DISCUSSION DOCUMENT

GENETICS AND MENTAL ILLNESS –

A LOOK AT SOME OF THE RECENT LITERATURE ABOUT THE POSSIBLE LINK BETWEEN GENETICS AND SOME OF THE MAJOR MENTAL ILLNESSES

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Introduction

The subject of genetics and its link with mental illness is one that causes a lot of controversy.

For some people the causes of mental illness are an area laden with emotion.

There are people who see mental illness as being primarily caused by the worlds we live in, whether that is through the experience of past trauma or through trying to manage in a harsh and unfriendly society.

There are others who see mental illness as a purely biological phenomenon with as little difference to its manifestation as occurs with an illness such as Diabetes.

The two sides of the debate can cause a great deal of friction and argument and when the idea that some mental illnesses may have a genetic component is added, then emotion can become high.

For some people the very idea of genetics and mental illness brings up memories and fears of the abuse of science. For instance the idea that the eugenics movement of the 1930's and 1940's may occur again and for pressure to then arise to select out the existence of people with a mental illness.

The idea of a link between genetics and mental illness may also make people fear that if there was such a clear link, then there could be unfavourable treatment of people with a mental health problem in such things as the job market or getting insurance, or in labelling young people before they even get symptoms of illness.

Other people see the issue as an irrelevancy. It distracts from the principle task of getting on with life whatever the condition or disability a person may have. It medicalises and gives a negative edge to people's lives.

However other people have the opposite opinion. If there were to be a clear way of describing the link between genetics and mental illness then perhaps cures could become possible in the future. Informed decisions could be taken about whether to have children or not and people at risk could have strategies in place to provide early intervention if they ever did become ill which, would help diminish the impact of the illness.

This paper was stimulated by the interest a volunteer with HUG had in the subject. It is an attempt to look at some of the literature on the subject and to give a broad overview of some of the current evidence about the link between genetics and mental illness.

We hope to follow this up with a further document giving some of our opinions and some of the arguments in favour of and against seeking a genetic test for mental illness.

GENETICS AND MENTAL ILLNESS

Human genetics is still a young science. The term was first coined in 1905 and although some essential pioneering work was done in the 19th century, most of the work has taken place in the 20th century. The modern study of genetics began with the botanical experiments of Gregor Mendel which were published in 1866. His findings were ignored at first and rediscovered in 1900 when they became the beginnings of the new science.

In the last 30 years there has been much discussion as to whether various aspects of human experience and behaviour are due to genes or environmental influences. Genes are one of the factors controlling hereditory. They are coded messages that instruct the growing body in how to develop and function.

Genes are too small to be visible even under a microscope. They are carried by chromosomes, which are visible under a microscope. Chromosomes are tiny structures that carry genes. They can be thought of as a string of beads, with each bead representing a gene. A specific gene is always found at a particular site on a particular chromosome. Chromosomes are carried by DNA, so DNA carries the genetic codes for all forms of life.

Environmental influences include culture, family, diet, and chemical influences of all kinds. The two elements of genes and environment are closely interlinked in all aspects of our lives, for instance, height is something that is inherited, but also depends upon diet. There are some medical conditions which are clearly genetic but whose development depends on the environment: for instance, a disease, such as schizophrenia or manic depression, which might develop due to a genetic disorder may be prevented by some environmental intervention, or may only manifest itself in certain conditions.

In these last decades, there has been a growth of knowledge following the advent of "the new genetics" of DNA technology. New advances in DNA technology have stimulated a rapid increase in the amount of research aimed at identifying genetic markers linked to schizophrenia. If it succeeds in identifying a disease pathway, then this would enable new treatments to be designed that would act on the pathway.

There is now increased public awareness of the importance of genetics. There are several different types of genetic disorders: chromosomal disorders, single-gene disorders, multifactorial disorders, somatic cell genetic disorders, and mitochondria disorders. Multifactorial, or complex, traits are determined by the interaction of a number of genes each with a small but additive effect, together with environmental factors.

It was once thought that searching for genetic aetiology (genetic causes) for psychiatric disorders was pessimistic. There is now enthusiasm for using molecular biological approaches to resolve many etiological issues, which in the past seemed intractable. Psychiatric genetics is now being researched on a scale far greater than at any time before. The tasks of psychiatric genetics are to discover whether genes contribute to psychiatric disorder, and to discover how genes result in disorder – to understand the way in which they act, and to unravel how they interact with ones environment and experience.

GENETIC STUDIES

It has long been established that some forms of mental illness tend to run in families. Much effort has gone into determining that this is mainly determined by genetic factors, environment or a combination of the two. McGuffin et al 1994 suggested that it is unwise, when dealing with psychiatric disorders, to focus on nature and avoid nurture. Most psychiatric disorders are complex traits. Traditional methods of study in psychiatric genetics involve investigations in families, twins and adoptees. These are important methods of allowing it to be known whether genetic influences are the cause of an illness or not. Family studies involve investigation of the relatives of people suffering a mental illness and assessing the risk that they too will develop the disease. This risk is then compared to the risk that someone in the general population will develop the disorder. Family studies allow it to be said whether familial aggregation (family similarity) occurs and to what extent. Twin and adoption studies provide "natural experiments" which allow the effects of shared genes and shared environment to be teased out. K. Darton 1997 says that studies clearly show that there is a genetic component to at least the more serious forms of mental distress, such that the life-time risk of developing these conditions is increased in people with affected blood relatives. Studies into the genetics of people with mental illness may lead to benefits – it may add to the understanding of their underlying causes, improve diagnosis, enable the development of treatments, and allow treatments to be tailored more accurately to individuals.

It has been suggested by T. Giethiel that the uncovering of a genetic basis to mental illnesses will tend to turn the associated stigma of a mental illness into a 'real disease', one worthy of care and treatment rather then shame and stigma. He illustrates this by mentioning Alan Bennett's play 'The Madness of King George', which is also a film now. At the end of the play, it is explained that the king probably suffered a metabolic disorder (porphyria) and therefore was not 'really' mad – as the title of the play and film suggest. Other examples he mentions are in Alzheimer's disease where its molecular neurobiology and molecular genetics are now more understood and many more ordinary people see it as a type of illness. He also

mentions schizophrenia and manic depression and says that public perception of these mental illnesses are changing too.

Schizophrenia and manic depression are both considered to be multifactorial traits, complex traits, having many factors, as are a large number of physical illnesses. For schizophrenia and other types of mental distress the genetic component is generally thought to be an inherited predisposition to develop the condition in response to stress and other triggering circumstances.

However, it is stated, by Darton l997, that 89% of people diagnosed with schizophrenia have no parent with the same diagnosis, 81% will have no close relatives affected, 63% will have no family history of the condition at all. She also stated that for manic depression, the concordance, the degree of similarity, in identical twins is 70%, and for fraternal twins 15%. The frequency of manic depression in first degree relatives – parent or brother, sister - is 15%, second degree relatives – grandparent, uncle or nephew - is 5%, third degree relatives – great grandparent, cousin - is 3.5% and the general population, 1%.

LIFETIME RISK OF DEVELOPING SCHIZOPHRENIA

General population	1%
Child with 1 affected parent	18%
Child with 2 affected parents	46%

89% of people diagnosed with schizophrenia have no parent with the diagnosis.
81% of people diagnosed with schizophrenia have no close relative with the diagnosis.
63% of people diagnosed with schizophrenia have no family history of the condition at all.

With regard to manic depression, The Old Order Amish, who are a religious sect in America, are interesting. This is because they are a close knit community in whom the environmental, or triggering circumstances, that go along with the genetic factors which trigger a mental illness are lacking. It is very rare for the Amish to be associated with alcoholism, drug abuse, unemployment, divorce or any violence. Yet the Amish have the same number of people with manic depression as any other community of a similar size. Also, all the active cases were shown, by research, to have family histories of the disease going back several generations. Although these facts are discussed by McGuffin and Murray 1991 and Egeland 1987, they agree that it is still not known how manic depression, with little environment influences, comes about – more work needs to be carried out. The Amish themselves refer to manic depression as being 'in the blood'.

Almost all family studies have shown that the more closely related an individual is to the patient with schizophrenia, the greater the risk of development of schizophrenia becomes. However, familial aggregation of the illness does not, of course, confirm genetic transmission. It is suggested that it could be that children learn an abnormal form of behaviour from the schizophrenic parent or that familial transmission is via an infectious agent such as a virus. However, it is suggested by McGuffin et al 1994 that schizophrenia is a disorder with a strong genetic component, although the results of studies so far are contradictory and confusing.

The 'lifetime morbid risk' of a condition is the degree of risk that someone will develop it at some time in their life. If genetic factors are important in the development of schizophrenia, it would be expected that morbid risk would be higher in relatives of people with the illness than in the general population. Gottesman 1991 drew data from 40 European studies and found that the risk does vary with the extent of the gene sharing. The risk was greatest in identical twins of people diagnosed with schizophrenia, and decreases in the children of 2 parents with the diagnosis, first, second and third degree relatives, and finally in the general population.

Sham, Gill and Murray say that most mental disorders are likely to have complex or even heterogeneous aetiology – different forms of cause. The relationship between gene and disorder is unlikely to be one-to-one. It is probable that several genes contribute to one disorder and that one gene could contribute to several disorders. Also the interaction between gene and environment may be complex. For example, a gene may lead to a disorder only if a particular environmental event occurs at a particular time in development.

The data suggest that genetic factors are important in the development of schizophrenia but that they do not provide a complete explanation of its occurrence. Monozygotic, or identical, twins are genetically identical, but both will develop schizophrenia in less than half of cases where one does. A concordance rate for monozygotic twins of less than 100% indicates that genes are not sufficient to be the only cause of schizophrenia. What is inherited is a predisposition to develop the disorder. In fact, 89% of subjects with the diagnosis do not have a parent with the condition, and 63% have no relative with the illness. This could suggest that the gene involved is a new mutation and is not inherited or that cases of schizophrenia could exist without a genetic basis, indicating that genetics are not a necessary cause either. It is also suggested that a number of genetic factors may be required to occur together before schizophrenia could occur, so that if, say, 6 factors were required, 3 could come from each parent, neither of whom would be affected, but the child could become affected.

The advent of molecular genetics changed the area of genetics from being abstract and remote to being a 'hot' area of psychiatric research. Now it is possible to work out susceptibility to psychiatric disease at a molecular level.

McGuffin (1991) said that there are analyses which reveal that most of the variance in liability, responsibility, for manic depression can be accounted for by genes, while neurotic depression probably receives a large input from family environment, which provides clear leads to further studies.

Further studies are also needed to look into neurotic disorders, including depression, anxiety, panic, phobic, obsessive compulsive, personality, and eating disorders, because the genetics of these have been poorly studied. McGuffin et al 1994 say that there is evidence that neurotic disorders show familial aggregation, and that twin studies suggest that this is at least partly a consequence of genetic factors. Sim and Owens 1993 say that genetic and environmental factors contribute to the formation of neurotic disorders also stating that most authorities agree that environment is of greater importance than genes. However, studies of twins by Kendler et al 1987, found evidence for a genetic contribution to anxiety and depression. They were able to confirm their findings in 1992, in another study, which also appeared to show that familial environment, played no role in either condition.

An Australian twin study was carried out by Andrews et al 1990, which failed to find evidence of a genetic contribution to obsessive compulsive disorder. However, studies have been carried out by others, (Lenane et al 1990 and Karno et al 1988 – to name but two), who found different results – so as yet, no results are conclusive. McGuffin et al 1994 say that there is a genetic contribution to phobias and fears, even though the area has been understudied as yet.

Regarding personality disorder, some family, twin and adoption studies have been carried out, the findings of which suggest that genetic factors are involved, together with environmental factors. Questionnaire studies have been carried out by Lechlin et al 1988 and Plomin and Rende 1991 to look at personality, and nearly all the results suggest that personality is in part genetically determined.

Sims and Owen 1993 say that there is some evidence for a genetic cause for eating disorders, although they also say that psychological factors are probably the most important cause.

METHODS OF STUDY

The traditional methods of study in genetics involve investigations of families, twins and adoptees. Family studies allow it to be said whether familial aggregation occurs and to what extent. However, familial aggregation does not necessarily mean that the disorder is genetic. Family studies do not differentiate between genetic affects and those arising from shared family environment. Twin and adoption studies allow the effects of shared genes and shared environment to be teased apart. Over the last 30 years, these studies have provided very strong evidence that both genes and environment play a part in mental illness.

Family studies compare the frequency of a disorder in the relatives of affected people with the frequency seen in a sample of individuals drawn from the general public. Various approaches have been used, and the most satisfactory approach has been found to be to interview personally all available relatives, called the family study method.

Twin studies are carried out using both identical and fraternal twins. Identical twins are the products of the fertilisation of a single egg by a single sperm and therefore have 100% of their genes in common. Fraternal twins are from two eggs and two sperms and share on average 50% of their genes. Assuming both types of twins share common environmental effects to a similar extent, any greater similarities for a particular disease shown by identical twins compared to fraternal twins will be due to genetic influences.

One of the most frequent criticisms of twin studies is that identical twins may be treated more alike by their parents than fraternal twins, that they may be dressed more similarly, and may share a special environment, more so than fraternal twins. This problem has been studied to some extent by Leohlin and Nichols 1976, and McGuffin et al 1993. Both these studies found that identical twins were slightly more similar than fraternal twins, but concluded that these differences would not account for differences in illness.

It is suggested by McGuffin et al that adoption studies provide a cleaner, crisper separation between the effects of genes and those of family environment. Attention is focused on individuals who were adopted in early life and on both the adopted and biological families. Three commonly used study designs are:

1. The adoptee study – the adopted away child of affected parents are studied and compared with other adoptees of other non-affected parents.
2. The adoptees family study – adoptees who have developed a disorder are studied by comparing their biological and adopted relatives.
3. The cross fostering study – the rates of illness in adoptees who have affected biological parents but were raised by unaffected adoptive parents are compared with

the rates of illness in the offspring of normal parents brought up by adoptive parents who themselves become affected – this is the least common design.

Studies of adoptees has been used to investigate the possibility that the risk of developing schizophrenia is greater in someone whose parent has the diagnosis because they are being brought up by that parent. Studies have shown that the lifetime risk of developing the condition is not decreased by adoption. This also suggests that being brought up by a parent with schizophrenia does not have a significant role to play. It has also been shown that the concordance rate for the illness in identical twins is no lower in twins who are raised separately than in those who are raised by their parents together.

GENETIC COUNSELLING

There are two aims of genetic counselling: to try to lighten, or relieve, the adverse effects of genetic disorders, and to reduce the possible recurrence of the disorder. It is the process by which patients and relatives at risk of a mental illness with a genetic component are advised of the consequences of the disorder, the probability of transmitting or developing it and the ways in which the disorder can be prevented, avoided or ameliorated. The goal is to provide the maximum amount of information to make ones own informed decisions. The scope and consequences of genetic counselling depend upon just how much the genetic mechanisms underlying the disorder are understood. It is hoped and expected that with further advances in molecular genetics future advances will be made to help some people, but as yet this stage has not been reached.

As Angus Clarke 1994 says, genetic counselling is what happens when an individual, a couple or a family ask questions of the genetic counsellor about a condition or disease that is, or may be, genetic in origin. They may want information about a condition that has affected one or more relatives. Might they be affected by it? What treatment is available? In the event of a pregnancy, could testing for the condition be carried out, to see whether the child would be affected?

In responding to these questions, information is provided that could help decide about plans for having children in the future, or about making other important decisions.

Genetic counsellors at the moment adopt a non-directive educational approach, to help people as much as they are able, by informing and teaching. Therefore, a genetic counsellor could say to a couple who want to have children, one of whom has a schizophrenic parent, that the risk to a child of theirs could be 3%, which would be 3 times greater that the general population. It would then be the decision of the couple to decide whether they would accept this risk, which they could ascertain for

themselves was a low risk. However, as Moldin and Gottesman 1997 say, there are multiple genetic and non-genetic factors that may increase or decrease ones risk of developing schizophrenia, therefore, there is unlikely to be a way to predict with any certainty who will or will not become affected. So there is no indication that prevention of reproduction for people with schizophrenia will decrease the number of people who become schizophrenic. They suggest that when an individual inherits an amount of predisposing factors, and when the environment is sufficiently unfavourable, for any reason, illness may result.

Once people attending a genetic counsellor have been given information they request, that may be the end of the counselling. However, if they wish to make reproductive decisions on the basis of the information, they may find it helpful to discuss and talk things through. This provision of support during the process of decision making is also an aspect of genetic counselling. Another aspect is to provide ongoing support to all families living with decisions that have been made, and to individuals affected by, or at risk of developing a genetic disease.

Genetic counselling is a specialist service provided by clinical geneticists and other trained professionals. The counsellor may be medically qualified, but need not be.

Unfortunately, there are few centres where genetic counselling is available, so it occurs fairly rarely. Research and practice in the field of genetic counselling are only in the early stages of development, and they must continue to evolve.

People attend genetic counselling with concerns regarding a potential risk to their children, having had them, or to decide whether to have children or not. However, future advances in molecular genetics could change this, as the advances may allow pre-symptomatic and prenatal diagnoses in some families and also other possibilities of medical intervention.

These developments would raise ethical issues.

ETHICAL ISSUES

Ethics means the science of morals. Its meaning has more recently been broadened, so that it encompasses the science of human duty in its widest extent.

The study of genetics and mental illness offers an exciting approach to understanding causes and discovering cures for these diseases. However as McGuffin (1994) says, there are some ethical thoughts about the ability to avoid and treat genetic diseases.

One thought comes from a reaction to the eugenics movement in the early part of the twentieth century. Eugenics was based on the notion that the knowledge of genetics

could enable the abolition of certain diseases and lead to the improvement of the human stock in general. (Carlson 1987, Roll & Hanssen 1988). Some find it difficult to escape from the idea that geneticists still have the improvement of stock in their minds. Eugenics was used by the German Third Reich in evil ways around the time of the Second World War.

Another thought is the view that genetic explanations of psychiatric disorders are unacceptably mechanistic and very simple, often ignoring the influences of poverty, child abuse, poor education and interpersonal relations. This thought is often allied to another, which claims that genetic theories reduce the richness and complexity of human experience and also, that genetic mechanisms must be impossible to treat and are unlikely to be susceptible to psychological intervention.

A related concern is that molecular genetics could lead to neglect of non- biological, potential remedial contributions to mental illness (Pelosi & David 1989).

Another area of ethical concern relates to the question of availability of genetic information to third parties, such as relatives, employees and insurance companies. This could pose problems in the future, when susceptibility genes become identified.

The ability to understand the genetic basis of some mental illnesses, if it does come about, would have a profound beneficial effect on treatment and prevention of those mental illnesses, although there are these ethical issues to consider too.

REFERENCES

M Weller and M Eysenck 1992 The Scientific Basis of Psychiatry

S Bloch, P Chodoff, S Green 1999 Psychiatric Ethics

McGuffin, Murray 1991 The New Genetics of Mental Illness

McGuffin, Owen, O'Donnovan, Thapar, Gottesman Psychaitric Genetics

E Slater, V Cowie 1971 The Genetics of Mental Disorder

K.Dart 1997 Genetics Factsheet Mind Publication

S.O.Moldin, I.I.Gottesman 1997 At Issue: Genes, Experience and Chance of Schizophrenia – Positioning for the 21st entry. Schizophrenia Bulletin 24 (4) 547 – 561 National Institute of Mental Health

A.Dorfman, D.Thompson 1987 Is Mental Illness Inherited Time

A.Sims, D.Owens 1993 Psychiatry

A.Clarke 1994 Genetic Counselling Practice and Principles