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The human genetics of anorexia nervosa

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Abstract

Anorexia nervosa is a severe eating disorder characterised by restricted eating, the relentless pursuit of thinness and obsessive fears of being fat. The involved risk factors are probably numerous, but the existence of a genetic vulnerability has been proposed for decades. The heritability in the broad sense is computed on the basis of aggregation studies, treated twin samples and twin studies from the general population. Many difficulties make this heritability estimation problematic, but the convergence of the results (from family studies and two types of twin studies) gives the most convincing evidence in favour of a major role of genetics in the vulnerability to anorexia nervosa, with a heritability around 70%. Regarding the analysis of candidate genes, the most frequently studied is the *5-HT$_{2A}$* gene, with positive and negative results. We thus propose a meta-analysis showing that a large heterogeneity between samples exists, but the main effect of the −1438A allele persists even when extracting this contaminating effect (p=0.003). Furthermore, the absence of significant correlation between odds ratio and time after first publication of each sample, and size of each sample, is in accordance with the fact that the A allele is a risk factor. In order to explain the high heterogeneity between the nine studies yet performed, an alternative explanation such as a ''modifying the phenotype'' effect is proposed.

Keywords: Eating disorder; 5-HT$_{2A}$ receptor gene; Heritability

1. Introduction

Anorexia nervosa predominantly occurs in women (nine women for one man affected) and is characterised by restricted eating, the relentless pursuit of thinness and obsessive fears of being fat. Anorexia nervosa is a chronic relapsing illness with high mortality rate (10% per decade), severe weight loss and profound psychological distress being observed.

The list of potential risk factors in anorexia nervosa is important and has been changing in the last decades (Fairburn et al., 1999). Premorbid experiences with adverse parenting (low contact, high expectation, parental discord) were previously seen as major risk factors. In fact, many other risk factors are now recognised for anorexia nervosa, such as sexual abuse, family dieting, critical comments about eating, shape or weight from family and others, and occupational and recreational pressure to be slim. Premorbid characteristics were also propo-sed, such as low self-esteem, perfectionism and anxiety disorders.

The presence of family history of an eating disorder has also been considered as a risk factor and has been confirmed through numerous aggregation studies. Eating disorder of any type, depression and obsessive–compulsive disorder in the relatives are also associated with an increased risk of anorexia nervosa, emphasizing that the limit of the transmitted phenotype is still unknown. Recently, genetic factors were found to explain a large part of this familial risk, initially on the basis of treated samples (which detected a high heritability), and further confirmed on twins recruited from the general population. The importance of genetic factors in the vulnerability to anorexia nervosa can be indirectly measured through aggregation and twin studies.

2. Heritability of anorexia nervosa

The variation of a trait in relatives of affected probands compared to the evaluation of the same trait in relatives of

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Table 1
Frequency of anorexia nervosa among relatives of anorexic subjects from controlled studies

Authors	Relatives of affected proband			Relatives of controlled proband		
	Probands	Affected relatives		Probands	Affected relatives	
	N	*N*	%	*N*	*N*	%
Gershon et al., 1984	2	2/99	2.0	43	0/265	0.0
Strober et al., 1985	60	6/60	10.0	95	3/95	3.2
Herpertz-Dahlmann, 1988	42	3/69	4.0	37	0/61	0.0
Logue et al., 1989	17	0/132	0.0	13	0/107	0.0
Stern et al., 1992	34	2/153	1.3	34	0/140	0.0
Strober et al., 1990	97	16/387	2.1	107	0/738	0.0
Halmi et al., 1991	54	2/169	1.2	62	0/178	0.0
Lilenfeld et al., 1998	26	1/93	1.1	44	0/190	0.0
Strober et al., 2000	152	10/290	3.4	181	1/318	0.3
Grigoroiu-Serbanescu et al., 2003	68[a]	2?/185	1.0	68	0/198	0.0
Total	574	44/1637	2.7	684	4/2290	0.2

[a] Anorexia nervosa with the restrictive type only.

controlled probands indirectly depends on genetic liability for this trait. Some authors (Falconer, 1965; Reich et al., 1972) used this statement to measure heritability on the basis of categorical traits (such as morbidity), categorical morbidity reflecting dimensional liability. This estimation can be used with specific limitations such as in the absence of impact of shared familial environment, which seems respected in anorexia nervosa. We previously assessed the heritability in the narrow sense of anorexia nervosa on the basis of controlled family studies (Kipman et al., 1999) and found a relatively high impact of genetic factors (h^2=0.71, standard deviation=0.06). When adding three new samples (Table 1), including the largest sample yet published from Strober et al. (2000), the frequency of anorexia nervosa in the relatives of a proband with the same disease is 2.69%, compared to 0.18% in the relatives of healthy controls. The relative risk is 15.8, 95% CI [5.66–44.02], which is significantly above 1 (p<0.0001). The new evaluation of heritability is still high (h^2=0.69, standard deviation=0.04), in the same range of the previously published estimations (Holland et al., 1984; Treasure and Holland, 1990; Strober and Katz., 1988; Wade et al., 2000; Kipman et al., 2002; Ben-Dor et al., 2002), close to what is computed at the dimensional level for traits such as 'body mass index' and 'drive for thinness' (Rutherford et al., 1993), and included in the confidence interval of the estimated additive genetic effect derived from twin studies recruited from the general population (Table 2).

Table 2
Estimating the heritability of anorexia nervosa on the basis of population based twin studies (from Fairburn and Harrison, 2003)

Authors	Additive genetic	Shared environment	Individual-specific environment
Wade et al., 2000	58 (33–84)	–	42 (16–68)
Kortegaard et al., 2001	48 (27–95)	–	52
Klump et al., 2001	76 (35–95)	–	24 (5–65)

Table 3
Concordance for anorexia nervosa in monozygotic versus dizygotic twins in clinical samples

Author(s)	Monozygotic twins		Dizygotic twins	
	Concord	Discord	Concord	Discord
Holland et al., 1984	9	17	1	17
Holland et al., 1988	14	25	1	20
Schepank, 1997	6	8	0	5
Total	29	50	2	42

For twin studies, a certain discrepancy can be observed between studies based on the general population (Table 2) versus those using treated patients (Table 3). Bulik et al. (2000) in a review of twin studies on anorexia nervosa concluded that it is not possible to draw firm conclusions regarding the precise contribution of genetic factors. Ascertainment difficulties, statistical power and other specific limitations in the analysis of rare disorders, quality and representativity of the recruited samples, paucity of large samples (twins or families) effectively make the estimation of heritability difficult. It is the convergence of these results (from aggregation studies and two types of twin studies), much more than the conclusion of a single high-quality study, that gives the most convincing evidence in favour of a major role of genetics in the vulnerability of anorexia nervosa. The heritability of anorexia nervosa would thus be around 70%. Regarding such high heritability, the next step would logically be the search for the genes involved.

The number of candidate genes in anorexia nervosa is important regarding the significance of available data from the epidemiological, physiological, biochemical and pharmacological fields (Gorwood et al., 1998; Hinney et al., 2000). The choice of candidate genes should take into consideration the fact that anorexia nervosa (1) is an eating disorder with clinical specificities such as abnormal evaluation of shape and weight, (2) is higher in females, (3) appears predominantly during adolescence, (4) has an onset after a dieting period or a restricted energy intake and (5) is frequently comorbid with obsessive–compulsive and mood disorders. Even if the heritability is high, many unresolved questions explain the difficulties in depicting the genes potentially involved in the vulnerability to anorexia nervosa. One of the major problems concerns the unknown phenotype boundaries.

3. What are the phenotype boundaries of anorexia nervosa

This question could be considered of limited importance, when the recruitment of pure non-comorbid cases of anorexia nervosa might elude the problem. As the lifetime psychiatric comorbidity of anorexia nervosa is fairly large, comorbid psychiatric disorder being the rule more than the

exception (Halmi et al., 1991; Rastam, 1992; Braun et al., 1994; O'Brien and Vincent, 2003), the presence of a causal relationship between anorexia nervosa and comorbid conditions has to be assessed.

3.1. Comorbidity with other eating disorders

Unrelenting obsessions about inexplicable fear of weight gain and fatness are characteristic of anorexia nervosa, when binge eating episodes without abnormally low body weight because of compulsive self-induced vomiting, or other forms of compensation for the excess of food ingested, are typical of bulimia nervosa. Beyond these differences, the core psychopathology could nevertheless be shared by both anorexia and bulimia nervosa, namely that patients judge their self-worth largely, or even exclusively, in terms of their shape and weight and their ability to control them (Fairburn and Harrison, 2003).

In fact, 25–30% of patients with bulimia nervosa who visit treatment centers have a prior history of anorexia nervosa, and a wide range of psychiatric comorbidity is shared by the two types of eating disorders, such as depression, anxiety, low self-esteem, dependence and obsessive–compulsive disorders (O'Brien and Vincent, 2003). Furthermore, episodes of binge eating ultimately develop in a significant proportion of people with anorexia nervosa (Halmi et al., 1991), and a small proportion of typical bulimia nervosa will eventually develop anorexia nervosa (Hsu and Sobkiewicz, 1989).

From the genetic point of view, anorexia nervosa and bulimia nervosa probably have much in common. Indeed, a large aggregation study showed that the risk of bulimia nervosa in the first-degree relatives of a proband with anorexia bulimia nervosa is 3.5, and the risk of anorexia nervosa in the first-degree relatives of a proband with bulimia nervosa is 12.1 (Strober et al., 2000). All odds ratios were significantly above 1 and were comparable for each specific disorder in the relatives, whether the proband had bulimia nervosa or anorexia nervosa. Furthermore, the cotwin of a twin affected with anorexia nervosa is 2.6 times more likely to have a lifetime diagnosis of bulimia nervosa compared to cotwins of unaffected twins (Kendler et al., 1991; Walters and Kendler, 1995).

Anorexia and bulimia nervosa have thus much in common, and potentially share some of their vulnerability genes.

3.2. Relationship with mood disorders

Symptoms of depression are often prominent in bulimia nervosa, and associated in anorexia nervosa with irritability, liability of mood, impaired concentration and loss of sexual appetite (Fairburn and Harrison, 2003). The increased prevalence of depression (Lilenfeld et al., 1998; Strober et al., 1990) in eating disorder could thus be potentially attributed to common genetic factors. Indeed, there is an excess of major depressive disorder in relatives of probands with anorexia nervosa (7%–25%) compared to relatives of controls (2%–3%), the same pattern being observed in relatives of bulimia nervosa (Kaye et al., 1998). Nevertheless, the affective illness is more likely to be transmitted by probands with this same diagnosis comorbidity, the two conditions thus do not seem to express a single shared transmitted liability (Lilenfeld and Kaye, 1998). Nevertheless, the fact that major depressive disorder still appears after long-term recovery of the eating disorder is not in favour of a secondary effect (Hsu et al., 1992), and a bivariate structural equation modeling to a broad definition of anorexia nervosa and lifetime major depression showed that their comorbidity is likely, due to genetic factors that influence the risk for both disorders (Wade et al., 2000).

3.3. Association with obsessive–compulsive traits, personality and disorder

Clinically, patients with anorexia nervosa, particularly those with the restrictive type, frequently have obsessive traits such as counting calories, food verifications, ritualized feeding. In fact, many studies showed that obsessive–compulsive personality and disorder are found in excess in patients with anorexia nervosa (Gartner et al., 1989; Halmi et al., 1991; Rastam, 1992; Skodol et al., 1993; Braun et al., 1994; Vitousek and Manke, 1994). Altogether, female patients with anorexia nervosa have an obsessive–compulsive disorder comorbidity ranging between 25% and 69% (Rothenberg, 1986; Hudson et al., 1983; Halmi et al., 1991; Cavallini et al., 2000), the expected frequency of). Altogether, female patients with anorexia nervosa have an obsessive in the general population being around 1% (Bebbington, 1998). Such large comorbidity could be explained by common vulnerability genes. In fact, obsessive–compulsive traits such as perfectionism persist after recovery from eating disorders (von Ranson et al., 1999; Casper, 1990; Srinivasagam et al., 1995; Kaye et al., 1998) and could exist before the onset of the eating disorder, thus constituting a risk factor (Fairburn et al., 1999; Anderluh et al., 2003). Furthermore, persons with a high level of perfectionism are over-represented among healthy first-degree relatives of patients with eating disorders (Lilenfeld et al., 1998). Obsessive–compulsive disorder was also significantly more prevalent in anorectic mothers compared with control mothers (Halmi et al., 1991). By applying a complex segregation analysis to 141 families of probands affected with eating disorder (including 89 with anorexia nervosa), a Mendelian dominant model of transmission could be valid when joining eating disorder and obsessive–compulsive disorder within one single phenotype (Cavallini et al., 2000).

The relationship between anorexia nervosa and obsessive–compulsive disorder is thus a particularly sensitive case. The risk for obsessive–compulsive disorder is significantly elevated in anorexia nervosa (odds ratio >10) compared to healthy controls, but also to other eating disorders

and major depressive disorder, and tended to precede the onset of anorexia (Bulik et al., 1997). Detection of obsessive comorbidity (for traits, personality and disorder) is important when studying anorexia nervosa. It could be important to include in the analyses age at onset of the different diagnoses.

Looking for risk factors could be a way to disentangle such complex relationships between anorexia nervosa and comorbid conditions. This could be particularly true for a candidate gene that has been involved at least once in all these different disorders, namely mood disorders (Zhang et al., 1997), obsessive–compulsive disorder (Walitza et al., 2002), bulimia nervosa (Ricca et al., 2002) and anorexia nervosa, such as the *5-HT$_{2A}$* gene.

4. Is the *5-HT$_{2A}$* gene (−1438A allele) associated with an increased risk of anorexia nervosa?

Existence of an altered serotonin neurotransmission in anorexia nervosa is now generally admitted (for reviews, see Brewerton, 1995; Wolfe et al., 1997; Kaye et al., 1998), many studies trying to depict which serotonin receptor subtype could be involved. Dynamic studies with serotoninergic probes such as the *meta*-chlorophenylpiperazine (*m*-CPP) showed that 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors could be more specifically concerned (Brewerton and Jimerson, 1996), as *m*-CPP has an agonist effect for the 5-HT$_{2C}$ receptor and also binds to the 5-HT$_{2A}$ receptor (Hamik and Peroutka, 1989). A decreased synaptic serotoninergic responsivity that may involve these receptors has been suggested in anorexia nervosa (Wolfe et al., 1997; Kaye et al., 1998), although the role of nutritional status and body weight could act as confusing factors. A direct approach of the 5-HT$_{2A}$ receptors has also been used in anorexia nervosa, with the model of platelet 5-HT$_{2A}$ receptor (Elliott and Kent, 1989). 5-HT$_{2A}$ receptor-mediated platelet aggregation and platelet 5-HT$_{2A}$ receptor-coupled intracellular signal transduction were higher in a sample of patients with eating disorders, including some patients with anorexia nervosa (McBride et al., 1991; Okamoto et al., 1995). More recently, the B_{max} and K_d for [^{3}H]LSD (lysergic acid diethylamide) binding to platelet 5-HT$_{2A}$ receptors were increased in 10 patients with anorexia nervosa (Spigset et al., 1999). These three results are in favour of enhanced 5-HT$_{2A}$ receptor binding in anorexia nervosa.

Accordingly, the *5-HT$_{2A}$* gene has been analysed in patients with anorexia nervosa and the distribution of its promoter polymorphisms (−1438A/G) compared to healthy controls. Two sequence changes resulting in protein alterations have been identified in the *5-HT$_{2A}$* gene, Thr25Asn and His452Tyr, the exact role of the promoter polymorphism still being unclear (Erdmann et al., 1996; Kouzmenko et al., 1999). Four studies detected an excess of the −1438A allele in patients (Collier et al., 1997; Enoch et al., 1998; Sorbi et al., 1998; Nacmias et al., 1999), but five independent studies could not confirm this result (Hinney et al., 1997; Campbell et al., 1998; Ziegler et al., 1999; Kipman et al., 2002; Nishiguchi et al., 2001) (Table 4).

When many different samples are analysed for a candidate gene, it is important that a meta-analysis is performed, in order to conclude for the presence or the absence of a significant impact of the vulnerability gene, and depict what should be attributed between samples heterogeneity and the specific impact of the allele on the risk for the disorder (Fig. 1). In the nine studies performed, 872 patients were compared to 1656 controls. In total, the frequency of the −1438A allele of the *5-HT$_{2A}$* gene is 46.8% in patients with anorexia nervosa and 43.6% in controls, a global excess which is significant (χ^2=49.9, *df*=9, p=1.14×10^{-7}).

Table 4
Allele frequencies of the −1438G/A polymorphism within the promoter region of the 5-HT$_{2A}$ receptor gene in patients with anorexia nervosa and controls

First author	Origin	Study group	*N*	Allelic distribution		OR [95% CI]
				−1438A	−1438G	
Collier et al., 1997	British	Patients	81	83 (0.51)	79 (0.49)	1.51 [1.06–2.17]
		Controls	226	185 (0.41)	267 (0.59)	
Hinney et al., 1997	German	Patients	100	79 (0.40)	121 (0.60)	0.89 [0.64–1.22]
		Controls	355	301 (0.42)	409 (0.58)	
Campbell et al., 1998	British	Patients	152	146 (0.48)	158 (0.52)	1.26 [0.91–1.74]
		Controls	150	127 (0.42)	173 (0.58)	
Sorbi et al., 1998	Italian	Patients	77	87 (0.56)	67 (0.44)	2.36 [1.54–3.60]
		Controls	107	76 (0.36)	138 (0.64)	
Enoch et al., 1998	American	Patients	68	69 (0.51)	67 (0.49)	1.81 [1.12–2.94]
		Controls	69	50 (0.36)	88 (0.64)	
Ziegler et al., 1999	German	Patients	78	53 (0.34)	103 (0.66)	0.82 [0.55–1.22]
		Controls	170	131 (0.39)	209 (0.61)	
Nacmias et al., 1999	Italian	Patients	109	119 (0.55)	99 (0.45)	2.18 [1.48–3.21]
		Controls	107	76 (0.36)	138 (0.64)	
Kipman et al., 2002	French	Patients	145	123 (0.42)	167 (0.58)	0.80 [0.56–1.15]
		Controls	98	94 (0.48)	102 (0.52)	
Nishiguchi, 2002	Japanese	Patients	62	57 (0.46)	67 (0.54)	0.73 [0.50–1.07]
		Controls	374	403 (0.54)	345 (0.46)	

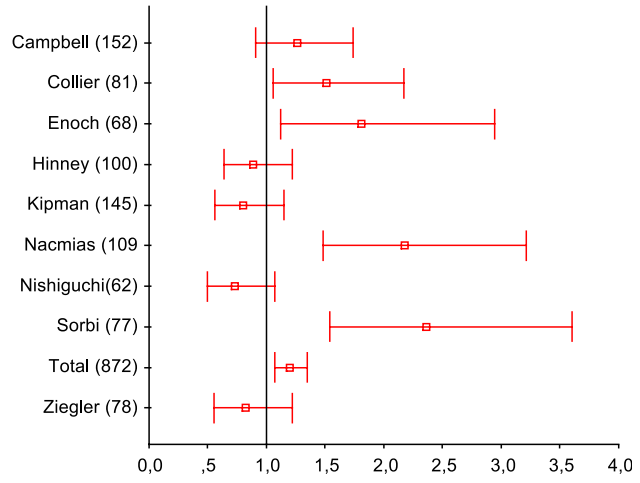

Fig. 1. Odds ratio of the association studies analysing the −1438A allele of the *5-HT$_{2A}$* gene in anorexia nervosa and controls in nine studies, and for total samples derived from a meta-analysis. ORs are given with their 95% confidence interval for the nine samples which are labelled by the name of the first author (with the number of recruited patients). Significance of the association means their 95% confidence interval does not reach the 1 odds ratio line.

A high inter-studies heterogeneity is also present (χ^2=41.7, *df*=8, $p=1.51\times10^{-6}$), which only partly explains the global association. Indeed, when excluding this heterogeneity in the association (Woolf, 1955), a specific association persists (χ^2=8.14, *df*=1, p=0.0043), with a corresponding odds ratio of 1.20 (95% CI [1.07–1.35]). The large variation of the −1438A allele in controls (from 0.36 to 0.54), the diversity of inclusion criteria and the differences in clinical characteristics of the samples (comorbidity, age of onset…) may introduce a large source of variance which could dilute (contaminate) the impact of the 5-HT$_{2A}$ gene. For example, when excluding the study based on non-Caucasian subjects (Nishiguchi et al., 2001), the odds ratio of the meta-analysis increases (odds ratio=1.27, 95% CI [1.12–1.44]) and the significance of the specific association is higher (p=0.0003). With such an odds ratio (1.27), the attributable role of the −1438A allele is 10.0% (Coughlin et al., 1994). The −1438A allele of the 5-HT$_{2A}$ gene could thus constitute a vulnerability marker for anorexia nervosa, some publications being negative because of lack of statistical power, or different types of recruited patients. Indeed, there is no correlation between the detected odds ratio and the size of the sample (r=−0.165, p=0.68), showing that the odds ratios do not significantly decrease with larger sample size (Ioannidis et al., 2001). No correlation with time after first publication (r=−0.449, p=0.24) was either detected, showing that the odds ratios are not significantly decreasing with more recent studies. Regarding presence of independent replications of a first positive association, a positive meta-analysis and the important role of serotonin, and potentially of the 5-HT$_{2A}$ receptor per se, in eating disorders in general and in anorexia nervosa in particular, the role of the −1438A allele has to be further analysed. Replications with different approaches, such as family-based association studies, are needed.

In order to depict the role of this potentially vulnerability gene in anorexia nervosa, a collaborative work from six European centers (“Factors in Healthy Eating” consortium) recruited 316 trios, trying to detect an excess of transmission of this allele from the parents to the affected probands. The transmission disequilibrium test did not find any significant excess of transmission of the −1438A allele (Gorwood et al., 2002), with 133 transmissions compared to 148 times the allele was not transmitted (p=0.59). As the transmission disequilibrium test approach is protected from the stratification bias, one hypothesis is that the positive case-control association studies were biased by the ethnic origins of patients and/or controls. An alternative and important aspect that has to be considered is that, if the transmission disequilibrium test is probably more specific than case-control association studies, the sensitivity of these two approaches are different. In this respect, Risch and Merikangas (1996) showed that for low genotypical relative risk (bellow 3), linkage approaches based on multiplex families require an unattainable number of families, and the required number of sibpairs and trios are much higher than cases and controls. If the genotypic relative risk (1.52) is computed on the basis of the first positive finding of Collier et al. (1997), the corresponding number of required sample is 14,817 multiplex families, 882 trios and/or 439 sibpairs. On the other hand, the 10% difference in patients and controls present in the same sample for the vulnerability allele only needs, for the case-control association approach, 212 patients and the same number of controls, with a classic α risk of 5% and a β power of 10%. Within this perspective, case-control association studies may be more adequate to test the role of candidate genes that have a moderate impact on a complex disorder.

One way to take into account the phenotypical heterogeneity of anorexia nervosa is to look at different clinical traits. Interestingly, in our sample for which we did not find any global effect for the risk of anorexia nervosa (Kipman et al., 2002), we observed that patients with the A allele had a significantly later age at onset of the disease (p=0.032). Furthermore, the A allele also appeared to be transmitted with an older age at onset (p=0.023) using a quantitative-trait transmission disequilibrium test approach. Thus, a subgroup of patients could be more specifically associated with the vulnerability allele. As late age at onset is observed in different subgroups of patients, for example, with more comorbid personality disorder and worse outcome (Ratnasuriya et al., 1991), clinical heterogeneity still needs further clarification before rejecting the role of the *5-HT$_{2A}$* gene.

5. Conclusions

The estimation of anorexia nervosa heritability is based on various studies, none of them being completely protected

from all the biases potentially involved. The different studies performed, such as population-based and treated patients based twin studies and also family aggregation studies, converge on a 70% heritability, in accordance with our global estimation. Nevertheless, the phenotypical relation between anorexia nervosa on one hand, and frequently comorbid disorders such as mood disorders, other types of eating disorders and obsessive–compulsive disorder on the other hand, has been poorly assessed at the genetic level.

The −1438A allele of the *5-HT$_{2A}$* gene is significantly associated (according to the current meta-analysis of case-control studies) but not linked (according to a transmission disequilibrium test on a large sample of trios) with anorexia nervosa. This vulnerability allele could have a complex impact on anorexia nervosa (such as a ''modifying the phenotype'' effect), and should thus be re-assessed taking into consideration a broader phenotype including these comorbid disorders, which potentially share common vulnerability gene(s).

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