Investigations into the genetic aspect of bipolar disorder among mood disorders

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Introduction

Bipolar disorder (BD), also known as manic depressive illness, is a complex mental disorder whose core feature is extreme disturbances in mood, ranging from mania to severe depressive episodes.

A subject's first episode can develop at any time in their life, however due to the redundancy of BD symptoms in other mental illnesses, diagnosis is complex and often changes throughout a patient's life.

In current clinical practice, anticonvulsants and antidepressants constitute the main treatments for BD, although these act more along of the lines of stabilizers rather than treatments.

Certain medication may also induce rapid cycling, where the patient may suffer four or more episodes of separate mood disturbances within a 12-month period.

Heritability and overall genetics

Relatives of patients with BD have a relatively high risk of developing mood disorders, indicating a genetic correlation. Accumulation of BD within families is also often found in large group studies.

No concrete causative genes for BD have been identified to date, considering most gene studies seek to study the impact of common stabilizers and find more targeted treatments. The discovery of the association of single-nucleotide polymorphisms (SNPs) with BD has however been celebrated in the research community, as these small changes in our DNA can lead to much larger mutations.

Table 1. Approximate lifetime rates of mood disorder in various classes of relative of bipolar probands.

Degree of relationship to bipolar proband	*Risk of bipolar disorder (%)*	*(Additional) risk of unipolar depression (%)*
Monozygotic co-twin	40–70	15–25
First degree relative	5–10	10–20
General population (ie, unrelated)	0.5–1.5	5–10

Figure 1. Summation table of the lifetime risks of bipolar disorder as well as risks of unipolar depression based on the degree of relationship to the affected individual including monozygotic co-twin, first degree relative and unrelated to the affected individual.
Adapted from "Genetics of bipolar disorder" by N. Craddock and I. Jones, 1999, *Journal of Medical Genetics*, 36:585-594.

Genes of interest

CACNA1C is a gene which codes for a component of calcium ion channels. Calcium ion channels allow for calcium to travel through membranes and are involved in many neurological processes such as nervous cell guidance and signal transmission in the brain. The rs1006737 SNP is the most studied in association with BD and its presence is related to decreased CACNA1C functioning, resulting in faulty calcium ion channels and further neurological damage.

ODZ4 is the site of the rs12576775 SNP, another common variant associated with BD. The ODZ4 gene codes for a protein that is found across membranes and plays a large role in the regulation of brain cell connectivity during development. This SNP is however also associated with many other complex mood disorders, including depression and autism spectrum disorders.

NCAN is the last gene discussed, however not all studies have been able to reproduce results confirming association of the rs1064395 SNP, located on this gene, and BD. This gene codes for a large protein secreted from many cellular components and involved in cell adhesion and migration, including brain cells. Although some studies have shown association of this mutation with BD, others have shown patients with the mutation that were unaffected.

Association to other genes such as ANK3 and TRANK1 has also been suggested, however further research is needed before making any conclusions.

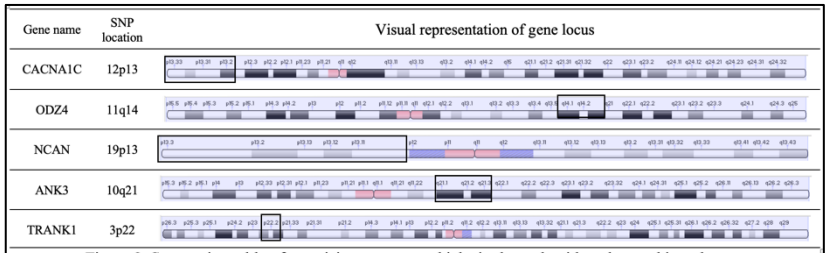

Figure 2. Summation table of promising genes on which single nucleotide polymorphisms have been associated with bipolar disorder, including chromosome visual representation.
Author's own work. Screenshots taken from Genome Data Viewer, *National Center for Biotechnology Information*, Retrieved April 10, 2021, from https://www.ncbi.nlm.nih.gov/genome/gdv/browser/gene/?id=7157

Limitations and next steps

Due to wide spectrum of symptoms and overlap with other mood disorders, identification of a causative element has still not ben achieved. Lack of larger pools of data from subjects with BD and relatives also impedes investigations in common biological markers to identify BD and find targeted treatments.

Further research concerning the promising genes will confirm their association with BD and indicate the respective next steps to take in accordance with the biological markers identified.

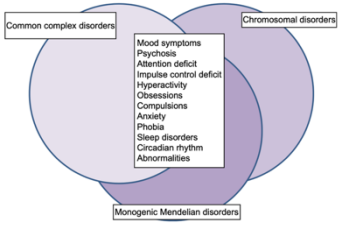

Figure 3. Symptoms of mood disorders are shared among common complex disorders, rare chromosomal disorders, and monogenic Mendelian disorders. Although many common complex disorders and rare Mendelian disorders share psychiatric symptoms, they do not always share the same genetic risk factors. Common complex disorders, such as bipolar disorder, are likely influenced by many genetic variants with small effect, in addition to the environmental risk factors. Rare chromosomal disorders are characterized by large chromosome deletions and duplications, which could potentially affect hundreds of genes. Rare monogenic Mendelian disorders are caused by characteristic mutations in a single gene. These differences in genetic risk factors have important consequences for risk prediction, genetic testing, and counseling.
Adapted from "Genetics of bipolar disorder" by B. Kerner, 2014, *The Application of Clinical Genetics*, 7:33-42.

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