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Perspective

An evolutionary perspective on complex neuropsychiatric disease

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SUMMARY

The forces of evolution—mutation, selection, migration, and genetic drift—shape the genetic architecture of human traits, including the genetic architecture of complex neuropsychiatric illnesses. Studying these illnesses in populations that are diverse in genetic ancestry, historical demography, and cultural history can reveal how evolutionary forces have guided adaptation over time and place. A fundamental truth of shared human biology is that an allele responsible for a disease in anyone, anywhere, reveals a gene critical to the normal biology underlying that condition in everyone, everywhere. Understanding the genetic causes of neuropsychiatric disease in the widest possible range of human populations thus yields the greatest possible range of insight into genes critical to human brain development. In this perspective, we explore some of the relationships between genes, adaptation, and history that can be illuminated by an evolutionary perspective on studies of complex neuropsychiatric disease in diverse populations.

INTRODUCTION

Among the most puzzling questions of human experience are why mental illnesses exist, why they persist, and why they demonstrate such a wide spectrum of severity and variability. An evolutionary perspective on neuropsychiatric conditions may offer some insights. In this perspective, we examine the evolutionary factors that influence complex neuropsychiatric conditions, with illustrations from current research in diverse populations.

Dobzhansky wrote, "Nothing in biology makes sense except in the light of evolution."[1] Complex human disorders are subject to the same forces that drive all of evolution. For all species, allele frequencies are influenced by the evolutionary forces of mutation, migration, selection, and genetic drift (or random changes in allele frequencies influenced by population structure). These processes operate locally and reflect adaptations to geography, climate, and infectious disease. Studying complex human disorders in populations from many different places reveals alleles that are the result of the local impacts of these influences. For understanding complex human conditions, studies of diverse populations are informative for a simple reason: adaptation is local, but human biology is universal. An allele of clinical importance to a phenotype in any one population reveals a gene of importance for that phenotype in all populations.

MUTATION

The genetic architecture of complex psychiatric traits reflects the influences of evolution and/or population genetics on the biology

of the developing brain.[2] A single genomic event may be associated with phenotypes of different severity (or no phenotype) in different persons.[3–5] Whether or not a mutation causes disease, and the severity of that disease, depends not only on the mutation's immediate impact on gene function but also on how and in what tissues the allele is expressed during development, the essentiality of the gene to normal development, potential interactions between the mutant allele and other genetic factors (e.g., oligogenic and epistatic effects[6–9]), and either exacerbating or protective features of the individual's physical and social environments.

Mutations with severe disabling effects on the developing brain do not survive long in evolution (much more about this below), so each one is individually rare, some even private to one patient or family. The consequence is that no single mutation or single gene explains psychiatric disease for more than a small number of patients.[10–15] Where do these mutations come from?

De novo mutation

Every person carries dozens of *de novo*, or new, mutations—that is, variants that were not present in either parent.[16] Most *de novo* mutations are neutral or slightly deleterious and persist (or not) over subsequent generations by chance.[17,18] As human population size has increased since the origins of agriculture, the number of *de novo* mutations entering our species has increased in parallel, so that most human protein-coding variants that exist today are evolutionarily recent and rare and, compared with ancient variants, are enriched for damaging alleles.[19] In expanding populations (compared with static populations), a greater proportion of the genetics responsible for traits that impact reproductive fitness is predicted to be due to combined effects of these very rare events.[20]

Among *de novo* mutations that are severely damaging to gene function, but are nonetheless compatible with life, some affect neurodevelopment and therefore can lead to severe neuropsychiatric conditions, including schizophrenia, autism, obsessive compulsive disorder (OCD), Tourette disorder, and bipolar disorder.[21–27] *De novo* mutations responsible for neuropsychiatric conditions may be either conventional single base-pair mutations and indels or structural genomic variants.[28] Some *de novo* structural variants, particularly those leading to autism and related pediatric developmental conditions, tend to reoccur in particularly vulnerable genomic "hotspots."[29] However, *de novo* mutations responsible for most mental illnesses are unique events, private to one person or to one family, if the mutation is inherited for a few generations. Different *de novo* mutations may occur in the same gene in different patients.[11] The number of *de novo* mutations in any individual child is strongly influenced by paternal age,[16] and consequently, conditions such as autism and schizophrenia are disproportionately observed among children of older fathers.[30,31]

The puzzling persistence of mental illnesses with significantly reduced fecundity[32,33] can be explained by the constant influx of *de novo* mutations. This constant resupply, combined with the very large number of genes essential for normal neurodevelopment, sustains a high prevalence of these conditions, each characterized by extreme genetic heterogeneity. That is, the thousands of genes critical to normal human brain development create many sites that are vulnerable to damaging new mutations. To take an imaginary counter-example, if only a few genes were critical to human brain development, autism and schizophrenia would be vanishingly rare because only a very small fraction of damaging *de novo* mutations would occur at vulnerable sites.

A major goal of mutation discovery is to reveal genes and pathways that are targets for treatment, not only for the patient with the original mutation but also for any patient with a mutation of similarly damaging effect in the same or related pathways. Occasionally, the link between mutation and treatment is immediately clear. For example, a genomic triplication of the glycine decarboxylase gene, *GLDC*, was discovered in a patient with schizoaffective disorder and in his mother, who had bipolar disorder with psychotic features.[34] The triplication was predicted to reduce the availability of glycine and D-serine, resulting in hypoactivity of the N-methyl-D-aspartate (NMDA) receptor. Treatment with glycine and D-cycloserine, each separately in a double-blind placebo-controlled trial, led to significant improvements in mood and psychotic symptoms for both patients.

Somatic mutation

Somatic mutations are *de novo* mutations that occur after fertilization of the zygote and hence are present in some but not all cells of the body (Figure 1). Somatic mutations may eventually prove to have a major influence on neuropsychiatric disease. These mutations are difficult to detect because they are generally not present in accessible tissue[35] but have nonetheless already been linked to several different neuropsychiatric conditions, including severe focal epilepsy in children,[36] medial temporal lobe epilepsy in adults,[37] intellectual disability, autism spectrum disorder, schizophrenia, and Alzheimer's disease.[38–40]

A relationship between somatic mutation and neuropsychiatric illness is supported by the frequency of somatic events in the tissues of affected individuals. Whole-genome sequencing of post-mortem brain tissue of individuals with no mental illness found ~80 somatic single nucleotide variants on average per person (similar to estimated numbers of *de novo* germline mutations[16]), with ~50% of individuals carrying at least one function-altering somatic mutation in a gene expressed in the cortex.[41] Individuals with schizophrenia and autism, compared with controls, were found to have higher numbers of protein-altering and/or regulatory motif-altering somatic mutations in post-mortem brain tissue.[41–43] The same was true for somatic events detectable in blood, for both point mutations in coding sequence and structural variants that disrupt critical genes. Individuals with autism, compared with their healthy siblings, were enriched for deleterious somatic coding mutations in brain-expressed critical exons,[44,45] whereas somatic copy-number errors disrupting *NRXN1* and *ABCB11* were detected in multiple individuals with schizophrenia.[46]

Repeat expansions of short sequences of DNA that alter expression of critical genes are a special class of somatic mutations. At these loci, DNA sequences of unaffected individuals include a moderate (often polymorphic) number of repeats, whereas extreme expansions lead to disease.[47] Expansions of DNA trinucleotide repeats (*CAG*, *CTG*, or *CGG*) are responsible for multiple severe neurodegenerative disorders, including

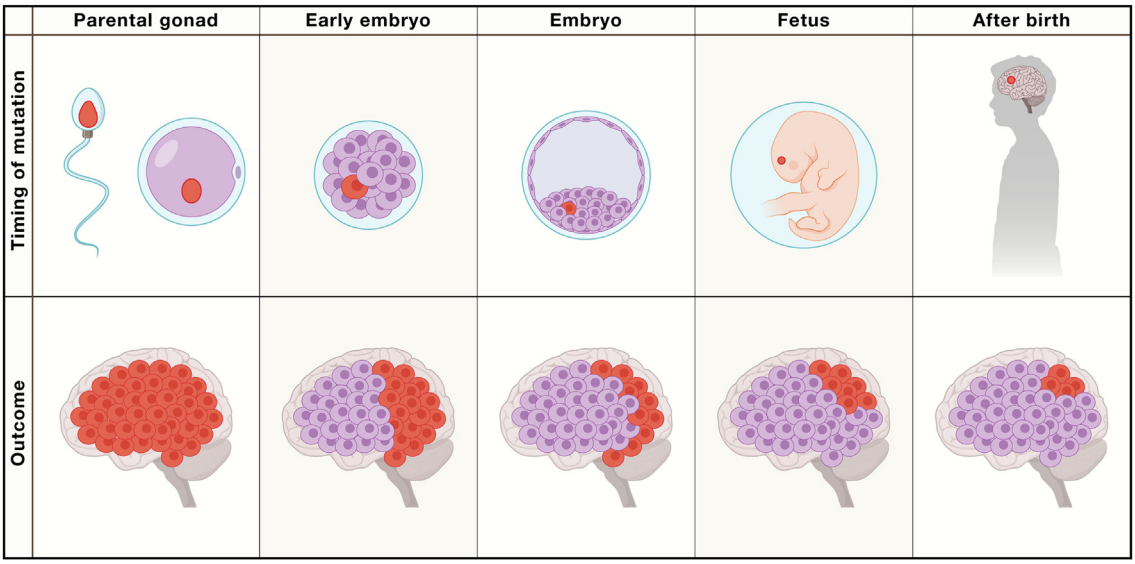

Figure 1. Somatic mutations and mental illness

Somatic mutations may appear *de novo* at any time during development of gametes, embryonic or fetal development, or after birth. The nature and severity of the illness depend both on the mutation and its timing of occurrence during development. As shown in the figure, for genes critical to brain development, the earlier the time of occurrence of the mutation during development (red dots in the top panels), the greater the proportion of brain cells that are affected (red cells in the lower panels). Somatic mutations are an extremely common cause of disease. For example, almost all cancers involve somatic mutations in critical genes in critical tissues. The role of somatic mutations in severe mental illness has been much more difficult to evaluate because somatic mutations causing mental illness are likely to arise in the brain, which is virtually inaccessible in living patients.

Fragile X syndrome (*FMR1*), Huntington's disease (*HTT*), cerebellar ataxias (*ATXN1* and *ATXN3*), and myotonic dystrophy (*DMPK*). Some trinucleotide repeat expansions are both unstable at meiosis and display somatic mosaicism, with the size of the repeat varying across brain regions.[48] This tissue-specific variation might explain some of the variation in clinical severity among individuals with the same apparent size of expansion.[49]

SELECTION

Human evolution has been in large part defined by selection for social and cognitive capacities enabling adaptation to climatic, geographic, and social pressures. These capacities included toolmaking, language, social cooperation, increased mobility, and the ability to recognize and solve complex problems.[50,51] Brain adaptations progressed from motor skills in higher primates to attention in ancient hominoids and hominids to language in early hominins to more strategic planning in modern humans.[52] Anatomically, advances in functional brain networks progressed from subcortical to cortical brain regions associated with excitatory neurons and synaptic functioning.[53] Human neurons have greater dendritic size, structural complexity, and subtype diversity than neurons of other species, enhancing neuronal capacity and connectivity for information processing.

Major selective pressures: Climate and infectious disease

Specific alleles critical to evolution of brain function have been difficult to identify, but experience with other traits suggests patterns that may also be relevant for brain genes. Selection acts on the individual, who either survives and reproduces or not. Selective forces on individuals are also selective forces on their alleles and, therefore, on allele frequencies of populations. For example, alleles regulating skin color have been subject to strong selection by latitude and climate, based on exposure to sunlight. In consequence, differences in allele frequencies of the ~40 genes regulating skin color are now the major genetic differences among continental populations.[54]

Infectious diseases are the other major player on this stage. Multiple alleles of hemoglobin beta (*HBB*) protect their carriers against malaria,[55] and at least two alleles of apolipoprotein L1 (*APOL1*) protect their carriers against trypanosomiasis (sleeping sickness).[56] As a result, high frequencies of these protective alleles are found in populations where the infectious diseases are endemic. The strength of selection for the resistant alleles of each of these genes is reflected by their persistence, despite severe pleiotropic effects: sickle cell anemia, thalassemia, and end-stage kidney disease.

Mutations with possible selective effects on human brain evolution

With increasingly complete sequences of ancient hominin and modern primate genomes, it is now possible to compare human genomes to those of our closest relatives in order to identify genetic features specific to the human lineage that may have been critical to human evolution.[57] The possible causal roles in human evolution of any of these genomic events are inevitably "just-so" stories, but for some features, the combination of genomic and experimental data suggesting meaningful adaptive effects is quite compelling. Each of these observations is consistent with the hypothesis that critical genetic events in human evolution involve alterations of regulatory mechanisms controlling the

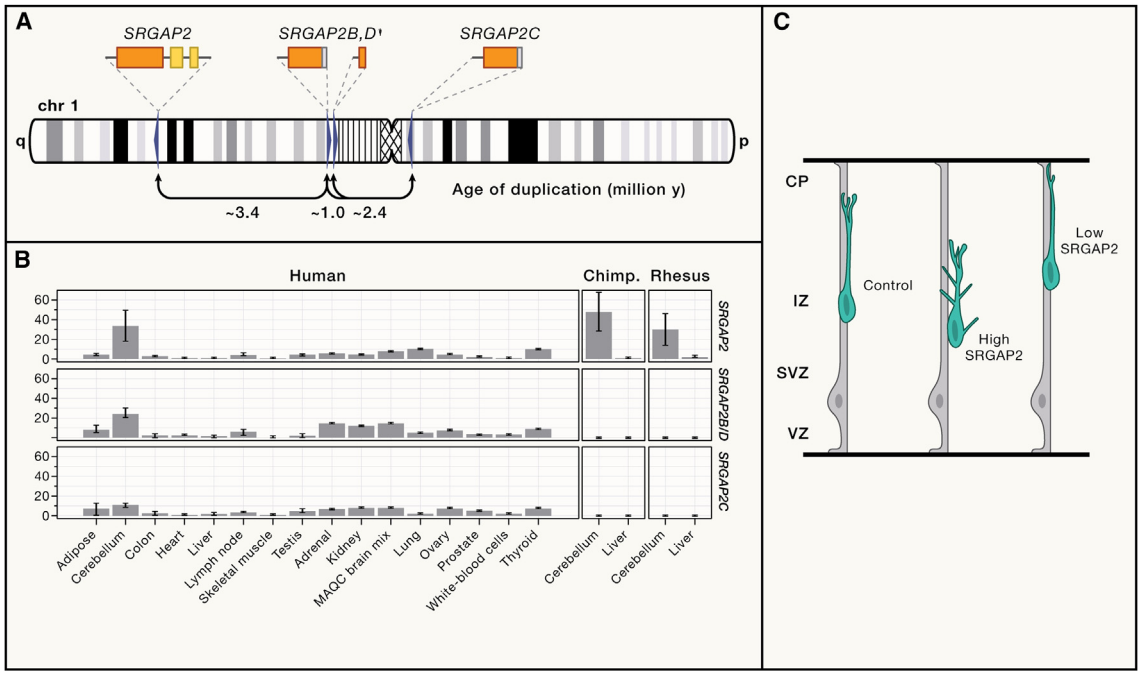

Figure 2. Human-specific duplications of *SRGAP2* and evolution of the neocortex

The *SRGAP2* gene on chromosome 1 encodes the SLIT-ROBO Rho-GTPase-activating protein, which controls migration of neurons and dendritic formation in the cortex. *SRGAP2* has been duplicated three times during human evolution.

(A) Timing of *SRGAP2* duplication events. ~3.4 million years ago (mya), *SRGAP2* was partially duplicated to form the less active *SRGAP2B*; ~2.4 mya, *SRGAP2B* was duplicated to form *SRGAP2C*, which lacks the GTPase-activating domain of *SRGAP2* and acts antagonistically to it; and ~1.0 mya *SRGAP2C* was duplicated to form *SRGAP2D*, a pseudogene.

(B) RNA expression levels of *SRGAP2* genes in various tissues of humans, chimpanzees, and rhesus monkeys. Expression levels are based on RNA sequencing (RNA-seq) data mapped using gene-specific sequences. *SRGAP2A* is expressed in the brains of all three species, but *SRGAP2B* and *SRGAP2C* are expressed only in the human brain. *SRGAP2D* is a pseudogene.

(C) Effects of differences in SRGAP2 protein levels on neuronal migration. SRGAP2 protein regulates neurite formation and branching by forming filopodia on neurons in the ventricular zone (VZ) and subventricular zone (SVZ) of the cortex. In a mouse model, high levels of SRGAP2 protein inhibit migration of neurons to the cortical plate (CP) compared with control. By contrast, SRGAP2C protein binds to and antagonizes SRGAP2, leading to prolonged period of neuronal migration to the CP. In the mouse model, reduction of SRGAP2 was associated with the emergence of human-like features in the neocortex, including a prolonged phase of maturation of dendritic spines and therefore a prolonged phase of maturation of the neocortex. Data and figure from Guerrier et al.,[60] Dennis et al.,[61] and Charrier et al.[62]

timing and level of gene expression during development.[58] We give three examples.

Jaws

Loss of function of the sarcomeric myosin gene *MYH16* gene in the human lineage approximately 2.4 million years ago (mya) led to drastic reduction of muscle and bone mass of the mandible in humans compared with the jaws of other primates.[59] The frameshift mutation responsible for loss of function of *MYH16* is unique to, and fixed in, the human lineage. The loss of the massive masticatory apparatus in the skull may have removed an anatomical constraint on brain size relative to body size (encephalization).[59]

Dendrites

Duplication specifically in the human lineage of the gene *SRGAP2* may bear on the evolution of brain development (Figure 2). *SRGAP2* encodes a GTPase-activating protein that controls migration of neurons and dendritic formation in the neocortex.[60] Between 3.4 to 1.0 mya, *SRGAP2* was duplicated three times in the human lineage. The duplications occurred only in the human lineage and are now fixed.[61] All copies of *SRGAP2* are expressed in human developing neocortex. Experiments introducing human *SRGAP2* genes into mice indicated that the duplicated mutant *SRGAP2* inhibits function of the parent gene, resulting in a prolonged phase of maturation of dendritic spines and therefore a prolonged phase of maturation of the neocortex.[62]

Neocortex

Human brain evolution is thought to involve the enlargement of the subventricular zone of the neocortex, with increased numbers and/or the prolonged proliferation of basal radial glial cells during development. This hypothesis led to a search for genes with high expression in radial glial cells compared with other neuronal cells. Many mammalian genes have this profile, but only one is specific to humans: *ARHGAP11B*.[63] This human-specific gene is a duplication of the parental pan-mammalian *ARHGAP* gene that encodes a RHO-GTPase-activating protein. The human-specific duplicate has a mutation leading to loss of this activity. Experimental expression of *ARHGAP11B* in developing mouse neocortex led to the expansion of the subventricular zone, to the amplification of basal radial glial cells, and to the folding (mimicking gyrification) of the neocortex, significantly increasing the cortical area. A similar experiment in

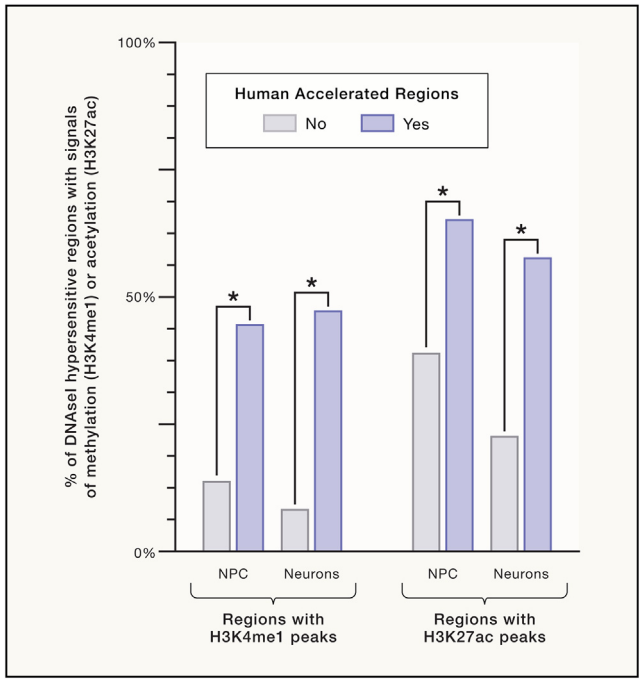

Figure 3. Human accelerated regions (HARs) are enriched for neurodevelopmental enhancer elements

HARs are genomic regions that are conserved across all human populations but differ between humans and all other species. In human neuroprogenitor cells (NPC) and neurons, HARs that are potentially regulatory (i.e., are DNaseI hypersensitive sites) are more likely than other DNaseI hypersensitive sites to include active regulatory elements (i.e., H3K4me1 signals of methylation or H3K27ac signals of acetylation). *$p < 0.001$; Z test for proportions (figure from Girskis et al.[70]).

marmoset also led to increased numbers of basal radial glial progenitors in the outer subventricular zone, to increased numbers of upper-layer neurons, and to enlarged and folded neocortex.[64] The duplication of *ARHGAP11* is estimated to have occurred 5.0 to 5.5 mya. The duplication in itself may have had no effect, but a much later single nucleotide mutation in the duplicated copy of *ARHGAP11* led to abnormal splicing, loss of the RhoGAP function, and substitution of an alternate carboxy terminus with a different function that fostered expansion of the subventricular zone.[65]

Evolutionarily dynamic noncoding regions

Evolutionary adaptations of the human brain involve many of the same pathways and mechanisms that go awry in mental illness. Genomic analysis can reveal links between these evolutionary adaptations and neuropsychiatric disease.[66] Although it has long been recognized that most evolution in the human lineage involves noncoding changes,[58] recent analyses have revealed regions of the human genome that are highly conserved across all human populations but highly divergent between humans and other species. Such elements include "human accelerated regions" (HARs), "human-specific conserved deletions" (hCONDELs), and "human ancestor quickly evolved regions" (HAQER), among others.[67–69] Importantly for understanding neuropsychiatric disorders, these regions are enriched for neural regulatory elements, with greater distinctiveness of human sequences often associated with marked changes in activity of neuronal enhancers (Figure 3).[70]

Variations in these evolutionarily dynamic regions are implicated in neuropsychiatric disease. For example, HARs, HAQERs, and hCONDELs are all enriched for regions of common variation implicated in schizophrenia risk.[67–69] Individuals with autism are significantly more likely than their healthy siblings to harbor *de novo* copy-number variants in HARs.[71] In consanguineous families in which autism is more likely to be inherited as a recessive trait, affected children are more likely than their unaffected relatives to carry rare alleles in HARs.[71]

Mutation-intolerant genes

Alleles that significantly increase risk for neuropsychiatric disorders, whether in HARs or elsewhere in the genome, occur disproportionately in genes that are not tolerant of naturally occurring variation—that is, genes in which missense and loss-of-function mutations occur at lower frequency than expected by chance, given gene size and structure.[22,72] Depending on the genotype and phenotype, negative selection on these alleles can be reflected in early mortality, reduction in fertility, or reduction in fecundity. For neuropsychiatric disorders, selection against damaging alleles of variation-intolerant genes is associated with a significant increase in childlessness among affected males, apparently mediated by cognitive and behavioral difficulties.[73]

Reduced fecundity as a selective mechanism

Neuropsychiatric traits such as schizophrenia and autism spectrum disorder are subject to negative selection due to reduced fecundity. Studies based in the Swedish birth and medical registries indicate that fecundity varies substantially across psychiatric disorders.[32] The largest reduction of fecundity was associated with schizophrenia (for affected males, 23% of the birth rate as compared with the general male population, and for affected females, 47% as compared with the general female population), whereas the effect was much less pronounced for persons with depression (95% for males and no significant effect for females).

Differential selection in females and males

Some features of neuropsychiatric illness are more severe in males than in females.[74,75] Gender differences may be due in part to diagnostic biases in assessment tools and sociocultural factors, but multiple lines of evidence support a female protective effect at the biological level. (1) Siblings of female probands with autism spectrum disorder are more likely to be diagnosed with autism compared with siblings of male probands. (2) Unaffected mothers of probands have higher polygenic risk scores compared with unaffected fathers.[76] (3) Female versus male probands with autism spectrum disorder have a 2-fold enrichment of *de novo* loss-of-function variants in highly constrained genes[72] and a 3-fold enrichment of the most damaging autosomal copy-number variants.[77] (4) Damaging copy-number mutations responsible for autism are much more frequently inherited from unaffected mothers than from unaffected fathers.[77] Each of these observations suggests that females must be more

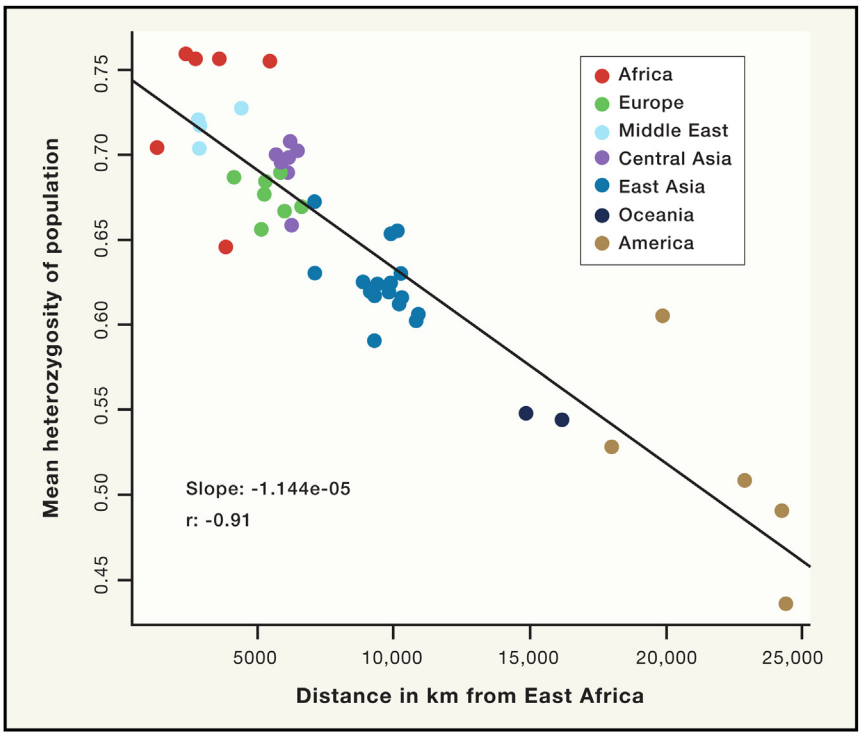

Figure 4. Genetic variation in human populations as a function of distance from East Africa

Heterozygosity genome-wide is highest in East Africa and decreases worldwide with distance from that point. The reason for the richness of human genetic variation in Africa is that people have lived in Africa longer than anywhere else (figure from McClellan et al.[80]).

severely affected genetically for the autism phenotype to be expressed. Females are also protected against the effects of rare *de novo* copy-number mutations affecting intellectual functioning, with significantly less severe effects on IQ compared with males with the same mutations.[78] These observations may explain the less severe reduction in fecundity for females versus males. Given equal burdens of damaging genetic variation, females may be less severely affected and hence more able than males to engage socially.

MIGRATION

Migration and genetic architecture

Ancient human migrations underlie patterns of genetic variation in modern human populations. After the divergence in Africa of humans and chimpanzees 5–6 mya, ancient hominins continued to evolve across the African continent. Modern humans emerged approximately 200,000 years ago, with small groups of individuals beginning to migrate out of Africa approximately 100,000 years ago, ultimately populating six continents.[79] Because 99% of human evolutionary history occurred in Africa prior to the out-of-Africa migrations and because few individuals left Africa compared with the number who remained, far more human genetic variation is found in Africa than anywhere else.[80] This is evident in population profiles of heterozygosity, which are highest in Africa, by far, and decrease as a function of geographical distance from East Africa (Figure 4).[18]

Both ancient and recent human migrations have influenced modern distributions of common and rare alleles worldwide and have yielded an intriguing paradox. Common polymorphisms (SNPs) found in all human populations are ancient variants, dating back to the shared evolution of our species in Africa or even before our separation from chimpanzees. SNPs of the HapMap vary in frequencies from place to place but are essentially polymorphic everywhere. At the other extreme, in recent human history, genetic variation has accumulated locally on all continents with rapid population expansion since the advent of agriculture.[81] Therein lies the apparent paradox: most human genetic variation is ancient and shared, but most alleles are recent and individually rare.[2]

Lessons from Africa

Given their rich genetic diversity, ancestral African populations are highly informative for detecting alleles responsible for complex human traits.[80] With advances of modern sequencing platforms, the challenge for gene discovery in medicine is to identify causal variants against the vast background of neutral genetic variation. In this context, unaffected individuals of African ancestry are highly informative controls for studies based in any population, as they harbor far more tolerated benign genetic variation than do participants from other populations. This wealth of benign variation enables a more powerful evaluation of candidate risk alleles in case-control designs from any population.

For example, in comparing individuals with schizophrenia to unaffected controls, the statistical power to detect enrichment of ultra-rare deleterious variants was far greater in an ancestral African population compared with a European cohort.[82] The study, based on an African population, demonstrated with a modest sample size (~900 cases and 900 controls) that genes disrupted in persons with schizophrenia were disproportionally involved in synaptic functioning and that the collective burden of intolerant genes disrupted by ultra-rare mutations increased the risk of illness. These observations were consistent with findings from European cohorts, but similar significance was only demonstrated with much larger sample sizes.[13,14]

Populations of African ancestry have been informative for other complex traits as well. Rare alleles associated with low high-density lipoprotein (HDL) cholesterol and a higher risk of coronary disease,[83] and rare alleles associated with low low-density lipoprotein (LDL) cholesterol and a lower risk of coronary disease,[84] were first established in large part from studies of individuals of African ancestry. Once identified, the findings were confirmed in other populations. As with schizophrenia, the informative nature of African populations for these complex traits was

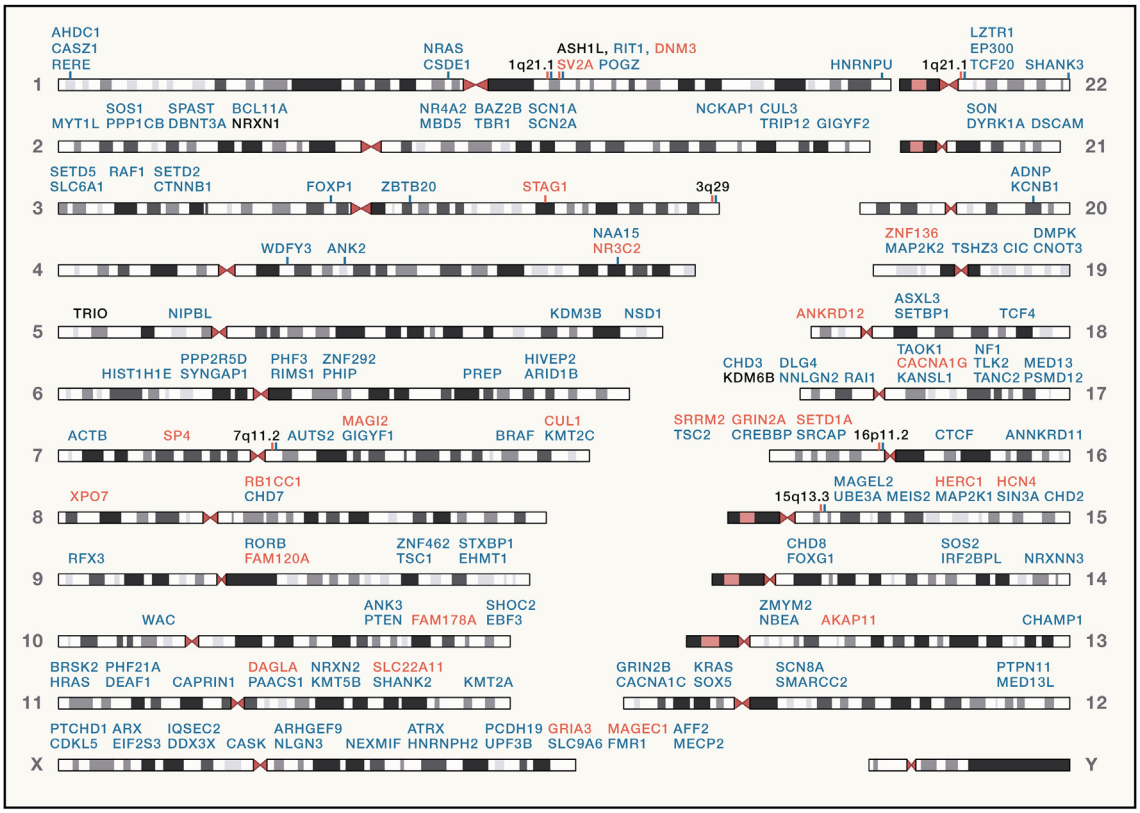

Figure 5. Genetic heterogeneity of severe mental illness

Individually rare and *de novo* point mutations and structural variants (deletions, duplications, inversions, and translocations) in many different genes have been causally associated with schizophrenia (red), autism (blue), or both (black). The list of affected genes is growing rapidly. No individual damaging variant appears in more than a small number of cases. Hotspots for structural variants include chromosomes 1q21.1, 15q13.3, 16p11.2, and 22q11.2. Figure updated from McClellan and King[2] with data from Turner et al.,[6] Singh et al.,[11] Zhou et al.,[15] and Marshall et al.[88]

not based on differences in risk of disease but on the power of filtering candidate alleles against the full backdrop of human evolutionary history in order to detect biologically meaningful effects.

Because human evolution in Africa occurred in highly diverse environments across the continent, African populations are also informative for studying gene-environment interactions. For example, as first mentioned above, persons of African ancestry are especially susceptible to end-stage kidney disorders. The increased risk is largely due to two common variants that have been positively selected for thousands of years because they confer protection against trypanosomiasis (sleeping sickness) in regions of Africa where it is endemic.[85] These variants, in the apolipoprotein L1 (*APOL1*) gene, encode for proteins that lyse the internal vesicles of *Trypanosoma brucei rhodesiense*, a major cause of trypanosomiasis, whereas the proteins encoded by the ancestral alleles permit growth of the parasite. However, the variant *APOL1* alleles lead to a higher risk in later life of end-stage kidney disease because the variant proteins also lyse glomerular cells of the kidney. The relationship between end-stage kidney disease, trypanosomiasis, and *APOL1* is an example of gene-environment interaction during evolution involving one gene and two severe common diseases, with positive selection for variant alleles in regions of endemic trypanosomiasis despite a much higher risk of kidney disease at post-reproductive ages.

GENETIC DRIFT

Genetic drift refers to changes in allele frequencies due to chance.[86] The strength of genetic drift is driven primarily by population structure, including changes in population size over time, geographic and social isolation, and mating patterns. Genetic drift is strongest in small populations, and in isolated populations, it can lead to high frequencies of damaging alleles by chance. In populations of any size, drift can lead to differences by chance in frequencies of benign alleles due to neutral alleles that "surf" on haplotypes during population expansions.[87] (Figure 5.) Population-specific surfing leads to differences in allele frequencies due simply to population of origin. This form of population stratification in allele frequencies is a major confound for association studies focused on alleles of very small effect sizes. In such studies, subtle differences in allele frequencies between individuals of different ancestries, even from the same continent, can lead to falsely attributing frequency differences to disease status rather than to ancestry.[2]

In human societies, nonrandom patterns of mating are major influences on population structure. These nonrandom patterns

of mating include consanguinity, endogamy, and assortative mating.

Consanguinity

Mate choice based on consanguinity, or genetic relatedness, leads to far higher incidence of recessive traits.[89] Mutations of severe effect on recessive traits, including mutations in noncoding regulatory regions, can be revealed by analysis of consanguineous families with multiple affected children.[90] As with the study of *de novo* mutations in probands from otherwise healthy families, studies of consanguineous families rely for the power of their analysis on retaining the family structure in the study. The genomic analysis is meaningful in the context of comparisons of children, parents, and other informative family members, not only cases and controls.

Endogamy

Populations may be genetically isolated as the result of endogamy—that is, mate choice based on the membership in the same group, whether defined by culture (such as language or religion) or genetics. If endogamy is accompanied by migration of the endogamous group, the population is likely to be further isolated. Endogamy can lead to occurrence at high frequency of either recessive or dominant alleles, and endogamous populations have proven particularly informative for genetic characterization of human disease.[91] Disease-associated alleles at high frequency in population isolates, but rare or absent elsewhere, have revealed genes important for neuropsychiatric disorders. These discoveries include an allele of topoisomerase *TOP3β* enriched in schizophrenia in the Finnish population,[92] an allele of the RNA-binding-motif protein *RBM12* associated with psychosis in Iceland,[93] and of the role of cadherins, particularly an allele of *PCDH3A*, in schizophrenia in the Ashkenazi Jewish population.[94] Each of these alleles was observed in one endogamous population, but the genes harboring them are critical to brain development in all populations.

Assortative mating

Assortative mating is the tendency for individuals to prefer mates with similar phenotypic characteristics and occurs across a range of traits including physical attributes (such as height) and social or cultural factors (such as language or religion).[95] Assortative mating also occurs frequently among individuals with psychiatric illnesses, both within and across disorders.[96–98]

Within-trait assortative mating substantially increases the risk of the same illness to offspring compared with the risk in the general population.[99] It may also contribute to the persistence of disorders with reduced fecundity, such as autism spectrum disorder and schizophrenia.[32,98] The increases in risk could be due to genetic causes, environmental causes, or both, with different combinations of influences in different families.

Because random mating is an assumption of all SNP-marker-based heritability estimators, such as linkage disequilibrium (LD) score regression[100] and residual maximum likelihood (REML),[101] assortative mating can yield significant overestimation of heritability.[102] Within-trait assortative mating may also account for some of the biases of Mendelian randomization[103] and to differences in findings between family-based and population-based genome-wide association studies (GWASs).[104–106]

Cross-trait assortative mating tends to increase with the number of diagnoses in the proband.[98] Consequently, cross-trait assortative mating, rather than shared biology, may underlie the apparent "genetic" correlation between pairs of illnesses. Cross-trait assortative mating is very highly correlated with estimates of shared genetic effects associated with different illnesses ($R^2 = 0.94$),[107] suggesting that reported genetic correlations between pairs of illnesses may be inflated by assortative mating. These findings have implications for understanding of the genomic architecture of psychiatric disorders, their shared biological basis (or lack thereof), and to study design considerations, such as whether highly genetically correlated diseases can reasonably be jointly analyzed to boost statistical power.[107]

IMPLICATIONS FOR GENE DISCOVERY

The premise of this commentary is that factors that drive evolution also shape the genetic architecture of complex traits, including psychiatric disease. In this section, we explore how an evolutionary perspective can inform the design of studies aiming to understand these genetic causes.

A very short history of the search for genetic causes

Questions about inherited causes of disease have been asked for thousands of years, but genetic approaches to answering them are very recent. In 1865, Mendel's presentation *Experiments in Plant Hybridization* to the Brünn Society for Natural Science described basic principles of genetics (albeit without the word "genetics"), with the recognition that dichotomous traits are inherited independently and with hypotheses of dominance, segregation, and independent assortment.[108]

The same year, unaware of Mendel's work, Francis Galton published *Hereditary Talent and Character*, which posited that "the qualities of each individual are due to the combined influences of his two parents, and the remarkable qualities of the one may have been neutralized in the offspring by the opposite or defective qualities of the other."[109] Galton founded the biometric approach to understanding heredity and over several decades applied statistical methods to the study of continuous, quantitative anthropomorphic traits in families.[110] He observed that many traits are approximately normally distributed, are correlated among relatives, and that values among offspring compared with parents often reflect regression to the mean ("regression to mediocrity").[111]

Galton's work had an enormous impact on statistics, genetics, and psychology but also provided the foundational rationale for eugenics. He wrote that "…if talented men were mated with talented women, of the same mental and physical characters as themselves, generation after generation, we might produce a highly bred human race, with no more tendency to revert to meaner ancestral types than is shown by long-established breeds of race-horses and fox-hounds."[109] Over the subsequent 130 years, his work and its elaboration by many others were used to justify colonialism, racism, apartheid, institutionalization, sterilization, and genocide.[112]

With the rediscovery of Mendel's work in the early 1900s, yet still without the concept of a gene, two very different approaches emerged for the study of inherited traits. Mendelians viewed traits as qualitative, often dichotomous, and biometricians (following Galton's model) viewed traits as quantitative, generally with underlying normal distributions. In 1918, R.A. Fisher proposed to reconcile these views with an "infinitesimal," or polygenic additive, model, positing that a large number of individually infinitesimal Mendelian factors could collectively explain a continuous trait.[113] Under this model, variance explained by any one factor would be negligible compared with overall genetic variance.[111]

In the 1960s, with the concept of gene firmly in mind but still without molecular biology to give it physical reality, D.S. Falconer extended Fisher's model by proposing a polygenic additive liability model, positing that the underlying liability for a qualitative trait might be normally distributed, with weak contributions from multiple genetic and environmental risk factors.[114] Whether or not a person developed an illness would then depend on the whether the total "dose" of liability exceeded a critical threshold.[115] The liability model was predicated on dominance and epistatic effects being negligible and with no individually large-effect environmental or genetic influences. In this context, Falconer also pointed out that the concept of heritability was intended to estimate the proportion of variance contributed by total genetic and total environmental influences, not to identify specific genetic or environmental causal factors.

When Falconer applied his model to data on prevalence and familial clustering of diabetes, he recognized that its practical usefulness was limited. He found that an additive polygenic liability model did not fit the empirical data on diabetes. Heritability estimates, which were intended to be stable estimates of the proportion of variance contributed by genetic factors, in fact differed for early-onset versus late-onset illness.[114] He suggested that the model failed because different genetic factors influenced early- and late-onset diabetes (genetic heterogeneity) and because environmental risk factors varied both among individuals and with age. Modern statistical geneticists have applied Falconer's argument to explain the failure of polygenic models to capture the genetic architecture of complex traits.[116]

Polygenic models in the genomic era

During the early years of the Human Genome Project, the least expensive high-throughput, widely available approach to evaluating genetic variation in human disease was to genotype thousands (soon millions[117]) of common single nucleotide polymorphisms (SNPs) in cases and controls, then to compare allele frequencies between the two groups. The goal was to identify common variants that contributed to disease or that were in LD with unknown variants that would ultimately prove to contribute to disease. These GWASs[118] shared as their theoretical rationale the polygenic liability models of Galton, Fisher, and Falconer. GWASs led to thousands of reports of tens of thousands of SNPs statistically associated with hundreds of traits, prominently among them psychiatric disorders,[119] including schizophrenia[120,121] bipolar disorder,[122] major depression,[123] autism spectrum disorder,[124] OCD,[96] ADHD,[125] and anxiety disorders,[126] and from subsequent pooling projects and meta-analyses, associations shared across disorders.[127–130]

Despite the vast number of reported statistical associations, for most common diseases, most heritability (in the original sense of proportion of total variance) is not explained by GWASs.[131] With the recognition of this "missing heritability," extensions of GWASs were developed to yield "polygenic risk scores," the sum of risk alleles weighted by their effect size.[132] Polygenic risk scores (PRS) were developed for hundreds of traits, including psychiatric disorders[133] and even social and economic status.[134] However, simulation studies indicate that the statistical significance of the apparent association between a PRS and a disease phenotype is inflated when the same cohort is evaluated both for the original GWAS and in construction of the PRS.[135] Perhaps not surprisingly, PRS developed in one population generally do not predict risk for the same trait in other populations.[136,137]

Given the failure of PRS to replicate across diverse ancestries, some recommend defining different polygenic risk scores for different populations.[138] Others suggest that PRS represent non-genetic correlates of ancestry-associated differences in risk driven by social and economic factors rather than reflecting underlying biological risk.[139,140] To the extent that this second explanation is correct, the use of polygenic risk scores sustains systemic discrimination by falsely ascribing to genetics differences in ancestry-correlated risk that are in fact driven by social inequities.

Causal alleles: Common

Debates regarding the genetic causes of complex disease are often framed as a dichotomy between rare alleles of individually severe effect versus common alleles of individually small effect, a recapitulation of the argument of 120 years ago. An evolutionary perspective suggests that this dichotomy fails to capture all the possibilities. Common alleles can have a clinically meaningful influence on disease, including neuropsychiatric disease, if their effects appear only at post-reproductive ages and thus influence a phenotype that is neutral in evolution even if devasting to affected individuals.

The most striking example of a common allele with a devastating post-reproductive effect is apolipoprotein E (*APOE*), of which the allele *APOE4* (Cys130Arg), with worldwide frequency 0.14, conveys significantly elevated risk of Alzheimer disease, especially among homozygotes.[141] Alzheimer disease influenced by *APOE4* is late onset, virtually always post-reproductive. The critical role of post-reproductive onset in the persistence of the damaging *APOE4* allele is supported by the observation that all mutations leading to early-onset Alzheimer disease are individually rare.[142]

The relationship between age-related macular degeneration and *CFH* is another well-characterized example of a disorder caused by a common genetic variant. The causal allele of complement factor H (CFH Tyr402His) confers a 2- to 5-fold increased risk of late-onset macular degeneration. The histidine allele at this site reduces the capacity of CFH to bind malondialdehyde epitopes, thereby reducing protection of the retina against oxidative stress and inflammation.[143]

Common alleles with devastating effects on post-reproductive conditions are more likely to persist if they carry strong protective effects at younger ages. The *APOL1* alleles that protect

from schistosomiasis but contribute to end-stage kidney disease are examples of this phenomenon.[56] As with *APOE4* and *CFH*, these *APOL1* alleles are associated with substantial increased risk for disease of nearly always post-reproductive onset, thus avoiding negative selective pressure while conferring positive selective pressure among younger people in schistosomiasis-endemic areas.

By contrast, for severe mental illnesses such as schizophrenia and autism, which are associated with a marked reduction in fecundity,[144] any allele increasing disease risk, even slightly, faces strong negative selection. How could such alleles become common? Proposed explanations include (1) possible selective advantage to carriers of common risk alleles who remain unaffected,[145] (2) LD between predisposing alleles and neighboring, functionally unrelated advantageous alleles, (3) hitchhiking of risk alleles in genomic regions harboring genes intolerant to loss of function and therefore conserved by selection,[146] or (4) changes over time or in different environments of the risk associated with individual alleles.[145] As of yet, no functional studies support any of these hypotheses.

An alternative "omnigenic model" proposes that the vast majority of variants reported by GWASs are not specific to any disorder but rather collectively disrupt highly interconnected regulatory networks, which ultimately disrupt expression of a smaller number of core genes related to the disorder in question.[147] This hypothesis is consistent with the diffuse patterns of GWAS-reported SNPs near genes with no apparent biological relevance. However, the model does not explain the persistence of common variants that are hypothetically causally involved, directly or indirectly, in complex traits with decreased fecundity.

Meta-analyses of GWASs report significant enrichment of common variants near the same genes that harbor rare alleles with demonstrated functional effects.[121] Nonetheless, demonstrating biological effects for individual GWAS-reported SNPs remains a challenge. Two lines of evidence have been proposed for their disease relevance: (1) for many phenotypes (not only mental illness), genes reported to be the nearest GWAS hits have a nearly 60-fold enrichment for the presence of rare variants associated with the same phenotype, compared with the second nearest gene (10-fold) and third nearest (3.6-fold),[148] and (2) genes near SNPs from GWASs of schizophrenia are disproportionately expressed in frontal cortex and hippocampus compared with hypothalamus, substantia nigra, or spinal cord and are substantially more likely to be expressed in cell-types of high relevance to schizophrenia, including CA1 pyramidal cells, medium spiny neurons, and interneurons.[121]

A caveat for these lines of evidence is that the genomic position of a variant in the general vicinity of a gene does not guarantee that the variant influences the neighboring gene's function.[149] Further, since most human genes are expressed in brain,[150] brain expression in a nearby gene does not confirm a functional role. Even if a nearby gene is critical for neurodevelopment, the question is not the function of the gene; the question is the functional impact of the variant. Proximity and statistical association by themselves do not establish biological relevance.

A recent study assessed the proportion of GWAS variants for psychiatric disorders that impacted gene transcription by assaying all variants in LD blocks seeded by these SNPs using massively parallel reporter assays (MPRAs).[151] Less than 1% (26/2,899) of sites demonstrated a difference in regulatory activity between the predicted risk allele versus the reference allele. For comparison, expression quantitative trait locus (eQTL) analyses of unselected variants genome-wide, with no reported association with a disease phenotype, yielded approximately the same proportion of variants (~1%) with allelic differences on gene expression.[152]

Causal alleles: Rare

The challenge of demonstrating causality for rare alleles of severe effect is the converse of the challenge for common alleles. Patients with schizophrenia, autism, and other severe neurodevelopmental disorders more frequently harbor individually ultra-rare (often *de novo*) mutations of clear functional impact on genes critical to neurodevelopment (Figure 5).[11–14] The biological rationale for many of these alleles is individually compelling, but statistically significant enrichment for damaging mutations in any single gene requires combining information from many cohorts.[10,11] Even then, severe mutations in any one gene explain only a small proportion of affected individuals.

Several genomic regions have been identified that are particularly susceptible to recurrent *de novo* copy-number errors as the result of their genomic structure.[29] Genomic lesions in these hotspot regions are causally associated with neuropsychiatric conditions including schizophrenia, autism, and intellectual disability at some genomic sites with syndromic effects.[29,88,153]

For point mutations and small insertions and deletions, biological and statistical evidence must be integrated to establish the effect of individually ultra-rare variants of severe effect. For example, network analyses based on genes harboring rare damaging mutations, each in a different patient, reveal pathways important to fetal brain cortical development and to neuronal postsynaptic signaling.[22,82,154–156] In comparison, analyses of rare damaging variants in controls, or of benign variants in cases or controls, do not converge in biologically meaningful networks. The network approach is appealing because evolution is biology. Mutations in genes that share biological functions are likely to lead to related clinical outcomes.

Statistical versus biological significance

In an era of big data and pan-omics, genetics has tended to devolve into computational modeling. The limitations of significance testing and the biological relevance of hypothesis testing focused on p values have long been emphasized by senior statisticians. 70 years ago, Yates noted that it is easy to fall into the trap of paying undue attention to the results of tests of significance and too little attention to the estimates of the magnitude of biological effects.[157]

This problem has become more dramatic than Yates could have imagined. With the very large sample sizes enabled by high-throughput genomics, tiny differences in allele frequencies reach statistical significance. For example, a GWAS of autism spectrum disorders reported on >10,000 subjects of European ancestry.[158] In this study, the risk SNP with the most significant p value had a frequency of 0.35 in the discovery case series, 0.38 in the replication case series, and 0.39 in the control series, yielding a chi-square p value of 2.1E−10. That is, the extremely large sample

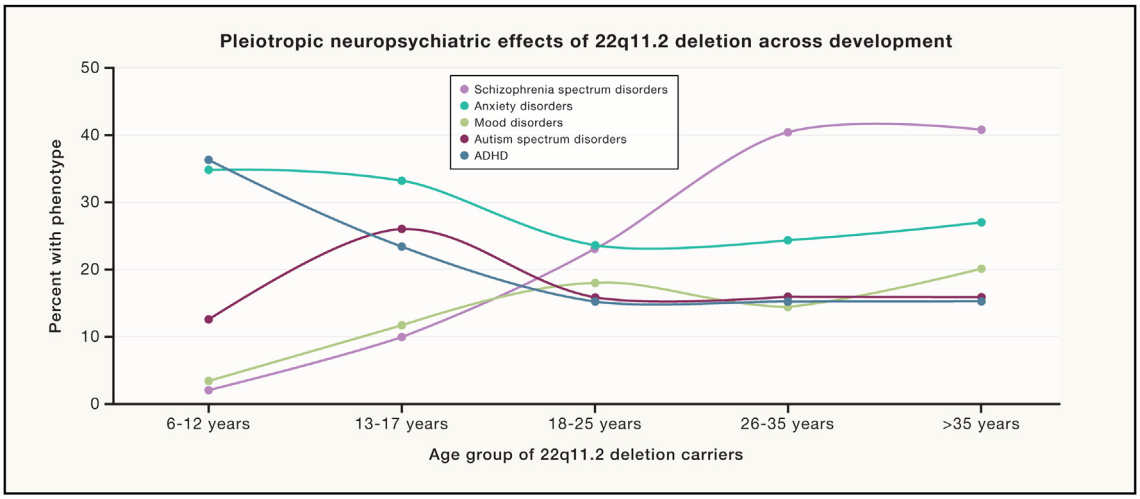

Figure 6. Clinical heterogeneity and pleiotropy among patients with deletion of chromosome 22q11.2
Prevalence rates by age for several neuropsychiatric disorders among 1,402 individuals with 22q11.2 deletions, evaluated by the International 22q11DS Brain Behavior Consortium (IBBC).

size yielded a highly significant p value for a trivial difference in allele frequencies. Meanwhile, the frequency of the same SNP across populations of Europe ranges from 0.30 to 0.79 and across populations of the world from 0 to 0.79. Because the differences in SNP frequencies across populations are so much greater than differences in SNP frequencies between cases and controls, the difference attributed to disease status could easily have been due to subtle differences in ancestry between cases and controls. More fundamentally, even if the difference between 0.35 and 0.39 were not confounded by ancestry, what would it mean?

Statistically significant but biologically false associations can cause clinical harm.[159] For example, five common variants classified as risk alleles for hypertrophic cardiomyopathy are in fact benign and, by chance, are found much more often in people of African ancestry. The studies reporting these variants as disease-associated apparently included a small number of patients of African ancestry without appropriate numbers of controls. Because the frequency of each allele is several-fold higher in African populations than in non-African populations, the initial positive associations were due to population stratification, not to disease risk. The failure to adequately control for population diversity, even for a few cases, resulted in benign variants being characterized as pathogenic on clinical genetics tests and, subsequently, in healthy persons of African ancestry being misinformed that they were at genetic risk for serious heart disease.

WHY MENTAL ILLNESS EXISTS AND PERSISTS

Just as human evolution is defined by adaptations to ecological diversity, mental illness often reflects disruptions, lags, or perturbations in the same adaptive capacities. Our strengths are our vulnerabilities. The cost of brain complexity is the vast number of mechanisms that can go wrong, contributing to disruptions in neurodevelopment and to the development of psychiatric conditions.

Humans share repertoires of emotional and behavioral responses to loss, adversity, frustration, and unmet demands. In an evolutionary context, emotional and behavioral regulation, distress tolerance, and strategic planning are necessary for creating and maintaining social networks; hunting and gathering food; negotiating conflict; mating; ensuring proximity to caretakers, offspring, and loved ones; avoiding danger and loss; and, in general, getting one's needs met. Social cooperation, language, and abstract thinking are built on foundational capacities including facial recognition, working memory, emotion/impulse control, selective attention, action planning, and theory of mind.[52] Disruption of these traits defines different classes of psychiatric disorders.

Biological complexity and clinical heterogeneity

The complexity of human brain function is reflected in both the heterogeneity and the comorbidity of psychiatric disease.[160] For example, deletion of chromosome 22q11.2 is among the strongest genetic risk factors for schizophrenia, yet patients with this deletion vary a great deal in phenotypic expression[161] (Figure 6). In addition to increasing the risk for several different neuropsychiatric disorders, the prevalence rates of these conditions vary across the lifespan.[162] Not surprisingly, prevalence rates of these conditions among patients with the deletion also vary by method of participant ascertainment: for example, clinical referrals versus population-based studies.[163] These complexities are not unique to the 22q11.2 deletion. Variable expressivity of phenotypes across the lifespan is likely to be revealed for most genes and structural variation underlying neuropsychiatric disease.

Among psychiatric syndromes defined as independent conditions, biological boundaries are often not clear. For example, some patients with seemingly distinct conditions such as major depressive disorder (MDD), panic disorder, social anxiety disorder, bulimia nervosa, and OCD all respond favorably to the same class of medication (serotonin reuptake inhibitors) and to the same modality of psychotherapy (cognitive behavioral therapy). Diagnostic and Statistical Manual (DSM) and International

Classification of Diseases (ICD) nosologies are not based on biological mechanisms but rather on symptom reports and observable behaviors, which to some degree are subjective and context dependent. Environmental and genetic risk and protective factors play a role in these presentations, as well as in responses to treatment, outcomes, and quality of life. Although certainly not resolving these complexities, an evolutionary perspective may offer useful insights.

The timing and dose of disruptions in brain development, of genetic and/or environmental origin, influence the nature of neuropsychiatric conditions. Clinical heterogeneity exacerbates the difficulty of characterizing the genetic architecture underlying any disorder.[164] The greater the impact on neurodevelopment, the more likely symptoms represent a marked departure from baseline functioning (or the failure to achieve independent function), regardless of context, setting, and culture. Not surprisingly, then, the evidence supporting the role of large-effect damaging *de novo* and rare mutations is strongest for conditions with earlier onset and greater impact on brain function, such as autism, intellectual disability, schizophrenia, and early-onset dementia, e.g, Ganna et al.,[12] O'Roak et al.,[30] Bird et al.,[142] Walsh et al.,[154] Reichenberg et al.,[165] and Antaki et al.[166]

The greater the breadth and variability of clinical presentations, the greater the challenge for gene discovery. For example, depression is highly heterogeneous, ranging in clinical settings from sadness and demoralization due to life circumstances to melancholia, catatonia, and suicide. Even more dramatically, the definition of bipolar disorder has expanded over the past few decades, ranging from classic manic-depressive illness (a severe episodic mood disorder with onset in young adulthood) to moodiness and irritability in children (with some researchers making the diagnosis in toddlers).[167] Similarly, the estimated prevalence of autism spectrum disorders has risen markedly over the past two decades, from one in 150 to one in 36 children by 8 years of age.[168] Very broad application of diagnostic criteria may enable greater access to care, greater advocacy for afflicted individuals and their families, and greater numbers of potential subjects for research projects. However, expanding the boundaries of psychiatric diagnoses exacerbates the already substantial heterogeneity of these conditions and frustrates the search for specific causal mechanisms.

The inherent variability in measurement and diagnosis further complicates gene discovery. MDD encapsulates many of these challenges. There are more than 945 possible symptom combinations that meet diagnostic criteria for MDD, and in the DSM-5 field trials, highly trained psychiatrists agreed on a diagnosis of MDD in only 4% to 15% of cases.[169] Two individuals can meet DSM-5 criteria for MDD without sharing a *single* symptom. These diagnostic challenges could substantially impact the genetic architecture of MDD. To this point, in order to recruit extremely large samples efficiently, GWASs often use minimal phenotyping strategies, defining case status based on a small number of self-reported items. These shortcuts have consequences: one comparative analysis found that SNP heritability estimates for MDD based on minimal phenotyping differed nearly 3-fold from heritability estimates for severe, recurrent MDD.[170] This reflects a bedeviling problem for psychiatry: the lack of any independent gold standard for diagnosis. Epidemiological surveys using different methods may find similar prevalence of illness in a population, but there is no assurance that the same individuals are identified as case or control by different methods.[171] Furthermore, when the same standardized questions are used for diagnosis across diverse populations, there is no assurance that the questions are understood in the same way across cultures and contexts.

Clinical presentations representing maladaptive or extreme reactions based on otherwise normal human responses (e.g., depression versus misery and grief, anxiety versus threat awareness/adherence to social norms, aggression versus self-preservation) suggest dynamic responses to environmental, social, and cultural risk factors and stressors rather than a broken gene or faulty brain network. This does not imply that genetics plays no role in the risk for, or protection from, suffering or worry or maladaptive behavior but rather that the interplay between genes and environment is so complex and individually unique that current diagnostic nosology may not be sufficient to identify underlying biological causes.

Changes in selective pressures

Changes in selective pressures over time may influence the prevalence of neuropsychiatric conditions. As an example, modern-day substance abuse may paradoxically be the consequence of prior adaptive success. The ability to tolerate and metabolize substances available in nature is an adaptive trait. More than a million years ago, hominids developed the capacity to metabolize alcohol as an adaptation to diets that included fermented fruit.[172] In much more recent human history, tolerance of alcohol may have conferred an advantage in times and places where water was contaminated.[173] Alcohol has enormous and complex impacts on social structure by lessening inhibitions, leading both to increased aggression and increased sexual activity. Depending on the individual, the social setting, and the culture, the same substance may promote reproductive success or social disruption or early death.[174] Genetics plays a role, in that individual variation in alcohol metabolism influences risk of alcohol dependence. For example, carriers of the alcohol dehydrogenase *ADH1B*2* allele (ADH1B Arg48His, with frequency >0.75 in East Asian populations and <0.05 among Europeans and Africans) have lower rates of alcohol consumption and dependence.[175] More generally, substance abuse highlights the complex interactions between genetic and environmental risks. Parental substance abuse confers both risk of *de novo* genetic damage via *in utero* exposure to toxins and the risk of child maltreatment and social chaos. Histories including both genetic and environmental risks are common among individuals with severe emotional and behavioral disturbances.

Other adaptive behaviors may also have been subject to changes in selective pressures. In hunter-gatherer societies, increased motor activity and aggressive responses to environmental cues (characteristics associated with ADHD) may have aided success in food gathering and avoiding predators, whereas in modern societies, these same traits often impair the ability to focus on complex tasks and can disrupt social interactions.[176] This said, it is important to distinguish between traits that are adaptive in some social and cultural contexts versus illnesses that are clearly disadvantageous in all contexts.[177] For

example, behaviors like checking, counting, cleaning, and hoarding are advantageous in detecting threats, preventing infection, finding and preserving food, and organizing possessions in confined spaces,[178] whereas OCD causes significant social dysfunction and impairment and is associated with lower fecundity,[96] with a continuing new supply of *de novo* mutations contributing to its persistence.[24]

Not every symptom, dysfunction, or tragedy is a disorder. DSM and ICD systems are useful for organizing clinical presentations, communicating observations, and quantifying practice. Yet consensus-derived clusters of symptom-based criteria, despite administrative and clinical utility, are generally not based in biology because causes of psychiatric illnesses remain for the most part unknown. Although well meaning, defining disorders has consequences. A shared name implies shared risk factors, causes, outcomes, and treatments. Although clinical and causal heterogeneity are widely acknowledged, there is nonetheless a tendency to focus on conditions with the same name as though they are homogeneous with shared underlying biology. This is not the case.

The deep end of the genome

Trying to discover genetic causes for highly variable dynamic human behaviors is diving into the deep end of the genome. An enormous amount of money and resources have been spent investigating psychiatric diagnostic categories that are widely acknowledged to have no biological validity. We suggest that the search for large-effect mechanisms, common or rare, genetic or environmental, should be prioritized for the most rigorously defined severe phenotypes. This does not mean foregoing diagnostic categories altogether but rather following the teachings of Kraepelin and Osler, narrowing the focus to more severe, homogeneous clinical presentations based on observable characteristic patterns of symptom presentation, course of illness, mental status changes, and treatment response rather than broadly applied consensus-based checklist criteria. For example, with schizophrenia, the power to detect rare damaging mutations was enhanced by focusing on patients with more severe, treatment-resistant forms of the illness.[179] Discovering the causes of illness for these exceptional patients will shed light on actionable biological mechanisms and guide the next generations of treatment development.

The success of precision medicine depends on the discovery of actionable mutations with clear impact on biological processes. Whole-exome and whole-genome sequencing approaches have identified thousands of rare pathogenic variants responsible for Mendelian and complex phenotypes and provided new insights into diagnostic, prognostic, intervention, and prevention strategies. In many ways, psychiatric disorders are more difficult to understand than other illnesses but can be approached with the same evolutionary perspective. With current sequencing technologies, the challenge is no longer to identify variants statistically associated with disease—the challenge is to determine which variants matter and why. The goal is to test causality for candidate genetic variants, including those in noncoding regions, and once established, to translate individual causal events into effective treatment strategies. Understanding how mutations causing neuropsychiatric disorders arose and why they persist are evolutionary questions that will aid in this translation.

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REFERENCES

1. Dobzhansky, T. (1973). Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. *35*, 125–129.
2. McClellan, J., and King, M.C. (2010). Genetic heterogeneity in human disease. Cell *141*, 210–217.
3. Coe, B.P., Girirajan, S., and Eichler, E.E. (2012). The genetic variability and commonality of neurodevelopmental disease. Am. J. Med. Genet. C Semin. Med. Genet. *160C*, 118–129.
4. Stefansson, H., Meyer-Lindenberg, A., Steinberg, S., Magnusdottir, B., Morgen, K., Arnarsdottir, S., Bjornsdottir, G., Walters, G.B., Jonsdottir, G.A., Doyle, O.M., et al. (2014). CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature *505*, 361–366.
5. Huang, Y.F. (2020). Unified inference of missense variant effects and gene constraints in the human genome. PLoS Genet. *16*, e1008922.
6. Turner, T.N., Coe, B.P., Dickel, D.E., Hoekzema, K., Nelson, B.J., Zody, M.C., Kronenberg, Z.N., Hormozdiari, F., Raja, A., Pennacchio, L.A., et al. (2017). Genomic patterns of de novo mutation in simplex autism. Cell *171*, 710–722.e12.
7. Webster, G., Puckelwartz, M.J., Pesce, L.L., Dellefave-Castillo, L.M., Vanoye, C.G., Potet, F., Page, P., Kearns, S.D., Pottinger, T., White, S., et al. (2021). Genomic autopsy of sudden deaths in young individuals. JAMA Cardiol. *6*, 1247–1256.
8. Guo, H., Wang, T., Wu, H., Long, M., Coe, B.P., Li, H., Xun, G., Ou, J., Chen, B., Duan, G., et al. (2018). Inherited and multiple de novo mutations in autism/developmental delay risk genes suggest a multifactorial model. Mol. Autism *9*, 64.
9. Wang, T., Zhao, P.A., and Eichler, E.E. (2022). Rare variants and the oligogenic architecture of autism. Trends Genet. *38*, 895–903.
10. Singh, T., Kurki, M.I., Curtis, D., Purcell, S.M., Crooks, L., McRae, J., Suvisaari, J., Chheda, H., Blackwood, D., Breen, G., et al. (2016). Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. Nat. Neurosci. *19*, 571–577.
11. Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M.A., Barchas, J.D., Bass, N., Bigdeli, T.B., Breen, G., Bromet, E.J., et al. (2022). Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature *604*, 509–516.
12. Ganna, A., Satterstrom, F.K., Zekavat, S.M., Das, I., Kurki, M.I., Churchhouse, C., Alfoldi, J., Martin, A.R., Havulinna, A.S., Byrnes, A., et al. (2018). Quantifying the impact of rare and ultra-rare coding variation across the phenotypic spectrum. Am. J. Hum. Genet. *102*, 1204–1211.
13. Genovese, G., Fromer, M., Stahl, E.A., Ruderfer, D.M., Chambert, K., Landén, M., Moran, J.L., Purcell, S.M., Sklar, P., Sullivan, P.F., et al. (2016). Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. Nat. Neurosci. *19*, 1433–1441.

14. Purcell, S.M., Moran, J.L., Fromer, M., Ruderfer, D., Solovieff, N., Roussos, P., O'Dushlaine, C., Chambert, K., Bergen, S.E., Kähler, A., et al. (2014). A polygenic burden of rare disruptive mutations in schizophrenia. Nature *506*, 185–190.

15. Zhou, X., Feliciano, P., Shu, C., Wang, T., Astrovskaya, I., Hall, J.B., Obiajulu, J.U., Wright, J.R., Murali, S.C., Xu, S.X., et al. (2022). Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes. Nat. Genet. *54*, 1305–1319.

16. Jónsson, H., Sulem, P., Kehr, B., Kristmundsdottir, S., Zink, F., Hjartarson, E., Hardarson, M.T., Hjorleifsson, K.E., Eggertsson, H.P., Gudjonsson, S.A., et al. (2017). Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature *549*, 519–522.

17. Kimura, M. (1968). Evolutionary rate at the molecular level. Nature *217*, 624–626.

18. Li, J.Z., Absher, D.M., Tang, H., Southwick, A.M., Casto, A.M., Ramachandran, S., Cann, H.M., Barsh, G.S., Feldman, M., Cavalli-Sforza, L.L., et al. (2008). Worldwide human relationships inferred from genome-wide patterns of variation. Science *319*, 1100–1104.

19. Tennessen, J.A., Bigham, A.W., O'Connor, T.D., Fu, W., Kenny, E.E., Gravel, S., McGee, S., Do, R., Liu, X., Jun, G., et al. (2012). Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science *337*, 64–69.

20. Lohmueller, K.E. (2014). The impact of population demography and selection on the genetic architecture of complex traits. PLoS Genet. *10*, e1004379.

21. Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., Yamrom, B., Yoon, S., Krasnitz, A., Kendall, J., et al. (2007). Strong association of de novo copy number mutations with autism. Science *316*, 445–449.

22. Gulsuner, S., Walsh, T., Watts, A.C., Lee, M.K., Thornton, A.M., Casadei, S., Rippey, C., and Shahin, H.; Consortium on the Genetics of Schizophrenia (COGS); PAARTNERS Study Group (2013). Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. Cell *154*, 518–529.

23. Fromer, M., Pocklington, A.J., Kavanagh, D.H., Williams, H.J., Dwyer, S., Gormley, P., Georgieva, L., Rees, E., Palta, P., Ruderfer, D.M., et al. (2014). De novo mutations in schizophrenia implicate synaptic networks. Nature *506*, 179–184.

24. Halvorsen, M., Samuels, J., Wang, Y., Greenberg, B.D., Fyer, A.J., McCracken, J.T., Geller, D.A., Knowles, J.A., Zoghbi, A.W., Pottinger, T.D., et al. (2021). Exome sequencing in obsessive–compulsive disorder reveals a burden of rare damaging coding variants. Nat. Neurosci. *24*, 1071–1076.

25. Willsey, A.J., Fernandez, T.V., Yu, D., King, R.A., Dietrich, A., Xing, J., Sanders, S.J., Mandell, J.D., Huang, A.Y., Richer, P., et al. (2017). De novo coding variants are strongly associated with Tourette disorder. Neuron *94*, 486–499.e9.

26. Goes, F.S., Pirooznia, M., Tehan, M., Zandi, P.P., McGrath, J., Wolyniec, P., Nestadt, G., and Pulver, A.E. (2021). De novo variation in bipolar disorder. Mol. Psychiatry *26*, 4127–4136.

27. Guo, H., Duyzend, M.H., Coe, B.P., Baker, C., Hoekzema, K., Gerdts, J., Turner, T.N., Zody, M.C., Beighley, J.S., Murali, S.C., et al. (2019). Genome sequencing identifies multiple deleterious variants in autism patients with more severe phenotypes. Genet. Med. *21*, 1611–1620.

28. Girirajan, S., Campbell, C.D., and Eichler, E.E. (2011). Human copy number variation and complex genetic disease. Annu. Rev. Genet. *45*, 203–226.

29. Itsara, A., Cooper, G.M., Baker, C., Girirajan, S., Li, J., Absher, D., Krauss, R.M., Myers, R.M., Ridker, P.M., Chasman, D.I., et al. (2009). Population analysis of large copy number variants and hotspots of human genetic disease. Am. J. Hum. Genet. *84*, 148–161.

30. O'Roak, B.J., Vives, L., Girirajan, S., Karakoc, E., Krumm, N., Coe, B.P., Levy, R., Ko, A., Lee, C., Smith, J.D., et al. (2012). Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature *485*, 246–250.

31. Brown, A.S., Schaefer, C.A., Wyatt, R.J., Begg, M.D., Goetz, R., Bresnahan, M.A., Harkavy-Friedman, J., Gorman, J.M., Malaspina, D., and Susser, E.S. (2002). Paternal age and risk of schizophrenia in adult offspring. Am. J. Psychiatry *159*, 1528–1533.

32. Power, R.A., Kyaga, S., Uher, R., MacCabe, J.H., Långström, N., Landén, M., McGuffin, P., Lewis, C.M., Lichtenstein, P., and Svensson, A.C. (2013). Fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse vs their unaffected siblings. JAMA Psychiatry *70*, 22–30.

33. Mullins, N., Ingason, A., Porter, H., Euesden, J., Gillett, A., Ólafsson, S., Gudbjartsson, D.F., Lewis, C.M., Sigurdsson, E., Saemundsen, E., et al. (2017). Reproductive fitness and genetic risk of psychiatric disorders in the general population. Nat. Commun. *8*, 15833.

34. Bodkin, J.A., Coleman, M.J., Godfrey, L.J., Carvalho, C.M.B., Morgan, C.J., Suckow, R.F., Anderson, T., Öngür, D., Kaufman, M.J., Lewandowski, K.E., et al. (2019). Targeted treatment of individuals with psychosis carrying a copy number variant containing a genomic triplication of the glycine decarboxylase gene. Biol. Psychiatry *86*, 523–535.

35. Levy-Lahad, E., and King, M.C. (2020). Hiding in plain sight — somatic mutation in human disease. N. Engl. J. Med. *383*, 2680–2682.

36. Bedrosian, T.A., Miller, K.E., Grischow, O.E., Schieffer, K.M., LaHaye, S., Yoon, H., Miller, A.R., Navarro, J., Westfall, J., Leraas, K., et al. (2022). Detection of brain somatic variation in epilepsy-associated developmental lesions. Epilepsia *63*, 1981–1997.

37. Khoshkhoo, S., Wang, Y., Chahine, Y., Erson-Omay, E.Z., Robert, S.M., Kiziltug, E., Damisah, E.C., Nelson-Williams, C., Zhu, G., Kong, W., et al. (2023). Contribution of somatic Ras/Raf/mitogen-activated protein kinase variants in the hippocampus in drug-resistant mesial temporal lobe epilepsy. JAMA Neurol. *80*, 578–587.

38. D'Gama, A.M., and Walsh, C.A. (2018). Somatic mosaicism and neurodevelopmental disease. Nat. Neurosci. *21*, 1504–1514.

39. Doyle, G.A., Crist, R.C., Karatas, E.T., Hammond, M.J., Ewing, A.D., Ferraro, T.N., Hahn, C.G., and Berrettini, W.H. (2017). Analysis of LINE-1 elements in DNA from postmortem brains of individuals with schizophrenia. Neuropsychopharmacology *42*, 2602–2611.

40. Downey, J., Lam, J.C.K., Li, V.O.K., and Gozes, I. (2022). Somatic mutations and Alzheimer's disease. J. Alzheimers Dis. *90*, 475–493.

41. Rodin, R.E., Dou, Y., Kwon, M., Sherman, M.A., D'Gama, A.M., Doan, R.N., Rento, L.M., Girskis, K.M., Bohrson, C.L., Kim, S.N., et al. (2021). The landscape of somatic mutation in cerebral cortex of autistic and neurotypical individuals revealed by ultra-deep whole-genome sequencing. Nat. Neurosci. *24*, 176–185.

42. Maury, E.A., Jones, A., Seplyarskiy, V., Rosenbluh, C., Bae, T., Wang, Y., Abyzov, A., Khoshkoo, S., Chahine, Y.; Brain Somatic Mosaicism Network, and Park, P.J. (2022). Enrichment of somatic mutations in schizophrenia brain targets prenatally active transcription factor bindings sites. Preprint at bioRxiv.

43. D'Gama, A.M., Pochareddy, S., Li, M., Jamuar, S.S., Reiff, R.E., Lam, A.-T.N., Sestan, N., and Walsh, C.A. (2015). Targeted DNA sequencing from autism spectrum disorder brains implicates multiple genetic mechanisms. Neuron *88*, 910–917.

44. Lim, E.T., Uddin, M., De Rubeis, S.D., Chan, Y., Kamumbu, A.S., Zhang, X., D'Gama, A.M., Kim, S.N., Hill, R.S., Goldberg, A.P., et al. (2017). Rates, distribution and implications of postzygotic mosaic mutations in autism spectrum disorder. Nat. Neurosci. *20*, 1217–1224.

45. Freed, D., and Pevsner, J. (2016). The contribution of mosaic variants to autism spectrum disorder. PLoS Genet. *12*, e1006245.

46. Maury, E.A., Sherman, M.A., Genovese, G., Gilgenast, T.G., Kamath, T., Burris, S.J., Rajarajan, P., Flaherty, E., Akbarian, S., Chess, A., et al. (2023). Schizophrenia-associated somatic copy-number variants from 12,834 cases reveal recurrent NRXN1 and ABCB11 disruptions. Cell Genom. *3*, 100356.

47. Orr, H.T., and Zoghbi, H.Y. (2007). Trinucleotide repeat disorders. Annu. Rev. Neurosci. *30*, 575–621.

48. Telenius, H., Kremer, B., Goldberg, Y.P., Theilmann, J., Andrew, S.E., Zeisler, J., Adam, S., Greenberg, C., Ives, E.J., and Clarke, L.A. (1994). Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. Nat. Genet. *6*, 409–414.

49. Ciosi, M., Cumming, S.A., Chatzi, A., Larson, E., Tottey, W., Lomeikaite, V., Hamilton, G., Wheeler, V.C., Pinto, R.M., Kwak, S., et al. (2021). Approaches to sequence the HTT CAG repeat expansion and quantify repeat length variation. J. Huntingtons. Dis. *10*, 53–74.

50. Fleagle, J.G. (2013). Primate Adaptation and Evolution, Third Edition (Elsevier).

51. Antón, S.C., Potts, R., and Aiello, L.C. (2014). Human evolution. Evolution of early Homo: an integrated biological perspective. Science *345*, 1236828.

52. Kaczanowska, J., Ganglberger, F., Chernomor, O., Kargl, D., Galik, B., Hess, A., Moodley, Y., von Haeseler, A., Bühler, K., and Haubensak, W. (2022). Molecular archaeology of human cognitive traits. Cell Rep. *40*, 111287.

53. Galakhova, A.A., Hunt, S., Wilbers, R., Heyer, D.B., de Kock, C.P.J., Mansvelder, H.D., and Goriounova, N.A. (2022). Evolution of cortical neurons supporting human cognition. Trends Cogn. Sci. *26*, 909–922.

54. Pavan, W.J., and Sturm, R.A. (2019). The genetics of human skin and hair pigmentation. Annu. Rev. Genom. Hum. Genet. *20*, 41–72.

55. Weatherall, D.J. (2013). The role of the inherited disorders of hemoglobin, the first "molecular diseases," in the future of human genetics. Annu. Rev. Genom. Hum. Genet. *14*, 1–24.

56. Friedman, D.J., and Pollak, M.R. (2020). APOL1 and kidney disease: from genetics to biology. Annu. Rev. Physiol. *82*, 323–342.

57. Krause, J., and Pääbo, S. (2016). Genetic time travel. Genetics *203*, 9–12.

58. King, M.C., and Wilson, A.C. (1975). Evolution at two levels in humans and chimpanzees. Science *188*, 107–116.

59. Stedman, H.H., Kozyak, B.W., Nelson, A., Thesier, D.M., Su, L.T., Low, D.W., Bridges, C.R., Shrager, J.B., Minugh-Purvis, N., and Mitchell, M.A. (2004). Myosin gene mutation correlates with anatomical changes in the human lineage. Nature *428*, 415–418.

60. Guerrier, S., Coutinho-Budd, J., Sassa, T., Gresset, A., Jordan, N.V., Chen, K., Jin, W.L., Frost, A., and Polleux, F. (2009). The F-BAR domain of srGAP2 induces membrane protrusions required for neuronal migration and morphogenesis. Cell *138*, 990–1004.

61. Dennis, M.Y., Nuttle, X., Sudmant, P.H., Antonacci, F., Graves, T.A., Nefedov, M., Rosenfeld, J.A., Sajjadian, S., Malig, M., Kotkiewicz, H., et al. (2012). Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. Cell *149*, 912–922.

62. Charrier, C., Joshi, K., Coutinho-Budd, J., Kim, J.E., Lambert, N., de Marchena, J., Jin, W.L., Vanderhaeghen, P., Ghosh, A., Sassa, T., et al. (2012). Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. Cell *149*, 923–935.

63. Florio, M., Albert, M., Taverna, E., Namba, T., Brandl, H., Lewitus, E., Haffner, C., Sykes, A., Wong, F.K., Peters, J., et al. (2015). Human-specific gene ARHGAP11B promotes basal progenitor amplification and neocortex expansion. Science *347*, 1465–1470.

64. Heide, M., Haffner, C., Murayama, A., Kurotaki, Y., Shinohara, H., Okano, H., Sasaki, E., and Huttner, W.B. (2020). Human-specific ARHGAP11B increases size and folding of primate neocortex in the fetal marmoset. Science *369*, 546–550.

65. Florio, M., Namba, T., Pääbo, S., Hiller, M., and Huttner, W.B. (2016). A single splice site mutation in human-specific ARHGAP11B causes basal progenitor amplification. Sci. Adv. *2*, e1601941.

66. Srinivasan, S., Bettella, F., Mattingsdal, M., Wang, Y., Witoelar, A., Schork, A.J., Thompson, W.K., Zuber, V.; Schizophrenia Working Group of the Psychiatric Genomics Consortium; The International Headache Genetics Consortium, and Winsvold, B.S., et al. (2016). Genetic markers of human evolution are enriched in schizophrenia. Biol. Psychiatry *80*, 284–292.

67. Mangan, R.J., Alsina, F.C., Mosti, F., Sotelo-Fonseca, J.E., Snellings, D.A., Au, E.H., Carvalho, J., Sathyan, L., Johnson, G.D., Reddy, T.E., et al. (2022). Adaptive sequence divergence forged new neurodevelopmental enhancers in humans. Cell *185*, 4587–4603.e23.

68. Pollard, K.S., Salama, S.R., Lambert, N., Lambot, M.A., Coppens, S., Pedersen, J.S., Katzman, S., King, B., Onodera, C., Siepel, A., et al. (2006). An RNA gene expressed during cortical development evolved rapidly in humans. Nature *443*, 167–172.

69. Xue, J.R., Mackay-Smith, A., Mouri, K., Garcia, M.F., Dong, M.X., Akers, J.F., Noble, M., Li, X.; Zoonomia Consortium†, and Lindblad-Toh, K., et al. (2023). The functional and evolutionary impacts of human-specific deletions in conserved elements. Science *380*, eabn2253.

70. Girskis, K.M., Stergachis, A.B., DeGennaro, E.M., Doan, R.N., Qian, X., Johnson, M.B., Wang, P.P., Sejourne, G.M., Nagy, M.A., Pollina, E.A., et al. (2021). Rewiring of human neurodevelopmental gene regulatory programs by human accelerated regions. Neuron *109*, 3239–3251.e7.

71. Doan, R.N., Bae, B.I., Cubelos, B., Chang, C., Hossain, A.A., Al-Saad, S., Mukaddes, N.M., Oner, O., Al-Saffar, M., Balkhy, S., et al. (2016). Mutations in human accelerated regions disrupt cognition and social behavior. Cell *167*, 341–354.e12.

72. Satterstrom, F.K., Kosmicki, J.A., Wang, J., Breen, M.S., De Rubeis, S.D., An, J.Y., Peng, M., Collins, R., Grove, J., Klei, L., et al. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell *180*, 568–584.e23.

73. Gardner, E.J., Neville, M.D.C., Samocha, K.E., Barclay, K., Kolk, M., Niemi, M.E.K., Kirov, G., Martin, H.C., and Hurles, M.E. (2022). Reduced reproductive success is associated with selective constraint on human genes. Nature *603*, 858–863.

74. Gur, R.E., Petty, R.G., Turetsky, B.I., and Gur, R.C. (1996). Schizophrenia throughout life: sex differences in severity and profile of symptoms. Schizophr. Res. *21*, 1–12.

75. Werling, D.M., and Geschwind, D.H. (2013). Sex differences in autism spectrum disorders. Curr. Opin. Neurol. *26*, 146–153.

76. Wigdor, E.M., Weiner, D.J., Grove, J., Fu, J.M., Thompson, W.K., Carey, C.E., Baya, N., van der Merwe, C., Walters, R.K., Satterstrom, F.K., et al. (2022). The female protective effect against autism spectrum disorder. Cell Genom. *2*, 100134.

77. Jacquemont, S., Coe, B.P., Hersch, M., Duyzend, M.H., Krumm, N., Bergmann, S., Beckmann, J.S., Rosenfeld, J.A., and Eichler, E.E. (2014). A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am. J. Hum. Genet. *94*, 415–425.

78. Sanders, S.J., Ercan-Sencicek, A.G., Hus, V., Luo, R., Murtha, M.T., Moreno-De-Luca, D., Chu, S.H., Moreau, M.P., Gupta, A.R., Thomson, S.A., et al. (2011). Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron *70*, 863–885.

79. Nielsen, R., Akey, J.M., Jakobsson, M., Pritchard, J.K., Tishkoff, S., and Willerslev, E. (2017). Tracing the peopling of the world through genomics. Nature *541*, 302–310.

80. McClellan, J.M., Lehner, T., and King, M.C. (2017). Gene discovery for complex traits: lessons from Africa. Cell *171*, 261–264.

81. Tishkoff, S.A., and Verrelli, B.C. (2003). Patterns of human genetic diversity: implications for human evolutionary history and disease. Annu. Rev. Genomics Hum. Genet. *4*, 293–340.

82. Gulsuner, S., Stein, D.J., Susser, E.S., Sibeko, G., Pretorius, A., Walsh, T., Majara, L., Mndini, M.M., Mqulwana, S.G., Ntola, O.A., et al. (2020). Genetics of schizophrenia in the South African Xhosa. Science *367*, 569–573.

83. Cohen, J.C., Kiss, R.S., Pertsemlidis, A., Marcel, Y.L., McPherson, R., and Hobbs, H.H. (2004). Multiple rare alleles contribute to low plasma levels of HDL cholesterol. Science *305*, 869–872.

84. Cohen, J.C., Boerwinkle, E., Mosley, T.H., and Hobbs, H.H. (2006). Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N. Engl. J. Med. *354*, 1264–1272.

85. Genovese, G., Friedman, D.J., Ross, M.D., Lecordier, L., Uzureau, P., Freedman, B.I., Bowden, D.W., Langefeld, C.D., Oleksyk, T.K., Uscinski Knob, A.L.U., et al. (2010). Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science *329*, 841–845.

86. Wright, S. (1955). Classification of the factors of evolution. Cold Spring Harb. Symp. Quant. Biol. *20*, 16–24D.

87. Coop, G., Pickrell, J.K., Novembre, J., Kudaravalli, S., Li, J., Absher, D., Myers, R.M., Cavalli-Sforza, L.L., Feldman, M.W., and Pritchard, J.K. (2009). The role of geography in human adaptation. PLoS Genet. *5*, e1000500.

88. Marshall, C.R., Howrigan, D.P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D.S., Antaki, D., Shetty, A., Holmans, P.A., Pinto, D., Gujral, M., et al. (2017). Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nature genetics *49*, 27–35.

89. Bittles, A.H., and Black, M.L. (2010). Evolution in health and medicine Sackler colloquium: consanguinity, human evolution, and complex diseases. Proc. Natl. Acad. Sci. USA *107*, 1779–1786.

90. Schmitz-Abe, K., Sanchez-Schmitz, G., Doan, R.N., Hill, R.S., Chahrour, M.H., Mehta, B.K., Servattalab, S., Ataman, B., Lam, A.-T.N., Morrow, E.M., et al. (2020). Homozygous deletions implicate non-coding epigenetic marks in autism spectrum disorder. Sci. Rep. *10*, 14045.

91. Peltonen, L., Palotie, A., and Lange, K. (2000). Use of population isolates for mapping complex traits. Nat. Rev. Genet. *1*, 182–190.

92. Stoll, G., Pietiläinen, O.P.H., Linder, B., Suvisaari, J., Brosi, C., Hennah, W., Leppä, V., Torniainen, M., Ripatti, S., Ala-Mello, S., et al. (2013). Deletion of TOP3β, a component of FMRP-containing mRNPs, contributes to neurodevelopmental disorders. Nat. Neurosci. *16*, 1228–1237.

93. Steinberg, S., Gudmundsdottir, S., Sveinbjornsson, G., Suvisaari, J., Paunio, T., Torniainen-Holm, M., Frigge, M.L., Jonsdottir, G.A., Huttenlocher, J., Arnarsdottir, S., et al. (2017). Truncating mutations in RBM12 are associated with psychosis. Nat. Genet. *49*, 1251–1254.

94. Lencz, T., Yu, J., Khan, R.R., Flaherty, E., Carmi, S., Lam, M., Ben-Avraham, D., Barzilai, N., Bressman, S., Darvasi, A., et al. (2021). Novel ultra-rare exonic variants identified in a founder population implicate cadherins in schizophrenia. Neuron *109*, 1465–1478.e4.

95. Robinson, M.R., Kleinman, A., Graff, M., Vinkhuyzen, A.A.E., Couper, D., Miller, M.B., Peyrot, W.J., Abdellaoui, A., Zietsch, B.P., Nolte, I.M., et al. (2017). Genetic evidence of assortative mating in humans. Nat. Hum. Behav. *1*, 16.

96. Mahjani, B., Klei, L., Mattheisen, M., Halvorsen, M.W., Reichenberg, A., Roeder, K., Pedersen, N.L., Boberg, J., de Schipper, E., Bulik, C.M., et al. (2022). The genetic architecture of obsessive-compulsive disorder: contribution of liability to OCD from alleles across the frequency spectrum. Am. J. Psychiatry *179*, 216–225.

97. Connolly, S., Anney, R., Gallagher, L., and Heron, E.A. (2019). Evidence of assortative mating in autism spectrum disorder. Biol. Psychiatry *86*, 286–293.

98. Nordsletten, A.E., Larsson, H., Crowley, J.J., Almqvist, C., Lichtenstein, P., and Mataix-Cols, D. (2016). Patterns of nonrandom mating within and across 11 major psychiatric disorders. JAMA Psychiatry *73*, 354–361.

99. Gottesman, I.I., Laursen, T.M., Bertelsen, A., and Mortensen, P.B. (2010). Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch. Gen. Psychiatry *67*, 252–257.

100. Bulik-Sullivan, B.K., Loh, P.R., Finucane, H.K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson, N., Daly, M.J., Price, A.L., and Neale, B.M. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat. Genet. *47*, 291–295.

101. Searle, S.R., Casella, G., and McCulloch, C.E. (1992). Variance Components (John Wiley & Sons).

102. Border, R., O'Rourke, S., de Candia, T., Goddard, M.E., Visscher, P.M., Yengo, L., Jones, M., and Keller, M.C. (2022). Assortative mating biases marker-based heritability estimators. Nat. Commun. *13*, 660.

103. Hartwig, F.P., Davies, N.M., and Davey Smith, G.D. (2018). Bias in Mendelian randomization due to assortative mating. Genet. Epidemiol. *42*, 608–620.

104. Kong, A., Thorleifsson, G., Frigge, M.L., Vilhjalmsson, B.J., Young, A.I., Thorgeirsson, T.E., Benonisdottir, S., Oddsson, A., Halldorsson, B.V., Masson, G., et al. (2018). The nature of nurture: effects of parental genotypes. Science *359*, 424–428.

105. Young, A.I., Frigge, M.L., Gudbjartsson, D.F., Thorleifsson, G., Bjornsdottir, G., Sulem, P., Masson, G., Thorsteinsdottir, U., Stefansson, K., and Kong, A. (2018). Relatedness disequilibrium regression estimates heritability without environmental bias. Nat. Genet. *50*, 1304–1310.

106. Lee, J.J., Wedow, R., Okbay, A., Kong, E., Maghzian, O., Zacher, M., Nguyen-Viet, T.A., Bowers, P., Sidorenko, J., Karlsson Linnér, R.K., et al. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat. Genet. *50*, 1112–1121.

107. Border, R., Athanasiadis, G., Buil, A., Schork, A.J., Cai, N., Young, A.I., Werge, T., Flint, J., Kendler, K.S., Sankararaman, S., et al. (2022). Cross-trait assortative mating is widespread and inflates genetic correlation estimates. Science *378*, 754–761.

108. Mendel, G. (1866). Versuche über Pflanzen-hybriden. Verhandlungen des naturforschenden Vereines in Brünn IV (Im Verlage des Vereines), pp. 3–47.

109. Galton, F. (1865). Hereditary talent and character. Macmillan's Magazine 1859–1907 *12*, 318–327.

110. Galton, F. (1889). Natural Inheritance (MacMillan).

111. Turelli, M. (2017). Commentary: Fisher's infinitesimal model: a story for the ages. Theor. Popul. Biol. *118*, 46–49.

112. Kevles, D.J. (1995). In the Name of Eugenics: Genetics and the Uses of Human Heredity (Harvard University Press).

113. Fisher, R.A. (1918). The correlation between relatives under the supposition of Mendelian inheritance. Transactions *52*, 399–433.

114. Falconer, D.S. (1965). The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann. Human Genet. *29*, 51–76.

115. Génin, E., and Clerget-Darpoux, F. (2015). Revisiting the polygenic additive liability model through the example of diabetes mellitus. Hum. Hered. *80*, 171–177.

116. Génin, E., and Clerget-Darpoux, F. (2015). The missing heritability paradigm: A dramatic resurgence of the GIGO syndrome in genetics. Hum. Hered. *79*, 1–4.

117. International HapMap Consortium, Frazer, K.A., Ballinger, D.G., Cox, D.R., Hinds, D.A., Stuve, L.L., Gibbs, R.A., Belmont, J.W., Boudreau, A., Hardenbol, P., et al. (2007). A second generation human haplotype map of over 3.1 million SNPs. Nature *449*, 851–861.

118. Hardy, J., and Singleton, A. (2009). Genomewide association studies and human disease. N. Engl. J. Med. *360*, 1759–1768.

119. Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Børglum, A.D., Breen, G., Cichon, S., Edenberg, H.J., Faraone, S.V., Gelernter, J., et al. (2018). Psychiatric genomics: an update and an agenda. Am. J. Psychiatry *175*, 15–27.

120. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature *511*, 421–427.

121. Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., Bryois, J., Chen, C.Y., Dennison, C.A., Hall, L.S., et al.

(2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature *604*, 502–508.

122. Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J.R.I., Gaspar, H.A., et al. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat. Genet. *51*, 793–803.

123. Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J.R.I., Hagenaars, S.P., Ward, J., Wigmore, E.M., et al. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. *22*, 343–352.

124. Grove, J., Ripke, S., Als, T.D., Mattheisen, M., Walters, R.K., Won, H., Pallesen, J., Agerbo, E., Andreassen, O.A., Anney, R., et al. (2019). Identification of common genetic risk variants for autism spectrum disorder. Nat. Genet. *51*, 431–444.

125. Demontis, D., Walters, R.K., Martin, J., Mattheisen, M., Als, T.D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Bækvad-Hansen, M., et al. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat. Genet. *51*, 63–75.

126. Purves, K.L., Coleman, J.R.I., Meier, S.M., Rayner, C., Davis, K.A.S., Cheesman, R., Bækvad-Hansen, M., Børglum, A.D., Wan Cho, S., Jürgen Deckert, J., et al. (2020). A major role for common genetic variation in anxiety disorders. Mol. Psychiatry *25*, 3292–3303.

127. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address:; Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell *179*, 1469–1482.e11. plee0@mgh.harvard.edu.

128. Brainstorm Consortium, Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P., et al. (2018). Analysis of shared heritability in common disorders of the brain. Science *360*.

129. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E., et al. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. *45*, 984–994.

130. Hatoum, A.S., Colbert, S.M.C., Johnson, E.C., Huggett, S.B., Deak, J.D., Pathak, G.A., Jennings, M.V., Paul, S.E., Karcher, N.R., Hansen, I., et al. (2023). Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. Nat. Ment. Health *1*, 210–223.

131. Manolio, T.A., Collins, F.S., Cox, N.J., Goldstein, D.B., Hindorff, L.A., Hunter, D.J., McCarthy, M.I., Ramos, E.M., Cardon, L.R., Chakravarti, A., et al. (2009). Finding the missing heritability of complex diseases. Nature *461*, 747–753.

132. Khera, A.V., Chaffin, M., Aragam, K.G., Haas, M.E., Roselli, C., Choi, S.H., Natarajan, P., Lander, E.S., Lubitz, S.A., Ellinor, P.T., et al. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat. Genet. *50*, 1219–1224.

133. Wray, N.R., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., Murray, G.K., and Visscher, P.M. (2021). From basic science to clinical application of polygenic risk scores: a primer. JAMA Psychiatry *78*, 101–109.

134. Abdellaoui, A., Hugh-Jones, D., Yengo, L., Kemper, K.E., Nivard, M.G., Veul, L., Holtz, Y., Zietsch, B.P., Frayling, T.M., Wray, N.R., et al. (2019). Genetic correlates of social stratification in Great Britain. Nat. Hum. Behav. *3*, 1332–1342.

135. Uffelmann, E., Posthuma, D., and Peyrot, W.J. (2023). Genome-wide association studies of polygenic risk score-derived phenotypes may lead to inflated false positive rates. Sci. Rep. *13*, 4219.

136. Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., and Daly, M.J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. *51*, 584–591.

137. Murray, G.K., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., and Wray, N.R. (2021). Could polygenic risk scores be useful in psychiatry?: a review. JAMA Psychiatry *78*, 210–219.

138. Ju, D., Hui, D., Hammond, D.A., Wonkam, A., and Tishkoff, S.A. (2022). Importance of including non-European populations in large human genetic studies to enhance precision medicine. Annu. Rev. Biomed. Data Sci. *5*, 321–339.

139. Kerminen, S., Martin, A.R., Koskela, J., Ruotsalainen, S.E., Havulinna, A.S., Surakka, I., Palotie, A., Perola, M., Salomaa, V., Daly, M.J., et al. (2019). Geographic variation and bias in the polygenic scores of complex diseases and traits in Finland. Am. J. Hum. Genet. *104*, 1169–1181.

140. Curtis, D. (2018). Polygenic risk score for schizophrenia is not strongly associated with the expression of specific genes or gene sets. Psychiatr. Genet. *28*, 59–65.

141. Tanzi, R.E. (2012). The genetics of Alzheimer disease. Cold Spring Harb. Perspect. Med. *2*, a006296.

142. Bird, T.D. (2008). Genetic aspects of Alzheimer disease. Genet. Med. *10*, 231–239.

143. Haines, J.L., Hauser, M.A., Schmidt, S., Scott, W.K., Olson, L.M., Gallins, P., Spencer, K.L., Kwan, S.Y., Noureddine, M., Gilbert, J.R., et al. (2005). Complement factor H variant increases the risk of age-related macular degeneration. Science *308*, 419–421.

144. Escott-Price, V., Pardiñas, A.F., Santiago, E., Walters, J., Kirov, G., Owen, M.J., and O'Donovan, M.C. (2019). The relationship between common variant schizophrenia liability and number of offspring in the UK Biobank. Am. J. Psychiatry *176*, 661–666.

145. van Dongen, J., and Boomsma, D.I. (2013). The evolutionary paradox and the missing heritability of schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet. *162B*, 122–136.

146. Pardiñas, A.F., Holmans, P., Pocklington, A.J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S.E., Bishop, S., Cameron, D., Hamshere, M.L., et al. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat. Genet. *50*, 381–389.

147. Boyle, E.A., Li, Y.I., and Pritchard, J.K. (2017). An expanded view of complex traits: from polygenic to omnigenic. Cell *169*, 1177–1186.

148. Backman, J.D., Li, A.H., Marcketta, A., Sun, D., Mbatchou, J., Kessler, M.D., Benner, C., Liu, D., Locke, A.E., Balasubramanian, S., et al. (2021). Exome sequencing and analysis of 454,787 UK Biobank participants. Nature *599*, 628–634.

149. Gallagher, M.D., and Chen-Plotkin, A.S. (2018). The post-GWAS Era: from association to function. Am. J. Hum. Genet. *102*, 717–730.

150. Kang, H.J., Kawasawa, Y.I., Cheng, F., Zhu, Y., Xu, X., Li, M., Sousa, A.M.M., Pletikos, M., Meyer, K.A., Sedmak, G., et al. (2011). Spatio-temporal transcriptome of the human brain. Nature *478*, 483–489.

151. Deng, C., Whalen, S., Steyert, M., Ziffra, R., Przytycki, P.F., Inoue, F., Pereira, D.A., Capauto, D., Norton, S., Vaccarino, F.M., et al. (2023). Massively parallel characterization of psychiatric disorder-associated and cell-type-specific regulatory elements in the developing human cortex. Preprint at bioRxiv.

152. GTEx Consortium; Laboratory, Data Analysis &Coordinating Center (LDACC)—Analysis Working Group; Statistical Methods groups—Analysis Working Group; Enhancing GTEx (eGTEx) groups; NIH Common Fund; NIH/NCI; NIH/NHGRI; NIH/NIMH; NIH/NIDA; Biospecimen Collection Source Site—NDRI (2017). Genetic effects on gene expression across human tissues. Nature *550*, 204–213.

153. Coe, B.P., Stessman, H.A.F., Sulovari, A., Geisheker, M.R., Bakken, T.E., Lake, A.M., Dougherty, J.D., Lein, E.S., Hormozdiari, F., Bernier, R.A., et al. (2019). Neurodevelopmental disease genes implicated by de novo mutation and copy number variation morbidity. Nat. Genet. *51*, 106–116.

154. Walsh, T., McClellan, J.M., McCarthy, S.E., Addington, A.M., Pierce, S.B., Cooper, G.M., Nord, A.S., Kusenda, M., Malhotra, D., Bhandari,

A., et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science *320*, 539–543.

155. Willsey, A.J., Sanders, S.J., Li, M., Dong, S., Tebbenkamp, A.T., Muhle, R.A., Reilly, S.K., Lin, L., Fertuzinhos, S., Miller, J.A., et al. (2013). Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell *155*, 997–1007.

156. Parikshak, N.N., Luo, R., Zhang, A., Won, H., Lowe, J.K., Chandran, V., Horvath, S., and Geschwind, D.H. (2013). Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell *155*, 1008–1021.

157. Yates, F. (1951). The influence of statistical methods for research workers on the development of the science of statistics. J. Am. Stat. Assoc. *46*, 19–34.

158. Wang, K., Zhang, H., Ma, D., Bucan, M., Glessner, J.T., Abrahams, B.S., Salyakina, D., Imielinski, M., Bradfield, J.P., Sleiman, P.M.A., et al. (2009). Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature *459*, 528–533.

159. Manrai, A.K., Funke, B.H., Rehm, H.L., Olesen, M.S., Maron, B.A., Szolovits, P., Margulies, D.M., Loscalzo, J., and Kohane, I.S. (2016). Genetic misdiagnoses and the potential for health disparities. N. Engl. J. Med. *375*, 655–665.

160. Sreeraj, V.S., Holla, B., Ithal, D., Nadella, R.K., Mahadevan, J., Balachander, S., Ali, F., Sheth, S., Narayanaswamy, J.C., Venkatasubramanian, G., et al. (2021). Psychiatric symptoms and syndromes transcending diagnostic boundaries in Indian multiplex families: the cohort of ADBS study. Psychiatry Res. *296*, 113647.

161. Fiksinski, A.M., Hoftman, G.D., Vorstman, J.A.S., and Bearden, C.E. (2023). A genetics-first approach to understanding autism and schizophrenia spectrum disorders: the 22q11.2 deletion syndrome. Mol. Psychiatry *28*, 341–353.

162. Schneider, M., Debbané, M., Bassett, A.S., Chow, E.W.C., Fung, W.L.A., van den Bree, M., Owen, M., Murphy, K.C., Niarchou, M., Kates, W.R., et al. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am. J. Psychiatry *171*, 627–639.

163. Hoeffding, L.K., Trabjerg, B.B., Olsen, L., Mazin, W., Sparsø, T., Vangkilde, A., Mortensen, P.B., Pedersen, C.B., and Werge, T. (2017). Risk of psychiatric disorders among individuals with the 22q11.2 deletion or duplication: A Danish Nationwide, Register-based study. JAMA Psychiatry *74*, 282–290.

164. Ganesh, S., Vemula, A., Bhattacharjee, S., Mathew, K., Ithal, D., Navin, K., Nadella, R.K., Viswanath, B., and Sullivan, P.F.; ADBS Consortium (2022). Whole exome sequencing in dense families suggests genetic pleiotropy amongst Mendelian and complex neuropsychiatric syndromes. Sci. Rep. *12*, 21128.

165. Reichenberg, A., Cederlöf, M., McMillan, A., Trzaskowski, M., Kapra, O., Fruchter, E., Ginat, K., Davidson, M., Weiser, M., Larsson, H., et al. (2016). Discontinuity in the genetic and environmental causes of the intellectual disability spectrum. Proc. Natl. Acad. Sci. USA *113*, 1098–1103.

166. Antaki, D., Guevara, J., Maihofer, A.X., Klein, M., Gujral, M., Grove, J., Carey, C.E., Hong, O., Arranz, M.J., Hervas, A., et al. (2022). A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex. Nat. Genet. *54*, 1284–1292.

167. McClellan, J., Kowatch, R., and Findling, R.L.; Work Group on Quality Issues (2007). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J. Am. Acad. Child Adolesc. Psychiatry *46*, 107–125.

168. Maenner, M.J., Warren, Z., Williams, A.R., Amoakohene, E., Bakian, A.V., Bilder, D.A., Durkin, M.S., Fitzgerald, R.T., Furnier, S.M., Hughes, M.M., et al. (2023). Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2020. MMWR Surveill. Summ. *72*, 1–14.

169. Regier, D.A., Narrow, W.E., Clarke, D.E., Kraemer, H.C., Kuramoto, S.J., Kuhl, E.A., and Kupfer, D.J. (2013). DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. Am. J. Psychiatry *170*, 59–70.

170. Cai, N., Revez, J.A., Adams, M.J., Andlauer, T.F.M., Breen, G., Byrne, E.M., Clarke, T.K., Forstner, A.J., Grabe, H.J., Hamilton, S.P., et al. (2020). Minimal phenotyping yields genome-wide association signals of low specificity for major depression. Nat. Genet. *52*, 437–447.

171. McClellan, J.M., and Werry, J.S. (2000). Introduction–research psychiatric diagnostic interviews for children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry *39*, 19–27.

172. Carrigan, M.A., Uryasev, O., Frye, C.B., Eckman, B.L., Myers, C.R., Hurley, T.D., and Benner, S.A. (2015). Hominids adapted to metabolize ethanol long before human-directed fermentation. Proc. Natl. Acad. Sci. USA *112*, 458–463.

173. Guthrie, J.S., and Ho-Yen, D.O. (2011). Alcohol and cholera. J. R. Soc. Med. *104*, 98.

174. Yu, C., and McClellan, J. (2016). Genetics of substance use disorders. Child Adolesc. Psychiatr. Clin. N. Am. *25*, 377–385.

175. Bierut, L.J., Goate, A.M., Breslau, N., Johnson, E.O., Bertelsen, S., Fox, L., Agrawal, A., Bucholz, K.K., Grucza, R., Hesselbrock, V., et al. (2012). ADH1B is associated with alcohol dependence and alcohol consumption in populations of European and African ancestry. Mol. Psychiatry *17*, 445–450.

176. Jensen, P.S., Mrazek, D., Knapp, P.K., Steinberg, L., Pfeffer, C., Schowalter, J., and Shapiro, T. (1997). Evolution and revolution in child psychiatry: ADHD as a disorder of adaptation. discussion 1679. J. Am. Acad. Child Adolesc. Psychiatry *36*, 1672–1679.

177. Stein, D.J., Hermesh, H., Eilam, D., Segalas, C., Zohar, J., Menchon, J., and Nesse, R.M. (2016). Human compulsivity: A perspective from evolutionary medicine. Eur. Neuropsychopharmacol. *26*, 869–876.

178. Polimeni, J., Reiss, J.P., and Sareen, J. (2005). Could obsessive–compulsive disorder have originated as a group-selected adaptive trait in traditional societies? Méd Hypotheses *65*, 655–664.

179. Zoghbi, A.W., Dhindsa, R.S., Goldberg, T.E., Mehralizade, A., Motelow, J.E., Wang, X., Alkelai, A., Harms, M.B., Lieberman, J.A., Markx, S., et al. (2021). High-impact rare genetic variants in severe schizophrenia. Proc. Natl. Acad. Sci. USA *118*, e2112560118.