Multiple affected Afrikaner families in a schizophrenia genetic study: environmental risk factors in interaction with genotypes

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Abstract

The authors report on six multiple affected Afrikaner families suffering from schizophrenia or schizoaffective disorders. These families form part of an ongoing study on genetics of schizophrenia. Three or more first degree relatives were affected in these families. In each family, the following will be reported on: a family tree, sociodemographic data, diagnostic features, substance abuse, early insults, early deviant behaviour, and longitudinal course of illness. Environmental risk factors in interaction with genotypes are discussed and it is emphasised that diseases will tend to cluster in families not because of a direct genetic effect, but because relatives are more vulnerable to the risk-increasing effect of a prevalent environmental risk factor. Progress in the study of environmental factors that interact with genes needs to go hand in hand with developments in molecular genetics.

Key words: Multiple affected founder families; genetics; schizophrenia; environmental risk factors

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Schizophrenia has a heritability in the 60% to 90% range. The search for chromosomal loci and genes has been slow and frustrating. The reason for this may be because there is multiple susceptibility genes involved, each of small effect. In many cases the development of the disorder may depend on the synergistic interaction among particular patterns of genes (epistasis) and not just on the cumulative additive effect of multiple susceptibility genes. The epigenetic processes and environmental factors act in conjunction with the multiple susceptibility genes, each of small effect. The empirical evidence shows that environmental influences are strong and pervasive but rarely determinative.

In the case of genotype-environment interaction, diseases will tend to cluster in families, not because of a direct genetic effect, but because relatives are more vulnerable to the risk-increasing effect of a prevalent environmental risk factor. Some of the affected probands to be discussed in this paper were raised by a schizophrenic mother or father, which could have exposed these probands to a dysfunctional family rearing environment. The Finnish Adoptive Family Study of Schizophrenia showed that the risk of developing schizophrenia spectrum disorders in high-risk adoptees was greater than for control adoptees, but only for those high-risk adoptees who were additionally exposed to a dysfunctional family rearing environment.

There are certain expectations that founder populations may be useful to circumvent some of these obstacles in schizophrenia genetic research. Founder populations may offer reduced genetic heterogeneity, a more uniform environment, and the potential for genealogical research. These populations have proven useful for mapping genes that underlie Mendelian disorders and should also facilitate the search for genes for schizophrenia.

In a recent report of an ongoing study of the genetics of schizophrenia it was concluded that the Afrikaner population is likely an appropriate founder population to map genes for schizophrenia using both linkage and linkage disequilibrium (LD) approaches. The authors are involved in this ongoing study.

Most previous quantitative genetic studies of schizophrenia have employed a phenotypic syndromal definition of this illness based on a single main lifetime diagnosis. Another approach requires a diagnostic hierarchy, with schizophrenia at the top, followed by schizoaffective disorder, then bipolar disorder. If, for example, in the early stages of an illness an individual shows symptoms that fulfill the criteria for a manic or depressive episode but later the clinical presentation becomes typical of schizophrenia, the main lifetime diagnosis is regarded as schizophrenia.
nia and the earlier mood symptoms are regarded as non-specific and not considered in further analysis. A hierarchical diagnosis should take all these diagnostic aspects of the psychotic equation into account. Supplementing the traditional approach of assigning a single main lifetime diagnosis, with information on within person co morbidity of psychotic syndromes, may provide valuable information about the familial aggregation of psychotic symptoms.5

We report on six multiple affected families (where three or more first degree relatives were affected) with schizophrenia or schizoaffective disorders. Certain sociodemographics, diagnostic features, substance abuse, early deviant behaviour, early insults and long-term outcome will be reported on. Aspects of the nature-nurture interplay in these families will be discussed.

Methodology
Since 1997 a collaborative study between the Human Neurogenetic Laboratory of The Rockefeller University, New York and the Department of Psychiatry, University of Pretoria, South Africa has been ongoing. Approval for the protocol was obtained from the IRB committees at both sites. All participants gave written informed consent.

Our current sample includes more than 300 probands of Afrikaner descent who meet diagnostic criteria for schizophrenia or schizoaffective disorder, according to the American Psychiatric Association 1994.6 Of the probands ± 20% are members of families with two or more affected individuals, while the rest are members of triads (affected individual and both biological parents). Families where three or more first-degree relatives are affected are scarcer and six such families were identified. In this paper certain data obtained from these six families will be discussed.

For the full detail of the sample collection, clinical evaluation and Genealogical Research the reader is referred to a paper by M Karayiorgou et al, 2004.4 In the multiple affected families an affected subject was recruited and then the other affected family members were approached for inclusion in the study. In other instances the researchers were notified from the start that it is a multiple affected family, and the members were then approached individually for inclusion in the study.

The clinical evaluation consisted of the following:-
1. The diagnostic interview for genetic studies (DIGS)7 was used for all diagnostic evaluations. Continued interviewer reliability and reduction in interviewer drift were ensured. Reliability of final diagnosis was found to be excellent. The diagnostic interviews were conducted in Afrikaans.
2. Following each interview, diagnosticians completed DSM-IV checklists for each category in which positive symptoms were identified in the DIGS.
3. A narrative chronological summary of prodromal traits, symptom onset, and functional impairment.

The following aspects were extracted from the above mentioned data in each multiple affected family: main psychiatric diagnosis and age of onset of illness, comorbid psychiatric conditions and age of onset, age at recruitment, substance abuse history, early life insults, early deviant behaviour (1-10 yrs) and long-term course and pattern of severity. In the results section a familytree will be presented for each multiple affected family as well as the above mentioned data for each numbered affected proband.

Results
The reason for not including certain data in family III & VI was the following:
In family III, subject 11:2 had passed away at the time of the initial interview and retrospective data was not available. In family VI, subject 1:1 was not prepared to participate in the study.
Family III

Discussion

Psychiatric diagnosis and age at onset of illness

In families II, IV and VI, diagnoses of schizophrenia were made in all of the probands. The diagnoses that were made in the other families were schizoaffective disorder and, in isolated affected probands, diagnoses of schizophrenia. There is evidence of familial co-aggregation between schizoaffective disorder and schizophrenia but no familial relationship was generally found between schizophrenia and bipolar disorder.

The diagnosis of schizoaffective disorder in this study was made according to the DSM IV criteria. The diagnostic criteria leave much to interpretation. Determining the exact length of each mood episode is not always easy or even possible. The term “substantial portion” referring to the time period of the mood episode in the total duration of the active and residual period of the illness, is not defined.

A reasonable conclusion from the available data is that patients suffering from schizoaffective disorder make out a heterogeneous group: some have schizophrenia with prominent mood symptoms, others have a mood disorder with prominent schizophrenic symptoms and still others have a distinct clinical syndrome. The hypothesis that schizoaffective disorder patients have both schizophrenia and a mood disorder, is untenable, as the calculated co-occurrence of the two disorders is much lower than the incidence of schizoaffective disorder.

In this study of molecular genetics of schizophrenia in Afrikaners, schizoaffective disorder has been included among affected relatives for linkage analysis. When gene loci are eventually identified, decisive evidence may be obtained for the genetic etiology and transmission of schizoaffective disorders. This will allow the determination of whether they are subtypes or genetic interforms of schizophrenia or mood disorders, or perhaps a combination of these possibilities.

In family I, IV, V and VI, where more than one generation had affected probands, the age of onset of illness of the youngest generation probands was at a younger age than that of the older generation. In the case of families V and VI, the younger generation probands with an earlier age of onset of illness, all abused cannabis.

Cannabis abuse

In a genetic study as reported here, the investigators cannot exclude underreporting of drug use because it was assessed by using self reported data in a high percentage of cases. We often see that where cannabis use data is reported in a social background report, data is not always reliable. Cannabis use/abuse was not confirmed with toxicological screening.

In the vulnerability model for schizophrenia an individual might be vulnerable to schizophrenia but not get the disease unless some life event stressor triggers it. The findings of the Swedish Conscripts Longitudinal Study suggest that cannabis may be such a stressor. According to this stress-vulnerability model, individuals differ in their sensitivity to adverse environmental circumstances, and genetically sensitive individual are more likely to develop symptoms when exposed to these environments than others.

In most of these families, where cannabis abuse was a positive factor (family II, V and VI) the onset of psychosis was at a younger age or may have triggered the psychosis as in family III. The earlier the onset of the psychosis the worse the outcome of the illness.

Psychosis outcome is more strongly predicted by a baseline lifetime history of use of cannabis than by recent use. This finding suggests that this association is not fully explained by the short term effects of cannabis leading to acute occurrence of psychotic experience.

Van Os hypothesized that the neurobiological changes in-
ducted by tetrahydro-cannabinol may interact with a preexisting vulnerability to dysregulation of the cannabinoid system or to other neurotransmission systems interacting with the cannabinoid system. In accordance with this hypothesis, their findings demonstrate that the impact of cannabis use on psychosis outcome is especially marked in subjects with an established vulnerability to psychosis. These multiple affected families will have such an established genetic vulnerability to psychosis.

The DSM IV exclusion criteria for schizophrenia and schizoaffective disorder states that the disturbance is not due to the direct physiological effects of a substance (e.g. drug of abuse, a medication) or a general medical condition. If one looks at the above mentioned dysregulation of the cannabinoid/neurotransmission systems hypothesis then the use of the DSM IV classification in genetic research becomes problematic and a hierarchical diagnostic system will be more valuable.

**Early deviant behaviour (one to ten years of age)**

In a previous study, early non-psychotic deviant behaviours, the demographics, syndrome course and symptoms of 109 Afrikaner probands who met criteria for DSM IV schizophrenia or schizoaffective disorder were compared to 109 age- and gender-matched US probands. Consistent with past findings, 68% of Afrikaner probands, as compared to 67% of age- and gender-matched US probands, reported one or more form of early non-psychotic deviance. These behaviours included poor socialization, extreme fears/chronic sadness, and/or attention learning impairment. The early non-psychotic childhood deviance distinguished a distinct subtype of patients and the forms of early deviance manifested were meaningfully linked to later disease outcome.

In families III and VI early deviant non-psychotic behaviours featured very prominently. An notable feature of all the probands who had this behaviour is that their onset of illness was before 20 years of age (ranging from 14 to 19 years). It has been found before that premorbid social impairments are more marked in child and adolescent onset schizophrenia than in other psychoses. There appeared to be developmental continuity from premorbid impairment to negative symptoms in this study. Most of the probands in this discussion who had early non-psychotic deviant behaviour also had a chronic deteriorating course of illness.

**Pregnancy and delivery complications**

Previous literature has linked abnormalities of pregnancy and complications of delivery with increased risk of adult schizophrenia. Examples of specific factors that have been recorded include delayed fetal growth, infections, poor nutrition, and hypoxic-ischemic damage. Many previous studies are compromised by recall and selection effects. Some cohort studies have failed to confirm this effect. It remains uncertain whether or not obstetric complications are the result of pre-existing fetal abnormalities. A recent study found no support for suggestions that pre-existent fetal abnormalities precede obstetric complications in the histories of individuals with schizophrenia.

Pregnancy and delivery complications as well as early insults were reported in family II, III and VI to a limited extent. Five of the six probands where these complications were reported, were males. Information in this regard was obtained from mothers and/or probands. Information obtained in this way is susceptible to bias. A study on maternal recall bias, obstetric history and schizophrenia suggested that studies that rely on maternal recall alone, are susceptible to bias. The excess of obstetric complications recalled by the mother, could be related to abnormal behaviour in their child rather than maternal illness, family history or psychotic symptoms.
ies have suggested that males exhibit more or different risk markers, more serious symptomatology, as well as poor prognosis, than do females.\textsuperscript{19}

The psychopharmacological treatment and longitudinal course of illness in these multiple affected families was discussed in a poster presentation at the CINP Conference June 2004 in Paris.\textsuperscript{20}

**Conclusion**

Recruitment of multiple affected families in psychiatric genetic research remains important. We reported on six multiple affected Afrikaner families where three or more first-degree relatives were affected with schizophrenia or schizoaffective disorders.

The number of multiple affected families reported on are small and no definite conclusions can be drawn from the results.

Although the heritability of schizophrenia is substantial, its estimates do vary, and its contribution to the schizophrenia phenotype cannot be understood without taking in account the importance of environmental factors.\textsuperscript{21} Furthermore, disease will tend to cluster in families, not because of a direct genetic effect, but because relatives are more vulnerable to the risk-increasing effect of a prevalent environmental risk factor.

There is evidence of familial co-aggregation between schizoaffective disorder and schizophrenia but no familial relationship was generally found between schizophrenia and bipolar disorder. It is emphasized that a hierarchial diagnostic approach would take all diagnostic aspects of the psychotic equation into account when doing genetic research in schizophrenia.

The exposure to cannabis in these genetic sensitive probands triggered an earlier age of onset of illness with a poor prognosis in some probands.

Developments in molecular genetics need to go hand in hand with progress in the study of environmental factors that interact with genes. Prevention of phenotypes by targeting environmental risk factors that interact with genotypes is both feasible and acceptable.\textsuperscript{11}

**References**


