associated with carcinogenesis via their roles in cell cycle regulation and centrosomal function.[268,269] Conversely, some well-known "cancer genes," including BRCA1 and APC, are highly expressed in the growing brain, with functions in cell cycle progression;[270–272] both of these genes exhibit evidence of positive selection along the human lineage.[87,273–275] BRCA1 is highly expressed in testis as well as brain and proliferating breast tissue[230] and knockout mice are small yet generally normal except for a complete lack of spermatogenesis and underdeveloped mammary glands.[276] APC, ASPM, BRCA1, and MCPH1 all exhibit tumor-suppressor roles, but with patterns of pleiotropy not yet adequately understood to evaluate the molecular-genetic and tissue-specific targets of selection upon their evolutionary dynamics. By contrast, antagonistic–pleiotropic effects on brain, gonad, and cancer development in females are epitomized by the Pro/Arg72 polymorphism of TP53, which mediates complex trade-offs between fertility, longevity, and cancer progression[277,278] that appear unique to the human lineage.[279] Atwal *et al.*[280] report evidence of positive selection on MDM4, a key TP53-interacting gene, that they use to identify functional haplotypes that may influence cancer risk (see also Ding *et al.*[281]); comparisons of derived and ancestral haplotypes for such genes should also yield important insights into the genetic architectures of pleiotropy involving neurodevelopment and reproduction, in recent human evolution.

Reproductive tissues and cancer risk

Human reproductive functions commonly involve rapid cell proliferation in the contexts of male–female, male–male, and mother–offspring conflicts, with strong, direct effects on fitness.[230] Such functions appear to potentiate and mediate a pleiotropic

axes of gene expression and function involving testis, placenta, ovary, prostate, and breast that involves increased risk of cancer. Three examples of such connections from the literature include cancer-testis antigens; similarities between placental growth and cancer; and positive selection, sexual conflicts, and cancer involving genes expressed in the prostate.

First, a large set of genes referred to as "cancer-testis antigen genes" are characterized by expression restricted to these two tissues, where they play roles in cell proliferation; these genes also exhibit a strong enrichment on the X chromosome and clear evidence of positive selection.[230,282,283] The expression of cancer-testis antigen genes in cancer appears to involve "co-option" of molecular functions that evolved in the context of rapid and effective spermatogenesis,[284,285] as such properties presumably convey advantages to cancer cells in proliferative growth. Evidence for a trade-off between male fertility and cancer risk comes from studies the Y-linked TSPY1 gene, which exhibits positive correlations of gene copy number with human male sperm count,[286] and aberrant high expression of the gene associated with a range of cancers.[287] More generally, mouse knockouts of tumor-suppressor genes that are not lethal exhibit a striking preponderance of differential phenotypic effects on fertility, especially in males.[288]

A second example of co-option of reproductive molecular-genetic functions in cancer risk is described by Ferretti *et al.*,[289] who demonstrate how the proliferative, invasive and migratory phenotypes of placental cells, and their underlying signaling pathways and gene-expression patterns, are extensively deployed by cancer cells for the development and evolution of their broadly similar cellular phenotypes (Fig. 5) (see also Bischof and Campana[290]). The extreme diversity of placental phenotypes among mammals, despite their shared, common function[161,291] attests to strong selection on the effects of gene expression in this organ, where effects of maternal–fetal conflicts, and genomic-imprinting conflicts, are known to be especially strong. Imprinted genes in particular are known to exert strong effects on cancer risk, because of their functional haploidy and roles in control of cellular growth and proliferation.[292,293] These considerations suggest that analyses of how placental–uterine interactions constrain placental growth, during normal development of this organ, should yield novel insights into therapeutic agents for control of cancer.[294]

The prostate apparently represents a third arena for strong positive selection with increased cancer risk as a by-product, although the normal functions of human prostate-specific gene expression have yet to be investigated in enough detail for robust links between adaptation and maladaptation to be drawn.[295] Across primates and some invertebrates, genes coding for protein components of seminal fluid show notably enhanced signatures of positive selection, with some combination of male–female conflicts and sperm competition driving rapid evolutionary change that is adaptive in exclusively antagonistic contexts.[203,296–298] Such antagonism should be exacerbated by enrichment to the X chromosome of not just brain and testis-expressed but also genes expressed in the prostate,[299] placenta,[300] and ovary,[301] given evidence for the X chromosome as a nexus for sexually antagonistic fitness effects[302] and other forms of genomic conflict.[303]

A primary implication of pleiotropic axes of gene expression and function involving brain, testis, placenta, ovary, prostate, and breast is that disease risk should commonly involve not just loss-of-function mutations, but also gain-of-function mutations, and pleiotropic effects of strong positive selection in tissues that do not themselves manifest the disease phenotypes. Such effects can be discerned via tests for positively selected alleles in disease-associated genes, followed by analyses of functional differences between ancestral and derived alleles and the effects of such functional differences in tissues where the gene is highly expressed.

Evolutionary origins of the genetic axis of evil

Uniquely human and human-elaborated phenotypes are most directly relevant to disease risk, but the origins of human disease risk, as mediated by genomic conflicts and strong positive selection, go back about 120 million years to the origin of eutherian mammals. The first eutherians exhibited a remarkable suite of evolutionarily novel traits, including (1) enlarged brain size (relative to body size) due to neocortex expansion and reorganization, including the origin of the corpus callosum;[304,305] (2) enhanced complexity of social interactions,[304]

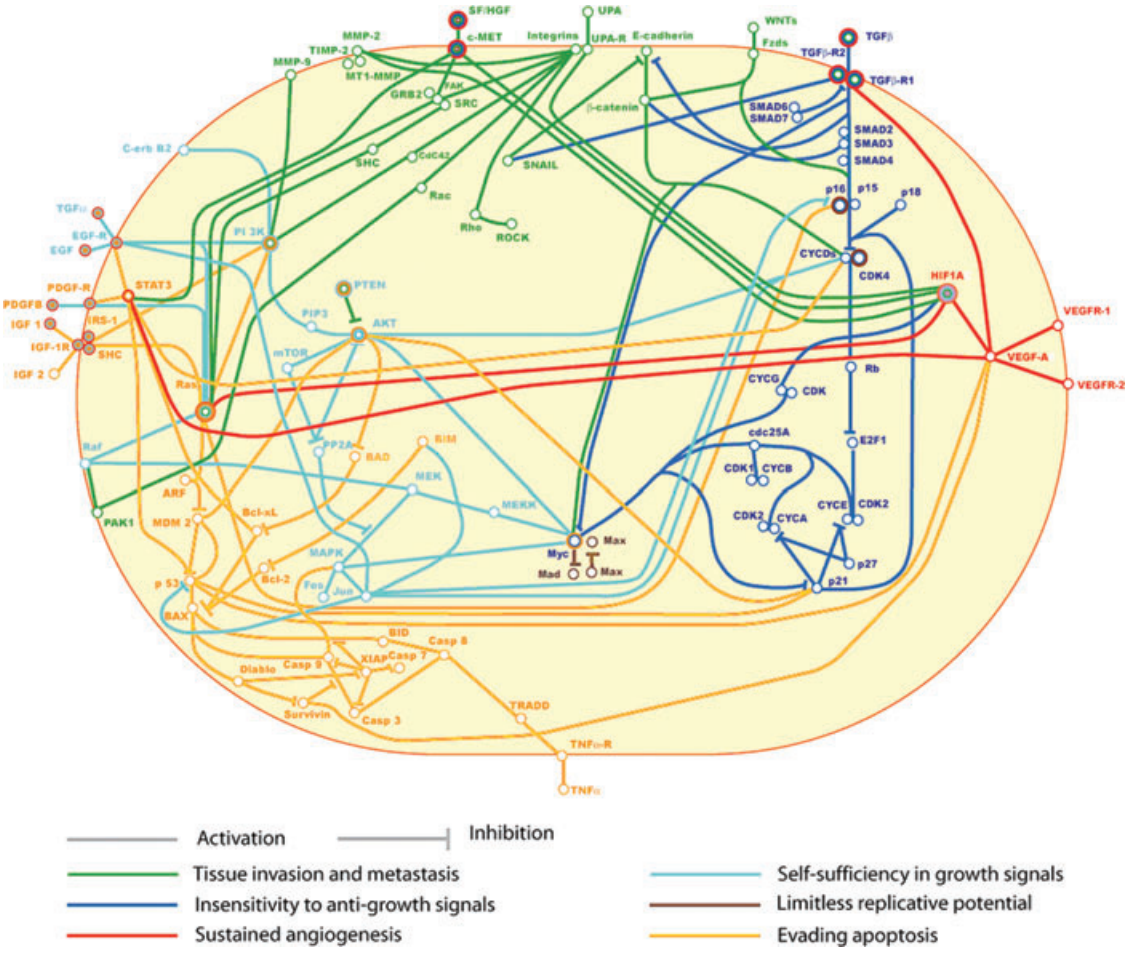

Figure 5. **Co-option of genetic pathways expressed in placentation by cancer cell lineages. All six of the hallmarks of cancer, shown as colored lines, are manifest in the growth-signaling networks that mediate placentation. From Ferretti *et al.*[289] with permission.**

apparently based initially on mother–offspring bonding; (3) origin of the neurohormone oxytocin, which mediates such bonding;[306,307] (4) origin of the invasive, hemochorial placenta,[161,308] serving to define the group; (5) origin of the breast, uterus, and vagina;[309,310] and (6) origin of the prostate gland.[311] The evolution of this concatenation of novel and expanded organs centers on increased levels of maternal energetic and behavioral investment in offspring, setting up profound male–female asymmetries in investment that have apparently potentiated male–female conflicts over control of female reproductive resources,[312,313] genomic-imprinting conflicts in the placenta and brain,[314] and increased levels of competition between males and between sperm in the female reproductive tract. Humans, with greatly enlarged brains and breasts, and especially invasive placentation, represent a eutherian epitome of high maternal investment; these adaptations, and continuous female receptivity selecting for continual high activity of testis and prostate tissues, should generate especially strong genomic conflicts in our species perhaps more than in any other mammal. Understanding how such conflicts have driven human genetically based disease risk demands novel integration of evolutionary biology with medical genetics, in the context of how modern humans have evolved. Indeed, as Hippocrates first sought the natural, proximate causes of disease, so must modern medical science begin to seek its ultimate causes, where our evolutionary past meets the present.

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Conflicts of interest

The author declares no conflicts of interest.

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