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Annotation

Genetic Counselling for Schizophrenia

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Summary: It is possible that genes contributing to the development of schizophrenia may be identified within the next decade. Genetic methods are improving rapidly, and are surrounded by great public interest. Requests for genetic counselling are keeping pace with this increased attention, but the problems faced by psychiatric genetic counsellors are complex, and the experience of offering such counselling and the issues involved are rarely discussed. In this context the paper describes a year's work counselling for schizophrenia in the Maudsley Hospital Genetic Clinic.

The last year has seen an increased public awareness of genetic methods. Not only have the possibilities and ethics of gene manipulation, prenatal diagnosis, and selective abortion been aired by the media, but in late 1983 a positive linkage was reported for the gene for Huntington's Chorea with a polymorphic DNA fragment from chromosome 4 (Gusella *et al,* 1983). The speed of this finding took the scientific world by surprise, and opened the door on a programme of research aimed at the eventual eradication of this disorder. Similar research to identify genes contributing to the major psychoses was recently suggested (*Lancet,* 1983) and is now under way. On present indications, it seems very possible that such genes will be located, and their gene products explored, before the end of the century, so that genetic counselling may soon become an essential part of our psychiatric repertoire.

However, counselling for schizophrenia and other psychiatric disorders is particularly difficult. Firstly, the definition of the illness often presents problems—is the condition in a given family schizophrenia at all, and should other psychiatric disorders in the family, such as possible 'schizophrenia spectrum' disorders, be included in calculation of the risk? Secondly, the chance of passing on 'schizophrenic' genes is by no means the only consideration when couples contemplate starting a family. Sometimes the possible teratogenic effects of neuroleptics in pregnancy (or the consequences if they are stopped), the effect of pregnancy itself on the mental state of a schizophrenic mother, or the couple's ability to bring up a child, are of overriding importance. Thirdly, there may be within a couple particular pressures on the individual from the 'schizophrenic' family: the spouse may wish to apportion blame, or sever relations with his/her in-laws, and suggest counselling in the hope of justifying this. Fourthly, many theories for the aetiology of schizophrenia have been put forward over the years. Families may be particularly sensitive or guilty, e.g. the concepts of the 'schizophrenogenic mother' or 'schizophrenogenic family' have been devastating for some parents. Thus, righting misconceptions may be as necessary as providing a full appraisal of the situation (Tsuang, 1978). Finally, the degree and pattern of the genetic contribution to schizophrenia is unknown, though speculation is widespread.

Interest in genetic counselling for schizophrenia may have been increasing because the publicity for genetic discoveries has led people to see possibly inherited disorders as treatable. In the little that has been written about genetic counselling for schizophrenia, most authors have considered the theoretical rather than the practical aspects of counselling. It seemed appropriate, therefore, in the present climate of increasing genetic optimism, to assess the work of a recently opened genetic clinic at the Maudsley Hospital, by examining referrals for schizophrenia for the year from April 1983 to March 1984.

The work of the psychiatric genetic clinic

Referrals to the clinic during 1983/84 were accepted from psychiatric colleagues (5), general practitioners (1), indirectly through the National Schizophrenia Fellowship (9) as well as from concerned individuals as self-referrals (8). It was decided to accept the latter after several personal approaches had been made. Among

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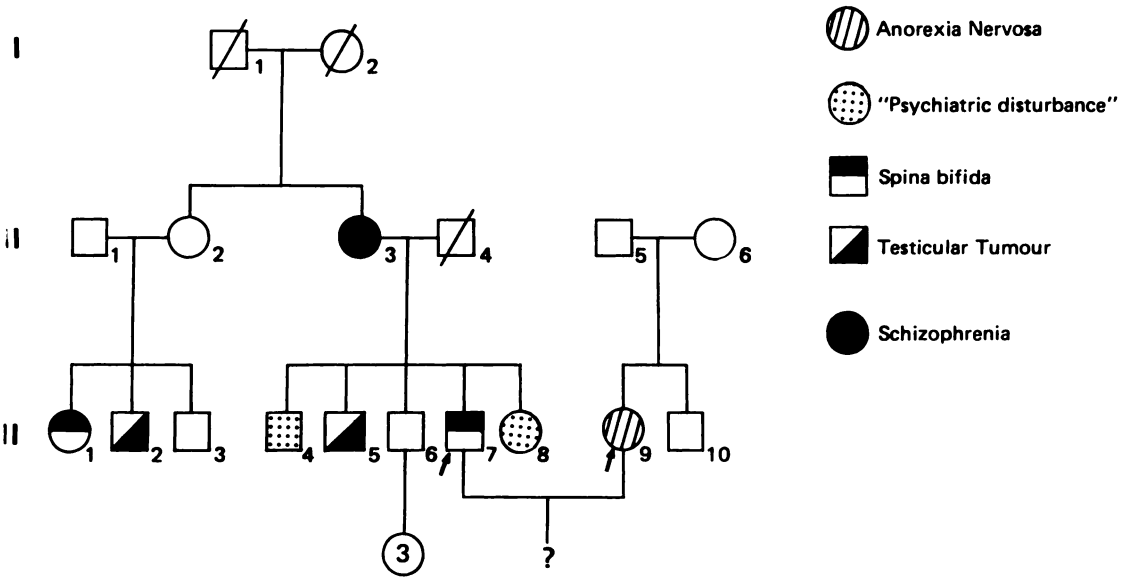


FIG. Pedigree of the A and O'G families

patients seen for various neurological and psychiatric conditions, 23 were counselled for schizophrenia, either in themselves or in their families, during the year of the study. Only one was not a bona-fide referral for an opinion or counselling, despite our policy of allowing self-referrals, (this was an elderly schizophrenic man who had developed a psychotic interest in twin research). Another schizophrenic referred herself for help with marital difficulties surrounding her decision to remain childless. Other inappropriate self-referrals from psychotic individuals were easily detected from the initial letter and directed elsewhere. Thus, the 23 were made up of four concerning the risk to the offspring where the potential parent was schizophrenic; 11 concerning the risk to the subject or offspring where a relative had schizophrenia; six for a 'genetic opinion', and two cases just mentioned.

Who seeks genetic counselling?

Eleven out of 23 subjects who used the genetic clinic in 1983/84 were not mentally ill, but wished to learn more about the risk of schizophrenia for themselves, their relatives, or for potential offspring. In four cases a schizophrenic patient, or his/her spouse requested counselling. (In one couple, both the potential parents were schizophrenics; their children would have a 50% chance of developing the illness (Slater & Cowie, 1971)).

Most relatives and schizophrenics who sought counselling were socially aware, responsible individuals who did not wish to risk disruption in the future lives of their family. They may have been in relatively less need of genetic counselling than those from more deprived backgrounds, but there were particular issues and stresses that seemed common in those attending our genetic clinic. For example, in several instances where a young couple were considering marriage or children the 'unaffected' partner or his family had insisted on an investigation of the risk. Subtle undertones of blame and guilt were often present. A potentially disruptive situation could often be defused by introducing an opportunity to ventilate such feelings, and when this was combined with the realisation that the risk was probably not as bad as expected, many couples became openly relieved.

When schizophrenics themselves and/or their partners seek advice, some counsellors invariably (Fuhrmann & Vogel, 1982) or usually (Erlenmeyer-Kimling, 1976) advise against having children. This policy is not adopted in our clinic, as in our view the role of a genetic counsellor is not to advise, but to provide an informed assessment of the risks, and allow the couple to make their own decision. Nevertheless the problems for schizophrenics as potential parents may be major ones. While the children may have a comparatively low risk of developing the disorder, the risk of drugs during pregnancy and the stresses involved in rearing a family may outweigh the desire for children. But a decision not to bear children may be tragic if the subject has not had schizophrenia at all. A man attending our clinic had been diagnosed as having a "schizophrenic reaction" as an adolescent, yet neither his casenotes, nor his current mental status provided any evidence for schizophrenia as generally diagnosed, though he was highly anxious.

The following case report illustrates some typical features of genetic counselling for schizophrenia, including the need for accurate diagnosis, the importance of collecting full family information and constructing a pedigree, and the need for psychiatric evaluation of those being counselled.

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Case report

KA, a 25 year-old design consultant, attended for genetic counselling with his wife of six months, AA, because his mother had schizophrenia. They referred themselves after reading a leaflet published by the National Schizophrenia Fellowship.

His mother developed schizophrenia at the age of 25, when her husband died in an accident, leaving her alone with five small children. Since that time, she had had a chronic illness, characterised by repeated hospital admissions. Her son explained that over the years, he had noticed bizarre behaviour (e.g. taking the dog for a walk at 3.00 a.m.), incongruous emotions, deterioration in personal habits and cleanliness, and complaints of hearing voices. She was given injections of flupenthixol at her local hospital which "make her more bearable".

The five children were all brought up together in a children's home. They saw their mother and maternal grandparents very frequently, and KA described his childhood as "not bad at all; we had happy times".

AA, a 33 year-old executive, accompanied her husband. She had been a difficult and disturbed young woman. After a traumatic adolescence, with treatment for anorexia nervosa, she had risen rapidly to an executive position in a marketing company, where she was seen as ambitious and 'a workaholic'. KA was eight years her junior, and at interview was dominated by his wife. She had precipitated the counselling session, she said, for two reasons, firstly, to "make sure" her children would not become schizophrenic, like his mother, and secondly because she wanted to keep KA away from his "crazy family". At interview, she focussed on the mental health of the A family. It was KA who told me that his wife had had prolonged psychiatric care. She found discussing this upsetting, and became tearful. Her problems, it turned out, had delayed their marriage for three years (during which they lived together). She was unsure about having children and had only agreed to do so because of her age ("If I don't do it now, I may lose the chance"). She was still attending a psychiatrist but considered herself well.

Family history

A. family (See Figure)

Father (II_4) died accidentally with no known illnesses.

Mother (II_3) has very probable schizophrenia, as described.

Mother's sister(II_2) is alive and well.

Maternal cousins: Female(III_1) has severe spina bifida. She is wheelchair-bound.

Male (III_2) had a testicular tumour. Apparently cured.

Male (III_3) is alive and well.

Siblings of KA:

III_4 described as a "loner" and "definitely off". Lives alone on social security, and is very suspicious of other people. Has never seen a psychiatrist, and will not speak to the rest of the family.

III_5 had a testicular tumour, which was resected. He is now well and lives alone.

III_6 alive and well with three healthy daughters.

III_7 KA himself. Has very mild spina bifida which is asymptomatic.

III_8 sister has attended psychiatrist for many years with depression. Has attempted suicide. She is divorced and lives with her mother.

O'G Family

Parents and two children. AA, (III_9) formerly A.O'G is the only one with any psychiatric contact.

Counselling session

Mental illness: As can be seen from the pedigree, the A family is full of medical and psychiatric illness. Nevertheless, KA and his wife saw his mother's schizophrenia as the most worrying condition, and it was this that they most dreaded in their potential children. KA had suffered a disrupted childhood; though he described it as "happy", he would not wish the same for his grand-children. He did not wish his mother to be informed, so I could not read her casenotes, but from his description, it appeared likely that she had chronic schizophrenia.

The psychiatric illness in KA's siblings is less easy to categorise. Should the "weird" brother, III_4 be counted as psychiatrically ill with schizophrenia? Does his sister, III_8 have a mental illness that is genetically related to her mother's? I adopted the stratagem of assessing the risk both ways, and giving these as upper and lower limits. Further, the mother's illness only became manifest after the early death of her husband. How much did this stress contribute to the development of her illness?

The A couple were informed that if II_3 (KA's mother) was the only schizophrenic in the family, and KA himself remained well, then the risk to their children was probably less than 3%. If KA's brother and sister were both considered to have a variant of schizophrenia, then the risk might be higher, but by conventional calculations, would still be considerably less than 10%. This would not be considered a significant genetic risk.

AA's anorexia nervosa and depression were not considered to contribute to the development of schizophrenia in her offspring, but is this really the case? Kay (1978) has examined studies of the spouses of patients admitted to mental hospitals, and has shown that approximately 30% may have some psychiatric illness or personality disturbance, and the risk of psychiatric disturbance in the offspring was greater in these couples. Anorexia is not considered to fall within the 'spectrum' disorders, though some forms of depression may do so (Rosenthal, 1974). Holland *et al*, (1984) have shown that there is no excess of psychosis in the families of anorexics, so it is unlikely, though still possible, that the A's were an example of assortative mating on the borders of schizophrenia. If this were the case, we would have underestimated the risk for their children.

Spina bifida: KA was not particularly concerned about this, saying "my cousin is wonderful with it", and "it hasn't bothered me". However, I suggested that AA should mention the family history to her obstetrician if she became pregnant, and informed her that tests were now available which might allow prenatal diagnosis, and that folic acid supplements during pregnancy might exert a

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preventive effect. Spina bifida is a condition which, like schizophrenia, appears to have a multifactorial aetiology. It is suggested that where a parent has the disorder, the risk to any offspring will be about 3% (Baraitser, 1982).

Testicular tumours: KA said again that he was unworried by this, though he had regular check-ups. Both his brother and cousin were considerd "cured", but both were probably infertile. Little is known about the inheritance of cancer, although some families have a very high incidence of cancer of various types. I explained to the As that I did not know the risk of his developing a testicular tumour, nor that for his children. I suggested that he keep having the check-ups.

An area that is particularly pertinent to genetic counselling of psychiatric disorders is the motivation behind the request for help. Are couples like the As seeking an excuse to avoid children, or to avoid relations with in-law's? Is there any evidence that the As future children should be kept from contact with their father's 'crazy family'? The study of Wender *et al* (1974) examined this issue by examining the offspring of normal individuals who were reared by schizophrenics. This group showed no increased rate of schizophrenia, despite close contact with the illness, so that the effect of schizophrenic grandparents, aunts or uncles is likely to be equally benign.

K and AA were very intelligent but troubled individuals, with a rather tense relationship. It was not possible to explore their problems fully in a 1 1/2 hour session, but they were encouraged to ventilate their feelings as much a possible, and to begin to consider all the other implications of having a family. Were they using the family history of schizophrenia as a scapegoat to cover other worries about raising a family? Did AA resist the idea of getting pregnant (and thereby gaining weight) and having to give up work for a while? Did KA see his wife as a mother figure, and thus resent the idea of a child? They clearly enjoyed having the opportunity to speak freely to each other on these issues during the counselling session, and left saying that they felt it had cleared the air and was very much worthwhile. They were given the clinic number and asked to telephone if further questions came to mind.

Discussion

It is not often that the risk to the potential offspring of a well relative of a schizophrenic will be great enough to warrant concern about reproduction. But the inheritance of schizophrenia is complex, and the genetic counsellor must judge the risks for a particular family from a range of theoretical and empirical information.

The mode of inheritance of schizophrenia

Where disorders with an apparent genetic predisposition do not have a simple mode of inheritance, alternative explanations have to be invoked. The situation is not unique to psychiatric illness, but is seen among most commonly occurring medical or congenital disorders. Examples include cardiovascular disease of middle life, diabetes mellitus, spina bifida, and congenital dislocation of the hip. The inheritance of such disorders is now generally supposed to be multifactorial (Vogel & Motulsky, 1982), where a number of unknown genetic and environmental influences may act in varying combinations to produce the illness. Within this concept, it is understood that a single major gene or an environmental influence may be involved as the only aetiological agent in some cases, so that the fundamental aetiology of such disorders may be heterogenous. Taken as a whole, however, multifactorial conditions behave as if the liability to develop each disorder (i.e. the accumulation of risk factors associated with that disorder) were normally distributed in the general population (Carter, 1969; Edwards, 1969). The all-or-none appearance of the condition is dealt with by the concept of a threshold (Falconer, 1982), beyond which there is manifestation.

Gottesman & Shields (1982) have recently urged the concept of multifactorial inheritance for schizophrenia, and before that an earlier version of a similar idea, the polygenic theory (1967), which proposes a large number of genes of small effect, acting in combination with the environment to produce the illness (without the additional single major genes or major environmental influence permitted under the multifactorial hypothesis). There have been other ideas, foremost among them Slater's (1958) suggestion that schizophrenia was due to possession of a single dominant gene which did not necessarily give rise to the illness (i.e. had incomplete penetrance). Do these alternative models for the aetiology of schizophrenia have any relevance for practical genetic counselling?

Theoretical models are relevant for counselling, since they can be used to derive risk figures for the relatives of schizophrenics. Computer programmes are available, (e.g. Smith's RISKMF (1971) used by Gottesman & Shields, 1982), which calculate the exact theoretical risk, based on the polygenic/multifactorial model, for varying combinations of affected and non-affected relatives, from the base population rate of 0.9% to over 50% where both parents and other relatives have the illness. At best, such theoretical risk figures provide a framework for counselling, at worst they may be completely erroneous. Morton *et al* (1979) have shown that alternative single major gene and multifactorial/polygenic models, incorporating a diagnostic spectrum of very mild to chronic schizophrenia, can generate risk figures that vary tenfold.

A further complication is that theoretical risk figures generated under a polygenic/multifactorial

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model assume a qualitative equality of risk, while in reality some families may be particularly vulnerable, and others have little inherited risk at all. Karlsson (1974) has described multigenerational pedigrees from Iceland which show precisely this effect. Thus, the widely accepted figure of a 10% occurrence of schizophrenia in siblings, parents, or children of a schizophrenic may be true overall, but for individual cases, almost always wrong.

In this situation, empirical pointers to inherited vulnerability assume great importance. In general, the more severe the schizophrenic illness in terms of chronicity and age of onset, the higher the risk of schizophrenia for others in the family (Slater & Cowie, 1971; Gottesman & Shields, 1982). On the other hand, where there are obvious organic disorders affecting cerebral function, such as epilepsy (Slater *et al,* 1963) or previous trauma (Schulz, 1932 reanalysed in Slater & Cowie 1971; Davison & Bagley, 1969), preceding the schizophrenic illness, the risk for relatives is very much lower and may be no higher than that found in the general population. From a research perspective, using a familial/sporadic dichotomy to categorise schizophrenics is finding increasing favour (Murray *et al,* 1984) and as a practical guideline for counselling, it has much to recommend it. Because the mode of inheritance is not understood, schizophrenia presents a different problem for genetic counselling from e.g., Huntington's Chorea, or Duchenne Muscular Dystrophy, where the mode of inheritance is known, but evaluating the risks in a particular case may present problems because of such factors as age-related penetrance or mutation rates. In these situations, computer programmes such as LIPED (Ott, 1974) (or its successor LINKAGE, Lathrop *et al,* 1984) have proved invaluable.

It is not the role of a genetic counsellor to advise individuals, but rather to present the evidence of risk, and provide enough information for those seeking counsel to make their own decisions. A single session is seldom enough to accomplish this; many people remember questions they meant to ask only after they left, so that a follow-up appointment or phone call is always offered (Tyler & Harper, 1983).

It was apparent that in some cases, patients were referred for genetic counselling when in reality a second opinion on the psychiatric illness itself was sought. Such referrals may be equally appropriate. Patients welcomed the opportunity to discuss all aspects of their illness and its treatment, as well as its inheritance, with an informed stranger who was able to assure them that their illness was frequently seen and their treatment standard. Many had private worries that they did not feel able to share with the doctors who were intimately involved with their care. For example, an elderly lady with a previous psychiatric breakdown felt mentally tortured and guilty because two of her three children had had similar illnesses. She explained, "I find it easy to talk to you, because I won't have to face you again".

Who should provide psychiatric genetic counselling?

Any genetic counsellor must draw on the skills of geneticist, marital therapist, psychotherapist, and general practitioner (Kessler, 1979) in an effort to meet the very individual needs of those seeking genetic advice. Psychiatric genetic counselling may be even more complex, (Tsuang, 1978; Targum, 1982) in view of the diagnostic and genetic uncertainties surrounding psychiatric disorders, and the possibility of actual or developing psychiatric illness in those counselled. It seems wise to continue to offer such a service in a psychiatric setting, perhaps on a regional basis or in major psychiatric centres.

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