REVIEW

The Genetics of Depression: A Review

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Major depressive disorder (MDD) is common and moderately heritable. Recurrence and early age at onset characterize cases with the greatest familial risk. Major depressive disorder and the neuroticism personality trait have overlapping genetic susceptibilities. Most genetic studies of MDD have considered a small set of functional polymorphisms relevant to monoaminergic neurotransmission. Meta-analyses suggest small positive associations between the polymorphism in the serotonin transporter promoter region (5-HTTLPR) and bipolar disorder, suicidal behavior, and depression-related personality traits but not yet to MDD itself. This polymorphism might also influence traits related to stress vulnerability. Newer hypotheses of depression neurobiology suggest closer study of genes related to neurotoxic and neuroprotective (neurotrophic) processes and to overactivation of the hypothalamic-pituitary axis, with mixed evidence regarding association of MDD with polymorphisms in one such gene (brain-derived neurotrophic factor [BDNF]). Several genome-wide linkage studies of MDD and related traits have been reported or are near completion. There is some evidence for convergence of linkage findings across studies, but more data are needed to permit meta-analysis. Future directions will include more intensive, systematic study of linkage candidate regions and of the whole genome for genetic association; gene expression array studies; and larger-scale studies of gene-environment interactions and of depression-related endophenotypes.

T he identification of genes that underlie susceptibility to nonbipolar depressive disorders would be a major advance in our understanding of pathophysiological mechanisms. Current studies focus on two phenotypes: major depressive disorder (MDD) and traits like neuroticism that predict increased risk of depression. We review here the genetic epidemiological rationale for these studies, genetic association studies of candidate genes (such as those with roles in monoaminergic neurotransmission), genetic linkage studies of MDD and of related traits, and alternative research strategies.

Genetic Epidemiology

MDD

The lifetime prevalence of unipolar MDD is at least 10%, with the risk in women twice that in men (Moldin et al 1991; Tsuang et al 1994; Weissman et al 1996). Heritability based on twin studies is 40% to 50% (Bierut et al 1999; Kendler et al 1993a, 2001; McGuffin et al 1991, 1996; Sullivan et al 2000; Torgersen 1986) and perhaps higher when measurement error is modeled based on repeated assessments (Kendler et al 1993a). Adoption studies provide some support for a role for genetic factors (Mendlewicz and Rainer 1977; Cadoret 1978; Wender et al 1986), although these studies have methodological limitations (Sullivan et al 2000). The relative risk (RR) (ratio of risks to first-degree relatives of MDD probands vs. the general population) is around 2 to 3 (Gershon et al 1982; Weissman et al 1984a; Maier et al 1992). The mode of inheritance is unclear (Price et al 1987; Moldin et al 1991; Marazita et al 1997). Potent environmental risk factors include childhood abuse and neglect and life stress (Kendler et al 2002, 2004).

The power of genetic mapping studies depends on the RR attributable to each specific gene or interaction (James 1971; Risch 1987). For multigenic mechanisms such as those that presumably underlie depression susceptibility, the largest RR attributable to any one locus cannot be known in advance, but presumably it is advantageous to identify characteristics that predict the largest possible total RR. For MDD, these include age at onset (AO) in the 30s or earlier (Cadoret et al 1977; Mendlewicz and Baron 1981; Weissman et al 1984a, 1984b; Bland et al 1986, Price et al 1987; Kupfer et al 1989; Weissman et al 1993) and recurrent episodes (Bland et al 1986; Gershon et al 1986; Kendler et al 1993a, 1994, 1999). The RR for recurrent *and* early-onset MDD (MDD-RE) is probably at least 4 to 5 (Weissman et al 1982, 1993; Bland et al 1986; Marazita et al 1997), although the population risk has not been clearly established for this specific subtype.

While relatives of bipolar disorder (BD) probands are at increased risk of MDD, the reverse is not the case (e.g., Maier et al 1992). McGuffin et al (2003) analyzed data drawn from separate twin samples with bipolar versus unipolar (MDD) probands and concluded that 71% of the genetic liability to mania is independent of the liability to depression. There is some evidence to suggest a familial-genetic relationship between MDD and bipolar II disorder (BD-II) (Gershon et al 1982; Endicott et al 1985), but we lack twin and large-scale controlled family data. Understanding of the genetic relationship between MDD and BD probably must await the elucidation of molecular mechanisms.

MDD, Anxiety Disorders, and Neuroticism

Neuroticism is a term introduced by Eysenck (1967) to describe a high-order factor in analyses of self-rated or observer-rated measures of personality, characterized by dysphoria, anxiety, tension, and emotional reactivity (e.g., McCrae and Costa 1985; DeNeve and Cooper 1998). Heritability is 40% to 50% (Floderus-Myrhed et al 1980; Jang et al 1996) and reasonably stable across adult life (Viken et al 1994). High premorbid neuroticism scores are a robust predictor of future onset of MDD (Kendler et al 1993b, 2004). Kendler et al (1993b) estimated that 55% of the genetic risk of MDD was shared with neuroticism. There may be common genetic factors (presumably, specific DNA sequence variations) that can predispose to MDD, neuroticism, and generalized anxiety disorder, and less clearly to panic disorder and social phobia, while obsessive-compulsive disorder and simple phobias are more independent (reviewed by Mineka et al 1998; also Kendler et al 1995; Weissman et al 2005). Thus, some genetic studies incorporate depressive and anxiety symptoms into a single phenotype, either with trait scores such as neuroticism or using categorical diagnoses.

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Association Studies of Candidate Genes

Monoaminergic Candidate Genes and Gene-Environment Interactions

Most of the published genetic association studies of mood disorders have focused on functional polymorphisms (DNA sequence variations that alter the expression and/or functioning of the gene product) in the loci encoding the serotonin transporter (SLC6A4), serotonin 2A receptor (5HTR2A), tyrosine hydroxylase (TH) (the limiting enzyme for dopamine synthesis), tryptophan hydroxylase 1 (TPH1) (serotonin synthesis), and catechol-o-methyltransferase (COMT) (dopamine catabolism). There are one or more recent meta-analyses of studies of these polymorphisms for MDD, BD, suicidal behavior, and/or for neuroticism, as summarized (for analyses of larger numbers of studies) in Table 1. Only three significant findings emerge across studies, all involving the short allele of the well-known serotonin transporter gene-linked polymorphic region (5-HTTLPR) 44-base pair (bp) insertion/deletion polymorphism: 1) a modest association (odds ratio [OR] = 1.13) with BD; 2) modest associations with suicidal behavior and particularly violent suicidal behavior, although the positive evidence was produced by studies of alcoholic rather than mood disorder patients; and 3) an association with depression-related trait scores, with one meta-analysis reporting an effect only in studies of neuroticism using the NEO Personality Inventory and a second meta-analysis (considering an overlapping set of studies but limited to nonpatient samples) reporting an effect only from studies of the harm avoidance factor of the Tridimensional Personality Questionnaire (TPQ) inventory. This polymorphism has not shown significant association overall with MDD, although a large positive study (OR = 1.26 for the short allele) (Hoefgen et al 2005) was published too recently for inclusion in the meta-analyses, and a significant small effect might be observed when these data are added.

More recently, Walther and Bader (2003) reported that a tryptophan hydroxylase 2 (TPH2) isoform (rather than TPH1, previously known as TPH) is the predominant form in brain, and Zill et al (2004a) reported that MDD was associated with 1 of 10 single nucleotide polymorphisms (SNPs) (global empirical p = .0051 for the set of 10 tests) and with 10 SNP haplotypes (global p = .0001) in TPH2 in 300 MDD patients and 265 control subjects. Association of the same SNP was observed in 263 suicide victims versus control subjects (global p = .01 for single SNPs and .0001 for haplotypes) (Zill et al 2004b). These findings await replication. Zhang et al (2005) reported a loss-of-function polymorphism in TPH2, which they found to be associated with MDD (but not BD) in 87 MDD cases versus 219 control subjects, a small sample size for a complex disorder. However, Zhou et al (in press) were unable to find this polymorphism in 403 major depression cases and 352 control subjects by direct sequencing or in 1740 depression cases by genotyping.

There are many other genes in which polymorphisms have been studied by one or several groups but with no recent meta-analyses to assess the evidence across studies. Also, the growing literature on monoamine-related gene polymorphisms and antidepressant responsiveness (reviewed by Malhotra et al 2004) is beyond the scope of this review, but as more powerful methods are brought to bear on pharmacogenetic studies, the findings could provide additional clues to etiological mechanisms.

5-HTTLPR, Stress and Depression

Caspi et al (2003) reported that in 847 subjects followed in a study of development from ages 3 to 26, the number of stressful life events from 21 to 25 predicted subsequent depression, and this relationship was predicted by the number of short alleles at 5-HTTLPR (p < .05 for scores, p = .056 for MDD diagnosis). A similar interaction was observed for the effect on depression of the number of positive childhood maltreatment indices between ages 3 and 11. Neither depression scores nor MDD were predicted by genotype alone. Thus, it appeared that 5-HTTLPR genotype influenced stress reactivity rather than directly "causing" depression. There is evidence to support this hypothesis, including an association between short alleles and depression following stress in 127 women (Mitchell et al 2004; Dr. Philip Mitchell, personal communication, October 2004); onset of depression following low-threat events for the short-short genotype (Kendler et al 2005); increased depression scores in maltreated children if they lacked social supports (Kaufman et al 2004); increased amygdala activation in response to aversive stimuli (Hariri et al 2002, 2005); and increased adrenocorticotropic hormone (ACTH) response to separation in female (but not male) rhesus monkeys with previous adversity (Barr et al 2004). However, Gillespie et al (2005) reported that in 1206 twins, stress predicted MDD but with no interaction with 5-HTTLPR genotype.

The 5-HTTLPR story raises several points about candidate gene research. While it should prove possible to unravel the behaviors associated with this functional polymorphism, the full complexity of the effects of this gene is far from clear. Short alleles produce fewer transporter molecules that have reduced serotonin uptake activity (Lesch et al 1996), although Shioe et al (2003) did not observe an association between 5-HTTLPR genotype and transporter binding measured by positron emission tomography. Hariri et al (2005) (for recent data and review) have reported an association between short alleles and hyperreactivity of the amygdala to images of fearful and angry faces in psychiatrically well subjects. It seems paradoxical for an effect that is produced by antidepressant drugs (reduced transporter activity) to be associated with increased emotional reactivity and perhaps depression. Hariri et al (2005) reviewed evidence suggesting that antidepressant effects are related to downregulation of serotonin receptor 1A (5-HT1A) autoreceptors rather than to increased synaptic serotonin, with reduced transporter activity (due to short alleles) producing the opposite effect through postsynaptic downregulation and resulting insensitivity to serotonin. It would seem that no clear explanation of these diverse findings and effects is currently available. Further, there are at least 24 known single nucleotide polymorphisms in SLC6A4, including at least 9 that produce amino acid changes (Hahn and Blakely 2002), and no study has addressed the effects of all possible sequence variations on behavior and gene function. It is only now becoming technologically feasible to study a large number of polymorphisms in any given candidate gene, and such studies are needed, both for genes selected based on mechanism and for those that emerge from systematic positional cloning studies.

Brain-Derived Neurotrophic Factor

Another more recent etiological hypothesis about depression is that neurotoxic effects (possibly related to excessive corticotropin activity and/or to the inflammatory effects of cytokines) damage or kill hippocampal cells, which in turn mediate many depressive symptoms, with deficient function of neuroprotective peptides. Genetic factors could alter the balance of neurotoxic and neuroprotective responses to stress, while antidepressants have been shown to enhance neuroprotective effects (for a review, see Manji et al 2001). Brain-derived neurotrophic factor (BDNF) is one such neuroprotective protein, and there were

Table 1. Meta-Analyses of Mood Disorder Genetic Association Studies

Polymorphism, Disorder	Ref	Studies	Cases/Control	Effect	OR	CI	p	Comments
COMT Val158/108Met								
BD:	a	12	NR	Met:	1.08	.95–1.23	NS	Omitted the first positive report
DRD3 Ser9Gly								
BD:	b	11	980/1100	Allele 1:	1.04	.90–1.21	NS	788 cases vs. 1100 control subjects, plus 192 trios
HTR2A T102C								
UP c-c:	c	7	768/959	Alleles:	.96	.84–1.11	NS	
BD c-c:	c	10	1095/1468	Alleles:	.98	.87–1.10	NS	
Suic vs. Cont:	d	9	596/1003	Alleles:	1.09	.93–1.27	NS	Also NS without 2 Asian samples
SLC6A4								
5-HTTLPR								
BD c-c:	e	15	2774/3652	S (short) allele:	1.13	1.05–1.22	.001	
BD c-c:	f	12	1356/1953	S; each GT:	NR		NS	Het+
BD TDT:	f	6	NR	S:	NR		NS	
UP c-c:	e	14	1961/3402	S:	1.05	.96–1.14	NS	Het+; No effect of ethnicity
UP c-c:	f	10	910/2017	S; each GT:			NS	Eur S/S OR = 1.16 ($p < .05$), dependent on one study; NS due to multiple tests; Het+
Suic vs. Cont:	g	17	1521/2429	SS + SL vs. LL:	1.21	.94–1.57	NS	NS for S allele; Het+; ethnicity
Suic vs. Cont:	d	12	1168/1371	S:	1.17	1.04–1.32	.009	Also significant for SS vs. LL, SS + SL vs. LL, the effect was for attempters not completers
Suic vs. non-suic pts:	g	8	511/831	SS + SL vs. LL:	1.55	1.15–2.10	.004	NS for S allele; GT effect in alcoholism, not mood or psychotic disorders
Violent suic vs. Cont:	g	5	190/733	SS + SL vs. LL:	3.32	1.51–7.31	.003	Also significant for alleles (OR = 1.67), and for violent vs. nonviolent suic (alleles or GT)
Non-violent suic vs. Cont:	g	5	375/733	SS + SL vs. LL:	.94	.71–1.25		NS for S allele
Neuroticism/	h,k	23	5629	NEO + TPQ:			.087	T scores (mean 50, SD 10); Het+
Harm Avoidance:				NEO only (10):			.000016	
Neuroticism (NEO):	i	11	2231[l]				NS	Also NS for GT, dominant or recessive
Harm Avoidance (TPQ):		13	2598[l]	SS vs. SL + LL			.0021	Also $p = .0082$ for SS vs. LL
Intron 2 VNTR								
BD c-c:	e	11	2292/1357	Length (contin):	1.05	.96–1.14	NS	Het+; No effect of ethnicity or instrument
BD c-c:	f	15	1605/2697	9, 10, 12 rpts:			NS	Het+; Each allele NS for Asian, Eur separately
UP c-c:	e	9	1817/653	Length (contin):	.99	.92–1.06	NS	
UP c-c:	f	11	706/2242	9, 10, 12 rpts:			NS	Het+; Each allele NS for Asian, Eur separately
TH Tetranuc Repeat								
BD:	j	9	583/745	Alleles 2, 3, 4, 5:			NS	Also NS for 846 BD + UP cases vs. 823 Cont
UP:	j	3	204/359	Alleles 2, 3, 4, 5:			NS	
TPH Intron 7 A218C								
BD:	a	5	NR	C allele:	1.12	.98–1.28	NS	Omitted the first positive report

All studies used random and/or fixed effects meta-analysis methods.

Ref, reference; Suic, suicidal; Cont, control subjects; OR, odds ratio; CI, 95% confidence interval; BD, bipolar disorder; Pub bias, publication bias (Egger model); Contin, allele length analyzed as continuous variable; c-c, case-control studies only; TDT, family-based studies only; Eur, European; GT, genotype; rpts, repeats; Het+, significant between-studies heterogeneity detected; NR, not reported; NS, not significant; pts, patients; NEO, NEO Personality Inventory; TPQ, Tridimensional Personality Questionnaire; UP, unipolar depression (major depressive disorder).

[a]Lohmueller et al 2003.
[b]Elvidge et al 2001.
[c]Anguelova et al 2003a.
[d]Anguelova et al 2003b.
[e]Lasky-Su et al 2005.
[f]Lotrich and Pollock (2004).
[g]Lin and Tsai (2004).
[h]Sen et al 2004.
[i]Munafo et al 2005.
[j]Furlong et al 1999.
[k]Similar conclusions reached by Schinka et al (2004), details not shown.
[l]Analysis included only general population samples (no patient samples), and excluded studies with deviation from Hardy-Weinberg equilibrium.

initial reports of reduced serum BDNF in MDD (Karege et al 2002) and of association between polymorphisms in BDNF and BD (Sklar et al 2002; Neves-Pereira et al 2002), but subsequent reports have been mixed for both disorders (Hashimoto et al 2004; Tsai et al 2003; Strauss et al 2004; Geller et al 2004; Kunugi et al 2004; Oswald et al 2004; Nakata et al 2003) and there are insufficient reports of the same polymorphism and MDD phenotype to support a meta-analysis. This and other genes relevant to this hypothesis will be receiving more intensive study.

Genetic Linkage Studies

An alternative to the study of mechanism-based candidate genes is the positional cloning strategy–the systematic study of the genome, either with genetic linkage studies of informative pedigrees followed by association studies of candidate regions (e.g., using very dense maps of single nucleotide polymorphisms) or systematic genome-wide association studies. The latter have not yet been attempted for depression, but several linkage studies have been or will soon be reported for MDD and related traits. A comparison of these studies illustrates the diverse strategies available for this problem.

The sample sizes and phenotype definitions of these studies are summarized in Table 2. All studies used 9 to 10 cM microsatellite marker maps, except that the Abkevich et al (2003) and Camp et al (2005) analyses are from the same study, which used a 5 cM map. The clinical characteristics of an additional industry-sponsored study of 470 recurrent MDD (MDD-R) affected sibling pairs (ASPs) have been published (Farmer et al 2004), with a stated goal of

collecting 1000 ASPs, but genome scan results are not yet available. Holmans et al (2004) published a report on around half of their large sample, with results from their full sample of around 650 MDD-RE pedigrees to be published shortly.

Table 3 describes findings that have received some support in more than one study. In the absence of data to compare identical phenotypes and statistical methods, "positive" results have been selected simply based on the top 10 findings (or lod [logarithm of the odds ratio] scores >2 without covariates) in two or more studies, to gain a rough idea of the degree of support for chromosomal regions across studies. Each study produced additional interesting findings that might prove to be important as more data appear. This compilation falls far short of a formal meta-analysis or combined analysis, which might be valuable once the full Farmer et al (2004) and Holmans et al (2004) results are available. The reader is referred to the original papers for further details of these studies.

In the three MDD scans, approaches to analysis have varied. Holmans et al (2004) analyzed a single diagnostic model (MDD-RE, with age at onset less than 31 for probands and 41 for other cases) with one primary linkage analysis (multipoint allele-sharing analysis using ALLEGRO [Gudbjartsson et al 2000]) and empirical genome-wide p-values. Abkevich et al (2003) and Camp et al (2005) published separate analyses of the same linkage study of large Utah pedigrees selected for having multiple MDD cases. Abkevich et al (2003) considered all MDD and BD cases as affected and analyzed male subjects and female subjects separately, correcting for two tests. Camp et al (2005)

Table 2. Linkage Studies of Major Depression and Neuroticism-Related Personality Traits

Author, year	Families	Cases	Phenotype(s)
MDD			
Zubenko et al 2003a	81	NA	MDD-RE,[a] MDD-R, "major" mood disorders, "all" mood disorders, "depressive spectrum" disorders
			Sex and "2q linkage" as covariates
Holmans et al 2004	297	819	MDD-RE[a]
Utah Study[b]			
Abkevich et al 2003	110	1,107	MDD or BD-I or BD-II
Camp et al 2005	87 (19–112)[c]	75–718[c]	MDD-RE[a]; MDD-RE[a] or anxiety disorder; MDD-RE[a] plus anxiety disorder
			Secondary analysis divided by sex
Personality		N (genotyped)	
Cloninger et al 1998	105	987	Harm avoidance (in alcoholism pedigrees)
Fullerton et al 2003	561	1,122	Neuroticism
			Extreme concordant-discordant pairs drawn from a population sample of 88,141
Nash et al 2004	283	757	Composite index of anxiety and depression; neuroticism
			Extreme concordant-discordant pairs drawn from a population sample of 6,387 sibships
Neale et al 2005	129	343	Neuroticism (12-item)

Shown are the sample characteristics and phenotype definitions in linkage genome scans of major depression and of neuroticism and related personality traits.

MDD-RE, recurrent, early-onset major depression; MDD-R, recurrent major depression; MDD, major depressive disorder; BD-I, bipolar I disorder; BD-II, bipolar II disorder.

[a]Before age 25 in Zubenko et al (2003a); before age 31 in Holmans et al (2004) (before 41 for cases other than probands) and in Camp et al (2005). Fullerton et al (2003) studied pairs in which each sib was in the top or bottom 2.5 percentile of scores; Nash et al (2004) selected the 10% "most informative" pairs.

[b]Abkevich et al (2003) and Camp et al (2005) drew their pedigrees from the same Utah sample. Abkevich et al (2003) considered all MDD cases plus BD-I and BD-II as affected, and selected families with four or more such cases. Camp et al (2005) considered MDD-RE cases (and/or, in alternative analyses, all DSM-IV anxiety disorders) as affected, excluded BD cases, and selected families with three or more MDD-RE cases.

[c]Eighty-seven large families were studied. The p-values were corrected for multiple testing: for each of three diagnostic models, pedigrees were split for analysis by limiting the genealogies to 3, 4, 5, or 6 generations. The n of "independent" families and of "affected" cases varied with diagnostic model and genealogical rule.

Table 3. Depression and Neuroticism Linkage Findings with Support in More Than One Genome Scan

Chr	Region (cM)	Best Linkage Evidence	Supportive Evidence
1	126–137	Neuroticism[a]: 2nd best	Neuroticism[b]: 2nd best
3	105	MDD-RE/Anx, MDD-RE[c]: Best	Neuroticism[b]: 4th best
4	151–176	Neuroticism[a]: 3rd best	MDD-RE/Anx[c]: lod > 2 (females)
6	31–47	Neuroticism[d]: Best	MDD-RE + sex[e]: 2nd best M-M
8	8–26	Harm avoidance[f]: Best	Neuroticism[a]: 7th best; best in males
			MDD-RE + sex[e]: 4th best; best M-M
11	85–99	Neuroticism[a]: 6th best	MDD-RE[g]: lod > 2
12	100–105	MD + BD[h]: Best (males)	Neuroticism[a]: Best; best in females
15	105–115	MDD-RE[e]: Best	MDD-RE[c]: Best in males
18	75–88	MDD-RE/Anx[c]: 2nd best	MDD-RE[c]: 5th best
			Mood Dis[g]: lod > 2 (Also harm avoidance[f], 3rd best at 109 cM)

Results are described in most cases in terms of relative strength of evidence for linkage, i.e., the best, 2nd best, etc., linkage score in a primary scan analysis (if no specific subtype listed) or for a phenotype (if listed), or by lod score (without covariates) > 2 (see text).

MDD-RE, recurrent early-onset major depression (onset <31 in references *c,e;* <25 in reference *f*); MDD-RE/Anx, the lod score was maximized over three diagnostic models (MDD-RE alone, MDD-RE or any anxiety disorder, MDD-RE plus any anxiety disorder); MD + BD, analysis of families with multiple MD probands, with BD (bipolar disorder) relatives included as affected; same sample as reference *c;* MDD-RE + sex, MDD-RE with sex of the affected pair entered as a covariate in logistic regression analysis; Mood Dis, any mood disorder (broad diagnosis); M-M, male-male affected pairs.

[a]Fullerton et al (2003).
[b]Neale et al (2005).
[c]Camp et al (2005).
[d]Nash et al (2004).
[e]Holmans et al (2004).
[f]Cloninger et al (1998).
[g]Zubenko et al (2003a).
[h]Abkevich et al (2003).

excluded BD relatives and considered dominant and recessive genetic models for three alternative phenotypes (MDD-RE [age at onset before 31] alone, MDD-RE *or* any anxiety disorder, MDD-RE *plus* any anxiety disorder), each for four methods of splitting their large multigenerational pedigrees for analysis (limiting genealogical connections to three to six generations). They computed empirical genome-wide lod score thresholds using regression analyses (Camp and Farnham 2001) to estimate the number of independent tests. Male subjects and female subjects were analyzed separately in a secondary analysis. Note that Camp et al (2005) grouped all anxiety disorders together, regardless of the weight of evidence for genetic relatedness to depressive disorders; however, most of the anxiety diagnoses were categories (panic disorder, agoraphobia, social phobia) that have shown such a relationship (Mineka et al 1998).

Zubenko et al (2003a) carried out multipoint allele-sharing linkage analyses (LODPAL [Olson 1999; Goddard et al 2001]) for five diagnostic models: MDD-RE (onset before age 26); MDD-R; all MDD and BP; "major and minor" mood disorders; and "depressive spectrum" disorders (details of the included diagnoses and numbers of cases are not provided). Table 3 includes their MDD-RE and MDD-R results. Each phenotype was also analyzed with two covariates (sex and positive or negative family lod score on distal chromosome 2q). Empirical genome-wide lod score thresholds were computed for each analysis, without correction for multiple tests. This reviewer encountered several difficulties in interpreting the results: 1) unusually low simulation-based lod score thresholds (1.72–2.47 depending on model) were reported for analyses without covariates, but it is likely that the true thresholds were higher, particularly with multiple testing taken into account; 2) analyses using covariates produced several scores above 6, with no mention that lod scores are increased by the increased degrees of freedom; these should not be confused with scores from single-degree-of-

freedom analyses without covariates; 3) the highest score of 8.19 on chromosome 2q (MDD-R) was statistically confounded, because positive versus negative family lod score on 2q was a covariate in the analysis, so that for 2q the sample was essentially predivided in a way that could only produce a high score; 4) additional 2q markers from a different lab were added to the genome scan dataset prior to analysis, which prevents examination of the consistency between scan and fine-mapping results; and 5) these authors refer to "association" and "linkage" with the cyclic adenosine monophosphate (cAMP) responsive element binding protein-1 (CREB1) gene which lies in the distal 2q region of interest (Zubenko et al 2002, 2003a, 2003b), but all of their evidence is for linkage, which can never implicate a specific gene but only a broad chromosomal region containing many genes. The CREB1 is a plausible depression candidate gene (Laifenfeld et al 2005). No association was observed between any of five CREB1 polymorphisms and childhood or adolescent mood disorders in rather small samples (195 nuclear families and 112 cases vs. control subjects), with both unipolar and bipolar disorders included in the first sample and both MDD and dysthymic disorder in the second sample (Burcescu et al 2005).

All of the trait-based scans used quantitative multipoint analyses to study linkage to factor scores derived from personality questionnaires and then computed empirical genome-wide statistical thresholds. Two studies (Fullerton et al 2003; Nash et al 2004) used the strategy of selecting extremely concordant and extremely discordant sib pairs recruited from large population-based samples, elegantly demonstrating the potential efficiency and power of trait-based designs. Neale et al (2005) analyzed neuroticism scores in a smaller sample recruited to study nicotine dependence. Cloninger et al (1998) analyzed scores for the harm avoidance factor of the Tridimensional Personality Questionnaire, which is related but not identical to neuroticism (Svrakic et al 1993).

The results summarized in Table 3 suggest in a highly

preliminary way that linkage studies might prove successful in identifying chromosomal regions that contain genes involved in susceptibility to depression. As is the case for all linkage findings in complex disorders, one cannot predict which will prove to be true positives in the long run. Some of the "supportive" findings are sufficiently far apart that they might not be related to the same genetic loci. Two of the regions have also produced evidence for linkage to bipolar disorder: chromosome 12q (see Shink et al 2005 and Green et al 2005 for recent data and reviews), which produced strong evidence for linkage in the Utah sample when BD cases were included (Abkevich et al 2003) but not when they were excluded (Camp et al 2005), and chromosome 18q (see Fallin et al 2004 for recent data and a review). Bipolar findings in both regions are spread over rather wide areas, and it is not known whether there are susceptibility genes common to MDD and BD disorders in these or other regions. But there is sufficient convergence at this point among linkage studies of MDD and of related personality traits to support optimism about the future of these efforts.

One fundamental problem is power. For categorical traits like MDD or its subtypes, power analyses suggest that samples of 900 to 1000 ASPs are required to reliably detect a locus that causes a 25% to 30% increase in risk to siblings of probands (Hauser et al 1996; Levinson et al 2003). It is quite possible that no one single locus has an effect this large. Initial positive linkage reports tend to overestimate the true genetic effects, particularly with smaller samples (Goring et al 2001). For quantitative linkage, the extreme concordant-discordant approach clearly increases power, but Nash et al (2004) comment that with 283 families, their power was modest. Fullerton et al (2003) did not report statistical power, and although they detected multiple significant effects, it is likely that there were false-negatives as well. Thus, the full impact of genetic linkage findings on the search for depression susceptibility genes might come from combined analyses of multiple datasets.

Future Directions

Depression is a complex and multifactorial trait with important genetic and nongenetic contributory factors. Many methods and strategies will be applied, some of them not yet feasible or even imagined. However, a number of directions can be anticipated which are likely to be fruitful, including (at least) the following.

The positional cloning strategy will certainly be pursued using increasingly powerful methods to scan the genome for regions likely to contain relevant genes and then to search for DNA sequence variations in genes in those regions which are associated with the disease or trait. Scanning has usually involved genetic linkage studies of multiply affected families, like those described above. Linkage analysis is less powerful than analysis of association to specific sequence variants (Risch and Merikangas 1996), but only whole-genome linkage studies have been feasible until recently. Linkage scans are likely to miss many weakly contributory loci, but identification of some loci (Levinson 2003) can begin the process of unraveling the underlying mechanisms. Meta-analyses of multiple genome scans can be used to confirm regions of linkage (Levinson 2005), so that additional linkage genome scans of depression and related traits would be valuable.

Whole-genome association studies are now becoming feasible (Craig and Stephan 2005), but many questions remain about their design and power. These studies search across the genome for single nucleotide changes or polymorphisms which influence the disease or trait (direct association) or which are in linkage disequilibrium (LD) with causative variant(s) (indirect association, which results from specific SNP and causative alleles being so close that they are rarely separated by meiosis). It is not yet known how often common (e.g., >10% frequency), less frequent (1% to 10%), and/or very rare (<1%) SNP variants are relevant to complex diseases. It is now feasible to study maps of SNPs that are in LD with many of the common variants in the genome (Gabriel et al 2002; Cardon and Abecasis 2003) or that include most known SNPs in coding regions (exons) with a frequency of at least several percent (Pritchard 2001; Botstein and Risch 2003). It is not yet feasible to scan all sequence variation, which could include multiple very rare variants in susceptibility genes, but enormous advances in sequencing technology are expected in the near future (Kan et al 2004; Edwards et al 2005). At the very least, it should become possible to study most or all sequence variation within specific candidate genes, although relevant statistical methods are still under development (Marchini et al 2005; Neale and Sham 2004). All of these issues will be explored in studies of complex disorders like depression.

Newer hypotheses about the mechanisms of depression susceptibility (see above) are producing new sets of candidate genes (e.g., those involved in neurotrophic and neurotoxic processes, inflammation, regulation of cortisol secretion by the hypothalamic-pituitary axis, sleep, and circadian rhythms). With the advent of more powerful molecular and statistical methods, sequence variation in these genes will be intensively studied in large samples of families or of cases and control subjects for depression and related phenotypes. It should also become possible to study gene-environment interactions (e.g., accounting for factors like childhood trauma and life stress), by conducting larger-scale molecular studies on samples drawn from longitudinal or epidemiological cohorts and by measuring these variables in samples collected for genetic studies. There should be more intensive study of measures that might serve as endophenotypes relevant to depression susceptibility (Hasler et al 2004), perhaps including cortisol hypersecretion (Ehlert et al 2001), dysregulation of sleep (Riemann and Berger 2001), structural changes in the hippocampus and subgenual prefrontal cortex (Drevets 2001; Botteron et al 2002), electroencephalographic (Bruder et al 2005) and psychophysiological (Grillon et al 2005) measures, and other measures related to newer neurobiological hypotheses. There has been very limited study of the variation of these measures in clinically unaffected relatives of depression probands (Sitaram et al 1987; Giles et al 1988; Modell et al 1998), which would be a prerequisite to large-scale genetic studies. Because these measures are generally expensive and intrusive, they present a challenge for large-scale studies, but technological innovations could increase their feasibility. Genetic studies of animal models of depression, anxiety, and antidepressant response may be important in providing initial clues or convergent evidence to augment results of human studies. Gene expression array and proteomic methods are also rapidly evolving.

It is critical that the next generation of genetic studies of depression remain focused on *systematically* querying DNA sequence variation, whether through whole-genome linkage and association studies, dense LD mapping of all genes in a candidate region or in an extensive network of interacting genes detected by an unbiased method (and still denser mapping or sequencing of specific candidate genes that emerge from previous studies), whole-genome or whole-network gene expression studies, proteomic methods, or convergent evidence from two or more systematic strategies, etc. Most previous genetic studies of de-

pression, limited by available technologies, have focused on a small number of genes and polymorphisms selected on the basis of existing hypotheses. Current and near-term technology liberates us from this limitation, permitting us to query the genome in ways that could produce entirely new hypotheses and mechanisms about this complex susceptibility.

In conclusion, although it will be a challenging problem to uncover the genetic mechanisms underlying susceptibility to depression and related traits, it appears likely that the challenge can be met using technology that is either feasible now or that should be available quite soon.

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