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Bipolar I: The Causes and the Unknown

In 2007, the Archives of General Psychiatry published a study measuring the lifetime prevalence of psychotic disorders in a general population. Lifetime prevalence, or LTP, is the number of individuals in a population that at one point in life experience something, in this case a psychotic disorder, in comparison to the total number in the population. In this study, a population of 8,028 people above the age of thirty was screened for both psychotic and bipolar I disorders. The LTP of psychotic disorders was between 3.06 - 3.48%. Bipolar I accounts for .24% of the population. (1)

Bipolar disorder is a lifetime disorder characterized by episodes of mania and depression. Bipolar I disorder manifests with manic or mixed episodes lasting at least seven days. Usually, the severity of the symptoms requires immediate hospital care. Depressive episodes last approximately two weeks. Other forms of bipolar disorder, according to the National Institute of Mental Health (NIMH), include:

“**Bipolar II** Disorder is defined by a pattern of depressive episodes shifting back and forth with hypomanic episodes, but no full-blown manic or mixed episodes.

Bipolar Disorder Not Otherwise Specified (BP-NOS) is diagnosed when a person has symptoms of the illness that do not meet diagnostic criteria for either bipolar I or II. The symptoms may not last long enough, or the person may have too few symptoms, to be diagnosed with bipolar I or II. However, the symptoms are clearly out of the person's normal range of behavior.

Cyclothymic Disorder, or Cyclothymia, is a mild form of bipolar disorder. People who have cyclothymia have episodes of hypomania that shift back and forth with mild depression for at least two years. However, the symptoms do not meet the diagnostic requirements for any other type of bipolar disorder.”

Researchers agree that there is no single cause for bipolar I disorder, but rather a combination of different factors (2).

Diagnosis begins in ruling out other mood altering ailments, such as brain tumors and strokes. If the symptoms cannot be explained by a physical ailment, the next step is a mental health evaluation, which can be done by a trained mental health professional, such as a psychiatrist who is trained in the diagnosis and treatment of bipolar disorder. Since people suffering from bipolar disorder are most likely to seek help during a stage of depression and not mania an extensive familial history of mental health is required to rule out unipolar depression. Once diagnosed, there is no cure. Most people are able to control mood swings with mood stabilizing medications (including: Lithium, Depakote, Neurotin, Trileptal, and other anticonvulsant medications), atypical antipsychotic medications (including: Zyprexa, Abilify, Seroquel , Risperdal and Geodon), antidepressant medications (including: Prozac, Paxil, Zoloft, and Wellbutrin), and psychotherapy (including: cognitive behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, and psychoeducation). However, for the individuals for which medication does not work other treatments, electroconvulsive therapy, sleep medications, and alternative forms of medicine like herbal supplements (2).

Causes

Genetics

Some of the genes associated with bipolar disorder are catechol-O-methyltransferase (COMT), dopa decarboxylase (DDC), pericentrin (PCNT), asparagine-linked glycosylation 9

(ALG9), reelin (RELN), neuregulin 1 (NRG1), FXYD domain containing ion transport regulator 6 (FXYD6), regulator of G-protein signaling 4 (RGS4), and tryptophan hydroxylase 2 (TPH2)

(3). A person with an immediate relative who has bipolar disorder is four to six times more likely to develop the illness. However, a majority of the children with a familial history of bipolar disorder will not develop the disorder. The Bipolar Disorder Phenome Database serves to collect information and link visible signs of the disorder with genes. Since the creation of the database, researchers found many common symptoms including, substance abuse, consistent age of first manic episode, and frequency in manic episodes. Studies including twins hint towards the importance of environmental causes, however, these findings are not thoroughly understood (2).

As of last year, an international team of scientists reported abnormal copy number variants (CNVs) in sequences of DNA. Led by the University of California, San Diego School of Medicine, the researchers believe that these CNVs appear to play a significant role in the risk for early onset bipolar disorder. CNVs are alterations within the human genome in which there are too few or too many copies of a section of DNA. Genetic mutations not inherited from parents known as *de novo*, or spontaneously occurring CNVs, are known to significantly increase the risk of neuropsychiatric conditions like, schizophrenia or autism. However, their role was unknown bipolar disorder. However, the studies show a significant genetic risk in 5% of early onset bipolar disorder cases with CNVs. Previous studies focused on common inherited variants in order to identify susceptible genes. Met with little success, researchers believe that the recent focus on CNVs show “convincing” contributions to the development of early onset bipolar disorder (4).

Brain

With the help of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) researchers are able to see the brain like never before. These imaging technologies show that the brains of the people affected with bipolar disorder differ from the brains of healthy people. One study shows that the brain development of children with bipolar disorder is similar to children with a multi-dimensional impairment, a disorder which causes symptoms similar to those of bipolar disorder and schizophrenia. This particular type of brain development may be linked with a risk for unstable moods.

In 2005, *The British Journal of Psychiatry* published an article entitled “Regional Volume Deviations of Brain Structure in Schizophrenia and Psychotic Bipolar Disorder.” The article contained the findings of a computational morphometry study in which the brains of 25 people with schizophrenia, 37 people with bipolar disorder, and 52 healthy volunteers were scanned through magnetic resonance imaging (MRI). The results showed that individuals with bipolar disorder had no significant regions of grey matter abnormality, but did have anatomically overlapping white matter deficits in regions usually occupied by major longitudinal and interhemispheric tracts. Structurally, the brain of a person suffering from bipolar disorder had anatomical abnormalities in the white matter regions (5).

The Unknown

GWAs

In a Genome-wide association study, or GWA, common genetic variants are examined in differing individuals to determine the existence of a variant with a trait. The common genetic variants, typically single-nucleotide polymorphisms (SNPs), are analyzed to compare the DNA of two groups of individuals. The two groups are divided into people with the disease and people

without. If one allele is more frequent in the people with the disease, then an ‘association’ can be made. These associated regions are marked and considered to be influential in the risk of a disease (6).

In a 2009 article in *Molecular Psychiatry*, two GWAs studies were conducted with the purpose of identifying genetic factors in the cause(s) of bipolar disorder. One study involved participants on European ancestry (EA; n=1001; control: n=1033) , while the other included participants of African ancestry (AA; n=354; control: n=670). SNPs were collected from all groups and the results support of previous findings in ANK3 and at 15q14 influencing susceptibility to bipolar disorder. Additional regions containing NAPS, NTRK2, SLITRK2, and ROR1 will require follow-up studies. Researchers believe that the SNPs and regions all have such a small effect size that the majority of genetic variations influencing bipolar disorder are yet to be discovered (7).

In younger populations with bipolar disorder, evidence indicates quantitative, but not categorical differences in cognitive impairments in patients with either schizophrenia or bipolar disorder. The methods are as follows:

“We compared the cognitive abilities of older, community-living schizophrenia patients, controlling for their state of symptomatic remission, with those of older euthymic patients with bipolar I disorder. The study included 67 patients with schizophrenia (20 in symptomatic remission, 47 not in symptomatic remission; mean age 68 years) and 74 euthymic bipolar I patients (mean age 70 years), who were compared using analysis of covariance on clinical and neuropsychological variables (e.g., attention/working memory, verbal memory, executive function and verbal fluency) and contrasted with 69 healthy controls.”

The conclusion indicates that in both older patients with schizophrenia and with bipolar disorder may share major phenotypic similarity in later life (8).

Affecting between 1-3% of the general population, bipolar disorder usually begins to affect men and women between the ages of 15-25. The cause is unknown, but events such as, childbirth, periods of sleeplessness, recreational drug use, or even steroids and antidepressive medications are considered potential 'triggers' for bipolar disorder (9). Eric Salvatierra, the PayPal executive recently killed on the Caltrain tracks, suffered from depression and bipolar II disorder. He lived in Palo Alto with his family, and although the incident has not yet been ruled an accident or a suicide, Salvatierra's family decided to come forth with his illness in an effort to support others suffering with mental illness. Salvatierra was diagnosed only last year with depression and bipolar II disorder. He had been married for twenty years and had three daughters (10).

Bipolar can affect anyone and have a range of effects on a person's life. An article published this morning on the *Science Daily* reports the gained insight of why lithium salts are effective at treating bipolar disorder. For the past 60 years, lithium salt has been a treatment for bipolar disorder with little research as to why it is effective. A new study shows an effect of lithium in increasing the amplitude of clock rhythms. Lithium increases the strength of the clockwork in cells by up to three-fold by blocking the enzyme glycogen synthase kinase or GSK3. These findings encourage scientists to pursue the manufacture of medicines mimicking the effects of lithium salt to a greater extent and perhaps find a treatment for bipolar disorder that will not potentially trigger a worse side-effect (11). Perhaps one day, genomics will one day be able to identify the cause of bipolar disorder and prevent the illness, forever replacing treatments with side effects.

Works Cited

1. <http://archpsyc.ama-assn.org/cgi/content/abstract/64/1/19>
2. <http://www.nimh.nih.gov/health/publications/bipolar-disorder/complete-index.shtml>
3. <http://ghr.nlm.nih.gov/search?query=bipolar+disorder&show=genes>
4. <http://www.sciencedaily.com/releases/2011/12/111221140347.htm>
5. <http://bjp.rcpsych.org/content/186/5/369.short>
6. <http://www.genome.gov/20019523>
7. <http://www.nature.com/mp/journal/v14/n8/full/mp200943a.html>
8. <http://www.ncbi.nlm.nih.gov/pubmed/22407730>
9. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001924/>
10. http://www.contracostatimes.com/technology/ci_20159824
11. <http://www.sciencedaily.com/releases/2012/03/120313103922.htm>