Genetics of Unipolar Major Depressive Disorder

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ABSTRACT

Major depressive disorder (MDD) is a heterogeneous, highly prevalent, and moderately heritable disorder. A complex and diverse genetic-environmental interplay converges to set apart a significant minority that is susceptible to MDD, from among those who experience shorter lived and less recurrent intensive and incapacitating forms of sadness. The major technological advances of deciphering the human genome reference sequence and its common gene variations are beginning to allow cost effective genetic studies of unprecedented scale, applying increasingly denser genome wide mapping to increasingly larger case control samples. This effort is now at the initial stages of unraveling the genetic architecture of several complex phenotypes. Despite a tardy beginning, MDD genetic research is maturing from modest scale candidate gene association studies to include family-based linkage studies, and will soon allow genome wide case control association studies. Replicated risk conferring gene variants discovered so far exert a modest effect size that appears to contribute to overt phenotype expression in the context of a highly intricate concert of interrelated epigenetic and epistatic modifiers. The unraveling of additional previously unimplicated MDD risk conferring genes, that will throw light on molecular mechanisms mediating such susceptibilities, is necessary for progressing beyond current generation monoamine modulating antidepressant drugs. The review outlines basic concepts and current progress briefly overviews major replicated gene findings that to date mostly stem from hypotheses driven candidates, and ends with a discussion of current directives, including sample size and phenotype considerations and advancement of systematic studies of the functional significance of implicated gene variants, beyond their current exploratory stage.

INTRODUCTION

Basic understanding of MDD pathophysiology is limited, and has been driven in large part by extrapolating from putative mechanisms of drugs found to possess antidepressant efficacy. Genetics circumvents the need to access the relevant molecular pathophysiology, by associating sequence variation with phenotype, thus offering an important window for discovering previously unimplicated mechanisms. The completion of the genome reference sequence and increasing availability of genome scale molecular tools is beginning to transform all areas of medicine. Our understanding of complex psychiatric phenotypes such as MDD has much to gain from this genomic revolution, as the majority of common psychiatric disorders as we currently define them, based on clinical presentation and subjective symptom resemblance, show considerable heritability.

HERITABILITY

Family twin and adoption studies are used to estimate the extent of heritable contribution for a phenotype of interest. MDD aggregates in families as demonstrated by a 2.84 increased risk for a broad MDD phenotype among first degree relatives of affected probands (1). Whereas mere familial clustering of cases does not distinguish between a shared environmental vs. a shared

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genetic cause, a heritable effect is demonstrated when concordance for sharing the phenotype among relatives increases as a function of increased sharing of genetic sequence (e.g., as occurs among relatives with decreasing familial distance, or when comparing monozygotic twins that share the same DNA sequence, with dizygotic twins that share half of their sequence on average, as would any sibling pair). Heritability estimates for MDD based on monozygotic vs. dizygotic twin concordance differences exhibit a modest heritable contribution of 37% (1) with a greater estimated contribution of 42% for women vs. 29% for men (2). Limited adoption studies point to an important genetic impact of parental depression (3), but also a significant environmental impact of maternal depression in mediating depression among adopted adolescents (4). Although the heritable contribution for broadly defined MDD is about half of that found for bipolar disorder or schizophrenia, its prevalence is several fold higher, and its permissive phenotype definition may be more prone to the inclusion of multiple etiologies, if these share a sufficient number of similar diagnostic criteria. Such heterogeneity may be one reason behind the low rates of response to generic antidepressants that target monoaminergic neurons (5). Increased severity, high recurrence rate and early onset phenotype characteristics exhibit increased heritability (as gauged by the observation that such characteristics among index probands predict higher rates of depression among their relatives) (6). When applying such model fitting and accounting for measurement error, heritability estimates for a restrictive MDD phenotype can be shown to increase to over 70% (reviewed in 7). Chronic illness course has also been shown to be associated with increased familial aggregation among recurrent, early-onset MDD pedigrees (8). Restrictive phenotype aspects have been applied to guide ascertainment considerations in several linkage based genome scan studies described below. Another important facet of diagnostic specificity relates to disorders that share some phenotypic aspects with MDD, such as bipolar disorder, anxiety disorders or internalizing personality traits. It is clear that some cases observed to satisfy diagnostic criteria for unipolar depression may have differing etiologies (e.g., bipolar disorder is one example). Misdiagnoses potentially carry important treatment implications (e.g., bipolar depression is better treated with mood stabilizers), and there is an ongoing debate as to their prevalence (9). There is evidence for familial aggregation and some shared heritability for MDD with both BPD (10) and anxiety disorders (11). Neuroticism, to name a different diagnostic construct, reflects in large part genetic liability for MDD (12). As these partially overlapping phenotype distinctions are likely polygenic in etiology (13, 14), we might expect that a single small effect gene could contribute in a modular way to more than one categorical phenotype, depending on individual constellations of interactive epistatic and epigenetic modifiers. Such a possibility is supported both by evidence for some shared inheritance between these phenotypes, as well as some overlap in clinical presentation (e.g., some shared symptoms, medication response, etc.). Indeed, as detailed below, some gene polymorphisms, such as the serotonin transporter promoter polymorphism and neurotrophic tyrosine kinase receptor 3 (NTRK3) gene variations, have been shown to predispose to more than one categorical phenotype. Currently employed categorical phenotype definitions are formulated using threshold-based descriptive symptom clustering that mostly relies on subjective self report and lack valid biomarkers, resulting in permissive boundaries that constrain our ability to ascertain cases sharing homogeneous biological underpinnings. From a geneticist's point of view, this compromises our odds for locating common causative gene variations. Issues of phenotype definition for genetic studies are further discussed in more detail below.

GENES

STRATEGIES FOR LOCATING INVOLVED GENES

Once a heritable contribution has been established, we may turn to locate the actual genes or, more precisely, genomic template nucleotide sequence variations that transmit such heritable risk. Historically, efforts for locating disease risk conferring genes have either focused on hypothesis driven candidates or employed an unbiased exploration using linked polymorphic markers that span the whole genome in search of previously unimplicated loci. Allele and genotype frequencies of nucleotide sequence variations within a candidate gene, that is thought to possess a priori relevance to MDD pathogenesis, may be compared between cases vs. ethnically matched healthy unrelated controls in search of association (or by using parental DNA in search of deviation from expected even transmission rates to affected offspring). Genome wide linkage is based on genome scale systematic mapping of the inheritance patterns of evenly spaced polymorphic markers in

search of linked markers that are co-inherited with a risk conferring gene variant among affected family relatives, thus implicating susceptibility linked chromosomal regions harboring a causative variant. Allelic variants in both adjacent marker and risk gene loci may be co-transmitted if their proximity on the same chromosome impedes crossing over between them during meiosis, resulting in deviation from independent assortment. The completion of the human genome reference sequence and increasingly detailed knowledge of single nucleotide polymorphisms (SNPs) now allow genome wide association studies through dense mapping at a range of 10^6 SNPs. Here adjacent SNPs that are in linkage disequilibrium with a risk conferring polymorphism form haplotype blocks that also show association with the phenotype and may be used to fine-map the co-transmitted risk variant. Alternatively, a functional SNP that has a causative role may be directly detected by showing deviant allelic frequencies among affected individuals as compared with controls. SNP microarrays thus allow cost effective genome wide association studies (GWAS) using increasingly larger case control samples. Furthermore, genomic microduplications and microdeletions, also known as structural variants or copy-number variants (CNVs), have been demonstrated to have a high prevalence as well as a causative role in mediating complex psychiatric disorders (15), and genome scale copy-number variation can be studied alongside single nucleotide variation using a single microarray platform (16).

MODIFICATION OF GENE VARIATION EFFECTS

An implicated gene sequence variation may or may not acquire functional significance for conferring risk to a phenotype of interest, in the context of a complex interchange that includes several players. Genes are transcribed into mRNA and translated into protein in a cell X time X function specific manner. Epigenetic modifications of the template DNA nucleotide sequence are a set of environmentally modulated complex molecular interactions (e.g., DNA methylation, chromatin remodeling) regulating the where, when, and to what extent a certain gene may be expressed. A Gene X Environment (GXE) interaction occurs when nucleotide sequence variations become important in mediating risk for a phenotype in the context of relevant exposure, as has been arguably demonstrated for the serotonin transporter gene promoter polymorphism and discussed in detail below. The impact of a risk conferring gene variation may be further modified by interactive effects of other variations in the same gene or in other relevant genes. Epistasis or Gene X Gene (GXG) interaction takes place when the action of one gene is modified by that of another or several other (e.g., modifier) genes, and the phenotypic consequences of any one allele may generally depend on multiple other alleles in a highly complex interactive manner.

IMPLICATED MDD RISK GENE VARIANTS

GENOME SCALE STUDIES

Despite its high prevalence, the study of MDD has lagged behind and has been less extensively addressed by genome wide studies, as compared with the less frequent but more heritable psychiatric disorders (e.g., schizophrenia and bipolar disorder). A number of MDD linkage studies have been performed to date (17-20, 21-24) with several chromosomal regional implications reported by more than one study (e.g., reviewed in 22, 25, 26). Most of these studies ascertained familial cases with homogeneous restrictive and highly heritable phenotypic characteristics (e.g., featuring early age at onset, high recurrence rate, a more severe and chronic clinical course, high familial loading, gender specific sub analyses etc.), that are more likely to share common genetic underpinnings. In addition to the lower statistical power of linkage based analysis (see, for example, 27), a major limitation of family based linkage studies is an inherent difficulty to ascertain sizable numbers of families with multiple affected relatives sharing restrictive phenotype characteristics that will allow a large enough sample powered to detect variants with a small effect size. Further, large chromosomal regions shared among family members constrain the narrowing down of a linkage signal sufficiently to identify a causative gene. Both within a cohort and between cohorts, the percentage of families sharing a similar founder effect may be limited, despite efforts to ascertain cohorts with a homogeneous ethnic background (e.g., in both North American and Northern European populations there is little evidence for founder effects, 28). Detection of a genomic signal may thus be muted in a large cohort in which only some of the families carry a certain risk conferring variant, and replication of reported signals may be limited by genetic heterogeneity in different cohorts (29). Genome wide MDD case control association samples (GWAS) are currently being ascertained (30, 31), with an emphasis on large scale samples (e.g., incorporating a growing understanding in the field of

genetics of complex traits that even several thousand cases and controls may not be enough to capture modest risk conferring variants). The long-term effort required for ascertaining such exceedingly large samples may be very much worth while, as they are likely to eventually shed new light on the largely uncharted biology of MDD.

NTRK3 gene localization through positional cloning. The Genetics of Recurrent Early-Onset Depression (GenRED) linkage project reported preliminary genome scan evidence from 297 families implicating the 15q25.3-26.2 chromosomal region with a restrictive phenotype of recurrent early-onset MDD (17). This region was independently implicated by two other independent linkage studies that focused on a similar restrictive phenotype, the European-U.S. Depression Network (DeNt) study (21) with 497 affected Sibling pairs, and a linkage study of 87 extended pedigrees from Utah (24), as well as in a final extended genome scan analysis (23, 32). Linkage fine mapping of this region with SNPs in 631 families produced genome-wide significant evidence for linkage (32). The authors further genotyped 1,195 individuals from 300 informative European ancestry pedigrees with multiple relatives with recurrent early onset MDD, for 795 SNPs, applying linkage disequilibrium mapping, and located several nominally significant candidate genes in the region (33). One of these, the NTRK3 gene, encodes a receptor that binds neurotrophin 3 (NT3), and may be involved in MDD pathogenesis.

The NTRK3 finding was recently replicated in a sample consisting of 603 families with 723 affected children and adolescents diagnosed with a mood disorder with onset of the first episode by age 15 (34). The NTRK3 gene thus represents a potentially important candidate gene successfully arrived at through linkage derived positional cloning. The gene encodes trkC which is preferentially expressed in relevant brain regions and constitutes a particularly attractive candidate that fits elegantly with the neural plasticity theory of antidepressant treatment mechanism and depression (35, 36), and warrants further replications attempts, and functional characterization.

CANDIDATE GENES

A specific gene may either be implicated as a candidate for conferring risk to a phenotype through a previous hypothesis that purports its function may possess pathogenetic implication, or is identified through being linked with an informative marker in the context of a genome screen (positional cloning, such as with NTRK3). Hypotheses driven candidate gene search is difficult to conduct when the disorder at hand has little in the way of known pathobiology. Important leads that have attracted extensive interest in terms of generating hypotheses for MDD candidate gene search include antidepressant drug targets and the neuroendocrine and neuroimmune pathways. Currently available antidepressants act to increase monoaminergic neurotransmission, and may exert a therapeutic effect in part through augmenting neural plasticity processes (37). Sequence variations in genes encoding antidepressant drug targets constitute immediate candidates for influencing therapeutic and adverse response patterns, but may also impact on risk for MDD. Candidate gene associations with MDD have been recently reviewed (38, 39). Lopez-Leon et al. reviewed MDD association studies reported in 183 papers that studied 393 polymorphisms in 102 genes (38). Only 22 of these polymorphisms were investigated by three or more studies allowing a meta-analysis, of these they found significant evidence for association for *APOE*, *DRD4*, *GNB3*, *MTHFR*, *SLC6A3* and *SLC6A4* (38). Below we review some of the candidate gene findings replicated in several studies or meta-analyses, and important initial findings from larger scale studies.

The serotonin transporter. The serotonin transporter gene solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4) gene located on chromosome 17q11.1–q12, is the exclusive therapeutic target for the derived second generation selective serotonin reuptake inhibitor class of drugs. Several sequence variations have been described in the gene, the most extensively studied is 5-hydroxytriptamine transporter-linked polymorphic region (5-HTTLPR) a 43 base pair Insertion/Deletion short/long (S/L) polymorphism in the promoter (40), which together with rs25531 an A/G substitution within the Longer allele creates a functional AP2 transcription-factor binding site reported to interact to reduce gene expression to a level comparable to that of the short allele (41). Additional variations have been described in the same polymorphic region that may result in a further effect on transcription (42, 43). The ancillary pharmacogenetic arm of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest single study to date with 1,953 participants, could not confirm association with therapeutic response, but reported a positive association of the grouped short allele

and long-G allele combination (e.g., alleles reported to reduce mRNA expression) with adverse effect burden induced by the SSRI citalopram (44). A recent meta-analysis summarizing nine studies with 2,462 participants found significant evidence for association of the 5-HTTPLR with antidepressant response, as well as for additional polymorphisms in smaller overall samples, including the serotonin transporter intron 2 (STin.2) and sequence variations in the serotonin receptor genes HTR1A, HTR2A, the tryptophan hydroxylase gene (TPH1) and the brain derived neurotrophic factor (BDNF) gene (45). The serotonin transporter promoter variation has also been associated with suicidality (46), and with bipolar disorder, albeit with a modest OR of 1.12 (46). Evidence of association with anxiety related personality traits of harm avoidance (47) and neuroticism (48) (e.g., shown to possess partly shared heritability with depression) does not appear to hold for harm avoidance, and requires further study for neuroticism (e.g., 49, 50).

Stressful events have been shown to increase risk for MDD (51), and different adverse events are causally associated with distinct depressive symptoms (52). Caspi et al. (53), employing a follow up study of 1,000 children through young adulthood, demonstrated 5-HTTLPR short allele carriers were more prone to serious depression if experiencing stressful life events either during childhood or during the years preceding the depressive episode, suggesting a GXE interactive effect whereby the capacity of early stress exposure to alter the brain's susceptibility for depression, depends in part on 5-HTTPLR genotype. This report was followed by numerous reports investigating a role for stress exposure as a modifier of 5-HTTPLR impact on depression, with inconclusive over all replication results to date (e.g., reviewed in 54), and more recently refuted in a large meta-analysis (55). Proposed methodological strategies for gene environmental studies have been previously reviewed (56), and further investigation of the molecular mechanisms mediating such GXE interactive effect remains an important field for further study requiring much larger sample sizes (57).

Other MDD risk genes. Lopez-Leon et al. found positive evidence for association for the MTHFR C677T with MDD employing a meta-analysis of six association studies with a total of 875 cases and 3,859 controls with a combined OR of 1.20 (CI, 1.07–1.34) for the T allele (38). They also found the *APOE* epsilon2 allele to show a significant protective effect for MDD in a meta-analysis of seven studies including a total of 827 cases and 1,616 controls, with a pooled OR of the epsilon2 allele compared to the epsilon3 of 0.51 (CI, 0.27–0.97) (38). Lopez-Leon et al. (38) further calculated positive associations for the dopamine D4 receptor gene (DRD4) 2 allele with unipolar disorder and mixed affective (bipolar and unipolar) disorder in a meta-analysis of 12 samples with a total of 917 affective patients and 1,164 controls, the GNB3 C825T using three studies with a total of 375 cases and 492 controls (T allele OR, 1.38; CI, 1.13–1.69); and the dopamine transporter gene (SLC6A3) 40 base pair VNTR showed positive association calculated from three studies including a total of 151 cases and 272 controls, with a pooled OR for the 9/10 genotype compared to the 10/10 genotype of 2.06 (CI, 1.25–3.40) (38). The G72 gene, previously associated with schizophrenia and BPD, was reported to associate with MDD and neuroticism (58). Several immune related gene associations with MDD have been reported. The P2RX7 gene is located within a region on chromosome 12q24.31 that has been identified as a susceptibility locus for affective disorders by linkage and association studies. P2RX7 is a purinergic ATP-binding calcium channel that modulates monocyte/macrophage-induced inflammatory response and is also expressed in neurons and glia. A non-synonymous coding SNP in the P2RX7 gene (rs2230912) resulting in amino acid substitution (Gln460Arg), that was previously found to be associated with bipolar disorder (59), was significantly associated with MDD, among 1,000 German Caucasian patients compared with controls (60). Proteasome beta4 subunit (PSMB4), and TBX21 (T bet) genes important in T lymphocyte function (61), and cyclic nucleotide phosphodiesterases PDE9A and PDE11A genes (62) were also reported to associate with MDD risk. All these association reports await further replications.

Endophenotype gene associations. Endophenotypes represent more elementary phenotypic measures that may be more likely to correlate with small effect sequence variants. Depression may be associated with hippocampal volume reduction, in part through a reduced capacity for neurogenesis, and neurotrophic factors including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) have both been implicated in modulating hippocampal plasticity (35, 63). There is no consistent evidence associating common BDNF gene polymorphisms with MDD, although significantly smaller hippocampal volumes were observed for patients and for controls carrying the BDNF Val66Met Met allele (64-66). Similarly VEGF gene SNP variations have been shown to corre-

late with hippocampal volume among healthy subjects (67). The 5-HTTPLR short allele has been reported to correlate with augmented amygdala activation to fearful stimuli which may be related to trait negative affectivity and depression (68). A summary of several replication attempts provides some support to this finding (69).

To conclude, antidepressant drug targets and also neuroimmune and neuroendocrine modulators have been extensively invoked to guide candidate gene selection for MDD association studies. Methodological aspects of candidate gene association studies have progressed to employ increasingly larger case control samples or meta-analytic summaries to increase sample size (38, 70). The majority of reported studies to date have failed to incorporate comprehensive scans encompassing all known sequence variations in any gene of interest. As an example, although the SLCA4 gene contains multiple known variations (42, 43), the majority of studies focused on promoter variations (e.g., mostly 5-HTTLPR). Studies that examined additional SLC6A4 SNPs and haplotypes reported their relevance for both gene expression (42, 43) (71) as well as for mediating stress X SLC64A genotype effects on the depressive phenotype (72). Further, few studies have looked for epistatic interactions between different candidate susceptibility loci (72-76). Such studies generally would require larger samples unless a large effect size is produced by interactive loci.

The following step of unraveling the biological significance of implicated risk variations is currently at its beginning stages. It follows both that functional knowledge of gene variations is currently too scant to justify premature focus of phenotype associations on any single sequence variant, and that reciprocal systematic input from such studies would result in a more informed focus on risk conferring gene variations for functional studies. Recent initiatives for ascertainment of large scale samples for genome wide association studies may yield new findings of previously unknown MDD risk conferring genes in the near future.

CURRENT DIRECTIVES FOR STUDY

With few exceptions, replicated MDD gene association findings to date derive from modestly sized meta-analyses that combine small case control samples with non-uniform ascertainment characteristics. Further, a majority of studies to date address hypotheses driven candidates that mostly revolve around known mechanisms of antidepressant drugs. As noted, such studies have prematurely devoted disproportionate focus to few highly reported polymorphisms (e.g., such as the 5-HTTPLR promoter variation), neglecting comprehensive coverage of the coding and promoter regions of the gene of interest. Despite the extensive efforts described and some progress made, the hypotheses driven candidate gene strategy is unlikely to provide ground-breaking perspectives that will furnish a new understanding of the largely unknown biology of depression.

Elucidation of previously unimplicated genes may come from unbiased genome scale family based linkage studies, and eventually from genome scale case control studies once large enough samples (e.g., the lower limit of which is several thousands cases) have been ascertained, as has recently been the case for schizophrenia (77). A conspicuous finding from numerous recent replicated gene findings across several complex phenotypes such as schizophrenia (77-79), type II diabetes (80, 81), and rheumatoid arthritis (82) is the small effect size conferred by implicated gene variants. Such findings could only be reliably detected with employing exceedingly large case control samples, highlighting the importance of multicenter collaborative efforts and meta-analyses for meaningful GWAS results. This does not discount smaller family based linkage studies, as these may discover mutations that bear a higher relative risk for familial restrictive MDD phenotypes among a cohort that shares a founder effect, despite a lower overall sample size. A common genetic variant in the same gene may confer a much lower relative risk for sporadic MDD, in which case a population based GWAS may require a much larger unrelated case control sample to detect a minor effect size that exhibits genome wide significance level. The frustratingly low and variable relative risks attributable to implicated gene variations in the context of recent population based case control GWA studies of multiple complex disorders among samples sized at 104 subjects pose the immediate question of how relevant these true replicated findings may be for predicting actual risk for the disorder. The unfolding genetic landscape of schizophrenia thus far appears to be populated with both a prevalent polygenic type resulting from the convergence of several common polygene variants each contributing a minute relative risk to the sporadic disorder, as well as rare cases of copy number variations that hold a very high relative risk for carriers (15, 83, 84). This combination of cases may account for a stable rate of schizophrenia over generations despite reduced fecundity of those affected, as the heritable pool for common gene variations that confer risk to the sporadic phenotype lies with the unaffected

general population, whereas rare CNVs may mostly arise among affected individuals de novo, and are therefore independent of fecundity. Such patterns raise questions about future practicality of predictive tests, as inherited minute effect poly genes cannot be ascribed deterministic stigmatizing predictions for an individual carrier, but rather portray probabilistic propensities that may become conductive of a categorical phenotype only within a given epistatic and epigenetic context. If common gene variants each contribute so little to the biology of the complex phenotype, and rare structural variants apply to very few of the patients, what implications could such findings possibly have for guiding the development of novel targeted preventive and palliative molecular interventions that could be useful to the majority of patients?

Several of the structural variants as well as minor risk SNP variations discovered appear to converge in disrupting common neurodevelopmental pathways such as neuregulin signaling (e.g., 15), or the interactive DISC I and PDE4B genes, the disruption of either of which may result in a schizophrenia phenotype (85), leading to the suggestion that genes in such relevant pathways may either be severely disrupted leading to rare cases, or contain common minor variations contributing to the common polygenic phenotype (15). Discoveries of either type of variation may converge to implicate the same pathogenetically relevant genes and pathways that possess common relevance as targets for significant interventions.

CONCLUSION

Non-hypotheses driven GWA studies are transforming our understanding of the genetic architecture and pathophysiology of common complex medical disorders. Since 2005, nearly 100 replicated risk conferring gene variants have been reported for as many as 40 common diseases (86). This progress contrasts with the slow progress in complex trait research during the previous two decades, and largely stems from rapid increments in the ability to apply denser SNP mapping to larger case control samples. MDD research is currently on the verge of applying such large scale GWA studies. The published literature surveyed above is to date mostly compiled of reports stemming from modest case control samples exploring candidate gene association with categorical MDD, few of which withstand meta-analytic validation of independent replication attempts. In a similar vein, reviews of hundreds of association reports across multiple medical disorders demonstrate the importance of large scale independent replication and meta-analyses for teasing out replicated findings from frequent non-replications that may result from population stratification, phenotype differences, selection biases, genotyping errors, etc. (e.g., 87, 88). Detailed guidelines have recently been proposed for replicating genetic association (89) and for assessing the validity of cumulative evidence for genetic association findings (90, 91). Empirically derived statistical power estimates suggest that GWAS for complex phenotypes will typically require several thousands of cases to study main effects and several tens of thousands of cases to properly support the investigation of gene X gene or gene X environment interactions (92).

The modest relative risks conferred by hitherto discovered common gene variations in psychiatric genetics signify probabilistic propensities, with little if any practical diagnostic predictive value, and are not likely to bear deterministic (e.g., neither stigmatizing nor of practical clinical value) attributes for the individual. Future comprehensive knowledge of sets of multiple interacting small effect risk loci might have practical predictive implications, in the context of clinical risk factors and ethnic derivation. The small effect size of risk conferring gene variations makes a much harder case for efforts to decipher their incremental biological contribution to the pathogenesis of a polygenic multifactorial disorder. This is in contrast to karyotype abnormalities and CNVs that have been identified so far to result in very high relative risks for overlapping major psychiatric disorders and cognitive deficits, but apply to rare cases and may mostly arise de novo. Although unlikely to reform the next 2012 addition of DSM-V, genetics will definitely have an increasing input into diagnostic reclassification. More importantly, the discovery of risk loci will furnish the basis for a fresh understanding of the pathophysiology of these idiopathic conditions, offering hope for the design of selective molecular interventions for the prevention and treatment of psychiatric disorders.

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