Focus on
Rare genetic variants in bipolar disorder: how outliers help understand complex disorders

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There is a long-standing debate between those who support the Common Disease Common Variant (CDCV) approach to the study of disorders with complex inheritance and those who argue in favour of a search for rare variants [Common Disease Rare Variant (CDRV); Doris, 2002]. The CDCV approach is based on the well-accepted assumption that for most complex disorders, including schizophrenia and bipolar disorder, inheritance is multifactorial with several genetic variants interacting with each other and with the environment to cause the disease. Because these disorders are relatively common, it is assumed that causative variants should be common too. The high prevalence of these variants and the fact that each one of them is neither sufficient nor obligatory by itself to cause the disease makes them difficult to identify. Indeed, until today not one common genetic variant has been shown to be associated with psychiatric disease beyond doubt, at least to the same extent that ApoE4 is associated with Alzheimer’s disease. Supporters of the CDRV approach are not necessarily opposed to the idea that most cases of complex disorders are caused by common genetic variants. Rather, they suggest a ‘shortcut’ to the identification of the involved genes by the use of special outlier cases – extreme phenotypes, patients with chromosomal aberrations, or the study of large multiplex pedigrees. In all of these instances the hope is that inheritance is more Mendelian in nature, with a variant of major effect contributing to a large extent to the aetiology of the disorder. Even though these mutations are probably rare and do not explain most cases of disease, they might shed light on pathophysiological pathways that are shared by more common forms of the disorder.

The advantage of studying rare pedigrees is evident, for example from the successful study of hypercholesterolaemia. This common disorder is usually transmitted with a complex pattern of inheritance similar to what is seen with major psychiatric disorders. In rare pedigrees where inheritance is Mendelian, mutations with major effect were found in genes for the low density lipoprotein (LDL) receptor and associated proteins. This has led to a better understanding of altered cholesterol metabolism in more common forms of the disorder (Goldstein and Brown, 2001). Similar cases exist in psychiatric research. Velo-cardio-facial syndrome, a rare congenital multi-system disorder associated with a high rate of psychosis, is caused by a 22q11 deletion. This is congruent with replicated findings of linkage with schizophrenia for the same chromosomal region (Lewis et al., 2003) and identification of associated genes on 22q11 in the general population such as COMT (Shifman et al., 2002) or PRODH2 (Liu et al., 2002). Another example is of DISC1, a gene found to be disrupted by a balanced 1:11 translocation segregating with severe psychopathology in one extended pedigree from Scotland (Millar et al., 2000). Association with common single nucleotide polymorphisms (SNPs) within DISC1 are have since been found in samples of unrelated individuals with common forms of schizophrenia and bipolar disorder (Hennah et al., 2003; Hodgkinson et al., 2004).

In this issue of the International Journal of Neuropsychopharmacology, Meyer et al. (2005), provide another example of the usefulness of studying rare

See Meyer et al. (this issue). Rare variants of the gene encoding the potassium chloride co-transporter 3 are associated with bipolar disorder.
forms of psychiatric disorders. In the past this group has found linkage to chromosome 15q14-21 for periodic catatonia, an extreme phenotype of psychosis, characterized by fluctuating levels of mobility and mood. They conducted mutation screening of candidate genes located within this large linked region (15 Mb) and failed to identify disease-causing mutations in the CX36 and nicotinic alpha7 receptor (CHRNA7) genes. In the present study this group examined another strong candidate – the gene encoding the potassium-chloride co-transporter 3 gene (KCC3 or SLC12A6). Interest in this gene stems not only from its location but also from its role in a different severe neurological disorder. Recessive mutations in SLC12A6 were shown to cause Andersen syndrome, a rare disorder characterized by neuropathy and agenesis of the corpus callosum (ACCPN). ACCPN is associated with psychotic symptoms. Also, there are reports of abnormalities of the corpus callosum in schizophrenia. Meyer et al. (2005) screened the coding domain of SLC12A6, as well as flanking intronic regions and the putative promoter, in two patients from one large pedigree that contributed to the linkage finding, and in three controls. They did not find any non-synonymous mutations (amino-acid-changing variations). On the other hand, three newly described polymorphisms segregating with disease were discovered, two SNPs in the putative promoter region and 5'-UTR, and one base-pair insertion in intron 4. These were then studied in a large cohort of patients with either schizophrenia (n = 114) or bipolar disorder (n = 72) from the same region in Germany and compared to ethnically matched controls (n = 350). The rare form of the promoter SNP (32418760G), by itself or as part of haplotypes with the other two variants, was found to be significantly associated with bipolar disorder. The association withstood a conservative correction for multiple testing, even though the authors could have argued that their observations are not independent of each other. On the other hand this super-conservative correction can address the possible argument regarding the significance of their results given that this group studied two other genes in this locus previously. Associations were weaker for the other two variants, and these could be explained as stemming from linkage disequilibrium (LD) with the promoter variant. No associations were found with schizophrenia, and the trend for associations in the combined group of patients probably came from the bipolar group. Not finding any mutation causing structural change of the encoded protein led the authors to suggest that the promoter SNP by itself, or in combination with the 5'-UTR SNP, affects pathogenesis through a regulatory role. Indeed, they state that they have preliminary results to support such a role for 32418760G/A. The authors discuss the possibility that a true causative variant can still be present in a different gene in the vicinity of SLC12A6, and cause association with these SNPs if they are in LD with it. They reject this explanation claiming that LD cannot extend for more than 3–100 kb in outbred populations. While this might be true, it still does not exclude the existence of a mutation within a different unrecognized transcript or regulatory element of SLC12A6 or in a much closer unknown gene.

While it is necessary to use caution in interpreting the biological significance of the results, this work shows clearly how studying ‘outliers’ can be relevant for understanding complex disorders. One large pedigree where an extreme phenotype of psychosis is transmitted in a Mendelian fashion, led to identification of a rare variant within a candidate gene that co-segregates with disease. This rare variant was found in 11% of patients with bipolar disorder compared to 4% in controls, carrying an odds ratio of 3.54. Thus, the association with disease in one large pedigree with a narrowly defined phenotype was replicated for a broadly defined phenotype in the general population. The relevance of the finding from the rare pedigree is even more appreciated when taking into account the report of the authors that the bipolar patients carrying the rare SNPs were not different clinically from patient who did not carry them.

The association with bipolar disorder and not with schizophrenia of the rare alleles identified in a pedigree affected with periodic catatonia might be surprising. Catatonia was originally considered to be a subtype of schizophrenia. More recently it has been recognized that many cases can be seen as expression of mood disorders (Taylor and Fink, 2003). This is especially true when one uses Leonhard’s classification to diagnose periodic catatonia, in which bipolarity of symptoms is more pronounced (Leonhard, 1999). In this regard it is evident that studies such as this can assist in defining clearer borders between diagnostic entities. It is also interesting to note that these rare variants were not found in patients from the other 11 pedigrees with periodic catatonia that contributed to the linkage finding on chromosome 15q, possibly pointing to genetic heterogeneity even within narrowly defined phenotypes. Another intriguing finding is that different mutations in the same gene can lead to different forms...
of neuropsychiatric disorders. Rare structural mutations in SLC12A6 cause autosomal recessive ACCPN. More common variants in non-coding regions may cause changes in genes expression and lead to a different neurodevelopmental disorder. This phenomenon is well recognized in other cases. For example, carriers of pre-mutations in the fragile X gene (FMR1) are at increased risk to develop a tremor/ataxia syndrome at old age (Jacquemont et al., 2004).

Before accepting the association of the rare form of the SLC12A6 promoter (32418760G) with bipolar disorder the finding should be replicated in other large cohorts. Moreover, the functional significance of the polymorphism should be elucidated. Once this is accomplished it could prove an important contribution to the diagnosis and treatment of bipolar disorder. Moreover it would demonstrate again that ‘rare’ is not insignificant, at least for the genetics of complex disorders.

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Statement of Interest

None.

References


