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The Missing Heritability Puzzle of Schizophrenia: Hypothesis and Plausible Sources

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Abstract

Genetic research on schizophrenia, a common psychiatric disease with complex etiology and high (56-80%) heritability, has failed to identify causal genes, variants or causative mechanisms. Given the extensive effort and limited success to date, it is imperative to review potential reasons for this missing heritability. We argue that a successful elucidation of hereditary mechanisms in schizophrenia will likely involve attention to the role of neurodevelopment and cell differentiation and consideration of the genome structure, including temporal and spatial patterns. The identification of discrete endophenotypes, the,accommodation of environmental effects at the level of gene expression, including any sex differences and patterns of mutations, including de novo events, and the use of analytic techniques that go beyond genome-wide association studies. Identification of the heritable component of schizophrenia is needed to understand the cause of the disorder and to facilitate the development of effective corrective and possibly preventive measures.

Keywords: Missing heritability; Schizophrenia; Genome wide association studies (GWAS); Single nucleotide polymorphism (SNP).

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INTRODUCTION

Missing heritability

Over the last four decades, the search for causal genes for a large number of Mendelian disorders have been remarkably successful and has led to a better understanding of the biological causes of these disorders. This understanding has been instrumental in developing several preventive and corrective measures, some currently in practice with still others under development. It has launched a new era in diagnosis, treatment, and prediction of the prognosis based on genetic mutations and their functional consequences and has fueled

hopes that similar strategies will be effective in localizing genes and mutations underlying susceptibility to common and complex diseases. Advances in molecular technology have led to a shift away from DNA marker-based strategies towards genome wide association studies (GWAS). These assess the potential association of hundreds of thousands to millions of genetic markers with the disease phenotype in a single experiment. GWAS approaches are not hypothesis-based and used for testing different and unrelated genetic models. This approach is suitable where we have little understanding of the biological pathways involved. In contrast, candidate gene studies are entirely dependent on an accurate understanding of the underlying biological mechanisms, a factor that may account for the failure to replicate the results of the candidate gene studies. The underlying rationale for GWAS is the 'common disease, common variant' (CD-CV) hypothesis.[1] Early GWAS on complex phenotypes were inadequate in two ways. First, they used too few (thousands) genetic markers, and second, they studied a relatively small number (hundreds) of patients. Other limitations included imprecise phenotyping and control groups of questionable comparability. Today, GWAS have been aided by comprehensive 'Single-nucleotide polymorphism chips' with millions of markers that are able to capture most (if not all) common variation along the complete genome. They also use thousands of patients, and some have moved to international collaborative experiments. Finally, these are becoming financially less expensive.

However, over 400 GWAS studies[2] have been published to date for various complex common disorders viz., psychiatric diseases, both forms of diabetics, auto-immune diseases, and asthma, to name a few. The results of these studies have failed to offer a persuasive an explanation as anticipated and have not resulted in identifying a single gene for each of the disorders (with a few exceptions). Further, the most common variants identified, confer relatively small increments in risk (1.1-1.5). Another fallout of the studies is that the identification of causal variations to date cannot account for estimates of heritability. As an example, over 40 genes were identified for human height, which accounts for only 5% of the heritability estimate[3], while only five loci were identified for macular degeneration, which explains over 50% of the heritabilityestimate.[4] This begs the question: Where are the genes and genetic mutations that contribute to the high heritability estimates of most complex phenotypes and disorders? A review by Génin E. (2020)[5] has termed this phenomenon missing heritability. Manolio (2009)[6] argues that there are many contributors to missing heritability. They range from experimental efficiency to biological assumptions regarding the genetic and environmental architecture of the disorder. Several studies were plagued by low power. Genetic predisposition may involve a large number of variants with small effects and/or rare variants with larger effects. Given the complex inheritance pattern and the potential of gene-gene and gene-environment interactions were not included in several studies. Furthermore, some complex disorders, such as neuropsychiatric disorders, have no biological diagnostic tests, and are especially prone to diagnostic uncertainty and error. This is particularly problematic in situations where subjects are assessed by different diagnosticians, when samples are pooled in order to achieve sufficient numbers for analysis. Finally, most GWAS have been undertaken on European populations rather than using a representative sample of humans.

Each complex disorder poses a unique set of challenges in exposing heritability at the level of genetic or epigenetic variation. In this paper, we will focus specifically on the missing heritability in schizophrenia, a disease where attempts thus far have not led to expected success.

Schizophrenia: a complex disorder

Schizophrenia (SCZ) (MIM 1815000) is a severe neuropsychiatric disorder characterized by abnormalities in the perception, and experience of reality and social dysfunction. Individuals affected by SCZ present with auditory hallucinations, paranoid, or bizarre delusions, and disorganization. SCZ is a complex disorder with overlapping yet diverse symptoms. Diagnosis is based on the symptoms outlined in the diagnostic and statistical manual of mental disorders (DSM IV) rather than on any biological markers, and thus relies on the patient's self-reported experiences and observed behavior. Furthermore, there is uncertainty about whether the diagnosis represents a single disorder or a number of discrete syndromes with different causes. Studies suggest that genetics and early environmental and social processes are important factors contributing to causation.[7] Recreational and some prescription drugs can

cause or worsen symptoms.[8] Given its worldwide and lifetime prevalence of 1%,[9] it is a major health and societal burden. It is notable that monozygotic (MZ) twins, who apparently share 100% of their genetic makeup is concordant in only ~50% of cases.[10] Moreover, the degree of manifestation in terms of timing and severity may vary among individuals affected by this disease, even in the same family. The disease clusters in some families, and genetic relatedness to an affected individual is one of the greatest risk factors[11,12] assessed the heritability of SCZ from twin data. They found evidence for substantial additive genetic effects, with an 81%(95% confidence interval) and 73%(90% confidence interval) estimate of heritability in liability to SCZ. These results are similar to most other published results. Recently, Lichtenstein *et al*. (2009)[13] used familial relationships to assess the heritability of SCZ and bipolar disorder. They found that the heritability for SCZ and bipolar disorder was 64% and 59%, respectively. Shared environmental effects were modest (SCZ: 4.5%, 4.4%, 7.4%; bipolar disorder: 3.4%, 2.3%, 6.2%) for both disorders. The comorbidity between disorders was mainly (63%) due to additive genetic effects common to both disorders. It suggests that components of genetic variation, particularly additive genetic variation, may account for up to 80% of the phenotypic variability in the population, and some causal genes may have pleiotropic effects. The results are consistent with a view of SCZ as a complex trait that results from genetic and environmental etiological influences.

What is heritability?

The heritability of a trait is defined as the proportion of phenotypic variance in a population attributable to genetic factors (broad sense heritability, H) or additive genetic factors (narrow sense heritability, h^2). Estimating the heritability of a trait is useful for guiding genetic research. Further, it helps in defining "the genetic component of the trait" (G) also could be used to anticipate the theoretical limit of the polygenic risk score (PRS). This helps us to the ascertain completeness of the analytical model of a trait's genetic architecture. This ratio of variances is used to assess if genetic variations play a significant role in explaining the observed phenotypic variation of a trait or disease.[14] For most traits, heritability will vary across environments and populations and over time, depending on the manifestation and degree of genetic variation. In humans, it is typically estimated from the discordance between MZ and dizygotic twins (DZ) [broad sense heritability as (DZ-MZ)/DZ] or familial relatedness, [narrow-sense heritability as additive genetic variance (VA)/phenotypic variance (VP)]. Here, the estimate of narrow-sense heritability is based on presumed familial relatedness, which may not be realistic. For example, full sibs are expected to share on average half their genetic complement, but this proportion can vary; in one large study, the value ranged from 0.37 to 0.6212. The underlying assumptions permit over and under estimations of heritability, butmore often than not, such estimates are misinterpreted as transmissibility. In the future, it will be possible to refine these estimates using actual genetic relatedness based on the degree of genetic sharing from genomewide assessments.

What do we know about the genetics of SCZ?

Over 40 years of genetic research on SCZ ranging from early biochemical markers, protein polymorphism to DNA markers (Microsatellite to SNP, CNV), cytogenetics, linkage and association studies to the recent GWAS have established that the disease is multifactorial and genetically heterogeneous. A number of genes that predispose to the development of schizophrenia,[15] and most have relatively small effects.[16] This dilemma is exemplified by the results of a number of more recent and comprehensive studies that have concentrated on GWAS.[17] Recent studies of CNV indicate the involvement of a large number of rare or very rare variants of major effects.[18] There are two features of this dataset that deserve elaboration. First, these reports have, to date, identified over 30 risk markers. Second, many, but not all, markers have been identified in a single study. Collectively, these results appear to argue that SCZ is characterized by rare mutations at a large number of loci, and that no single gene or mutation is either necessary or sufficient for the development of this complex disease. Once again, consistent evidence for any single gene in a causal role for SCZ has not been unequivocally established. Such results are not compatible with the common disease common variant hypothesis. Further, some of the SCZ-associated variants argue fora pleiotropic effect, as some genetic variants are seen in a number of related psychiatric disorders.[19] SCZ research poses a few challenges: a. incomplete penetrance and variable expressivity;

b. clinical manifestations of "recessive alleles" (i.e., weak semi-dominance), c. allelic interactions (cis) or (trans), and their effects. Finally, considering the limitations of GWAS and the unfulfilled potential of these studies linger.

Multiple lines of inquiry highlight the role of immune mechanisms and infection susceptibility to the genetic architecture of severe mental illness. To this end, meta-analyses of the GWAS results of European descent[20,21] collectively show associations between SCZ and SNPs in or close to the major histocompatibility complex (MHC) on chromosome 6. The results have rekindled speculation that SCZ may be a response to infection, events early in life, such as perinatal infections, maternal malnutrition, and birth in the winter or spring, are also risk factors for SCZ. This highlights the role of G-X environment interactions during neurodevelopment. Several researchers have shown the role of retroviruses in psychiatric syndromes.[22-24] Another parallel observation is the delineation of a role for retroviruses or other infectious agents potentially interacting with the MHC locus. It is also noteworthy that, using GWAS, other diseases have shown 'hits' in the MHC, including neurological conditions (Alzheimer's disease),[25] and autoimmune disorders (Crohn's disease, both types of diabetes, and multiple sclerosis)[26] adding credence to the previous observations. Several such distinct observations offer a novel lead in the pathogenesis of this multifactorial-disease. Finally, still unknown and poorly understood genetic alterations during development, differentiation, and aging of brain can account for the noise.

Reviews by Kiran *et al*. (2013)[27] and Casey C. Fullard (2024)[28] summarize the SCZ genetics and various approaches employed.

Recent novel insights through twin studies in SCZ

Since the genomes of MZ twins are, at a minimum, almost identical, cases of discordance provide opportunities to identify factors that influence phenotypic differences. Most complex disorders display less than 100% concordance between MZ twins. SCZ is no different in that MZ twins show a concordance rate of ~50%, and DZ twins are concordant in only 16% of the cases.[29] The reduction in concordance from the genetic relatedness (100% for MZ and 50% for DZ twins) has often been explained by reduced penetrance and/or variable expressivity, which assumes that only a proportion of individuals with the causal genotype actually manifest any or even some of the SCZ symptoms. Not surprisingly, epigenetic mechanisms have been implicated in the discordance of MZ twins for SCZ,[30] and a number of reports have identified gene-specific DNA methylation differences between MZ twins discordant for the disease.[31,32] Epigenetic differences (loss or gain of CpG dinucleotide methylation) in promoter region methylation have been observed between MZ twins discordant for SCZ.[33] Recently, the significance of somatic mutations that create genetic diversity among developing neurons has been proposed to explain the discordance of MZ twins for a variety of behavior disorders, including SCZ.[34,35]

Recent studies have begun to challenge some of the genetic assumptions regarding MZ twins. For example, evidence is accumulating that MZ twins are not only different in epigenetic features but may also be different genetically. Using genomic DNA hybridization, Singh et al,[36] identified an 11-kb deletion in the cluster of cadherin genes (5p14-CDH 12 and CDH 18) in an affected member of a discordant MZ twin pair. The genomic region in the affected twin belongs to the type II cadherin gene family, which is involved in neuronal cell adhesion.[37] Further, Bruder *et al*. (2008)[38] reported that all of the 19 pairs of MZ twins he assessed were different for structural variations commonly referred to as copy number variation (CNV). Pathogenic and disease-prone CNVs alter gene dosage and their phenotypic expression, which often leads to human neuropsychiatric disorders.[39] Implicating structural *de novo* changes operating somatically may account for the discordance of MZ twins with SCZ. SCZ appears to be a neurodevelopmental disorder; however, neurodevelopment is poorly understood. It includes neuron formation, migration, synaptogenesis, pruning, apoptosis, and activity related changes.[40] These processes determine anatomical structures and establish neural connectivity and communication that maintain cognitive processes (attention, memory, language, and emotions). Various neurodevelopmental events may cause genetic mosaics.[41] It is often assumed that the neurodevelopmental process follows the developmental programs common to other organs and tissues. The prominent feature of these processes is that mitosis follows differentiation (due to differential gene expression), where all daughter cells are expected to be genetically identical. As discussed above, this may not always be the case. In fact, mitosis during

neuronal differentiation may yield genetically discordant daughter cells. This could be due to variable and individual-specific mosaicism caused by mitotic aneuploidy, CNV, and DNA methylation, or L1 transposition, among other mechanisms. Many of these mechanisms may be sensitive to environmental factors. For example, Westra[42] and Siyuan Liu[43] showed that aneuploid cells from mitotic nondisjunction are present in the proliferating cerebellum. In fact, they may account for 20% of the cells in different brain regions. Such mechanisms may cause MZ twins to be discordant for behavioral abnormalities, including SCZ. Supporting this observation Marie E Jönsson[44] demonstrated that neural progenitor cells undergo LINE1 (L1) retrotransposition in the hippocampus and several other regions of the brain, contributing to individual somatic mosaicism. The results suggest that *de novo* L1 retrotransposition events in the human brain may be programmed and not just an accidental occurrence. Finally, still unknown and poorly understood genetic alterations during development, differentiation, and aging of brain can add noise to the genetic investigation.

Explaining the missing heritability of SCZ

Genetic relatedness is the most important risk factor for SCZ, and the heritability estimates for the disease have consistently been high (56-81%).[45] However, an extensive search for causal genes, mutations, and mechanisms using traditional methods has been hampered by poorly understood genetic architecture, including epigenetics and the environment. As discussed above, the missing heritability for SCZ could be attributed to heterogeneous sources, and traditional methods (which have been successful in the search for causal genes in Mendelian disorders) have not been effective in identifying it. Could it be that some of the critical assumptions in these experiments have not been fulfilled? The answer to this question must be yes, as the inconclusive and hard to replicate results attest. Could it be that the estimate of heritability is unreliable and represents an over estimation? For a variety of reasons, the answer to this question is probably yes. Further, fundamental gaps in the molecular interpretations of estimates of quantitative genetics and the underlying heterogeneity in SCZ exists.

For example, all genetic relatedness (sibs, MZ twins, etc.) used in the calculation of heritability is presumed and not determined experimentally. Could it be that the diagnosis of SCZ has been problematic? The answer again is yes. It is based on a heterogeneous set of symptoms rather than a precise test for an entity called SCZ. Furthermore, not all individuals included in all DNA studies have been assessed by the same criteria or confirmed by following them over time. This may overestimate heritability, and the results generated from such samples will be difficult to replicate. An overestimation of heritability for SCZ will also result from the assumed genetic relatedness of individuals, including the genetic identity of MZ twins. The diagnostic heterogeneity and assumptions about the degree of genetic relatedness may also confound the biological hypothesis to be tested. In this case, the additive model involving multiple genes, each with the relatively small effect that forms the foundation for the CD-CV hypothesis, will require larger and more genetically heterogeneous samples to test in the future. Quantifying linkage disequilibrium variation between populations will be particularly relevant when amalgamating findings from multiple GWAS.[46]

A large number of alleles with weak individual associations with SCZ point to a polygenic model. These alleles are not shared with any non-psychiatric disorders but overlap with other psychiatric conditions[47] and contribute to at least ~3% of the heritability of SCZ. A finding of considerable interest is the increased mutational burden in SCZ as conferred by rare CNV.[48,49] Studies have also revealed up to an eightfold increase in the rate of *de novo* CNV in sporadic cases compared with familial cases and control subjects. This suggests that there may be distinct differences in the genetic determinations of sporadic versus familial cases of SCZ, which goes beyond the common disease common variant model, the dictum that has inspired many SNP association studies in SCZ. Such variants may be fully penetrant or involve allelic heterogeneity. It is thought that these rare alleles could be recurrent in the population (either inherited or sporadic), but would remain at low frequency due to the selective disadvantage they confer.

Re-appraisal of the common disease common variant (CD-CV) model

The common disease, common variant (CD-CV) model proposes that common alleles with small to moderate disease risks may have an additive or multiplicative effect on SCZ; this universally accepted dictum has inspired

many SNP association studies investigating common polymorphisms in SCZ.[50] The picture emerging from various whole genome sequencing studies is that, an abundance of rare and private variants are the major sources of variation. However, the CD-CV model alone has not been able to explain the genetic architecture of SCZ. Another proposed theory that has received increasing attention in the past decade is the CD-RV (common disease rare variant) model, which suggests heterogeneity of complex disorders. SCZ develops from multiple rare variants;[51,52] recent large scale association studies have successfully identified numerous risk variants.[53] Recent CNV studies corroborate that rare risk loci, individually or collectively, could predispose SCZ to supporting the CD-RV model. One implication of this realization is that recent mutations may have a greater influence on disease as a result of access to nutrition and not those conferred by variations that arose in distant ancestors. Apart from locus heterogeneity, CNV studies showed that even within the same disease associated genomic locus, there could be allelic heterogeneity. Some of these rare alleles could be recurrent in the population (either inherited or sporadic), but would remain at low frequency due to the selective disadvantage they confer, while others may be private events found only in singleton individuals or individual families.

Population genetics as a confounding factor in heritability estimates

A unified genetic model for human disease is that all human disease categories, including Mendelian disease, genomic disorders, and complex traits, and even chromosomal syndromes represent a spectrum of phenotypic manifestations. Reflecting the totality of pathogenic variants, ancestral alleles, and unique combinations inherited from parents, and *de novo* variants.[54] Hence, reproducing any novel discoveries from these genome wide scans in independent studies is now a prerequisite for the putative findings to be accepted. So, the current trend in genome wide surveys of common diseases and complex traits fundamentally aim to detect indirect associations where the single nucleotide polymorphisms (SNPs) carrying the association signals are not biologically active but are in linkage disequilibrium (LD) with some unknown functional polymorphisms. Genome wide analyses of LD variations between populations that allow the identification of candidate regions with a different pattern of LD are the new way to identify a disease association in a disparate population.

Meta-analyses of genome scans for the same diseases across different cohorts, in particular across different ethnic populations, will be greatly enhanced by first understanding the extent of LD differences in candidate regions between these cohorts, since true association signals can be weakened in the presence of significant variations in regional LD when the underlying causal variants exist on different haplotypic backgrounds.[55] The problem of the portability of associations in replicative studies or meta-analyses of the patterns of LD between populations is a confounding problem.

Other probable sources of missing heritability

a. Genetic interactions as a contributing factor

Quantitative geneticists have long known that genetic interactions can affect heritability calculations. Biological processes often depend on the rate limiting value among multiple inputs, such as the levels of components of a molecular complex required in stoichiometric ratios. Geneticists have harnessed the genetic interactions model and have identified several loci with additive effects in several human diseases, viz., Hirschsprung's disease, ankylosing spondylitis, type I diabetes, and SCZ.[56] The potential magnitude of missing heritability is well illustrated in Crohn's disease, for which GWAS has so far identified 71 risk associated loci.[57] Under the additive genetic architecture, these loci explain only 21.5% of the estimated heritability. In SCZ, several studies repeatedly highlight such interactions with drug response,[58] clinical variables,[59] and other forms of psychiatric syndromes (BPAD).[60] Collectively, all of these shed light on the additive effects of genes and polymorphisms on phenotypes which cannot be ignored, adding to the missing heritability pool.

b. Epigenetics

Epigenetics refers to modifications to DNA, histones, and nucleosomes that are reversible affected by the environment, and may persist over generations.[61] The determinants of phenomenon are hypothesized to include environmental factors and still unknown epigenetic mechanisms. Consistent components of complex traits, such as those linked to human stature or height, fertility, food metabolism, and hereditary defects have been shown to respond to environmental or nutritional

conditions and to be epigenetically inherited.[62] Further, altered balance of epigenetic networks has been reported to cause major pathologies in complex phenotype syndromes, viz., cancer[63] and SCZ.[64] Another a unique feature of epigenetics is its transgenerational inheritance, either in male or female gametes.[65] Similarly, some heritable genetic variants can lead to stochastic variation in epigenetic status (DNA methylation),[66] which may contribute to the low heritability of some phenotypes. Thus, epigenetic programs contribute to the "missing heritability" in studies of complex traits.

c. Other forms of variation could account for missing heritability

Human genome variation could involve large translocations, Indels, repeated DNA (CAG/CTG, VNTR, microsatellite), CNVs, and SNP. A classification based on the density of each of these polymorphisms. In the last few years' research has focused on single nucleotide polymorphisms (SNPs) and recently copy number variation (CNV) in the search for the underlying genetic etiology of complex disorders, enabling the interrogation of hundreds of thousands of SNPs and CNVs in one assay. Further, synonymus SNPs cannot fully explain the disease phenotype. However, SNPs are not the only form of genetic variation. Other forms of variation, such as variable number tandem repeats (VNTR) polymorphisms, and insertion/deletion (indels), have been consistently shown to be associated with complex disorders including SCZ and ignored as 'junk' DNA, viz., 1. VNTR lies within the third exon of the dopamine receptor D4 (*DRD4*) gene. 2. VNTR polymorphisms within the serotonin transporter (*5HTT*) gene and the monoamine oxidase A (*MAOA*) gene.[67] In summary, the investigation involving VNTR and other forms of repetitive DNA still holds substantial potential for a role in complex disorders via possible functional properties. These variations could perhaps account for the missing heritability. Recently, somatic mutations are increasingly being recognized as a major source of variation in many neuropsychiatric diseases. It is also likely that this type of genetic variation can lead to stochastic variation in epigenetic status, which in turn causes increased variability for a phenotype.[68] The differential mosaicism in developing brains[69] adds yet another source of genetic individuality.

d. Gender differences as contributors to missing heritability

Hypothesized[70] that sexual selection plays an important role in natural selection, highlighting the role of sex in evolutionary genetics. Several lines of evidence obtained from non-human model organisms, such as fruit flies, corroborate this observation. While males and females may share the same genes, their gene expression patterns[71] and interaction networks can differ significantly due to sex-limited expression, genomic imprinting and sex chromosomes.

The Sexual Selection – Sex Hormone Theory, provides an evolutionary framework for understanding how the differences in sex biased diseases and mental disorders have evolved over time.[72] There is now ample evidence of gender differences in basic neural processes and behaviors. Behaviors in mammals can be considered sexually dimorphic. It is proposed to be the end result of reciprocal influences between genes and the activational effects of neuroactive hormones and steroid receptors on the brain, as well as learning, social, and other environmental influences. Gender differences in central 5-HT neurotransmission appear to depend partly on sex related variation mechanisms.[73] Sex differences could result from linkage to sex chromosomes, genetic interaction, or differences arising from sex specific hormonal environments. Recently, several gender specific *de novo* variations have been implicated in SCZ, adding to the complexity burden.[74]

e. 1 Parent-of-origin effect

Although there are many associations between sequence variants and human traits have been discovered through genome-wide associations, the impact of parental origin has largely been ignored in complex disorders. The effects of susceptibility variants may depend on which parent they are inherited from. The allele that confers risk when paternally inherited is protective when maternally transmitted. The most obvious scheme is imprinting, in which the effect is limited to the allele inherited from a parent of a specific sex.[75] Most reports of genome wide association studies have treated the paternal and maternal alleles as exchangeable because the information required is often unavailable. As a result, it reduces the power of such studies to discover some susceptibility variants and underestimates the effects of others, contributing to unexplained heritability. Even when association can be established, the true effect is underestimated in SCZ.

Although many mechanisms can lead to parental origin-specific association with a

phenotype, sequence variants located close to imprinted genes are more likely to exhibit such behavior *a priori*.[76], in Icelanders the authors identified with detailed genealogical information along with phasing of haplotypes, identified a set of SNPs whose effect on the phenotype was dependent on whether they were inherited from the mother or the father. Thus, the ability to determine the parental origin of alleles in large samples opens new avenues to study associations between sequence variants and human traits.

f. Genetic drift

Genetic drift is a fortuitous occurrence due to bottleneck and/or founder effects that may result in the fixation of rare, harmful alleles modifying the genome of populations.[80] Further, the Hardy-Weinberg principle states that within sufficiently large populations, the allele frequencies remain constant over generations unless the equilibrium is disturbed by migration, genetic drift, mutations, gene flow, or selection. The effect of genetic drift is more notable when few copies of an allele exists, and the effect is less notable when many copies exist. Psychiatric diseases are highly disabling and appearing to decrease Darwinian fitness (Risk alleles for psychiatric disorders persist in the population) and fecundity. The variables of isolated populations, endogamy, assortative mating, and population history/bottlenecks have individual and additive roles in shaping the allelic spectrum in a given population. The evolutionary genetics model of mutation selection drift and balancing selection offers a testable framework for this dilemma.[81] Ashraf *et al*. (2014)[82] demonstrate that genetic drift can strongly affect the joint distribution of effect size and SNP frequency.

A study of South Asian Indians (with different population bottlenecks and admixture) that investigated the role of balancing selection using exome data from family members and archaic humans found an excess of SNPs in a gene set associated with the immune system, implicating evidence of selection in these families.[83] Hence, considering the evolutionary history of psychiatric disorders is important for generating new, testable hypotheses and understanding how best to design studies and analyze data. Thus, drift is a potential variable in the missing heritability jukebox.

2. Modifier genes or intermediate phenotypes

In complex disorders, many variants are expected to influence several intermediate traits termed modifiers.[77] Several such examples include the age-onset (AAO) $LRRK^{G2019S}$ mutation in Parkinson's disease.[78] Some individuals that carry disease alleles are nevertheless healthy despite affected family members in the same environment (example: DTNBPN1 haplotypes in SCZ).[79] Often referred to as endophenotypes, they promise in facilitating gene discovery for disease risk, with potential to index genetic liability, and contribute to our understanding of gene function and trans diagnostic etiology. Thus, identifying disease-associated modifier genes, genetic variants, and the background mode of action is essential to advance our understanding of complex traits and could shed light on heritability.

Caveats in definitions of heritability

Understanding heritability has become particularly important following recent scientific advancements in genetic science. Although widely used, the concept of heritability is still commonly misunderstood. It involves certain assumptions and nuances that are easy to miss or misinterpret. First, this definition does not naturally apply to binary traits (e.g., schizophrenia); it is typically assumed that there exists a continuous liability score underlying its manifestation (i.e., the trait manifests when the liability score is above a certain threshold).[84] Another important nuance is that heritability is (by definition) context specific and not a fundamental property of nature; it is defined for a specific population at a specific time and place.[85] As seen in the case of human height, income inequality, and socioeconomic status at birth vs. immutable genetic factors. Hence, it is expected that heritability is more of the variance and will be the result of access to nutrition and is not contingent on genetic differences.

CONCLUSION

In conclusion, the missing heritability in SCZ appears to be accounted for by a number of factors, not all of which have been addressed in the review. These include an imprecise diagnosis of the disease and/or its specific endophenotypes, a limited understanding of neurodevelopment, including the factors that may affect it, imprecision in the determination of genetic relatedness, the inclusion of patients, and controls representing diverse groups of humans, and a lack of consideration of the parental origin of genetic markers. Thus, such stochastic events during brain development, explain at least some of the missing heritability in SCZ.

Hence, in the era of complete individual

genomes future genetic models must take into consideration the impact of relatively small and variable effects of rare and singleton alleles and other forms of variation, viz., VNTR. Also, incorporating epigenetics and the parent of origin, models of population genetics, and evolutionary perspectives will add value to the gene-hunting exercise.

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