**Is Bipolar Disorder hereditary?**

**Marie Robbins (University Centre Grimsby)**

**Contact: robbinsm@grimsby.ac.uk**

Marie Robbins is the Programme Leader for the BSc (Hons) Applied Psychology programme and module tutor within several health programmes at the University Centre Grimsby. Marie is also the faculty ethics co-ordinator and has completed her HEA scholarship.

# Is Bipolar Disorder hereditary?

Bipolar is a serious mood disorder in which individuals experience episodes of depression and mania (Dick et al., 2003). This is diagnosed using the criteria within the ICD 10 or the DSM5 or DSM IV-TR. Although these manuals follow a medical approach to treatment, there is still mixed evidence when it comes to the aetiology of bipolar, with arguments presented from both the nature and nurture perspectives. Research has focused on areas which include: the loss of a parent or sibling during childhood (Mortensen et al., 2003); traumatic brain injuries, complications during childbirth, spring/winter birth, stressful life events and multiple sclerosis (Tsuchiya et al., 2003). Other research has focused on the biological argument investigating brain regions and more recently genetics (McIntosh, Hall, Lymer, Sussmann & Lawrie, 2009). It is the purpose of this paper to put forward evidence from a genetic perspective this will include both formal and molecular genetics.

Formal genetics are based on family, twin and adoption studies, these assess whether family members have higher rates of the condition than non-family members, whereas molecular studies aim to find gene and genome areas involved in the pathophysiology of the disorder, this is achieved by using linkage studies or association studies. Linkage studies “aim to find chromosomal areas in which are located genes of liability, by testing a large number of markers”, whereas association studies look for differences in alleles on specific genes amongst healthy controls and those affected by bipolar (Mandelli, Nivoli & Serretti, 2009, p.126).

Family, twin and adoptions studies are the initial way of identifying a genetic basis for bipolar (Shih et al., 2004). According to Jones, Kent and Craddock (2004, as cited in Juli, Juli & Juli, 2012) relatives are 5-10 times more likely to develop bipolar than non-relatives. However, family studies that investigate parents with bipolar and their children have been limited and have suffered from small sample sizes making them difficult to generalise (Preisig, 2006). To overcome this issue, Lapalme, Hodgins and LaRoche (1997, as cited in Preisig, 2006) conducted a meta-analysis which included 795 children. Findings revealed that 52% of the children with parents with bipolar had some form of psychiatric disorder and were four times more likely than children without parents with bipolar to suffer from a mood disorder. Nevertheless, this research fails to provide evidence for a genetic link between parents with bipolar and their children, it merely identifies the increase in mental illness among children with parents with bipolar. It can therefore be argued that family studies do not establish a genetic aetiology, as they do not determine between genetic and non-genetic factors (Alda, 1997).

Twin studies compare concordance rates for bipolar with monozygotic (MZ) and dizygotic (DZ) twins (Smoller & Finn, 2003). Findings tend to demonstrate higher concordance rates in MZ twins, which would suggest that there is a higher rate of heritability than environmental influences (Shih et al., 2004). However, early twin studies have been criticised because they fail to identify between bipolar and unipolar, they also have methodological flaws such as small sample sizes, lack of blinding, lack of specificity in diagnostic criteria and poorly structured assessments (Smoller & Finn, 2003).

Kieseppä, Partonen, Haukka, Kaprio and Lönnqvist (2004) eradicated these issues within their study which investigated concordance rates and heritability by using a population based twin study. Participants (n=19,124) born between 1940 and 1957 were screened by a psychiatrist and trainee psychiatrist using records from the "National Hospital Discharge Register and the Finnish Twin Cohort study in 1975, 1981 and 1990" (p.1815). They used the DSM-V criteria to make a diagnosis which was undertaken blind (zygosity was also determined in this manner). After this procedure a discussion was had (along with a senior psychiatrist when needed), and all diagnoses were agreed. Only those with a diagnosis of BPI or Bipolar type schizoaffective disorder were considered. This resulted in 26 pairs (27 probands, one pair had two probands) being invited to participate. The "Mx programme was used for biometrical model fitting to provide estimates of the genetic and environmental components of variance in the underlying liability to disease" (p.1816). Findings revealed that there was a high heritability of bipolar, which would suggest a stable between-population genetic contribution as "probandwise concordance rates were 0.43 (95% CI=0.10 to 0.82) for monozygotic twins" (MZ) with a correlation in liability of 0.85, and "0.06 (95% CI=0.00 to 0.27) for dizygotic twins" (p. 1814) (DZ) with a correlation in liability of 0.41. This study although representative, could be criticised for its ability to generalise due to its small sample size. However, as these findings support previous research such as that conducted by Cardno et al. (1999) who found correlations of 0.82 for MZ twins and 0.31 for DZ twins, it could be argued that these findings are therefore fairly reliable. Though concordance rates that are found to be less than 100% would suggest that the environment must also influence the phenotype (Smoller & Finn, 2003).

Genetics factors established within twin studies have also been found in adoption studies. These studies differ, as adoption studies attempt to differentiate between environmental and genetic influences by making comparisons between rates of the disorder with the biological family, to those of the adoptive family. The assumption is that if it is genes that influence the disorder then logically there would be greater resemblance within the biological family (Preisig, 2006). However, there has been very few adoption studies undertaken (Smoller & Finn, 2003). In a review of the literature by Preisig (2006) only two adoption studies were found, these were by Mendlewicz and Rainer (1977) and Wender et al. (1986). Both of these studies revealed a "threefold increased risk of bipolar" (p.367) amongst the biological relatives of bipolar patients compared with the adoptive relatives of bipolar patients. The research in this area tends to be lacking due to the difficulty in conducting this type of study. Confounding issues and obtaining samples are some of the problems encountered (Kendler, 1993 cited in Smoller & Finn, 2003).

Due to findings from formal genetic studies, linkage and association studies have attempted to identify the genes involved in bipolar. One early study conducted within an 'Old Order Amish kindred' identified the short arm of chromosome 11 (Egeland et al., 1987, as cited in Muglia et al., 2002). This sample was selected in order to eradicate possible extraneous variables found within other samples, such as alcohol or drug use; as the Amish lifestyle ensures that individuals within this community abstain from these indulgences, they were also chosen as the environment is relatively stable, meaning any changes in behaviour can be easily

identified (Georgi et al., 2014). However, findings failed to be replicated in reanalysis of the families (Egeland et al., 1987, as cited in Muglia et al., 2002); and other studies have mixed findings (Kelsoe et al., 1989). Nonetheless, this gene should not be eliminated, as the lack of replication may be due to lower power of linkage analysis to detect genes when they only partially contribute to the disorder (Greenberg, 1993). Due to this, Muglia et al. (2002, p.860) investigated "the short arm of chromosome 11 on p15.5 which has two dopamine system genes; d4 receptor (DRD4) and tyrosine hydroxylase (TH)". This study had a large sample size which consisted of 154 patients. Their DNA was taken from 'whole blood' samples. Findings revealed that there was a "biased transmission of the 2- and 4- repeat alleles which shows a parent origin effect (POE)" (p.864). This could indicate that the 2-repeat allele acts as a protecting factor when 'non-transmitted' from the mother, whereas the 4-repeat allele may indicate an amplified risk for bipolar. Interestingly, the TH did not reveal any transmission bias, therefore replication is required. This would however need polymorphisms within independent samples to be considered, which would aid in characterising the involvement of 11p15.5 (Muglia et al., 2002).

Other linkage studies initially identified ten candidate chromosomes regions (Ewald, Flint, Kruse & Mors, 2002), these included "4p, 10p, 12q, 13q, 16p, 18p, 18q, 21q, 22q, and Xq" (Dick et al., 2003, p.108), however more recent research has also identified 6q and 8q (Nurnberger, 2012). One study which has been able to provide some support for previous research findings was conducted by Ewald et al. (2002). This study used a genome-wide linkage analysis (GWA). Findings revealed 613 unique genotypes from 666 DNA markers. Non-parametric multipoint analysis and

parametric two-point linkage analysis was applied. Findings revealed a higher number than expected possible markers “significant linkage was obtained at chromosomes 12q24.3 (LOD 3.42, marker D12S1639)” additional chromosomes 1p22-p21 (2.75, marker D1S216), “along with additional loci on chromosomes 4p16, 5-8 and 16p13.3” (Ewald et al., 2002, p.734). Although this study consisted of a small sample (two families) and could therefore be criticised for its generalisability, a strength of this study lies within the data analysis as this study employed both parametric and non-parametric analysis. These findings support research previously conducted by Ewald, Degn, Mors and Kruse (1998). This research investigated linkage between bipolar and 16 microsatellite markers on chromosome 12q22-24 in two Danish families. A significant two point lod score (3.37) was identified on marker D12S1639. Degn et al. (2001) also investigated the 12q23-q24 using 17 microsatellite markers with a sample consisting of 14 participants with bipolar and 43 participants to act as a control group. They focused on findings with significance figures below p-values of 0.01 and identified the region around 6cM with markers D12S1614 and D12S1675, they also identified risk alleles on 10q26 and 18q23. Although these findings are interesting, it must be recognised that it is challenging making adjustments to statistical criteria and assessing statistical significance within association studies as the number and degree of linkage disequilibrium differs within different populations and genome regions (Schork et al., 2001, as cited in Degn et al., 2001).

It would appear that these findings are consistently supported. Dick et al. (2003) conducted a genome-wide linkage analysis from multiplex families with bipolar. The sample was collected from advertisements on advocacy group

websites, treatment facilities and professional organisations through “probands with bipolar I or siblings with bipolar I or schizoaffective disorder, bipolar type” (p.107). Participants (n=1,152, 250 families) were predominantly white (93%) with the remainder being African American (3.5) or other ethnicities (3.5). Informed consent was obtained prior to any interviews, relatives being contacted, or extraction of blood for DNA and cell lines. The ‘diagnostic instrument of genetic studies’ assessed participants, this according to Nurnberger et al. (1994, as cited in Dick et al., 2003) appears to have good test-retest reliability. Three models were developed for analysis within this study, these included: model one individuals with BPI or schizoaffective bipolar disorder (SABP), model two included individuals affected under model one plus those with the less severe BPII, and model three; individuals diagnosed under models one and two plus individuals with Unipolar depression recurrent type (UPR). Findings revealed that there were significant results on chromosome 17q (LOD 3.63, marker D17S92) and chromosome 6q (LOD 3.61, marker D6S1021), there was also some evidence to suggest linkage on other regions genome-wide on chromosome 2p, 3q and 8q. These findings suggest that several genes contribute to bipolar. There does however appear to be some issues within this study. For instance, this study has stated that it obtained informed consent, however it is not clear how this was achieved. Some studies (See Depp et al., 2007; Palmer et al., 2007) have used the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (Appelbaum & Grisso, 2001, as cited in DuBois, Bante & Hadley, 2011). Measures such as these are important particularly in this type of research as DuBois et al., (2011) found some individuals with bipolar have significantly lower scores than healthy controls, questioning therefore their ability to provide informed consent. This could therefore be seen as a weakness

within this study as not only is informed consent an ethical issue, it is also a legal requirement (DuBois et al., 2011), and as this information is missing from this research the replicability could be questioned. However, this study does appear to have good external validity due to its large sample size, which according to Allison et al. (1998, as cited in Juli, Juli & Juli, 2012) is important in linkage studies.

Although research has been able to identify some candidate chromosome regions and specific markers, linkage studies and association studies are not without their issues. These studies do not account for environmental factors which may play an important role in controlling the risk of developing bipolar, as it is evident that bipolar does not adhere to Mendelian rules (Mandelli et al., 2009). Some of the findings have failed to be replicated , and not one gene has been so far identified (Preisig, 2006), however due to the complexity of bipolar disorder, it is likely that it is more than one gene that accounts for bipolar disorder not a single gene, and these probably interact (Juli et al., 2012). Genome-wide association studies go only so far in explaining the phenotypic variability, whilst failing to resolve the issues relating to the lost heritability, this may be because the locus heterogeneity is so great that it may not be possible to separate it within linkage studies (Schulze, 2010).

Future research into bipolar may include endophenotypes; these are internal phenotypes that are described as “the intermediate component between complex disease and distal susceptibility genes” (Gateman and Gould, 2003, as cited in Sorbonne, 2012, p.22). These have previously been researched in schizophrenia (Juli et al., 2012), and may be useful in the future, not only within research but also in

enabling physicians to create more homogenous groups by subgrouping patients, leading to an individualist approach to medication or even possibly a cure (Soronen, 2012).

It would appear from the research discussed that there is some good evidence for a genetic aetiology within bipolar disorder. Formal genetics such as familial studies have identified that there is greater heritability within families, but fail to eliminate environmental factors, whereas twin and adoption studies aim to identify the amount of heritability. However, literature on adoption studies is limited and therefore leads to a large amount of generalisations regarding the few findings obtained. Twin studies seem more readily available but have been criticised previously for their methodological flaws. The research provided within this paper however as addressed these issues, and the results have matched those from previous studies.

Molecular studies have provided some interesting findings, even though sample sizes are generally small which according to Allison et al. (1998, as cited in Juli et al., 2012) is an issue and should be addressed particularly in linkage studies. Future studies may even see the increased use of endophenotypes as they have been successfully used within schizophrenia research (Juli et al., 2012). Even though some findings have failed to be replicated and not one particular gene has been identified, all of the studies discussed have provided interesting contributions to enable a greater understanding as to the role of genetics within bipolar disorder. These studies also demonstrate that there is no single method within genetic studies

that provide enough evidence to be definitive in the results, however this problem may be overcome with future technological advances (Preisig, 2006). Follow up linkage and association studies should be undertaken in future to enable replication of positive findings and keep clinical information up to date (Preisig, 2006).

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