Genetics and genomics of behavioral and psychiatric disorders

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Psychiatric conditions are to some degree under genetic influences. Despite the application of advanced genetic and molecular biological technologies, the genetic bases of the human behavioral traits and psychiatric diseases remains largely unresolved. Conventional genetic linkage approaches have not yielded definitive results, possibly because of the absence of objective diagnostic tests, the complex nature of human behavior or the incomplete penetrance of psychiatric traits. However, recent studies have revealed some genes of interest using multifaceted approaches to overcome these challenges. The approaches include using families in which specific behaviors segregate as a mendelian trait, utilization of endophenotypes as biological intermediate traits, identification of psychiatric disease phenotypes in genomic disorders, and the establishment of mouse models.

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Abbreviations

AS	Angelman syndrome
BDNF	brain-derived neurotrophic factor gene
CHRNA7	α7 neuronal nicotinic acetylcholine receptor subunit gene
COMT	catechol-*O*-methyltransferase gene
FOXP2	forkhead box P2 gene
GABRB3	γ-aminobutyric acid type-A receptor β3 subunit gene
MAOA	monoamine oxidase A gene
MRI	magnetic resonance imaging
NMDA	*N*-methyl-*D*-aspartate
NRG1	neuregulin 1 gene
OMIM	Online Mendelian Inheritance in Man
PRODH2	proline dehydrogenase 2 gene
PWS	Prader–Willi syndrome
QTL	quantitative trait loci
SLC6A4	solute carrier family 6, member 4 (serotonin transporter) gene
VCFS/DGS	Velocardiofacial syndrome/DiGeorge syndrome
WFS1	Wolfram syndrome 1 gene

Introduction

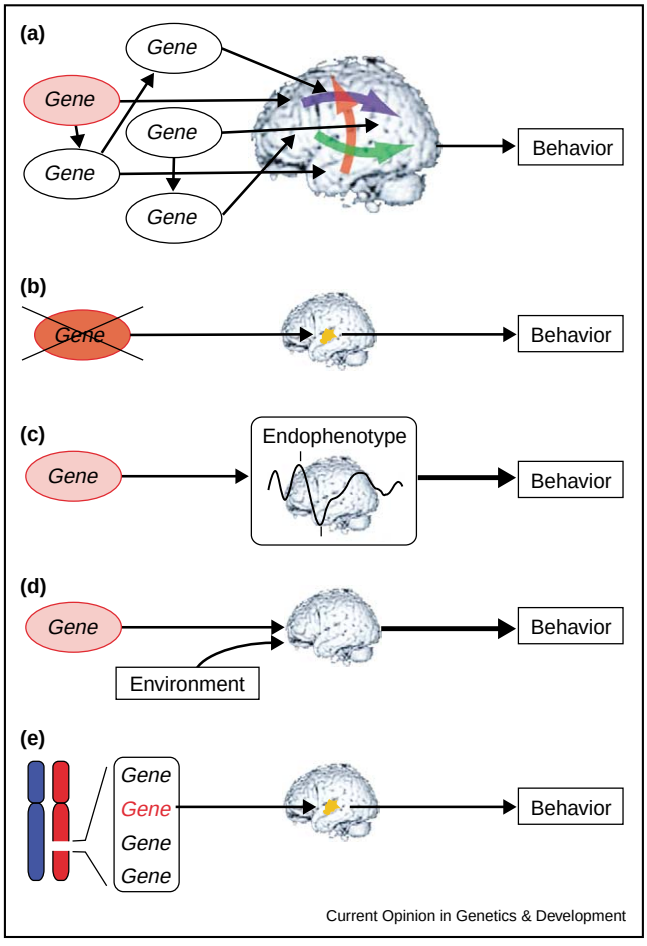
Findings from the family, twin and adoption studies of psychiatric disorders — including schizophrenia, bipolar disorder, autism, attention deficit hyperactivity disorder and addiction — have indicated that genetics plays a major role in the pathogenesis [1]. However, in the vast majority of families, the phenotype does not segregate as a simple mendelian trait, but rather displays patterns consistent with a complex trait. For such disease traits, multiple genetic and environmental factors may influence the susceptibility to the development of a phenotype [2]. Furthermore, a psychiatric disease phenotype may represent a final common pathway with multiple etiologies. Genetic heterogeneity could be substantial and in any given patient or family only one or a small number of genes may be contributing to the phenotype, but the specific gene may be different in different families. The genetic heterogeneity may be further complicated by low-penetrance alleles.

Despite substantive efforts to identify loci in the human genome and the genes responsible for these psychiatric conditions, the findings have been often controversial and inconsistent. Most candidate loci and genes for psychiatric diseases have failed to reproduce positive linkage or association and no single gene has been conclusively identified. One reason for this difficulty may arise from an oversimplified assumption that a gene and a behavioral phenotype can be reduced to a linear relation [3]. In fact, human behavior likely results from the interactions between complex genetic, cellular, anatomical and functional networks with environmental influences, representing a challenge for current genetic approaches (Figure 1). Recently, comprehensive reviews have summarized progress in the genetic analyses of each psychiatric disease [4–7]. Hence, by selecting examples of recent gene discoveries (Table 1), we here focus on how the challenges of going from behavioral/psychiatric trait to gene have been approached.

Behavior and psychiatric genetics in simple inheritance models

Single-locus disorders that segregate as mendelian traits may display a phenotype with similarities to a common disease representing a complex trait. Thus, alteration in the gene for the mendelian trait may contribute to the genetic basis of the common disease. The gene responsible for Wolfram syndrome, *WFS1* (OMIM 222300 [OMIM URL: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM]) may represent such an example. Wolfram syndrome is an autosomal recessive disease defined by juvenile-onset diabetes mellitus, diabetes insipidus, progressive optic

Figure 1



Schematic overviews of genetic approaches to study human behavioral traits. **(a)** The complex nature of a human behavior involves genetic networks and functional interactions (colored arrows) that are present between a susceptibility gene (pink oval) and a behavioral trait. This complexity has made the genetic study of psychiatric diseases extremely challenging. The panels below exemplify the approaches that have been taken to overcome these difficulties. **(b)** Single-locus disorders that segregate as a mendelian trait may result from a mutation in a gene (red oval). The mutation may result in a specific pathophysiology in the brain (yellow area) that is linked to a behavioral phenotype. This behavioral phenotype may have parallels to a common mental illness that represents a complex trait. **(c,d)** Considering an additional phenotypic parameter in the analysis may increase the statistical power of genetic analyses (thick arrows). (c) An allelic alteration in a gene may be reflected in a change of an objectively measurable biophysiologic parameter (endophenotype) that is tightly associated with a specific behavioral trait. (d) An environmental factor may enhance the effect of an allelic change in a candidate gene to an associated behavioral phenotype. **(e)** When a genomic disorder reveals a specific behavioral phenotype, genes in the chromosomal interval that is associated with the disease-specific genomic rearrangement (either deletion or duplication) represent strong positional candidate genes for the behavioral traits. One can focus on a specific genomic region for further extensive analyses using association, linkage and functional approaches.

atrophy and deafness. Patients with homozygous *WFS1* alleles also have a high prevalence of depression. Remarkably, heterozygous carriers have a 26-fold risk of psychiatric hospitalization [8]. Heterozygous *WFS1* carriers constitute ~1% of the population, thus it is possible that the *WFS1* gene may contribute as a susceptibility gene for psychiatric diseases.

Rare families in which behavioral phenotypes segregate as mendelian traits have been described. A positional cloning study in a large Dutch family with mild intellectual impairment and aggressive antisocial behavior segregating as an X-linked trait identified a mutation in the monoamine oxidase A gene (*MAOA*) [9,10]. As predicted by these human studies, mice lacking *Maoa* display aggressive behavior [11]. Furthermore, elevated levels of serotonin, norephinephrine, and dopamine observed in the brain of these mice provided clues to direct human research to either substantiate or refute the biochemical mechanisms for this specific phenotype in humans [11]. Stimulated by these findings, several association studies between *MAOA* and various psychiatric conditions have been carried out, but most of them were inconclusive. Notably, one study of a birth cohort of 1037 male children, whose development was followed to adulthood, considered an environmental factor — childhood maltreatments such as abuse and erratic parenting — into the association analysis in addition to the *MAOA* functional polymorphisms and antisocial behavioral outcomes [12••]. The results revealed a remarkable contribution of a *MAOA* genotype moderating the effect of maltreatment in childhood that leads to antisocial behaviors. Interestingly, environments may be contributing to the evolution of the human *MAOA* gene. *MAOA* appears to have undergone an ethnic population-specific positive selection, potentially resulting from local adaptation of particular *MAOA* haplotypes in association with corresponding behavioral phenotypes [13]. As with other organisms, human behavioral evolution may be mediated in part by positive selection of behavioral genes that may confer advantages to adapt to local environments.

The forkhead box P2 gene (*FOXP2*) encodes a forkhead transcription factor that may be involved in a behavioral trait. *FOXP2* mutations result in an impairment in fine orofacial movement and deficits in language processing and grammatical skills that transmits as an autosomal dominant trait [14•]. This discovery fomented studies of association and mutation analyses in patients with either autism or specific language impairment, especially because an autism locus (*AUTS1*) maps close to *FOXP2*. Unfortunately, studies indicated that *FOXP2* is not likely a strong contributor to either condition [15,16]. Molecular evolutionary studies revealed that *FOXP2* also appears to have undergone positive selection during primate speciation. Two human-specific amino acid alterations in the highly conserved coding sequence may enhance the protein function, resulting in modification of the ability to control orofacial movement and thus to develop language [17], although further confirmatory studies are required.

Table 1

Human gene and associated behavioral traits.

Gene	Locus	Variations	Phenotype when mutated	References
ALDGH2	12q24.2	Functional SNP	Alcoholism	[59]
BDNF	11p13	SNP	Hippocampus-related memory	[21]
COMT	22q11.2	Functional SNP	Schizophrenia	[20]
*DAAO**	12q24	LD	Schizophrenia	[60]
FOXP2	7q31.2	Mutations	Speech and language disorder	[14•]
*G72**	13q34	LD	Schizophrenia	[60]
*GABRB3**	15q11-q13	LD	Autism	[42]
MAOA	Xq11.23-11.4	Mutations, functional VNTR	Aggressive antisocial behavior	[9,10]
MECP2	Xq28	Mutations	Autistic behaviors and hand wringing (Rett syndrome)	[61]
MtDNA	Mitochondria	Mutations	Depression	[62]
*NRG1**	8p12	LD	Schizophrenia	[51••,52]
PRODH2	22q11.2	SNPs	Schizophrenia	[36•]
SLC64A	17q11.1-q12	VNTR	Anxiety	[18••,19]
WFS1	4p16	Mutations	Depression	[8]

LD, linkage disequilibrium analysis; SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat. *Candidate genes based on the positional and functional studies and no coding alterations in the gene were identified.

Endophenotypes as intermediate biological markers

The statistical power of linkage and association studies for behavioral and psychiatric traits may be improved by incorporating additional phenotypic parameters into the analysis. For example, the association of *MAOA* genotype and antisocial behavior was not clearly demonstrated until the environmental factor of maltreatment in childhood was considered [12••]. The use of endophenotypes — measurable biological traits that are associated with target behavioral phenotypes — also appears to be an effective solution to enhance the ability to detect genetic influence in behavioral phenotypes.

Local activity of the brain, which can be assessed by functional MRI, is one such example. Utilizing the response of the amygdala to fearful stimuli as an endophenotype for anxiety and fear behavior, a functional polymorphism in the serotonin transporter gene (*SLC6A4*) promoter was tested [18••]. In contrast to the modest effects of the *SLC6A4* haplotype on anxiety personality or fear behavior in previous simple association studies [19], the results of the endophenotype approach were remarkable. Differences between the two haplotypes on amygdala neuronal activity reached an effect size almost 10-fold higher than that observed in previous studies in which endophenotypes were not considered. Furthermore, the same approach was successfully applied to identify the association between the catechol-*O*-methyltransferase gene (*COMT*) and frontal lobe function, a hallmark for schizophrenia, and the association between *BDNF* and hippocampal function that reflect long-term memory [20,21].

Event-related potentials represent responses to various tasks and are altered in patients with psychiatric disorders and in their family members. Event-related potentials have been utilized as an endophenotype in genome-wide linkage studies of alcoholism and schizophrenia [22,23]. These studies have identified major loci with significant LOD scores [24•,25]. Follow-up studies on the chromosome 15 locus for schizophrenia identified *CHRNA7*, which encodes a nicotinic acetylcholine receptor subunit, as a functional candidate gene [26]. Other potential endophenotypes that can be utilized to increase the power of linkage and association studies for the psychiatric diseases have been summarized elsewhere [23,27].

Genomic disorders and psychiatric diseases

Genomic disorders are a group of genetic diseases caused by chromosomal rearrangements that result in either deletions or duplications of unique genomic segments that span up to 3–4 Mb [28,29]. Many genomic disorders, such as William syndrome [del(7)(q11.23q11.23)], Smith–Magenis syndrome [del(17)(p11.2p11.2)] and the phenotype resulting from the reciprocal duplication [dup(17)(p11.2p11.2)], Velocardiofacial syndrome/DiGeorge syndrome (VCFS/DGS) [del(22)(q11.2q11.2)], Prader–Willi syndrome (PWS) [pat del(15)(q11.2q13)] and Angelman syndrome (AS) [mat del(15)(q11.2q13)], present with unique behavioral features [30]. This suggests that dosage alteration, either loss or gain of gene(s) within the rearranged genomic interval, may predispose one to various behavioral phenotypes or, potentially, to specific personality characteristics. Such genes may be excellent candidates for studying common behavior traits.

Approximately 10–30% of the patients with VCFS/DGS — which is associated with a 3 Mb deletion on chromosome 22q11.2 — have psychiatric manifestations including schizophrenic behavior and mood changes [31•,32]. Independently, multiple linkage analyses suggested that both bipolar disorder and schizophrenia loci map to 22q11.2 [4]. Thus, gene(s) within this genomic deletion interval on 22q11.2 may increase susceptibility

to these behavior phenotypes. *COMT* appears to be one of the excellent candidate genes because of its function in metabolizing chatecholamines including dopamine [33]. After struggling with inconclusive association studies between a functional polymorphism in *COMT* and psychiatric conditions, two recent studies reveal what is potentially a major breakthrough. One study [20] applied an endophenotype as a target biological marker and the other [34] employed a large sample size in a population isolate, respectively, to improve the performance of genetic studies. Both studies confirmed significant association that has never been obtained using conventional genetic approaches.

Other studies utilized high-density haplotype mapping to narrow the schizophrenia susceptibility loci to two subregions within the VCFS/DGS deletion interval [35,36•]. Surprisingly, they excluded *COMT* from the critical region, but instead identified *PRODH2* as a strong candidate gene. Supporting this finding, *Prodh2* homozygous mouse mutants have deficits in sensorimotor gating, a biological hallmark of schizophrenia [37]. Interestingly, mice lacking a 1.1 Mb choromosomal segment equivalent to the VCFS/DGS critical interval because of a chromosome engineered deficiency show more severe sensorimotor gating deficits even in the heterozygous state [38], whereas mice with a 150 Kb deletion within this interval showed the opposite effect on sensorimotor gating [39]. This suggests a complex interaction of contiguous genes within this region in the behavior phenotype.

Chromosome 15q11.2-q13, which is frequently deleted in patients with PWS/AS, is another genomic region of interest to behavioral scientists. In addition to the characteristic behavioral features of PWS/AS, duplication of the same genomic segment, when derived maternally, appears to result in autism in some cases [40]. The duplication can result from interstitial duplication, dicentric, or derivative chromosomes [5]. These findings suggest the involvement of both gene-dosage and imprinting genomic mechanisms. The best candidate gene is *GABRB3*, which encodes a receptor subunit for an inhibitory neurotransmitter, GABA. Association between *GABRB3* and autism has been elusive [41,42], but a recent study [43] obtained a significant linkage between autism and *GABRB3* when using a statistical approach consisting of an ordered-subset analysis with an insistence on sameness as the endophenotype.

Although there has been limited success in determining the genetic etiology of anxiety disorders [44], a recently described genomic disorder may provide clues to this problem. Two forms of polymorphic large interstitial duplications spanning chromosome 15q24-26 appeared to be tightly associated with panic/phobic disorders accompanied by joint laxity [45•]. These duplications were found in 97% of unrelated patients with panic disorder/agoraphobia, in contrast to <10% in normal controls. Remarkably, the presence of mosaicism, two different forms of duplication within the same family, and absence of segregation between genetic makers in 15q24-q26 with duplication and a clinical phenotype indicate an unusual non-mendelian inheritance as a genetic basis of disease etiology [45•]. However, other studies have failed to reproduce these findings [46].

Mouse partial models of human behavior

Mouse models represent a tremendous resource for investigating the genetic basis of behavior because they can be genetically manipulated and genetic and genomic information is abundant. However, mouse models also present limitations for studies of psychiatric diseases because of the difficulties in modeling higher brain functions (e.g. language skill, self-concept and association of concept), or common psychiatric symptoms (e.g. hallucination, delusion, suicidal tendency or depression). Nevertheless, the evaluation of intermediate traits (endophenotypes) in mice can confer additional support for the involvement of human candidate genes in psychiatric diseases and may assist in the confirmation of a mutation's functional significance [47].

Forward genetics approaches — whereby mutations in specific genes are studied for behavioral phenotypes that can mimic human psychiatric disorders — have identified several genes important to behavioral traits [44,48,49]. Some human orthologs of these mouse genes map to the syntenic region of potential susceptibility loci and appear as strong candidate genes for psychiatric diseases (reviewed in [47,50]). Thus, these loci/genes are of particular interest to further investigate association with disease in human populations. The neuregulin 1 (*Nrg1*) knockout mouse model displayed behavioral traits that stimulated further the findings from human linkage studies, which identified *NRG1* as a strong positional candidate gene for schizophrenia [51••,52]. Hypomorphic mice mutated in *Nrg1* or its receptor, *ErbB4*, showed antipychotic-reversible hyperactive behavior and abnormal sensorimotor gating [51••]. Furthermore, *Nrg1* hypomorphic mice showed a reduction of functional NMDA receptors, a receptor family for the neurotransmitter glutamate, which recapitulated findings in the brains from schizophrenic patients. Interestingly, NMDA receptor hypomorphic mice also have a behavioral phenotype resembling schizophrenia [53]. Thus, findings in mouse studies corroborate independent findings from human studies.

In contrast to forward genetic approaches, reverse genetic approaches use the transmission of either traits or phenotypes to discover the underlying genes. Behavior phenotypes often represent multivariate complex traits with a spectrum of phenotype and multilocus inheritance and thus require specific mapping technologies. Quantitative trait loci (QTL) mapping may overcome such challenges [54]. Utilizing existing phenotypic variations between

different strains, QTL mapping aims to identify genes for differences in behavioral traits by comparing genetic variations of intercrossed strains. Recent progress in enriched genomic sequence, genetic marker and polymorphism information, high-throughput genotyping technologies, the development of QTL-mapping computational software, and the availability of mouse recombinant strains (congenic, consomic and advanced intercross strains) have advanced the utility of QTL mapping significantly in mice [47,55,56]. High-resolution QTL mapping and cloning holds great promise for behavior genetics in the next few years.

Despite the progress in QTL mapping in mice, variation that one can search for may be present only in mouse inbred strains but not in humans, thus it is possible that the QTL may only contribute to mouse behavior but not human psychiatric disorders [47]. This limitation can never be overcome unless mutations are introduced into the mouse genome. Ethyl-nitrosourea allows random, high-frequency mutagenesis of the mouse genome, thus one can perform genome-wide, phenotype-driven screening for specific traits [57]. Systemic approaches have been applied to screen massive numbers of mutants for behavior traits and to subsequently map the genes responsible [58].

Conclusions

It has been extremely challenging for geneticists to uncover the biological basis of psychiatric diseases because the nature of human behavior involves an intricate and complex series of neural networks and these diseases appear to represent complex traits thus limiting conventional genetic approaches. Nevertheless, recent progress in molecular genetic technologies continues to result in systematic and steady advances. As a result, the genetic bases of certain behavioral traits have begun to be elucidated. Exciting discoveries are imminent and these will further promote a better understanding of the biological basis of human behavior. Insights gained from such studies may provide a better understanding of abnormal behavior and open new avenues for the treatment of mental illness.

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