

The genetic basis of schizophrenia psychology essay



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Schizophrenia is a debilitating, psychiatric disorder. Primarily characterized by distortions to both thinking and perception, an individual suffering from this illness will experience progressive cognitive and behavioural impairment. Manifesting into psychosis, patients tend to develop an array of positive and negative symptoms that can ultimately leave a person totally withdrawn from society.

Coined by Eugen Bleuler in 1911, the term schizophrenia has developed significantly from the days of its classification as “dementia praecox” (Gottesman et al, 1982, p. 39). Thought once to be an incurable disease, antipsychotic medication and psychological therapy have estimated to prevent 1 in 5 individuals from experiencing a repeat, acute, schizophrenic episode (NHS, 2009). With a 0.7% lifetime risk of developing the illness, a significant amount of research has been undertaken towards studying the causation of schizophrenia (Tandon, 2008). Although the exact pathology behind this disorder is unknown, it is thought of being a multifactorial condition, with neurochemical imbalances, environmental triggers and even birth defects all being implicated. However, the most convincing evidence surrounding the pathogenesis of this disorder comes from that of molecular genetic studies.

Increasing efforts into understanding the genetics behind schizophrenia has proved to show that one's susceptibility can be up to 70% due to genetics alone (Freedman, 2003). Through the use of association and linkage analysis, a number of candidate genes have been implicated; the most important of which will be discussed within the breadth of this essay.

Examining how initial evidence surmounted from adoption and twin studies
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we will also explore the contribution of copy number variants, the understanding behind single-nucleotide polymorphism and even the recent impact of genome-wide association studies in pin-pointing further risk loci.

2. Genetic Vulnerability Studies

The genetic basis of schizophrenia first began to take effect in 1896 with the work of Professor Emil Kraepelin. A psychiatrist who worked with patients suffering from 'dementia praecox', Kraepelin began to hypothesise that between 50-70% of his patients had a clear hereditary predisposition to the disease. Through following up a number of his patients, he noticed that there was a certain degree of familial nature associated with the illness. Finding that a similar frequency of cases occurred in both brothers and sisters, he began to consider the possibility of the disease trait being passed down through successive generations. Working alongside Ernst Rudin in 1916, he therefore set out to decipher whether this disorder could fit into that of a Mendelian genetic framework. The "idea of a gene as a unit for transmitting characteristics" (Gottesman et al, 1982, p. 38) had only recently been introduced by Gregor Mendel, yet it formed the basis behind genetic transmission from a parent to their offspring. Kraepelin discovered that the presence of a dominant gene could not be feasible, as not every patient had a family history of an affected individual. On the other hand, testing for a recessive trait proved inconclusive due to a low correlation of risk between unaffected and affected individuals.

Having understood that schizophrenia does not follow a normal Mendelian pattern, over the next few decades, considerable amounts of research were

then carried out into the vulnerability of genetics. This is best explained in terms of family, twin and adoption studies.

2. 1 Family Studies

Family studies aim to compare the differences in incidence of a particular disease amongst different members of a family. As can be seen from figure 1. 0, schizophrenia has a high genetic component to it. Comparing the two extremes, the lifetime risk of the general population acquiring this psychotic illness is only 1%, whereas an identical twin has up to a 48% chance of developing it if their sibling is already affected. This evidence provides great support to that of the genetic theory. It shows that the greater the genetic link, the greater the risk there is of developing the condition.

Figure 1. 0 - Figure showing the percentage risk of developing schizophrenia in different classes of relatives.

Owen & O'Donovan (2008)

2. 2. Twin Studies

Twin studies have also been an important contributing factor to understanding the role of genetics within schizophrenia. The principle behind this method stems from the unique trait of monozygotic (MZ) twins sharing 100% of their genes and dizygotic (DZ) twins only sharing 50% (Jarvis et al, 2004). This property allows the basis of designing different types of twin studies. The most replicated study aimed to compare the similarities between MZ and DZ twins that have been reared together. This would

thereby eliminate any compounding influence that the environment could
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have on the results. Therefore, if MZ twins are more similar than DZ twins in the same environment, this provides strong evidence towards the importance of genes. Gottesman (1991) compared the results of 40 different twin studies spanning over a period of 60 years. By comparing the concordance rates of MZs and DZs for schizophrenia, he was able to show that MZs had a 48% concordance for the disorder, compared with only 17% in DZs (refer to figure 1. 0). This proved that MZs are more likely to share schizophrenia with their sibling than with DZs. However, this result also allows us to infer that schizophrenia is not solely a product of genes. If this were true, we would expect 100% concordance between MZ twins suffering from the same disease; yet we do not see this.

2. 3. Adoption Studies

An adoption study is a method by which one can isolate the influence of genetics and environment. In the situation where MZ twins are separated at birth and reared in different environments by different parents, it is understood that any similarities that resemble between the two siblings is primarily down to genetics, whereas any differences can be accounted to the environment. A study carried out by Tienari (1991) followed 155 adopted children, all of whom were known to have biological schizophrenic mothers. It found that 10. 3% of these children developed schizophrenia compared to only 1. 1% within a control group. Evidence such as this provides strong support towards the genetic theory as it isolates the influence of heredity and eliminates any environmental factors that could contribute to schizophrenia.

The impact of family, adoption and twin studies has led us to confidently conclude that genes play a key contribution to causing schizophrenia.

However, as of yet the exact mode of inheritance is still unclear. There could be several common alleles that could only pose a small risk, whereas a less common allele could possibly cause a greater risk (Williams et al, 2009).

3. Molecular Genetic Studies

Molecular genetic studies aim to locate specific genes that predispose an individual to a disease. Researchers have used a number of approaches to identify the specific loci that increase an individual's susceptibility. The main techniques that have been used to locate any implicated genes are via linkage analysis and association studies. These have been able to pin-point several loci within the human genome that confer a risk to schizophrenia.

Several studies that have combined both linkage and association analysis have been able to identify a number of key candidate genes such DTNBP1 and NRG1 (Riley & Kendler, 2006)

3. 1 Genetic Linkage Studies

Genetic linkage analysis is a technique used to identify specific regions of a genome that are " co-transmitted with the disease in families with two or more affected individuals" (Owen & O'Donovan, 2008, p. 417). Using this method, one is able to screen the whole genome for the presence of these specific regions using genetic markers. This type of study can be used to assess both major gene disorders (parametric linkage) and also complex diseases (non-parametric linkage) (Dawn Teare and Barrett, 2005).

This type of linkage is of great significance as it is able to detect genes of moderate to small effect. However on the downside, after locating and implicating the specific disease gene, extensive follow up association studies are needed to further prove that the specific loci conveys significant risk.

3. 2 Association Studies

Association studies aim to detect whether specific alleles are more or less common in patients within the general population (Owen & O'Donovan, 2008). Compared to linkage analysis, this method is more powerful in detecting genes with a weak effect. Furthermore, unlike linkage, the technique does not extend across large segments of the genome. Therefore it is necessary to genotype up to several hundred thousand markers (Williams et al, 2009).

4. Positional Candidate Genes

There are a number of genes that have been located at different chromosomal regions that have been linked to schizophrenia (figure 2. 0). The following genes that will be discussed within this essay have been selected due to a greater availability of papers that have been published supporting their influence within the disease. There are however a number of other genes such as regulator of g-protein signaling 4 (RGS4) and d-amino acid oxidase activator (DAOA) (G72) that have also been linked to schizophrenia but have not been discussed.

Figure 2. 0 - This figure represents the major chromosomal regions and genes that have been identified by linkage and association studies in schizophrenia”

O'Donovan & Owen (2008)

4. 1 Neuregulin 1 (NRG1)

Neuregulin 1 is a protein that is encoded by the NRG1 gene. This is a complex, candidate gene that has been identified on chromosome 8p22 (Steffansson et al, 2002). It was the first gene that was discovered to have an associative link to the development of schizophrenia and following its discovery, a number of association studies confirmed its existence by replicating the initial findings. Of the 44 studies published, 22 confirmed the existence of genetic variation within the region of NRG1. Ross et al, (2006, p. 145) summarized that “[t]he functional role of neuregulin 1 in schizophrenia is still uncertain, particularly since many different alleles and haplotypes have been implicated.”

4. 2 Dysbindin (DTNBP1)

Dysbindin (dystrobrevin binding protein 1) is a gene that has been identified through linkage to chromosome 6p22. 3. Known to code for a protein concentrated in post-synaptic terminals, it was first discovered in an analysis covering 265 Irish families (Straub et al, 1995). Since then, there have a number of further supporting studies that have confirmed the association between its locus and schizophrenia (Ross et al, 2006). Allen et al (2008) compared 118 meta-analyses in order to identify potential genetic risk

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factors in schizophrenia. The results confirmed a strong indication towards DTNBP1 being “ a primary susceptibility gene in schizophrenia” (Schwab & Wildenauer, 2009, p. 149). Although the function of DTNBP1 is unknown, dysbindin has been identified as influencing glutamate neurotransmission (Numakawa et al, 2004). This evidence supports a possible role within the disease due to the fact that the glutamate hypothesis of schizophrenia characterizes a decrease in glutamate mediated neurotransmission.

Two further studies carried out by Fanous et al (2005) and DeRosse et al (2006), underpinned an association between dysbindin risk haplotypes and high levels of negative symptoms within schizophrenia. These findings are supported with those found by Fallgatter et al (2006), as it is believed that dysbindin haplotypes may influence frontal lobe function; the frontal lobe being decreased in function in schizophrenia.

Genes disrupted by chromosomal translocations have been deemed to be very rare in causing schizophrenia (Ross et al, 2006). However, the main advantage from studying them comes from the fact that “ translocations produce a definable genetic lesion” (Ross et al, 2006, p. 146) meaning that one can study the effect of the resulting mutation by examining the final gene product. Ross et al, (2006, p. 146) described disrupted in schizophrenia (DISC) 1 to be the “ best supported candidate gene for schizophrenia” due to its potential for further research.

4. 3 Disrupted in schizophrenia (DISC) 1

DISC 1 is a gene that has been identified “ in the breakpoint of a balanced [1, 11] chromosomal translocation region” (Schwab & Wildenauer, 2009, p. <https://assignbuster.com/the-genetic-basis-of-schizophrenia-psychology-essay/>

151). It is known to code for an 854 amino acid protein that is highly expressed in the limbic structures of the brain. Furthermore, it is believed to play a role within cytoskeletal regulation, neuronal migration and even intracellular transport (Riley & Kendler, 2006). Due to this gene being highly implicated in neuronal function and brain development, extensive studies are being carried out to assess its potential as a susceptibility gene. Ekelund et al. (2001) have identified a locus on chromosome 1 within the DISC1 gene to be a potential risk factor. Studies such as this are implicating the gene to not only be involved in schizophrenia but also affective disorder.

4. 4 Catechol-O-methyl transferase (COMT)

A gene that has been discovered via linkage analysis on chromosomes 22q11 is that of the COMT gene. Catechol-O-methyl transferase (COMT) is an enzyme involved in the synthesis and degradation of monoamines. Using the example of dopamine, COMT introduces a methyl group into the catecholamine so as to convert it from dihydro-phenyl-acetic acid to homovanillic acid (the major metabolite of dopamine). COMT is “ functionally polymorphic, with a variable amino acid, Val158Met” (Riley & Kendler, 2006, p. 669). This polymorphism is a single nucleotide polymorphism that normally codes for COMT. Subjects with 22q11. 2 deletion syndrome are known to have a microdeletion in this area, which is known to result in larger amounts of dopamine within the brain (Gothelf et al, 2005).

5. Copy Number Variants (CNVs)

Copy number variants have been described to be “ a DNA sequence that is at least 1 kb in size...that can vary in dosage between individuals as a result <https://assignbuster.com/the-genetic-basis-of-schizophrenia-psychology-essay/>

of duplication or deletion of chromosomal material" (Williams et al, 2009, p. 67). It has been reported that up to 10% of the genome has been subjected to microduplications and deletions and that these copy number variants have a possible role within schizophrenia (Beckman et al, 2007).

6. Recent Advances and Future Directions

The recent advances in the search for schizophrenic susceptibility genes have come from the introduction of genome-wide association studies. This new technique has the ability to detect and identify risk genes of small effects within many different diseases.

In the future there are possibilities of conducting whole genome studies in order to detect associations with single nucleotide polymorphisms and also the rare copy number variants (Owen & O'Donovan, 2008). Furthermore, through further use of genome-wide association studies, one would be able to look into detecting copy number polymorphisms as well as rare variants. This will however depend on the availability of large patient samples and even more the ability to handle increasingly large data sets.

7. Conclusion

In 1911, Bleuler summarized that " heredity does play its role in the etiology of schizophrenia, but the extent and kind of its influence cannot as yet be stated" (Gottesman et al, 1982, p. 40). Within this essay we have highlighted the extent to which heredity plays a substantial role within schizophrenia, but also how as of yet there is still no definitive aetiology behind this multifaceted disorder.

After surmounting the evidence from family, twin and adoption studies, we have clearly demonstrated the greater impact of genetics compared to that of any other factor. After examining familial studies, we can see that the greater the genetic link, the greater the risk of susceptibility to schizophrenia. On the contrary however, because MZ twins do not have 100% concordance, it is evident that genetics alone cannot be considered the sole cause of schizophrenia and that factors such as the environment are also implicated.

Researchers have been able to identify several promising candidate genes through the combination of both linkage and association analyses. A number of regions within the human genome have shown consistent signs of linkage; most notably dysbindin, neuregulin 1 and DISC 1. Identification of these risk loci is still only the first step to proving a relationship between it and schizophrenia. With each new study that is published, further research needs to be carried out so as to enhance its validity. The more times a study is replicated, the more weighting it has in proving the existence of susceptibility genes. In several cases where new genes have recently been identified, the number of replication studies still remains small (Riley & Kendler, 2006).

It is also important to note that there still remain a number of limitations in some of the methods that have been used. Taking the example of twin studies, one must not neglect the possibility that if MZ twins share a more similar environment than DZs, then this factor, along with the influence of identical genes, could lead to a greater similarity between MZs. Considering the limitations of linkage analysis, it is important to understand that the <https://assignbuster.com/the-genetic-basis-of-schizophrenia-psychology-essay/>

resolution is extremely low, to the extent that millions of base pairs along the chromosomes are being examined at a time. Furthermore, the strongest linkage signals are only best detected in recessive and highly penetrant diseases,

The availability of meta-analysis and genome-wide association studies have provided researchers with the ability to review an increased range of data, some of which is also now available as part of public databases. Many studies have failed due to their sample sizes being very limited in numbers. With rare structural variations being very small, it should be known that “small effects require large samples of individuals” (Bertolino, 2009, p. 290).

To summarise our findings, I believe the best model to fit the genetic mechanism of schizophrenia to be that of the oligogenic model. This model illustrates how a limited number of small genes are implicated, and how they all interact with each other and the environment. At the moment, scientists are also in favour of this model with recent research into copy number variants strengthening its basis. Due to rare genetic structural variation a small number of risk loci are being implicated, all of which can be influenced by a number of factors other than by genetics alone (Schwab & Wildenauer, 2009).

Although there have been considerable amounts of research into the genetic basis of schizophrenia, no single gene has been consistently associated with a greater likelihood of developing the illness. Therefore, the “precise nature of the genetic contribution remains obscure at this time” (Tandon et al, 2008, p. 1)