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The Genetic Link between Schizophrenia and Bipolar Disorder

The link between schizophrenia and bipolar disorder has been debated for over a century. For decades many psychologists and researchers insisted that they were completely isolated disorders with no common ground; however, even before genetic analysis became feasible, the evidence was mounting that they were somehow linked. Psychiatrists defined an "intermediate" illness (schizoaffective disorder) with features of both conditions, and bipolar and schizophrenic patients were found to have similar brain scans with reduced white matter density.[1] One study from Denmark in 2003 found that patients with bipolar disorder were more likely to have family members with schizophrenia or schizoaffective disorder.[2] However, the researchers also found that some risk factors associated with schizophrenia did not have the same effect with bipolar disorder, suggesting that the two are separate to some extent.

In 2009, a study done on two million Swedish families showed that first degree relatives of probands with bipolar disorder or schizophrenia also had a higher risk of having either disorder.[3] Even half-siblings had a higher risk of either illness than the general population, although their risk is less than that of full siblings. For relatives of probands with bipolar disorder, "increased risks for schizophrenia were present for all relationships, including offspring adopted away." Overall heritability for schizophrenia was 64% and 59% for bipolar disorder.

Although it is now widely accepted that the two disorders are linked heritably, finding the actual connection – or even the genetic cause of each condition – has been slow. Many different studies have looked at single-nucleotide polymorphisms (SNPs) that appear to be somewhat

[1] http://www.ncbi.nlm.nih.gov/pubmed/15939409
[2] http://www.ncbi.nlm.nih.gov/pubmed/14662553
[3] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879718/

noteworthy, but only a few have actually reached statistical significance or are found in more than just a few patients. In one article published in 2013, the correlation found between schizophrenia and bipolar disorder was 0.68 (± 0.04 standard error).[4] This number was similar to the correlation within different groups of bipolar patients. While this correlation seems quite high, the authors noted these numbers may be altered by misdiagnosis – 15% of patients admitted to a hospital and originally diagnosed with bipolar were later rediagnosed with schizophrenia; 4% of "schizophrenia" patients were rediagnosed as having bipolar disorder. To be fair, this is likely a concern in every study regarding the two disorders.

Another 2008 article focused primarily on schizophrenic and bipolar patients with mental retardation.[5] It has been shown that people with mental disabilities have a higher prevalence of schizophrenia than the general population. The study did find some "candidate genes" that contribute to both disorders in patients with mental retardation, including *GRIK4* and *NPAS3*, which are both found at breakpoints in a chromosome translocation. While many studies have identified genes or chromosome regions linked to these disorders, the sheer number of results and lack of replication by other researchers suggest that these psychoses are very heterogeneous, with several different models of inheritance. One guess is that bipolar disorder and schizophrenia are not caused by one or even a few common mutations in the genome, but a multitude of infrequent mutations that may only be found in certain families: the "common disease, multiple rare variants" hypothesis.

When it first became feasible for the average research team, gene sequencing showed a lot of promise in helping find the causes of bipolar disorder and schizophrenia. Many different

[4] http://www.nature.com/ng/journal/v45/n9/pdf/ng.2711.pdf
[5] http://www.ncbi.nlm.nih.gov/pubmed/19073419

linkage studies have been done, to the point where loci "showing linkage with [bipolar disorder] have been found on every single chromosome" (for schizophrenia, 21 out of 23 chromosomes have regions linked with the disease).[6] However, "many proposed candidate regions did not reach genome-wide significance and most loci failed replication." Meta-analyses have been used to try to narrow the number of genes down, but many do not result in the same loci even though they use overlapping data sets. The same holds true for association studies – hundreds of different genes have been called "candidates" for either disorder but turned out to have both positive and negative associations with each condition.

With the advent of cheap(er), commercialized chips that could test for thousands of SNPs came the hopes that a genome-wide association study (GWAS) would finally be able to determine the genetic cause of bipolar disorder and schizophrenia. However, by 2009 only three SNPs came to achieve genome-wide significance by surpassing the generally accepted p-value threshold of 5×10^{-8}, and those were only in association with bipolar disorder. Some researchers have suggested that rather than looking at the "most significant" single SNP results in one study, multiple studies should be combined to identify results that are found to be less statistically significant, but are more commonly found. Using this approach, the Psychiatric GWAS Consortium identified several loci with strong associations for both schizophrenia and bipolar disorder: *ANK3*, the *NEK4-ITIH1-ITIH3-ITIH4* region, and *CACNA1C*.[7][8] Another criticism of the GWAS method is the tendency to look at each SNP separately, rather than finding the most significant combinations of polymorphisms. Additionally, if these mental disorders can be

[6] http://onlinelibrary.wiley.com/doi/10.1002/humu.21042/pdf
[7] http://www.ncbi.nlm.nih.gov/pubmed/21926974
[8] http://www.ncbi.nlm.nih.gov/pubmed/21926972

caused by a large number of rare gene variants, a GWAS may never be able to discern which SNPs are important.

Researchers have started to look at identifying copy-number variations (CNVs) as a way to find relevant genes. A CNV is defined as a "gain or loss of genomic segments—from over 1 kb up to several megabases—compared to a reference genome." Studies estimate a genome-wide occurrence of CNVs in healthy individuals between 5-10%. Some parts of the genome are more susceptible to these structural rearrangements than others. Most of the larger and more common rearrangements have likely been identified, but many smaller and rarer combinations still likely need to be discovered.[9] The role of CNVs in bipolar disorder and schizophrenia is still under investigation. It has been found that CNVs and deletions are found at increased frequencies in bipolar and schizophrenic patients compared to the general population. Some specific CNVs are detected only in these patients, indicating that they are "probably pathogenic and deserve further investigation."

Because the genes associated with schizophrenia and bipolar are numerous and none have a very high prevalence, it is difficult to determine the genetic mechanism behind either disorder. One of the genes also associated with mental retardation, *GRIK4* (Kainate-Type Glutamate Receptor Gene) was disrupted in a patient because it was located right at a breakpoint on chromosome 11. *GRIK4* forms part of a glutamate receptor which allows excitatory responses to travel between neurons.[10] It was already hypothesized that "reduced glutamate neurotransmission contributes to schizophrenia, based on observations that the ionotropic glutamate receptor antagonists phencyclidine and ketamine cause psychotic symptoms, and glutamate receptor

[9] http://onlinelibrary.wiley.com/doi/10.1002/humu.21042/pdf
[10] http://www.uniprot.org/uniprot/Q16099

expression in schizophrenia is reduced in post mortem brain studies."[11] A case control study looked at 27 *GRIK4* SNPs in 458 controls, 386 schizophrenic subjects, and 368 bipolar subjects. There was a significant association between markers for *GRIK4* in both schizophrenia and bipolar disorder. However, the SNPs associated with schizophrenia – at the center of the gene – were completely different than the ones associated with bipolar disorder, located towards the 3' end. Additionally, the SNPs associated with schizophrenia were associated with an increased incidence of the condition, while the SNPs associated with bipolar disorder appeared to have a protective effect.

Another gene associated with both disorders is *NPAS3* (Neuronal *PAS* Domain Protein 3 Gene[12]), which is located on chromosome 14 and can also be disrupted by translocation. Many studies had already linked this gene to bipolar disorder. In one family, the gene's translocation eliminated its transcriptional activation domain; it was predicted that there would be a 50% reduction in its protein (*Npas3)* levels in the cell. Mice lacking this gene show abnormal responses in a prepulse inhibition test – they typically display increased anxiety and locomotor activity – and have reduced recognition memory. Their nesting and nurturing behaviors are impaired and their social interactions with other mice are abnormal. All of these signs correlate to symptoms in human schizophrenic patients. Additionally, *Npas3* was discovered to mediate neurogenesis in the adult mouse hippocampus; mice lacking *Npas3* have virtually no neurogenesis there. Impaired function in the hippocampus has long been suspected as a factor in psychological illness.

[11] http://www.ncbi.nlm.nih.gov/pubmed/19073419
[12] http://www.uniprot.org/uniprot/Q8IXF0

Ultimately, our understanding of the link between schizophrenia and bipolar disorder is still quite lacking and limited by current technology. The ability of the GWAS system to detect association with rare SNPs is "significantly constrained by having predominantly common alleles (only about 12% of usable SNPs in the most commonly used GWAS system would detect infrequent alleles, that is, with a frequency less than 1%)."[13] CNV identification will hopefully improve our understanding of these conditions within the next few years. Since the first sequencing of the human genome, associated costs have declined exponentially. Within the next few years, entire genomes can be analyzed with ease and all CNV and SNP variants can be detected. Perhaps then the basis behind schizophrenia and bipolar disorder will be discovered, and with it a path to treatment.

[13] http://ajp.psychiatryonline.org/article.aspx?articleid=106785