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Genetics and genomics of depression

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Abstract

Depressive disorders are among the most common psychiatric diseases, with prevalence estimates ranging from 5% to a maximum of 20%. Despite their high prevalence and socioeconomic impact, little is known about their etiology. Heritability estimates demonstrate up to a 50% genetic component based on family aggregation and contrasting monozygotic and dizygotic twin studies. The low relative risk to siblings (λsib <1.5) makes the search for their genetic determinants very tedious. Gene-environment interaction has been recognized for a long time in the pathophysiology of depression, and its best biological substratum at present is represented by the serotonin transporter (5-HTT) gene, where several copies of its short allele culminate in depression and suicide in response to lifelong stress events. Many total genome scans have been performed with variable results, the most authoritative being the one of Utah pedigrees with a strong family history of major depression. It identified a locus on chromosome 12 encompassing a gene cluster and sex-specific predisposition. Nevertheless, recent genome scan meta-analysis yielded somewhat disappointing conclusions with a relatively low significance for quantitative trait loci on chromosomes 9, 10, 14, and 18. Studies on animal models have contributed to the chromosomal mapping of many behavioral traits, including anxiety, the stress response, and depression. Although F2 crosses constitute a classical approach, novel models of recombinant inbred strain and recombinant congenic strain animals allow for a rapid initial localization of any traits. This type of analysis has led us to uncover significant loci for the stress response and anxiety in rats and mice.

1. Introduction

Three thousand years ago, an Egyptian script reflected on the human condition, aging, and death in a very pessimistic way, but it was specifically at the time of Hippocrates, 5 centuries before our era, that this school coined the term *melankholia* (black bile), for one of the 4 humors. Following in the footsteps of the Greeks, Avicenna (Ibn Sina) described melancholic conditions in his textbooks, which have endured for several centuries as a canon of medicine, and attributed their origin to a somatic component, *splen* (Gk), from which the English word "spleen" was later derived [1].

Depression is one of the most common psychiatric diseases, with prevalence estimates ranging from 5% to 20%. It is recurrent, tends to have a chronic course, and is often comorbid in nature. Depression is a clinically heterogeneous disorder thought to result from an interplay of multiple genes interacting with environmental and developmental epigenetic components. It presents itself in 2 etiologically different forms, that is, bipolar disorder (manic depression) or unipolar disorder (a condition characterized by depression alone). Both forms are subject to a genetically overlapping and distinct genetic influence (for review, see Ref. [2]).

Depression comprises different symptoms, such as disturbance of mood, thinking, sleep, appetite, and motor activity, with suicidal thoughts or attempts that occur in different degrees of penetrance and intensity in depressed individuals [3]. The possibility that depression is best defined as a collection of syndromes rather than a single entity differing in the severity of its symptoms is plausible and may be supported by distinct genetic signatures. As with other polygenic traits, an additional difficulty in the identification of its genetic determinants resides in the fact that each individual gene has a modest effect, and the trait as a whole is often strongly modulated by the environment [4]. This is important with psychiatric disorders where there are additional impediments in the hunt for genes that include poor diagnosis, which is more often an art than a science. Cases are often identified on the basis of ambiguous symptoms, and individuals in a pedigree may be misdiagnosed. Another complication is phenotypic heterogeneity where a number of distinct genetic causes may result in a similar set of symptoms.

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It has been postulated that a dimensional rather than a categorical approach to the depressive phenotype definition would increase the probability of identifying its susceptibility genes. A recent exploratory factor analysis was thus performed to model depressive symptom dimensions [5]. In this study, undertaken in a large and well-defined sample of depressed subjects, 4 factors were identified: (1) mood symptoms and psychomotor retardation; (2) anxiety; (3) psychomotor agitation, guilt, and suicidality; and (4) appetite increase and hypersomnia. Three of the 4 dimensions suggested substantial familial and potentially genetic etiologies. It was concluded that the identification of depression symptom dimensions could provide the potential for a more refined phenotypic definition, such as that required in gene-mapping studies.

2. Unipolar depression

Major depressive disorder (MDD, unipolar depression) is a common disorder associated with increased mortality, particularly because of a high suicide rate [6]. It is the leading cause of worldwide disability among individuals between 15 and 44 years of age [7]. The lifetime prevalence of MDD is between 5% and 10% [8] with women almost twice as likely to be affected as men. The major depressive syndrome is characterized by its length, exceeding 2 weeks of depressed mood and/or reduced or absent capacity for pleasure accompanied by additional symptoms such as disturbed sleep and appetite, reduced concentration and energy, excessive guilt, slowed or agitated movements, and suicidal thoughts or acts [3]. Twin and adoption studies have confirmed its genetic inheritance [9-11]. Studies of monozygotic and dizygotic twin pairs suggest polygenic inheritance, with evidence of major locus effects and an overall heritability estimate between 40% and 70%, as confirmed by recent meta-analysis [12]. First-degree relatives of individuals suffering from MDD have at least a 2- to 3-fold increased risk of MDD compared with the general population [13,14]. Two clinical features of the probands can predict a greater MDD risk in first-degree relatives: recurrent episodes and early age of onset. The relationship between recurrent episodes and familial risk has been reported in several studies, and increased familial risk for early onset probands has also been observed in nearly 10 different studies. There is also a possible interaction between earlier age of onset and recurrence. Again, the definition of more homogenous disease phenotypes or clinical subsyndromes is required, and the study of population isolates may help increase genetic homogeneity.

3. Bipolar depression

Bipolar depression (BPD) can be subdivided into bipolar 1 (BP1) and bipolar 2 (BP2) disorders. Bipolar 1 is defined as having at least one lifetime episode of mania and usually (but not necessarily) episodes of depression, but may also include episodes of hypomania, whereas BP2 shows episodes of both hypomania and depression with no manic episodes [15]. Based on a broad definition of BPD, a prevalence rate of 11% has been reported, with a suicide rate between 10% and 15%, 15-fold higher than in the general population. Whether BP1 and BP2 represent distinct forms of the clinical and genetic condition or merely different points along a continuum of severity is still a matter of debate [15]. In most families, bipolar disorders are thought to be influenced by multiple genes as well as by environmental influences. Gene-gene and gene-environment interactions, therefore, complicate attempts to understand the cause of this complex disorder(s). Similarly to other complex traits [16], locus heterogeneity can also be a player. Again, it is important to determine whether a trait quantitatively influences the disorder or whether the trait is a syndrome of dimension of the disorder.

4. Overlap between unipolar and bipolar depression

One major impediment to the identification of susceptibility genes of depression is the misdiagnosis of cases, which is often based on ambiguous symptoms. The genetic relationships between unipolar and bipolar disorders remain unclear. Although unipolar and bipolar types of depression are genetically distinct syndromes, there is some genetic overlap between the 2. Thus, confusion may arise from misdiagnosis on the one hand and from genetic overlap between the 2 depression types within the same pedigree on the other hand. It is well known that some individuals with major depression episodes also have episodes of mania or hypomania (manic syndrome without substantial functional impairment), receiving a diagnosis of BP1 and BP2, respectively. In contrast, unipolar depression is much more common among relatives of BPD patients, and affective disorders tend to coexist with anxiety in many families [17,18]. First-degree relatives of BP1 and BP2 probands are at increased risk of both unipolar and bipolar disorders, but the relatives of MDD probands are not at increased risk of BP [13,19,20], and males and females are at equal risk of BP1, suggesting that unipolar and bipolar disorders are at least partially independent genetically. The status of BP2 is less clear. Relatives of BP2 probands are at greater risk of BP2 than BP1 [21-23], and BP2 lies between BP1 and MDD in clinical features and in the rates of BP1 and MDD in families of BP2 probands. It is difficult to differentiate reliably between BP2 and MDD with current methods. Partly for these reasons, the genetic determinants of these disorders have remained particularly elusive so far.

5. Linkage analysis

Numerous studies have investigated genetic linkage to BPD over the past 2 decades. As many as 10 chromosomes (chr) have been shown, through mapping analysis, to contain genes contributing to BPD. The earlier reports

suggested linkage to loci on chr 11, the X chr, and chr 18. Other linkage studies published later on identified candidate regions on a number of different chromosomes, including 1q, 4p, 10p, 12q, 13q, 18pq, 20q, 21q, 22q, and Xq. A first meta-analysis of all reported genome scans found the strongest multipopulational evidence for BPD susceptibility loci on chrs 13q and 20q [24]. A subsequent meta-analysis, which included more studies than in the earlier one and excluded some smaller studies that the previous study had included, concluded that no chromosomal region achieved statistical significance by several simulation-based criteria. The most significant loci were identified on chrs 9p, 10q, and 14q, with some suggestive loci on chrs 9p, 18p, and 18q. Narrowing these regions has proven to be difficult to date, and, as yet, no genes have been conclusively demonstrated for BPD, and we have to remember the well-recognized bias of the meta-analysis approach resulting from underreporting of negative data.

Abkevich et al [25] typed 628 microsatellite markers in 110 Utah families (large families with similar habits, including avoidance of coffee and alcohol) with 4 or more available affected cases ascertained through MDD probands. Linkage was analyzed for all cases first, and then for males and females separately. One significant quantitative trait locus (QTL) on chr 12q22-23 was observed in males only, where evidence for linkage to BPD had been reported [26-30]. Later on, Fullerton et al [31] performed a genome scan in 559 sibling pairs who were concordant or discordant for neuroticism scores, as a substantial overlap was estimated between the genetic factors underlying MDD and neuroticism [32-36]. In their study, significant evidence for linkage was observed on chrs 1q, 4q, 7q, 8p, 11q, 12q, and 13q. The 12q peak they found was essentially at the same location as the significant QTL results reported by Abkevich et al [25], except that the neuroticism linkage was observed primarily in females rather than in males. In a more recent study by Holmans et al [6] with a sample consisting of 297 informative families containing 415 independent affected sibpairs (685 informative affected relative pairs), affected cases had recurrent MDD with onset before the age of 31 years for probands or 41 years for other affected relatives. Mapping with 389 microsatellite markers identified a significant QTL at chr 15q25 for recurrent, early-onset MDD. Linkage was not sex-specific. No other significant QTLs were identified. The latter study did not confirm the QTL on chr 12q reported by the earlier studies mentioned above, even with sex as a covariate. It was noted that the clinical model was somewhat different between the studies, and the inconsistent results for MDD are again typical of complex traits for which the replication of linkage is difficult.

6. Candidate gene approach

Molecular and genetic research in depression has also relied on association analysis using candidate genes such as those coding for neurotransmitters, mainly serotonin and dopamine. The 5-HT (serotonin) system has received the most attention for its involvement in a myriad of processes, including brain development and synaptic plasticity. A variant of 5-HTT located on chr 17q, a protein critically involved in the control of 5-HT function, has been evaluated as a candidate gene. Allelic variations in the 5′ flanking transcriptional region of 5-HTT gene (5-HTTLPR which controls 5-HTT expression and function) have been associated with personality traits, including anxiety, depression, and aggressiveness. Short (S) and long (L) 5-HTTLPR variants differentially modulate the transcriptional activity of the 5-HTT gene promoter, protein concentration, and the resulting 5-HT uptake in lymphoblastoid cells. They also influence several other functions, such as 5-HT uptake and content in platelets and the response to pharmacological treatment, and even 5-HTT neuroimaging in the human brain, with the S variant being associated with lower 5-HTT expression and function (for review, see Ref. [2]). 5-HTTLPR polymorphism has been associated with increased risk of mood disorders, including depression and bipolar disorder, in several independent population- and family-based studies. However, this polymorphism has only a moderate influence on these traits corresponding to less than 5% of the total variance.

It has been suggested by Caspi et al [37] that although the 5-HTT gene may not be directly associated with depression, it could modulate the serotoninergic response to stress. This was based on 3 lines of experimental genetic research suggesting the hypothesis of gene × environment interaction. First, although there was no clear genotype-phenotype correlation in the absence of stress, homozygous −/− and heterozygous +/− mice with disrupted 5-HTT exhibited more fearful behavior and greater increases in the stress hormone ACTH in response to stress than homozygous +/+ controls. Secondly, in rhesus macaques in which the length of the gene variant is analogous to that of humans, the S allele is associated with decreased serotoninergic function only in those reared in stressful conditions. Thirdly, human neuroimaging indicates that the stress response is mediated by variations in 5-HTTLPR. Humans with 1 or 2 copies of the S allele exhibit greater amygdala neuronal activity to fearful stimuli compared with individuals homozygous for the L allele. In 2003, Caspi et al [37] reported a prospective longitudinal study of a representative birth cohort, supporting the hypothesis of a gene-environment interaction in which an individual's response to environmental insults is controlled by the number of copies of the HTT promoter polymorphism. Thus, individuals with 1 or 2 copies of the S allele of the 5- HTT promoter polymorphism presented more depressive symptoms in relation to stressful life events than individuals homozygous for the L allele [37] (see review by Wurtman [this issue] for more details). Furthermore, 2 nonsynonymous single-nucleotide polymorphisms (SNPs) that changed the coding sequence of 5-HTT gene were found to segregate with complex serotoninergic dysfunction–related phenotypes, including

obsessive compulsive disorder and other 5-HT-related disorders, or were associated with severe depression. A missense mutation resulting in conserved ILE-425-VAL substitution in 5-HTT gene was linked with obsessive compulsive disorder [38]. This substitution is located in transmembrane domain 8 of 5-HTT and may modify the α-helix secondary structure and, thus, have an effect on transport function. Functional studies have shown a gain in function through constitutive activation resulting in a 2-fold increase of 5-HT uptake [39]. Other variations and functional SNPs identified in the transcriptional control region of the gene of the 5-HT1A receptor have been reported to be associated with anxiety- and depression-related personality traits [40].

In 2002, Lander's team [41] at MIT's Whitehead Institute investigated 76 candidate genes of BPD. Only 1 gene, the NGF gene encoding brain nerve growth factor, proved to correlate with this disorder. Recently, gene expression, as controlled by putative loci impact, became a major tool for exploration (e-QTL). Gene profiling was performed in the human postmortem prefrontal cortex and demonstrated altered expression of LIM and HSPF1. In major depression and suicide, similar abnormalities were observed in lymphoblast cells. This observation revived an older notion of a major deletion in HSP70 gene, suggesting the importance of the cell survival pathway in major depression and suicide.

7. Experimental genetics of depression

Major difficulties in relying on animal models for the study of depression or other related psychological disorders stem from the fact that there is no conclusive evidence that what occurs in a rat or mouse brain is the same as what occurs in the human brain. Nevertheless, although imperfect, to be useful, a good animal model of affective disorders should fulfil the following criteria: (1) strong behavioral similarities; (2) common cause; (3) similar pathophysiology; and (4) common treatment as for the human pathology. A wide range of animal models have been developed to study the psychobiology of emotionality, and anxiety- and depression-related behaviors. A battery of tests have been developed to offer rigorous and standardized phenotyping in rodents, an utmost prerequisite for genomic analysis. A review by Crawley and Paylor [42] provided many examples of successful behavioral phenotyping of rats and mice and the application of these paradigms to the human pathology. These neurological and neuropsychological tests can be effective as a first screening for behavioral abnormalities and converted from rats to mice. Depression tests include the Porsolt swim immobility test and the learned helplessness test.

In rodents, models of depression comprise depressive behavior as a result of genetic selection/manipulation, environmental stressors during development, in adulthood or with pharmacological treatment. The genetic model of helpless behavior is an example of environmentally induced pathology. Animals exposed to uncontrollable stress may become helpless and subsequently fail to escape controllable stress. Helpless animals share several characteristics with depressed humans. Selective breeding of Sprague-Dawley rats led to the creation of a congenital helpless rat model [43]. Another novel model of depression is the Wistar-Kyoto rat which presents sleep abnormalities, a hallmark of depression [44]. A helpless mouse line has also been developed by selective breeding [45].

Experimental genetic studies of behavioral traits are currently under way in mice and rats. Monogenetic (single-gene analysis) investigations are being conducted in transgenic (gene addition) rodents or knockout (gene deletion) mice (no knockout rats have been produced up to now). Transgenic and knockout technologies make it possible to test the importance of a known gene coding for neurotransmitters, receptors, etc. However, because depression is a polygenic trait, models such as recombinant inbred (RI), congenic, and recombinant congenic strains are used to map behavioral phenotypes, the initial step for positional cloning and gene identification as well as gene × environment interaction studies. Polygenic rodent models are currently being tested to identify genetic loci which by syntenic analysis can help to identify orthologous genes in humans. Some RI strains include the following: the B6 strain shows higher open-field activity than the A/J group [46-52] as well as more transitions in the light/dark box [48,53] and hole-poking responses [50], higher open-arm duration in the elevated plus maze [52], and a higher number of cued and contextual fear-conditioning responses [54]. The A × B/B × A RI panel was formed by interbreeding B6 and A/J parental strains. By mapping each resulting RI strain with genomic markers evenly dispersed throughout the genome, QTLs were identified for baseline and diazepam-induced activity in open-field and light/dark box tests [55], as well as ethanol- [56] and cocaine-induced activation [57]. We have recently used the paradigm of recombinant congenic strains of mice with C57BL/6J (B6) and A/J (A) progenitors to map the QTL of emotionality and stress susceptibility [58]. Initial data showed the highest load scores on the chr 1 region for an emotionality index overlapping with stress susceptibility on chrs 1 and 15. Some of the mouse stress QTL displayed synteny with our previously observed stress susceptibility loci in humans and rats [59]. Quantitative trait loci on mice chr 1 and 15 confirm the overlapping linkage of emotionality and stress susceptibility.

Because the relationship between stress and depression is well recognized, increased knowledge of the genetic determinants of stress [60] should further advance the collaborative approach in the search for genes of depression. A relevant example has been published recently and proposed as a novel concept in the pathophysiology of depression [60]. In this study, Fuchs et al [61] from Gottingen University demonstrated that chronic psychological stress (in a tree shrew model of depression) reduced hippocampal

cell proliferation, and transcriptional analysis revealed the suppressed expression of genes involved in cell differentiation. These abnormalities were alleviated by administration of the antidepressant clomipramine. This is an example of current collaborative work between behavioral psychobiologists and geneticists. In addition, such studies argue for expression array technology as an optimal reflection of environmental influences [62].

8. Conclusion

Depression is a trait as complex as other common diseases such as hypertension or diabetes. However, given the psychobiological complexity of depressive disorders and of the gene-environment interaction paradigm, it is not surprising that identification of the genetic determinants of depression is extremely difficult. As with other complex traits, an amalgam of winning conditions has to be met before success can be reached. These conditions include (1) development of the novel discipline of comparative genomics, which takes advantage of the recent sequencing of the human, rat, and mouse genomes; (2) better definition of depression disorder, which will require exquisitely fine phenotyping in both human cohorts and genetically designed rodent models; (3) the study of relatively isolated populations, which may help decrease heterogeneity of the disease; (4) higher density of genotyping; a million SNP genotyping will be possible in the near future with a single microarray chip; (5) the revolution in bioinformatics required to analyze the mass of data that will be generated; (6) the integration of these emerging technologies; and (7) improved collaboration between neurologists, neurobiologists, and neurogeneticists with bioinformaticians.

It is expected that future advances in the genomics of depression and mood disorders will facilitate pharmacogenetic studies leading to personalized treatments and better prevention measures.

References

[1] Jacquart D. Les médecins et les secrets de la bile noire. L'Histoire 2004;285:44-7.
[2] Lesch KP. Gene-environment interaction and the genetics of depression. J Psychiatry Neurosci 2004;29:174-84.
[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association; 1994.
[4] Hamet P, Pausova Z, Adarichev S, Adaricheva K, Tremblay J. Hypertension: genes and environment. J Hypertens 1998;16:397-418.
[5] Korszun A, Moskvina V, Brewster S, Craddock N, Ferrero F, Gill M, et al. Familiality of symptom dimensions in depression. Arch Gen Psychiatry 2004;61:468-74.
[6] Holmans P, Zubenko GS, Crowe RR, DePaulo Jr JR, Scheftner WA, Weissman MM, et al. Genomewide significant linkage to recurrent, early-onset major depressive disorder on chromosome 15q. Am J Hum Genet 2004;74:1154-67.
[7] World Health Organization. The global burden of disease. Geneva, Switzerland: World Health Organization Press; 1996.
[8] Zubenko GS, Maher B, Hughes III HB, Zubenko WN, Stiffler JS, Kaplan BB, et al. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet 2003; 123B:1-18.
[9] Mendlewicz J, Rainer JD. Adoption study supporting genetic transmission in manic-depressive illness. Nature 1977;268:327-9.
[10] Cadoret RJ. Evidence for genetic inheritance of primary affective disorder in adoptees. Am J Psychiatry 1978;135:463-6.
[11] Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 1986;43:923-9.
[12] Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157:1552-62.
[13] Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. Arch Gen Psychiatry 1982; 39:1157-67.
[14] Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, et al. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University-National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 1984;41:13-21.
[15] Mitchell PB, Malhi GS, Ball JR. Major advances in bipolar disorder. Med J Aust 2004;181:207-10.
[16] Hamet P, Pausova Z, Tremblay J, Deng AY. Hypertension as a genetic disease. In: Mancia G, Chalmers J, Ferrari A, Julius S, Saruta T, Weber M, editors. Hypertension Manual. Robert Stevenson House, Scotland: Harcourt Brace & Co Ltd; 2002. p. 49-75.
[17] Merikangas KR, Chakravarti A, Moldin SO, Araj H, Blangero JC, Burmeister M, et al. Future of genetics of mood disorders research. Biol Psychiatry 2002;52:457-77.
[18] Thapar A, McGuffin P. Anxiety and depressive symptoms in childhood—a genetic study of comorbidity. J Child Psychol Psychiatry 1997;38:651-6.
[19] Maier W, Lichtermann D, Minges J, Hallmayer J, Heun R, Benkert O, et al. Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. Arch Gen Psychiatry 1993;50:871-83.
[20] Tsuang MT, Faraone SV. The genetic epidemiology of schizophrenia. Compr Ther 1994;20:130-5.
[21] Simpson SG, Folstein SE, Meyers DA, McMahon FJ, Brusco DM, DePaulo Jr JR. Bipolar II: the most common bipolar phenotype? Am J Psychiatry 1993;150:901-3.
[22] Heun R, Maier W. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. Acta Psychiatr Scand 1993;87:279-84.
[23] Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W. Bipolar II. Combine or keep separate? J Affect Disord 1985;8:17-28.
[24] Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 2002;7:405-11.
[25] Abkevich V, Camp NJ, Hensel CH, Neff CD, Russell DL, Hughes DC, et al. Predisposition locus for major depression at chromosome 12q22-12q23.2. Am J Hum Genet 2003;73:1271-81.
[26] Craddock N, McGuffin P, Owen M. Darier's disease cosegregating with affective disorder. Br J Psychiatry 1994;165:272.
[27] Dawson E, Parfitt E, Roberts Q, Daniels J, Lim L, Sham P, et al. Linkage studies of bipolar disorder in the region of the Darier's disease gene on chromosome 12q23-24.1. Am J Med Genet 1995;60:94-102.
[28] Morissette J, Villeneuve A, Bordeleau L, Rochette D, Laberge C, Gagne B, et al. Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in Quebec points to a locus of major effect on chromosome 12q23-q24. Am J Med Genet 1999;88:567-87.

[29] Ewald H, Flint T, Kruse TA, Mors O. A genome-wide scan shows significant linkage between bipolar disorder and chromosome 12q24.3 and suggestive linkage to chromosomes 1p22-21, 4p16, 6q14-22, 10q26 and 16p13.3. Mol Psychiatry 2002;7:734-44.
[30] Jones I, Jacobsen N, Green EK, Elvidge GP, Owen MJ, Craddock N. Evidence for familial cosegregation of major affective disorder and genetic markers flanking the gene for Darier's disease. Mol Psychiatry 2002;7:424-7.
[31] Fullerton J, Cubin M, Tiwari H, Wang C, Bomhra A, Davidson S, et al. Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. Am J Hum Genet 2003; 72:879-90.
[32] Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women. Reliability of diagnosis and heritability. Arch Gen Psychiatry 1993;50:863-70.
[33] Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. J Abnorm Psychol 1994;103:103-16.
[34] Duggan C, Sham P, Lee A, Minne C, Murray R. Neuroticism: a vulnerability marker for depression evidence from a family study. J Affect Disord 1995;35:139-43.
[35] Fava M, Alpert JE, Borus JS, Nierenberg AA, Pava JA, Rosenbaum JF. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. Am J Psychiatry 1996;153:1308-12.
[36] Enns MW, Cox BJ. Personality dimensions and depression: review and commentary. Can J Psychiatry 1997;42:274-84.
[37] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
[38] Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, et al. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. Mol Psychiatry 2003; 8(895):933-6.
[39] Kilic F, Murphy DL, Rudnick G. A human serotonin transporter mutation causes constitutive activation of transport activity. Mol Pharmacol 2003;64:440-6.
[40] Strobel A, Gutknecht L, Rothe C, Reif A, Mossner R, Zeng Y, et al. Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. J Neural Transm 2003;110:1445-53.
[41] Sklar P, Gabriel SB, McInnis MG, Bennett P, Lim YM, Tsan G, et al. Family-based association study of 76 candidate genes in bipolar diorder: brain-derived neutrophic factor. Mol Psychiatry 2002;7(6); 579-93.
[42] Crawley JN, Paylor R. A proposed test battery and constellations of specific behavioral paradigms to investigate the behavioral phenotypes of transgenic and knockout mice. Horm Behav 1997;31: 197-211.
[43] Shumake J, Edwards E, Gonzalez-Lima F. Opposite metabolic changes in the habenula and ventral tegmental area of a genetic model of helpless behavior. Brain Res 2003;963:274-81.
[44] Dugovic C, Solberg LC, Redei E, VanReeth O, Turek FW. Sleep in the Wistar-Kyoto rat, a putative genetic animal model for depression. NeuroReport 2000;11:627-31.
[45] Vaugeois JM, El Yacoubi M, Costentin J. Comments on an animal model of depression. Ann Pharm Fr 2004;62:332-42.
[46] Bolivar VJ, Caldarone BJ, Reilly AA, Flaherty L. Habituation of activity in an open field: a survey of inbred strains and F1 hybrids. Behav Genet 2000;30:285-93.
[47] Garrett KM, Niekrasz I, Haque D, Parker KM, Seale TW. Genotypic differences between C57BL/6 and A inbred mice in anxiolytic and sedative actions of diazepam. Behav Genet 1998;28:125-36.
[48] Gershenfeld HK, Neumann PE, Mathis C, Crawley JN, Li X, Paul SM. Mapping quantitative trait loci for open-field behavior in mice. Behav Genet 1997;27:201-10.
[49] Logue SF, Owen EH, Rasmussen DL, Wehner JM. Assessment of locomotor activity, acoustic and tactile startle, and prepulse inhibition of startle in inbred mouse strains and F1 hybrids: implications of genetic background for single gene and quantitative trait loci analyses. Neuroscience 1997;80:1075-86.
[50] Thifault S, Lalonde R, Sanon N, Hamet P. Comparisons between C57BL/6J and A/J mice in motor activity and coordination, hole-poking, and spatial learning. Brain Res Bull 2002;58:213-8.
[51] Trullas R, Skolnick P. Differences in fear motivated behaviors among inbred mouse strains. Psychopharmacology (Berl) 1993;111:323-31.
[52] van Gaalen MM, Steckler T. Behavioural analysis of four mouse strains in an anxiety test battery. Behav Brain Res 2000;115:95-106.
[53] Bouwknecht JA, Paylor R. Behavioral and physiological mouse assays for anxiety: a survey in nine mouse strains. Behav Brain Res 2002;136:489-501.
[54] Bolivar VJ, Pooler O, Flaherty L. Inbred strain variation in contextual and cued fear conditioning behavior. Mamm Genome 2001;12:651-6.
[55] Mathis C, Neumann PE, Gershenfeld H, Paul SM, Crawley JN. Genetic analysis of anxiety-related behaviors and responses to benzodiazepine-related drugs in AXB and BXA recombinant inbred mouse strains. Behav Genet 1995;25:557-68.
[56] Gill K, Boyle A, Lake K, Desaulniers N. Alcohol-induced locomotor activation in C57BL/6J, A/J, and AXB/BXA recombinant inbred mice: strain distribution patterns and quantitative trait loci analysis. Psychopharmacology (Berl) 2000;150:412-21.
[57] Boyle AE, Gill K. Sensitivity of AXB/BXA recombinant inbred lines of mice to the locomotor activating effects of cocaine: a quantitative trait loci analysis. Pharmacogenetics 2001;11:255-64.
[58] Wehner JM, Radcliffe RA, Bowers BJ. Quantitative genetics and mouse behavior. Annu Rev Neurosci 2001;24:845-67.
[59] Dumas P, Pausova Z, Kren V, Krenova D, Pravenec M, Dumont M, et al. Contribution of autosomal loci and the Y chromosome to the stress response in rat. Hypertension 2000;35:568-73.
[60] Hamet P, Tremblay J. Genetic determinants of the stress response in cardiovascular disease. Metabolism 2002;51:15-24.
[61] Fuchs E, Czeh B, Flugge G. Examining novel concepts of the pathophysiology of depression in the chronic psychosocial stress paradigm in tree shrews. Behav Pharmacol 2004;15:315-25.
[62] Dumas P, Sun Y, Corbeil G, Tremblay S, Pausova Z, Kren V, et al. Mapping of quantitative trait loci (QTL) of differential stress gene expression in rat recombinant inbred strains. J Hypertens 2000; 18:545-51.