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PERSPECTIVE

The emergence of human-evolutionary medical genomics

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Abstract

In this review, I describe how evolutionary genomics is uniquely suited to spearhead advances in understanding human disease risk, owing to the privileged position of genes as fundamental causes of phenotypic variation, and the ability of population genetic and phylogenetic methods to robustly infer processes of natural selection, drift, and mutation from genetic variation at the levels of family, population, species, and clade. I first provide an overview of models for the origins and maintenance of genetically based disease risk in humans. I then discuss how analyses of genetic disease risk can be dovetailed with studies of positive and balancing selection, to evaluate the degree to which the 'genes that make us human' also represent the genes that mediate risk of polygenic disease. Finally, I present four basic principles for the nascent field of human evolutionary medical genomics, each of which represents a process that is nonintuitive from a proximate perspective. Joint consideration of these principles compels novel forms of interdisciplinary analyses, most notably studies that (i) analyze tradeoffs at the level of molecular genetics, and (ii) identify genetic variants that are derived in the human lineage or in specific populations, and then compare individuals with derived versus ancestral alleles.

Introduction

Analyzing the causes of phenotypic adaptation and maladaptation represents a central goal in evolutionary biology (Williams 1966, 1992). This goal is usually pursued using organisms and clades well suited to the measurement of fundamental population-genetic processes and phylogenetic patterns, and experimental testing among alternative causal hypotheses. It is difficult to conceive of a species less amenable to the study of adaptive significance than humans, because of their long generation times, low fecundity, regulation of behavior, and physiology by hugely complex brains, acceleratingly novel environments, and general experimental intractability. Indeed, studies of human adaptation seldom deploy measurements of phenotypic selection as an analytic approach; more frequently, comparative methods are utilized, across human groups, or across primates, to infer the selective pressures that have mediated evolution along the human lineage. Neither of these methods – measurement of selection and comparative analysis – lacks severe limitations on the rigor of strong-inference hypothesis testing, given the problematic nature of reconstructing thousands or millions of years in history from snapshots of present-day variation and scraps in the fossil record. Demonstrating the presence and causes of deviation from maladaptation (Crespi 2000a; Nesse 2005), in the myriad forms of human disease risk, is even more challenging, because hypotheses of adaptation and adaptive tradeoff must be contrasted with hypotheses based on processes, such as drift, mutation, and gene flow, that can constrain or delay optimization by selection (Arnold 1992).

The primary goals of medicine are the prevention, alleviation, or repair of phenotypes that humans consider maladaptive, via well-substantiated therapies. As such, the uncertainties of most purported evolutionary insights into human health concerns usually preclude consideration serious enough to warrant clinical evaluation, and the practice of medicine defaults to the perspective of body and mind as organic machines subject to forms of physical, physiological, and psychological breakdown (Williams and Nesse 1991; Nesse and Williams 1994). Understanding how such a machine works requires deterministic dissection of component parts and

their interactions, with medical interventions structured by delineation of disease states, and therapy development based on substantiated causes and patterns of deviation from optimal function.

The blueprints for our human machine reside, or course, in the genome, and accelerating progress in genomic technology, and deciphering the genomic bases of disease risks, has put genetics at the forefront of recent studies in the etiology of polygenic disease. Genes underlying disease have, like all other genes, evolved under the influence of natural selection and other population genetic processes. What role, then, should evolutionary biology play in the design and interpretation of genetically based studies of disease risk?

In this paper, I describe conceptual frameworks for integrating two fields, the genetics of polygenic disease risk, and the genetic evolution of modern humans, that have developed in considerable isolation despite their reliance on the same forms of genomic data. I first provide an overview of theory for analyzing and understanding human polygenic disease risk, and summarize recent advances that provide the first clear pictures of its genome-scale landscapes of allelic risk effects. Next, I describe the development and structure of a parallel research enterprise, elucidation of the 'genes that make us human' through studies of positive Darwinian selection along our lineage. Third, I discuss how these fields can be dovetailed to accelerate progress in both endeavors. And finally, I present four basic yet nonintuitive principles for the nascent field of evolutionary medical genomics, each of which serves to integrate proximate, mechanistic perspectives with the ultimate evolutionary dynamics of risk alleles and disease phenotypes, in the origin and diversification of modern humans.

The genes that make us sick

Genetically based disease risk poses an apparent paradox, given that many disorders with notably negative impacts on survival and reproduction are both relatively common and highly heritable (Keller and Miller 2006; Blekhman et al. 2008). A primary motivation of the human genome project, and projects that characterize genetic variation across the genome (e.g. Manolio and Collins 2009), has been the discovery and characterization of disease risk alleles, to account for heritable risk, infer the causes of polygenic disease at the levels of development, physiology, and pathways, and guide strategies for treatment and prevention. Vulnerability to disease mediated by such alleles is usually construed in terms of mistakes and weaknesses in construction–*de novo* and segregating alleles that are each slightly deleterious, in comparison to simple Mendelian diseases of large negative effect.

Ongoing searches for the 'disease genes' and 'risk alleles' that underly human dysfunction are conceptually structured, and empirically focussed, by five main axes of genetic disease risk (Altshuler et al. 2008; Manolio et al. 2009):

1 Disease frequency, between vanishingly rare and common, with high frequencies mediated by genetic factors that may be dependent on environmental variation;

2 Disease severity, in the context of effects on age-specific survival, with earlier-onset and high mortality rates, or effects on reproduction, indicating more severe;

3 *De novo* versus segregating variation – how much of disease risk is attributable to new, necessarily rare mutations, detectable only by comparing affected offspring with parents, compared to segregating variation, with risk alleles having successfully passed through at least one generation;

4 Common versus rare allelic variants. For sites with segregating variation, are disease risk alleles relatively common (e.g. with minor alleles at frequencies of 1%, or 5%, or above) or more rare?

5 Penetrant versus nonpenetrant effects of risk alleles. How likely is someone harboring a risk allele to exhibit the disease – between 100%, as in some monogenic diseases, and several percent, at the threshold of statistical estimation that increased risk exists?

These five axes are inter-related by the expectation that mutation–selection balance, and purifying selection generally, will more rapidly remove relatively more highly deleterious alleles from populations. As a result, more common diseases should tend to be less severe, more likely due to segregating compared to *de novo* variation, and less penetrant in the effects of risk alleles. A simple graphical model showing effects of *de novo* and segregating variants is presented in Fig. 1, and the expected inverse relationship between effect size of a disease risk allele, and its expected frequency in a population, is depicted in Fig. 2.

The idea that more common diseases should be mediated by effects from large numbers of common, low-penetrance disease risk alleles was originally framed as the 'common-disease common-variants' hypothesis (Reich and Lander 2001; Pritchard and Cox 2002). This hypothesis has recently become subject to robust tests via the availability of technology for measuring relatively common allelic variants across the entire human genome – so-called GWAS (genome-wide association studies) (Corvin et al. 2010). A large suite of GWA investigations, over the past 4 years, has successfully identified common risk variants for diseases of high heritability, such as schizophrenia, cancer and type 2 diabetes (Stratton and Rahman 2008; Psychiatric GWAS Consortium Coordinating Committee 2009; Stolerman and Florez 2009; Cazier

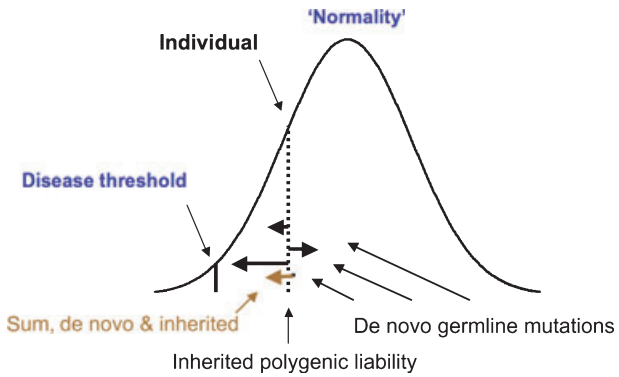

Figure 1 Polygenic disease risk for a given individual can be depicted as a combination of risk owing to alleles inherited from parents (inherited polygenic liability), and risk owing to new mutations (de novo germline mutation). Somatic mutation during development is also likely to be important, but has yet to be studied in detail.

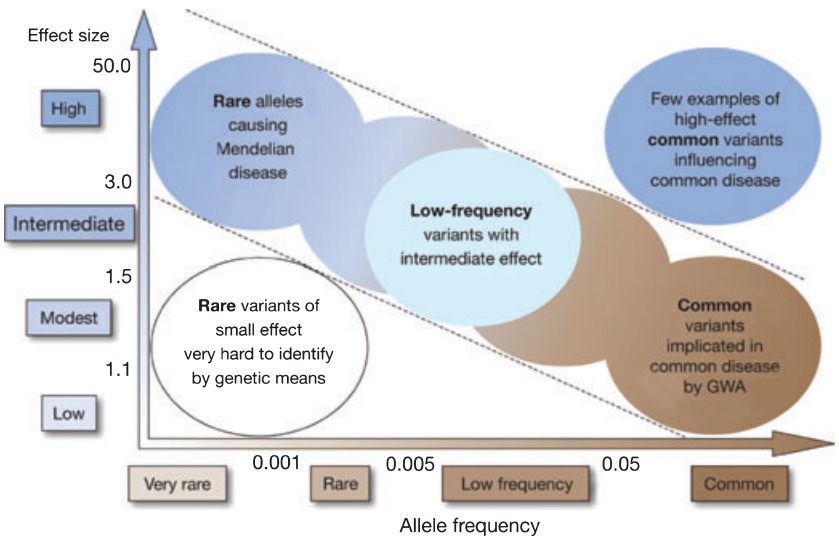

Figure 2 The frequency spectrum of human disease risk alleles includes alleles at all frequencies from rare to common, with effect sizes from high to low, with the relative importance in risk of different variants yet to be ascertained. From Manolio et al. (2009).

and Tomlinson 2010). The results of these studies, and comparable GWA analyses of height (McEvoy and Visscher 2009) and intelligence (Deary et al. 2009), convergently indicate that very large numbers – hundreds, thousands, or tens of thousands – of relatively common allelic variants with small effects mediate variation in polygenic human traits, but cumulatively account for <50% of estimated heritability (Goldstein 2009; Ku et al. 2010; Yang et al. 2010). The keys of 'missing' heritability may be hiding in any number of places (Weiss 2008; Manolio et al. 2009), with the street lamps of genomic technology now shining on rare variants of moderate to large effect (Fearnhead et al. 2004; Zhao et al. 2007; Bodmer and Bonilla 2008). Indeed, rare genomic copy number variants have been identified as penetrant risk factors for schizophrenia, autism, and intellectual disability, although they appear to account for only a small percentage of known risk (Wain et al. 2009).

Under the disease risk paradigms that guide GWA and rare variant investigations, mutation and purifying selection are normally considered, either implicitly or explicitly, as the primary population genetic and evolutionary genetic forces that modify the frequencies of disease risk alleles. But if thousands of alleles modify risk, for example, of schizophrenia – are they actually alleles 'for' this condition (Kendler 2005), or might they be better conceived as alleles 'for', say, the neurodevelopment of social cognition? More importantly, must such alleles, for any common disease, represent slightly malfunctional cogs in our human machine with respect to its functioning

overall, or might they also be advantageous, at least in some contexts?

The primary population-genetic processes that influence allele frequencies, in addition to mutation and purifying selection against deleterious alleles, or drift, are forms of positive selection and balancing selection. An additional, nonexclusive model for the generation and maintenance of genetic variation underlying polygenic disease risk, in addition to models based on some mixture of myriad segregating deleterious variants of small effect and rare deleterious mutations of larger effect (Fig. 2), is thus predicated on advantages, now or in the past, from alleles that influence such risk (Keller and Miller 2006; Kryukov et al. 2007). Variation can be maintained under this model by two main processes, ongoing positive selection and balancing selection, that can keep risk alleles at nontrivial frequencies either transiently as selection proceeds or at more or less stable equilibria. Support for the model comes from several recent studies that have demonstrated enrichments of positive selection on polygenic disease genes, compared to other genes, in human populations (Nielsen et al. 2007; Blekhman et al. 2008; Lappalainen et al. 2010); similarly, Amato et al. (2009) 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 hypotheses may plausibly explain enrichments of positive selection on polygenic disease genes.

First, common alleles that were advantageous in ancestral environments (for example, 'thrifty' genes affecting regulation of metabolism) are deleterious in current environments, and derived, formerly-maladapted alleles are now selected for (Di Rienzo and Hudson 2005; Di Rienzo 2006). 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 (e.g. Di Rienzo and Hudson 2005; Young et al. 2005; Helgason et al. 2007), and it provides a robust predictive framework for testing hypotheses on the dynamics of disease-related alleles. Positive selection in this context may involve phenotypes that are more or less fixed in humans, and adaptations because of geographically varying selective pressures that generate population differentiation (e.g. Novembre and Di Rienzo 2009; Adeyemo and Rotimi 2010). In humans, such selection should be recent, in the past thousands and tens of thousands of years (Hawks et al. 2007), and should involve strong selective pressures given that humans originated in equatorial Africa but spread worldwide across all climatic and ecological zones.

Strong, well-replicated patterns of positive selection on skin pigmentation and lactose tolerance genes represent paradigmatic examples of local adaptation (e.g. Harris and Meyer 2006), with additional examples of population differentiation apparently mediated by selection including sodium homeostasis (Young et al. 2005), body mass and shape (Katzmarzyk and Leonard 1998; Wu and Zhang 2010), and metabolic rate (Snodgrass et al. 2005). This suite of phenotypes subject to population differentiation and selection corresponds closely to the set of traits dysregulated in human metabolic disorders, including hypertension, obesity, dyslipidemia, and type 2 diabetes, that jointly define the human 'metabolic syndrome'. Hancock et al. (2008) indeed demonstrate strongly-enriched signals of population differentiation in 82 candidate genes for common human metabolic disorders, which they interpret primarily in terms of local selection from heat and cold stress. Selective pressures due to transitions from hunting and gathering to farming are also expected to strongly mediate susceptibility to polygenic disease, as suggested by signals of positive selection on celiac disease risk alleles (Barreiro and Quintana-Murci 2010), and the inferred time of origin for a positively-selected allele of TCF7L2, a gene that underlies risk of type 2 diabetes, near to the origin of agriculture (Helgason et al. 2007).

The ancestral-susceptibility model is generally conceived to apply to ecological factors, such as climate and diet, that are subject to selection for unidirectional transitions, at different scales of environmental variation in time and space from local to global. This model can, however, be generalized to other forms of selective pressures that generate evolutionary disequilibria, including genomic conflict situations where antagonistic coevolution generates more or less constant states of disequilibrial change (Crespi 2010a). The primary limitation of such models is the general lack of direct evidence regarding the targets and agents of selection – for example, do individuals bearing alternative alleles, for genes that show strong latitudinal allele frequency clines (Hancock et al. 2008), differ in both heat or cold tolerance, and risk of metabolic diseases? For loci showing evidence of genomic conflicts, what phenotypes are selected, and how do they benefit one party at a cost to the other? The striking among-population differences in patterns of positive selection, across the genome, shown by analysis of the human Hapmap data (e.g. Voight et al. 2006) suggest that local, recent selective pressures have substantially impacted human phenotypes and risk of disease. The pervasiveness of temporal and spatial variation in selective pressures, because of both ecological and non-ecological factors, also underscores the central importance of gene by environment interaction effects in the phenotypic expression and genomic analysis of human

disease risks (e.g. Andreasen and Andersen 2009; Wermter et al. 2010).

A second genetic process that may help to explain an enrichment of positive selection on polygenic disease genes is balancing selection mediated by antagonistic pleiotropy, or other processes including overdominance or frequency-dependent selection. Extensive pleiotropy is well documented as a universal mode of gene action (e.g. Knight et al. 2006; Barreiro et al. 2008), and a role for this process in patterns of positive selection and disease was suggested by Nielsen et al. (2005) in the context of 'selfish' mutations of tumor suppressor genes to increased rates of spermatogenesis that pleiotropically increase risks of cancer. More generally, under antagonistic pleiotropy, alleles exert positive effects in one developmental, physiological, of behavioral context, or at one time in the lifespan, that are stronger than, or balanced by, negative effects, expressed in some other context or later in life (Keller and Miller 2006; Kryukov et al. 2007), that manifest as risk of disease. Stronger advantages in one selective situation, such as one tissue or one life stage, can support stronger deleterious effects. Such deleterious effects are expected to be selected against (see e.g. Pavard and Metcalf 2007; Drenos and Kirkwood 2010), especially to the extent that they occur before reproduction and alloparental care-giving have largely ceased, they can be dissociated genetically via recombination, or they can be alleviated by selection and response at interacting loci. Antagonistically pleiotropic effects should thus often be evolutionarily transient.

A more fundamental, long-term form of pleiotropy involves intrinsic tradeoffs between opposing selective pressures, based ultimately on the necessity that energy, time, or molecular processes devoted to one biological function, such as some aspects of growth, reproduction, or defense and maintenance, must take away from others (Roff 2007). Tradeoffs are fundamental to life history theory in evolutionary ecology and can apparently maintain substantial levels of genetic and phenotypic variation in such contexts (Roff and Fairbairn 2006; Kruuk et al. 2008). At the levels of genes, proteins and developmental–physiological pathways, tradeoffs are expected to be no less pervasive, with alternative allocation of cellular resources to different functions, and degrees of low versus high pathway activation, mediating risk of alternative disease states (e.g. Stearns 2005; Caricasole et al. 2005; van Heemst et al. 2005; Reddy et al. 2009; Crespi 2010a). Tradeoffs associated with polygenic disease risk manifest in several important contexts, including the following: (i) associations of traits that are expected to be beneficial, such as higher birth weight, with diseases such as cancer (e.g. Maehle et al. 2010) that plausibly represent late-life pleiotropic effects of the favored phenotype; (ii) negative associations between diseases, such as genetically based inverse risk alleles, across multiple loci, for different autoimmune diseases (Sirota et al. 2009; Wang et al. 2010), and lower rates of cancer in individuals with schizophrenia (Dalton et al. 2005; Goldacre et al. 2005; Torrey 2006; Levav et al. 2007), Parkinson's disease (West et al. 2005), and Alzheimer's (Roe et al. 2010) than in matched controls.

Polymorphisms in several well-studied human genes provide putative examples of evolutionary genetic tradeoffs involving risk of polygenic disease. For example, (i) the Arg72Pro polymorphism in the tumor suppressor gene TP53 engenders lower fertility, but enhanced survival of individuals with the Pro allele (Ørsted et al. 2007; Kang et al. 2009); (ii) APOE gene E4 carriers have been shown in replicated studies to exhibit better verbal skills than individuals with alleles E3 or E2 when young, but higher risk of Alzheimer's and schizophrenia when older (Xu et al. 2006; Alexander et al. 2007; Akanji et al. 2009); and (iii) antagonistically pleiotropic, age-related effects of the Arg16Gly and Gln27Glu polymorphisms of the ADRB2 gene have been demonstrated for measures of cognition and age-related disease (Bochdanovits et al. 2009; Cagliani et al. 2009; Kulminski et al. 2010). These studies suggest that balanced polymorphisms may commonly be maintained under life history tradeoffs, with each allele providing benefits in the context of one component of fitness but costs, often expressed as disease, in the context of another. Such tradeoffs are also recognizable as negative genetic correlations between traits in quantitative genetic studies (e.g. brain size and gyrification in humans and baboons; Rogers et al. 2010), and as negative phenotypic correlations when potentially confounding effects are controlled. In contrast to selective sweeps, which may sometimes focus upon a specific trait undergoing adaptive change, balanced polymorphisms are expected to commonly involve multiple traits and tradeoffs between them. Balancing selection and antagonistic pleiotropy are commonly dismissed as population genetic forces that maintain variation across many loci, because of a perceived lack of evidence, but studies drawing on human genomic variation have uncovered a large suite of apparent cases over the past 10 years (Andrés et al. 2009; Table 1).

To the extent that changing environments, positive selection, antagonistic pleiotropy, and other forms of selection mediate risk of human disease, as well as generate and maintain genetic variation in risk, the evolution of human disease risk becomes inextricably linked with the evolution of modern humans. Similarly, the accumulation of human-specific and human-concentrated phenotypes along our lineage (e.g. Harris and Meyer 2006; Crespi 2010a) generates novel mutational targets for

Table 1. Examples of loci showing evidence for allele maintenance by long-term balancing selection and/or antagonistic pleiotropy, with alleles that affect medically relevant human phenotypes. HLA-locus genes other than HLA-G and C4B are not included (see Solberg et al. 2008 for these data). Disease risk alleles and alleles under balancing selection need not coincide. Andrés et al. (2009) list results from a genome-wide analysis of balancing selection.

Gene	Physiological function	Phenotypes	References, comments
ACE	Cardiovascular	Cardiovascular diseases	Cagliani et al. 2010
ADRB2	Catecholamine metabolism	Intelligence, autism, age-related diseases	Bochdanovits et al. 2009; Cagliani et al. 2009; Kulminski et al. 2010; antagonistic pleiotropy
APOE	Lipoprotein transport	Enhanced verbal skills in childhood, higher risk of Alzheimers, schizophrenia	Xu et al. 2006; Alexander et al. 2007 Akanji et al. 2009; antagonistic pleiotropy
APOL1	Cholesterol transport	Kidney disease, protection against trypanosomes	Genovese et al. 2010
AVPR1B	Neurohormone	HPA regulation, depression	Cagliani et al. 2009
BSG, CD55, CD151, SLC14A1	Blood group antigens	Infectious disease	Fumagalli et al. 2009a
CAPN10	Insulin signaling	Type 2 diabetes	Vander Molen et al. 2005; Harris et al. 2006
CCR5	Immunity, inflammation	Resistance to HIV	Bamshad et al. 2002
CPB2	Blood coagulation, fibrinolysis, inflammation	Cardiovascular, blood diseases	Cagliani et al. 2010
FMO3	Metabolism of xenobiotics	Unclear	Allerston et al. 2007
FSHB	Female reproduction	Female fertility	Grigorova et al. 2007
G6PD	Glucose metabolism	Malaria risk and G6PD deficiency	Verrelli et al. 2002
HBB	Hemoglobin chain	Malaria, anemia	Williams 2006
hCH	Reproduction	Miscarriage	Rull et al. 2008
HLA-G	Reproduction	Miscarriage	Tan et al. 2005
Interleukin genes	Immunity	Infectious disease, inflammatory diseases	Fumagalli et al. 2009b
IL10	Immunity, inflammation	Infectious disease, inflammatory diseases	Wilson et al. 2006
KIR locus genes	Immunity, inflammation	Infectious disease	Norman et al. 2004; Parham 2008
LMBR1	Limb, skeletal system development	Polydactyly	He et al. 2008
MEFV	Inflammatory system	Autoinflammatory disease	Fumagalli et al. 2009c
OAZ3	Polyamine synthesis	Male infertility	Christensen et al. 2006
Olfactory Receptors	Olfaction	Functional significance unclear	Alonso et al. 2008
PDYN	Neuropeptides	Epilepsy, schizophrenia	Babbitt et al. 2010
PKDREJ	Sperm–egg interaction	Fertility?	Hamm et al. 2007
PCDH genes	Protocadherins; brain development	Bipolar disorder	Noonan et al. 2003; Pedrosa et al. 2008
PTC	Bitter taste perception	Ingestion of bitter, toxic plants?	Kim et al. 2004
SDHA	Mitochondrial metabolism	Leigh's disease (mitochondrial)	Baysal et al. 2007
TLR genes CD14, others	Immate immunity	Infectious disease	Ferrer-Admetlla et al. 2008
TP53 pathway genes	Tumor suppressor, senescence	Fertility, survival, cancer risk	Kang et al. 2009; antagonistic pleiotropy
ZAN	Fertilization	Unclear	Gasper and Swanson 2006
Cases involving null alleles			
ABO blood group	Unclear	Infectious disease risk?	Greenwell 1997; Calafell et al. 2008
C4B	Immunity	Null alleles influence survival, autoimmune disease risk	Brai et al. 1994; Arason et al. 2003
FUT2	Blood antigen synthesis	Infectious disease, vitamin metabolism	Koda et al. 2000; Hazra et al. 2008 Carlsson et al. 2009
GJB2	Gap junction gene	Hearing loss, dysentery resistance	D'Adamo et al. 2009
LILRA3	Immunity	Autoimmune disease risk?	Hirayasu et al. 2006

human-specific and human-concentrated disease. How, then, might the spectrum and genetic causes of human disease risk be related to the genetic evolution of humans?

The genes that make us human

In a landmark paper, Clark et al. (2003) performed the first analysis, via comparisons of sequence data from humans, chimps, and mice, that allowed inference of the positively-selected genetic changes that have taken place along the human lineage. A plethora of subsequent studies, using diverse methods and datasets, has extended and refined the identification and analysis of putatively positively selected genes and other genomic elements, and gene expression differences, along the human lineage (e.g. Kelley and Swanson 2008; Oleksyk et al. 2008; Grossman et al. 2010; Sholtis and Noonan 2010). The primary outcome of these studies has been lists of genes, SNPs, genic regions, and enriched functional categories of gene, statistically inferred as candidates for positive selection – but virtually no information on causation, targets of phenotypic selection, or evolutionary trajectories (Hughes 2007).

For a small set of positively-selected 'microcephaly' genes, including ASPM, MCPH1, CENPJ, and CDK5RAP2, genetic data converges, and causally links, with data from developmental and medical genetics, phylogenetics, and paleontology: humans evolved greatly enlarged brains in part because of adaptive mutations across this suite of genes, most of which are involved in centrosomal function during neural development (e.g. Cox et al. 2006; Tang 2006; Kaindl et al. 2010). By contrast, for virtually all other genes and phenotypes, the causal nature of associations of positive selection at the gene level, with adaptation along the human lineage, remains almost entirely obscure. Part of this problem is some function of complexity in genotype–phenotype mapping, because of pervasive pleiotropy and epistasis in developmental pathways (Weiss 2008). But our ignorance regarding functional effects of the 'genes that make us human' may also arise, in part, from a 'genes-up' view of the evolutionary process, rather than 'phenotype-down' – how we know selection actually operates.

Evolutionary change along the human lineage can be depicted as a series of nested and overlapping allele frequency alterations, some of which are undergoing recent selective sweeps at local or global levels, some of which have become fixed by positive selection or other processes, and some of which involve recent or ongoing accelerated change in some region, compared to other primates. Each of these processes and forms of genetic variation, either within *Homo sapiens* or between *Homo sapiens* and our common ancestor with related species including chimps, Neanderthals, or other hominins (Green et al. 2010), can be exploited to infer the phenotypic effects of the substitutions, which provides insight into their potential roles in human phenotypic evolution and evolved risk of disease.

Selective sweeps and accelerated evolution

Recent selective sweeps provide opportunities for the most direct tests of correspondence between phenotypic and genomic adaptation: individuals with the putatively selected, derived haplotype or allele can be compared to individuals with ancestral haplotypes or alleles, either for a single trait (e.g, Mekel-Bobrov et al. 2007) for or a suite of traits that are hypothesized, based on gene functions, pathways, and tissue expression patterns, to represent potential targets of phenotypic selection (e.g. Grossman et al. 2004). Such studies rely on the rapidly developing field of phenomics – the quantitative analysis of phenotypic trait-space variation and covariation with the same comprehensive rigor as genomes (Houle 2010; Lanktree et al. 2010). Phenomic analyses coupled with inferences of selection turn a GWAS on its head, into what might be called a Phenotype Wide Association Study (PWAS), to determine the best phenotypic correlates of derived versus ancestral haplotypes. PWAS represents a logical extension of a much simpler application of positive selection data – using signatures of selection to identify putatively functional sites and variants – in the study of human disease risk (e.g. Ding et al. 2008; Atwal et al. 2009). The relationship of derived versus ancestral allele status to disease risk should depend upon the contexts and timing of positive selection: derived alleles may be expected to engender lower risk if the disease itself (or its subthreshold effects) represents a selective agent (e.g. Pavard and Metcalf 2007), or higher risk if disease represents a byproduct of strong, recent selection on some other component of survival or reproduction (Crespi 2010a). Most generally, PWA studies across the human genome can identify joint ongoing trajectories of recent human genetic and phenotypic evolution and evaluate the contributions of positive selection, compared to purifying selection and other processes, in risk of polygenic disease. Indeed, developmental and physiological phenomic targets of selection may provide more direct clues to gene and haplotype functions than do associations with disease, as they help to specify nonpathological and pleiotropic effects of genetic variation for common alleles.

The so-called human-accelerated regions represent DNA sequences that have evolved (and may still be evolving) especially quickly along the human lineage, compared to related lineages (Pollard et al. 2006; Prabhakar

et al. 2006). Such regions need not exhibit evidence of ongoing selective sweeps (which requires that certain conditions be met), but they can be inferred to exhibit functionality based on their genomic locations or regulatory features, which can serve to exclude hypotheses of rapid nonadaptive evolution. Accelerated evolution in the human lineage is expected to mediate risk of human-specific disease, as suggested by apparent associations of SNPs in the RNA gene HAR1A with auditory hallucinations in schizophrenia (Tolosa et al. 2008).

Fixed differences

Human-specific, derived alleles can be recognized via comparisons with related species (e.g. Nahon 2003; Kitano et al. 2004; Prabhakar et al. 2006; Green et al. 2010); analogously, human populations may also harbor unique, derived alleles (e.g. Baye et al. 2009). Fixed, human-specific alleles at sites that are otherwise highly conserved across primates are expected to subserve aspects of human-specific or human-concentrated phenotypes, such as the two amino acid substitutions in FOXP2 with effects on articulation and language via altered expression of a suite of target genes (Konopka et al. 2009). Analyzing adaptive functions of fixed differences relies on genotype–phenotype correlations involving natural mutational variation, or experimental, effects at the sites or gene of interest. For example, the transcription factor GTF2I shows evidence of strong upregulation in humans compared to chimps and other primates (Preuss et al. 2004), and deletion mapping of individuals with Williams syndrome, as well as mouse models, indicates a role for this gene in modulating social–behavioral interactions (Dai et al. 2009). Remarkably, this gene also shows genomic imprinting effects with preferential expression from the maternal chromosome (Collette et al. 2009), suggesting selective effects from mother-offspring social interactions that modulate maternal investment (Haig 2010). These diverse lines of evidence implicate GTF2I in human social evolution, and should motivate studies of its human-specific transcriptional targets and the social-behavioral effects of natural variation in expression levels. The degree to which natural or experimentally induced genetic variation recapitulates the context within which selection has acted over evolutionary time must remain more or less unclear. For humans, the best evidence should come from genome sequencing of archaic *H. sapiens* fossil DNA along our recent lineage, over the last few tens of thousands of years, and from study of genetic changes that involve bidirectionally altered gene dosages (Crespi et al. 2009).

In principle, human-specific derived alleles should underly some proportion of human-specific or human-concentrated disease risk (Crespi 2010a), with ancestral alleles, losses of function, or pleiotropic effects of derived alleles, associated with higher risk of disease. Such studies may also usefully consider the roles in disease of human-specific genes or isoforms (e.g. Nahon 2003; Kitano et al. 2004), as these may provide more substantial targets than SNPs or amino acids for both dysregulation and selection.

Do the genes that make us human also make us sick?

The relevance to human disease risk of positive Darwinian selection, and balancing selection, along the human lineage is an empirical problem that can be attacked with increasing power and precision as advances in genomic technology proceed. This question can be addressed by cross-referencing data on the status of haplotypes or amino acids as selected or derived and fixed in the human lineage (or in specific populations), with data from GWA studies on polygenic disease risk (e.g. Loe-Mie et al. 2010). Studies of positive selection can indeed be easily dovetailed with GWAS of disease, given that that same data – high-density SNP information, or whole-genome sequences – can be used for both. Answering this question, however, requires causal scaffolding from genes, to pathways, to human adaptations, and to risks of disease, because genetic variation exerts its effects on phenotypic variation, manifest in adaptation and maladaptation, via highly interactive pathways of development and physiology (Weiss 2008; Luo et al. 2010). In the study of human disease risk, such scaffolds have been built in two main ways. First, once enough disease risk genes are identified, concentration of genes in particular pathways can be statistically assessed, to ascertain which systems are most commonly dysregulated in disease, and which can serve as targets for drug development. Second, 'intermediate phenotypes' or 'endophenotypes' (e.g. Prasad and Keshavan 2008; Tan et al. 2008) – traits that are closely associated with disease states – represent intermediaries between genes, pathways, and disease risk, because they can causally link in both directions; for example, a subset of idiopathic autism has been associated with large head size, a suite of autism-related genes and copy number variants also influence head size, and several pathways have been recognized whereby these genes exert their effects (Crespi and Badcock 2008; Crespi et al. 2010).

In the study of positive selection, concentration of genes in particular, apparently selected pathways is commonly tested. Indeed, some pathways with concentrations of positive selection, such as NRG1-ERBB4 signaling (Voight et al. 2006) also appear to be targets of polygenic disease risk (e.g. in schizophrenia, Banerjee et al. 2010);

more generally, immune system genes demonstrate among the strongest overall patterns of positive selection in humans (e.g. Barreiro and Quintana-Murci 2010), attesting to the powerful selective role of infectious diseases in human evolution. However, as described above, the actual phenotypic targets of selection, which ultimately generate the signatures of selection in the genome, have almost never been investigated through comparing phenotypes of individuals with selected versus ancestral haplotypes, or individuals with fixed-derived versus mutated alleles. Similarly, the suites of traits associated with alternative genotypes at balanced polymorphisms have seldom been investigated in detail, despite increasing evidence from detailed genetic studies that balancing selection is considerably more pervasive than commonly presumed.

Three examples may illustrate the potential usefulness of jointly analyzing positive selection and disease risk. First, the well-known 'breast cancer' gene BRCA1 has been demonstrated as subject to positive selection in several studies (Fleming et al. 2003; Pavlicek et al. 2004), but more generally, the entire BRCA-FANC pathway in humans, which orchestrates DNA damage–repair responses, shows an apparent concentration of positive selection, with 6 of 13 pathway genes, ATM, BRCA1, CHEK2, FANCA, FANCE, RAD51, showing evidence of selective sweeps at 0.05 in one or more populations of the phase II human HapMap data (Voight et al. 2006); four other genes show significance at the 0.10 level. How do humans with derived and ancestral haplotypes differ for these genes? Second, a network that includes eight interacting schizophrenia-associated genes, recently identified by GWA studies, shows evidence of a remarkable concentration of positive selection and human-derived alleles (Loe-Mie et al. 2010). How do individuals that vary in their 'schizophrenia-risk' haplotypes, and patterns of pathway activation, differ in affect and cognition? Can ancestral/derived differences be used to help develop novel therapies, based on how natural selection has apparently dealt with disease risks in the past (e.g. Moalic et al. 2010)?

Associations between the recent genetic evolution of modern humans, and human genetic disease risks, can be assessed more or less directly by evaluating the roles in different forms of disease, and associated phenotypes, for genes inferred as positively selected in the human lineage. As a third example, I determined disease risk associations (both polygenic and monogenic) for genes inferred as positively selected from two recent analyses: (i) the Composite Multiple Signals test, a new, high-resolution test for alleles undergoing recent selective sweeps, over the past few tens of thousands of years (Grossman et al. 2010), and (ii) the tests for selective sweeps deployed by Green et al. (2010), which use the draft Neanderthal genome to localize inferred selective signals for the early evolution of *Homo sapiens sapiens*, on the order of 400 000 to 600 000 years ago with apparent, more recent gene flow. There was no evidence for concentrations of increased disease association for selected loci across all diseases for either data set. However, for the Green et al. (2010) data set, and for both data sets overall, the inferred, positively selected genes were significantly more frequently associated with neurological diseases (including schizophrenia, bipolar disorder, depression, dyslexia, autism, Alzheimers, Parkinson's and epilepsy) than were control genes (Table 2). These results suggest that recent

Table 2. Associations with disease, for genes inferred as positively selected via selective sweeps in Grossman et al. (2010, Table S5) or Green et al. (2010, Table S37), compared to sets of control genes. For selected genes, only single genes (or haplotypes associated with disease) were included, to avoid ambiguity regarding which gene was the apparent focus of selection. Disease and phenotype associations were obtained from PubMed searches (as of 31 May 2010) using gene names. As the goal is to compare selected vs control genes for frequency and nature of disease association, all associations are included, even if reported in a single study. Control genes were ascertained as the genes closest to 4 Mb from the focal selected gene, centromeric and telomeric.

	Numbers of genes shown, for each category (%)				
	Grossman et al. 2010 (recent sweeps)		Green et al. 2010 (sweeps after Neanderthal split)		
	Selected	Control	Selected	Control	
No association with disease	35 (53%)	77 (64%)	42 (59%)	76 (62%)	
Association with non-neurological disease	14 (21%)	26 (21%)	10 (15%)	30 (25%)	
Association with neurological disease	11 (17%)	12 (10%)	15 (21%)	14 (11%)	
Association with other phenotypes	6 (9%)	6 (5%)	4 (6%)	2 (2%)	Pooled analyses
Disease vs not disease, selected vs control	$\chi^2 = 0.8$, $P = 0.37$		$\chi^2 = 0.01$, $P = 0.91$		$\chi^2 = 0.29$, $P = 0.59$
Neurological disease genes vs other genes	$\chi^2 = 1.8$, $P = 0.18$		$\chi^2 = 3.17$, $P = 0.075$		$\chi^2 = 5.08$, $P = 0.024$*
Percent of disease genes neurological	$\chi^2 = 1.0$, $P = 0.31$		$\chi^2 = 5.20$, $P = 0.022$*		$\chi^2 = 3.94$, $P = 0.047$*

human evolution has been dominated by selection on cognitive–affective phenotypes, with direct implications for risk of neurological disease. The latter data set (Green et al. 2010) includes evidence for selection on several genes that mediate other phenotypes that may have been important in human evolution since our split with Neanderthals, such as craniofacial morphology (the ENPP1, TRPS1 genes) and the timing of tooth eruption (MSRB3) and puberty (DLK1). Disease-related, putatively selected genes represent excellent candidates for detailed phenomic and deep-sequencing studies, to more clearly infer the apparent phenotypic targets of selection, their genomic bases, and how disease risks relate to pleiotropy and human adaptations.

Principles of human evolutionary disease genomics

A key benefit from bridging between human medical genomics and human evolutionary genomics is reciprocal illumination of answers to two of the major unresolved questions in biology: how we evolved, and why we fall victim to cancer, schizophrenia, type 2 diabetes, and a suite of other polygenic, human-concentrated diseases. The primary challenges in constructing the required links are lack of in-depth background knowledge among evolutionary geneticists regarding causes of particular genetically based diseases, and lack of background among medical geneticists regarding the nuanced causes of evolutionary processes. The latter can be addressed with four straightforward, yet nonintuitive, principles of human evolutionary medical genomics, based within the larger field of evolutionary medicine (Nesse and Stearns 2008; Stearns and Koella 2008; Gluckman et al. 2011).

Human adaptations and disease risks have evolved together

Evolution along the human lineage is characterized by a suite of phenotypic changes including, for example, larger brain size, more advanced social cognition, more invasive placentation, continuous female receptivity, lower fertility per cycle, physical altriciality, neurological precociality and high levels of subcutaneous fat in infants, shorter interbirth intervals, longer childhood, and a peaked female age-specific fecundity distribution, with elongated postmenopausal lifespan in females (Crespi 2010a; Hawkes 2010). Each of these recently evolved human adaptations is expected to generate increased opportunity and scope for maladaptive dysregulation, with forms of disease reflecting human trajectories of evolution (Crespi 2010a). Evolutionary trajectories of genomic and phenotypic change can provide guidance concerning mechanisms of disease because they indicate how genes, genomes and traits that make up the human 'machine' have been modified and assembled, step by step, via selection and other processes along the human lineage. For example, advanced social cognition and emotionality have evolved along the human lineage via a series of nested genetic changes involving neurodevelopmental 'social-brain genes', so the genetic regions that have undergone, and are undergoing, such evolutionary changes should, as noted above, represent prime candidates in the etiology of autism and schizophrenia.

Most generally, these considerations suggest that the global landscape of human polygenic diseases, in terms of form, prevalence, severity, *de novo* versus segregating allelic etiology, mediation by common and rare alleles, and penetrance of alleles, should correspond, in part, to the landscape of recent human evolutionary genetic and environmental changes; for example, metabolic syndrome phenotypes appear to reflect, in part, dysregulated adaptations subsequent to human dispersal from Africa (Hancock et al. 2008) as well as more recent dietary changes. Disease genetic studies of hunter–gatherer and traditional horticultural human populations can be used to help parse recent environmental change effects from older adaptations (e.g. Gurven et al. 2008, 2009).

An important implication of such evolutionary perspectives on disease is that some so-called diseases may represent adaptations that increase reproductive success but decrease 'health', some may represent maladaptation because of recently altered environments (Nesse and Williams 1994), some may represent side effects of genomic conflicts (Haig 1993, 2006; Ubeda and Wilkins 2008; Crespi 2010a,b), and others may represent maladaptive, genetically based extremes of adaptations (e.g. Nesse 2004a). For example, mental health is often conflated with happiness, yet natural selection is expected to maximize not happiness, but striving for resources that have led, over recent evolutionary time, to increased reproductive success (Nesse 2004b; Nettle 2006). From this perspective, depression, or at least its mild manifestations in low mood, can be considered to subserve adaptive emotional functions that regulate motivation and modulate seeking of goals (Keller and Nesse 2006). Similarly, a central phenotype of bipolar disorder – mania – involves euphoria, racing thoughts, talkativeness, and high levels of sociability, mainly focussed around extreme, dysregulated pursuit of two proximately reproductive goals: money and sex (e.g. Johnson 2005). Does mania represent, in part, human striving for reproductive success run amok? Is hypomania (mild mania), in subclinical form, a behavioral target of selection in humans? Associations of bipolar disorder with high socioeconomic status (Coryell et al. 1989), high marks in school (MacCabe et al. 2010),

and aspects of creativity (Jamison 1993) support this hypothesis. Moreover, a recent study has demonstrated a significantly lower genome-wide 'burden' of presumably deleterious copy number deletions in bipolar patients compared to controls (Grozeva et al. 2010), which contrasts markedly with studies showing significantly higher burdens of copy number variants in two conditions, schizophrenia (ISC 2008; Kirov et al. 2009) and autism (Sebat et al. 2007), with less-direct links to fitness-related phenotypes. Such convergent findings should motivate studies that evaluate the cognitive, affective, and behavioral effects of bipolar genetic 'risk' variants in nonclinical populations, test for positive selection on such variants, and measure copy number burdens with regard to other heritable conditions involving exceptional human performance, such as high 'intelligence'.

Alleles, the primary units of natural selection, mediate the evolution of adaptation and disease risk via complex mixtures of conflict and cooperation, within and between loci and individuals

Explanations for adaptation based on the 'good of the group' or species were purged from evolution, ecology, and behavior in the 1960s and 70s, when it was demonstrated that alleles are the only entities in the hierarchy of biological life that persist long enough to have their frequencies adjusted or maintained by selection (Williams 1992; Keller 1999; Crespi 2000b). 'Good of the species' arguments persist, however, where one might least expect them – among geneticists, where the generation of variants is often seen as beneficial because it facilitates the efficacy of evolution. This viewpoint is intellectually pernicious because it blinds researchers to the processes that actually drive molecular evolutionary change and to well-established consequences of gene-level selection, such as genomic conflicts, that mediate a substantial proportion of human disease risk.

The sequelae to alleles as the primary units of selection, and consequent genomic confluence and conflicts of interest within and between individuals, are fundamental to understanding adaptation and disease in two central ways. First, from an evolutionary perspective, a 'gene' represents a haplotype variant of indeterminate size, with larger haplotypes more likely to exert greater phenotypic effects (that may be selected for or against) but less likely to avoid being broken apart by recombination. A positively selected haplotype may increase in frequency as a result of a single base-pair change along a megabase length, with linked, neutral, or deleterious variants dragged along until recombination happens to separate them. This hitch-hiking process has long been recognized in genetics, but its roles in adaptation and disease remain virtually unstudied. For example, a small section of chromosome 15 includes the eye-color gene OCA2, directly adjacent to the brain receptor gene GABRG3. Strong, recent positive selection has been reported for a blue-eyed haplotype of OCA2 (McEvoy et al. 2006), a series of studies has demonstrated associations of blue eyes with timid, inhibited behavior in children (e.g. Rosenberg and Kagan 1987; Coplan et al. 1998), and alleles of GABRG3 have been associated with autism (Menold et al. 2001). Has linkage disequilibrium between OCA2 and GABRG3, coupled with selection for blue eyes, generated associations of eye color with personality traits, autism, or both? Of course, the region of the human genome with among the strongest signals of selection, and the highest levels of linkage disequilibrium, is perhaps the most important for disease: the 3.6-Mb MHC region on chromosome six.

Second, genomically based conflicts are a fundamental outcome of gene-level selection, because different alleles at a locus, and alleles at loci with different patterns of inheritance and different patterns of genetic relatedness to interactants, can be selected for effects that 'benefit' the focal allele (increase its frequency) even at a replication cost to other alleles, or a fitness cost to individuals. Genomic conflicts come in two main types: (i) intragenomic (within-genome) conflicts include genomic imprinting, forms of drive (meiotic, meiotic stem cell, gestational, and centrosomal), sex–chromosomal interactions, and mitochondrial–nuclear relationships; and (ii) intergenomic conflicts involve competition between categories of individual, such as parent–offspring, maternal–fetal, sib–sib, male–female, female–female and male–male (Burt and Trivers 2006; Rice et al. 2008; Crespi 2010a). Costs of genomic conflicts may themselves manifest as disease, and more generally, evolved systems of conflict represent mechanisms that can become dysregulated via one party (allele, genomic element, or class of individual) 'winning' (reaching its optimum, while the other party suffers a frequency or fitness reduction), physiological costliness from dynamic tug of war (Haig and Graham 1991), new mutational targets from evolved conflict systems, and long-term, ongoing antagonistic coevolution. In each form of conflict, fitness differentials between competing parties are expected to be extremely strong (as for host–parasite interactions), also increasing the scope for deleterious pleiotropic effects of conflictually driven allele frequency change.

Genomic conflicts appear to be especially pervasive in the contexts of competition over reproductive resources that mediate differential survival and growth, such as maternal–fetal interactions (Haig 1993, 1996a,b, 1999, 2007), and meiotic and gestational drive (Zollner et al. 2004; Haig 1996a,b, 1997). For example, Haig (1993,

1996a,b, 2007) and Crespi (2010a) describe how the primary disorders of human reproduction, including infertility, early pregnancy loss, gestational diabetes, preeclampsia, and intrauterine growth restriction and show evidence of strong effects from genomic conflicts, as well as human-specific adaptation. Genomic imprinting effects in particular appear to play central roles in a suite of disorders including disrupted placentation (Fowden et al. 2006), cancer (Jelinic and Shaw 2007), altered metabolism of glucose and lipids, key currencies for fetal development (e.g. Chen et al. 2005; Haig 2008), and neurodevelopmental disorders (Crespi 2008; Crespi and Badcock 2008), as deleterious side effects of their roles in orchestrating prenatal and postnatal growth, and neurodevelopment (Ubeda and Wilkins 2008; Das et al. 2009; Crespi 2010b). Indeed, Kong et al. (2009) estimate from pedigree-based GWA data that 13–15% of the genetic risk for type 2 diabetes involves parent of origin effects (see also Voight et al. 2010), and some of the most penetrant and well-established risk factors for schizophrenia and autism involve imprinted genes (Crespi 2008; Crespi and Badcock 2008; Ludwig et al. 2009; Pun et al. 2010). The incidence of positive selection on imprinted compared to nonimprinted genes has yet to be systematically evaluated, but two of the genic regions inferred as positively selected in Grossman et al. (2010) are imprinted (see also Lo et al. 2007). Positive selection has also been reported in the imprinted genes C15orf2 (Wawrzik et al. 2010) and KLF14 (Parker-Katiraee et al. 2007), and alleles of this latter gene show strong links to carcinoma (Stacey et al. 2009) and plasma lipid concentration (Chasman et al. 2009) in recent GWA studies.

Some direct applications of genomic conflict theory to health practitioners include: (i) disease-related maternal or fetal phenotypes expressed in pregnancies that 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 (Haig 2004, 2007); (ii) diseases in offspring owing to noninherited maternal haplotypes that negatively impact fetal development (Haig 1996a,b, 1997; Johnson 2003); (iii) the importance of family-based studies, which can be used to detect parent of origin, imprinting effects that case–control analyses cannot; and (iv) recognition of novel, fundamental causes of psychological conditions, such as high levels of insecure attachment (psychosocial bonding) in childhood, because of parent–offspring conflicts commonly resolved in the parent's favor, that can reduce psychological well-being throughout later life (Crespi 2010b; see also Wells 2003). More generally, conflicts will usually not be observed unless explicitly sought, in part because they are invisible, senseless, or wasteful from the perspective of body and mind as coherent, unitary machines.

Strong natural selection early in life, from infectious diseases and interacting effects of nutritional status, is expected to sustain substantial negative effects on health in later life

Survivorship curves for poor, third-world human populations, and hunter–gatherer populations, drop precipitously from birth, with about 50% of children lost before the ages of 10–15 (Gurven et al. 2007; May 2007; see also Metcalf and Pavard 2007). Most of this mortality occurs in infancy, or soon after weaning, from infectious diseases and interactions of disease risk with poor nutrition (Wells 2009). Given that infectious disease risks, birth weight, and early weight gain show high heritabilities (Demerath et al. 2007; Kaslow et al. 2008; Beardsall et al. 2009), the forces of natural selection and genetic response must presumably have impacted more strongly upon genetic variants favoring early-life survival (even into the early-fetal stage) than upon virtually any other alleles or effects. A primary implication of this simple inference is that extremely strong, early selection can favor alleles that benefit early survival even if they engender substantial health and fitness costs later in life, owing to pleiotropy and linkage disequilibrium.

This is well-established theory, but its implications have yet to permeate the genetics of polygenic human disease. Thus, studies of senescence and life history evolution have focussed much more on laboratory demonstrations of antagonistic pleiotropy, and deciphering physiological mechanisms of age-related diseases, than on testing for pleiotropic, age-specific effects from specific, health-related alleles or developmental–physiological systems (Rose 2009). Similarly, GWA studies of common diseases sensibly compare cases and controls, for most diseases in adults, to identify 'risk' alleles. To the extent, however, that strong early-life effects and antagonistic pleiotropy actually operate, many so-called disease-risk alleles, especially common ones like the APOE, ADRB2, and TP53 variants in Table 1 are expected to also be alleles 'for' phenotypes that confer higher survival or other benefits in childhood. Similar considerations apply to gene by environment interactions, which may harbor much of the 'missing' heritability of polygenic disease (Manolio et al. 2009; Wermter et al. 2010); earlier environments, even into the fetal stage, are expected to impose stronger effects.

Several interesting implications follow from considering the demographics of ancestral and current third-world disease risks:

1) To the extent that early-childhood survival depends on resisting infectious diseases, alleles that enhance early infectious disease resistance should also frequently increase risk from later-life noninfectious disease; such processes may help to explain associations of HLA and other immune loci with human longevity (e.g. Naumova et al. 2007; Listì et al. 2010), and genetically-based tradeoffs between risks from infectious versus autoimmune and late-life disease (Sanjeevi et al. 2000; Dean et al. 2002; Correa et al. 2005; Fernández-Real and Pickup 2008; Van Bodegom et al. 2007; Mathieu et al. 2008; Wang et al. 2010). Indeed, it is only among polygenic autoimmune diseases such as rheumatoid arthritis and type 1 diabetes that a substantial proportion of genetically based disease liability has been accounted for (e.g. Hakonarson and Grant 2009; Imboden 2009), perhaps because of infectious diseases maintaining variation at the immune-related loci that underly risk.

2) To the extent that early survival has historically depended on relatively high birth weight, this phenotype should engender late-life costs underlain by pleiotropic alleles. For example, higher birth weight and large size have been associated with increased risk of some forms of cancer, at least in part because of alleles that enhance cell proliferation (Cnattingius et al. 2009; Oberg et al. 2009; Maehle et al. 2010). Similarly, the 8.1 'ancestral' HLA haplotype, found in about 10% of northern Europeans and apparently subject to strong, ongoing positive selection (Aly et al. 2006), is associated with both higher birth weight (Capittini et al. 2009) and increased risk from a large suite of autoimmune and other disorders (e.g. Price et al. 1999; Candore et al. 2002);

3) Under prenatal and early postnatal growth restriction, offspring should be under strong selection to partition available resources across different components of body organ and tissue growth to even more directly maximize early survival. Fetal 'programming' of adult disease was discovered by David Barker in the context of spatial epidemiological associations of low infant survival and low birth weight with increased rates of death from cardiovascular diseases and type 2 diabetes many years later (Barker 1998). A simple hypothesis for helping to explain this pattern involves a history of strong selection for genetically based, environmentally induced growth allocation patterns (e.g. relative allocation to brain, vascular system, insulin system function, immune function, etc.) that maximize early postnatal survival under adverse prenatal conditions, at a cost in later-life reproduction and survival. This hypothesis can help to explain genetically based associations of low birth weight with type 2 diabetes risk alleles (for the genes ADCY5, CDKAL1, GCK, and HHEX-IDE; Weedon et al. 2006; Freathy et al. 2009, 2010; Zhao et al. 2010) where such alleles mediate variation in tradeoff structure, in the additional context of birth weight benefits to offspring from such T2D risk alleles when present in the mother (Freathy et al. 2007, 2009; Lauenborg et al. 2009). Positive selection along the human lineage has been reported on alleles of the T2D risk genes TCF7L2 (Helgason et al. 2007), CDKAL1 (Teo et al. 2009), and ALMS1 (Scheinfeldt et al. 2009), but the relationships of selected versus ancestral alleles with relevant phenotypes remain largely unexplored. Such genetic effects are expected to be mediated in large part via conditionally adaptive responses to environmental variation, which involve epigenetic alterations that modify gene expression and developmental phenotypes (e.g. Bruce and Hanson 2010).

Compensatory childhood growth, which is known to likewise engender late-life costs (e.g. Ong and Loos 2006), should also be favoured by early-life selection under this tradeoff framework, and transgenerational effects of early-life adversity on birth weight and health (e.g. Kuzawa 2007; Kuzawa and Quinn 2009) may be explained in part by selection on early survival that is generally stronger than selection on investment in traits promoting female fecundity, leading via both genetic and plasticity effects to transgenerationally reduced investment in fecundity and late-life health.

Strong selection for early-childhood survival in humans may have important implications beyond genetically based health risks: thus, early-childhood survival and health have been strongly associated, in replicated studies among traditional and other societies, with measures of intelligence and education of the mother (Sandiford et al. 1997; Martin and Kubzansky 2005; Wachs et al. 2005; Čvorović et al. 2008; Webb et al. 2010). Was the recent evolution of brain development and intelligence in humans driven by selection on mothers for cognitive, affective, and behavioral phenotypes that enhance early-childhood survival? In turn, how much of the precocial neurological development of humans, coupled with physical altriciality, might be related to attracting early investment and health benefits from the mother (e.g. Hrdy 1999)?

Tradeoffs are molecular genetic as well as phenotypic, and uncovering the tradeoff structures of pleiotropic alleles should provide novel insights into both human evolution and disease risk

Tradeoffs between aspects of growth, maintenance, and reproduction have most frequently been analyzed at the levels of genetic and phenotypic correlations, but genetic correlations must be underlain by pleiotropy and linkage disequilibrium owing to genomic variation and molecular genetic mechanisms expressed in physiological and

developmental pathways. Indeed, tradeoffs are expected to exhibit hierarchical structure, and causal connections, from organisms to pathways to loci, at the following levels:

1 whole-body, life history tradeoffs involve differential allocation to growth, maintenance and reproduction, with lifetime inclusive fitness maximized under different regimes of total available time and energy and strength of tradeoffs (e.g. Jasienska 2009);

2 among-tissue tradeoffs involve differential growth of organs during development, and differential allocation to high-cost functions such as immunity and reproduction in adulthood (e.g. Fig. 3), with the brain retaining a privileged position as master controller subject to high costs from reduced allocation (Peters et al. 2004; Kuzawa 2010; Straub et al. 2010);

3 within-tissue tradeoffs involve differential specialized functions of specific tissues, such as fast-twitch versus slow-twitch muscles (MacArthur et al. 2007; North 2008), or brains relatively specialized for verbal versus visual-spatial task performance (Johnson and Bouchard 2007);

4 within-pathway tradeoffs, whereby upregulation, for example, of a growth-signaling pathway, enhances some physiological–developmental functions but decreases others, with consequent effects on disease risk in each case (e.g. Caricasole et al. 2005; Reddy et al. 2009; Crespi 2010a); and

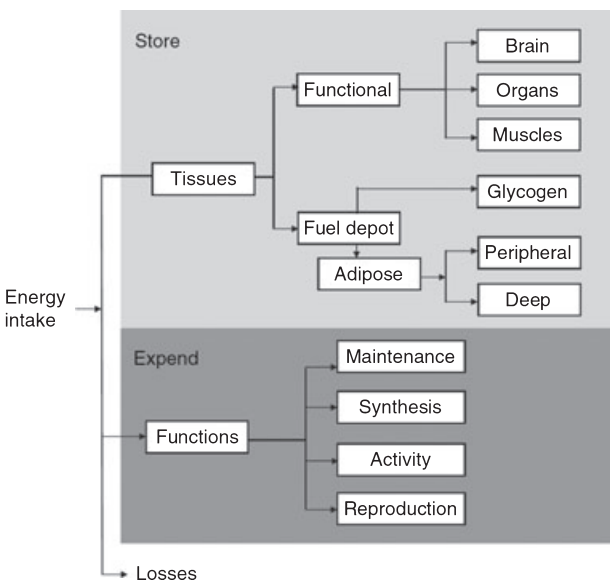

Figure 3 Storage and expenditure of resources for human growth, maintenance, and reproduction involve tradeoffs at multiple levels, from whole body to organs and tissues (shown here), and ultimately to cells and alleles. Such tradeoffs are expected to structure the evolution, development and expression of polygenic disease risks, just as they structure the evolution of human life history traits. From Wells (2009), with permission.

5 within-locus tradeoffs, whereby alternative genotypes engender different sets of benefits and costs; such tradeoffs should be mediated by mechanisms such as gene dosages, enzyme activities, and affinities for binding, and should involve risks of different diseases.

Within-locus genetic variation provides some of the best-known examples of molecular genetic tradeoffs, originally discovered because of their strong effects on disease risks; thus, the HBB locus mediates tradeoffs between risk of malaria and sickle-cell anemia, and TP53 mediates balances between reproduction, cancer, and senescence (Kang et al. 2009). One of the most interesting aspects of the data in Table 1 is that a substantial number of balancing selection cases involve losses of function for one of the alleles; loss of function alleles are expected to arise readily (given a larger set of mutational targets generating null phenotypes than differently functional ones) but increase disease risk because of deleterious effects in null homozygotes (see also Barreiro and Quintana-Murci 2010). Of course, not all cases of balancing selection need involve tradeoffs, as high allelic diversity can evolve for other reasons, but the role of this process in maintaining common alleles underlying disease risk deserves closer scrutiny. Indeed, the Val158Met polymorphism of an important schizophrenia-risk allele, COMT, has recently been shown to be subject to balancing selection effects, with heterozygotes demonstrating lower risk (Costas et al. 2010); do such effects generalize to other genes? Evidence for benefits from increased heterozygosity across many loci has been reported with regard to heart disease (Govindaraju et al. 2009); heterozygosity at a number of specific non-HLA loci has been shown to enhance survival of infectious or age-related disease (e.g. Kerlin et al. 2003; Dossou-Yovo et al. 2007; Gochhait et al. 2007; Hellemann et al. 2007; Catano et al. 2008; Livadas et al. 2009) and even low levels of inbreeding or homozygosity from other causes in humans lead to elevated risks from polygenic disease or death from infection (e.g. Lencz et al. 2007; Bacolod et al. 2008; Lyons et al. 2009a,b; Bittles and Black 2010; Mansour et al. 2010). Indeed, on a larger scale, increased homozygosity owing to founder effects in dispersal from Africa appears to account for a higher incidence of deleterious alleles in Europeans than Africans (Lohmueller et al. 2008).

Under life history theory, tradeoffs can be alleviated in part among a subset of individuals with high levels of fitness-enhancing resources (Reznick et al. 2000). With regard to human disease, high heterozygosity, low levels of *de novo* or rare deleterious, segregating mutations, high levels of developmental resources, and benign environmental conditions (e.g. Gurven et al. 2009) may each reduce the strength of tradeoffs involving components of fitness and disease risks. For example, tradeoffs between verbal

and visual-spatial skills are uncovered in 'normal' humans only after controlling for general intelligence (Ando et al. 2001; Johnson and Bouchard 2007), and a variety of neurogenetic conditions, including Turner syndrome, Klinefelter syndrome, and absence of the corpus callosum, involve tradeoffs between this pair of cognitive phenotypes (Brown and Paul 2000; Geschwind et al. 2000).

Conclusions

Evolutionary medicine represents one of the major conceptual advances in the health sciences over the past 25 years (Gluckman et al. 2011), but its penetration into the practice of medical research has been limited by: (i) inherent difficulties in developing and testing evolutionary hypotheses for human phenotypic adaptation and maladaptation, (ii) increasing specialization required for evolutionary biologists to contribute within any given medical research area, and (iii) ignorance and misunderstanding of how evolutionary approaches can inform the study of proximate mechanisms, and vice versa. These limitations can be overcome relatively effectively by studying the joint evolutionary genomic bases of human evolution and disease risk, which allows direct connections to be drawn between selection, adaptation, and maladaptive traits.

Emergence of a robust, interdisciplinary human evolutionary medical genomics will require integration of human disease genetics with conceptual and analytic approaches from evolutionary medicine, phylogenetics, molecular genetics, life history theory, and study of the genetic and phenotypic changes underlying modern human origins. The most directly useful insights should come from functionality of positively-selected and balanced haplotypes and human-specific fixed differences, increased focus on mechanisms of genomic conflict and their maladaptive sequelae, direct dovetailing of disease risk and positive selection phenomic studies, and considering the genomic landscape of common polygenic disease as a spectrum of multi-level, timing-dependent and tissue-dependent tradeoffs punctuated by deleterious mutations. Indeed, under this perspective much, if not most, of the common variants implicated thus far as disease risk alleles by GWAS may actually be beneficial overall or in many contexts – to fitness if not health. Human disease risks have evolved, and the nascent field of evolutionary medical genomics offers unique and powerful opportunities to bring proximate and ultimate approaches together, for discovering how and why.

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