Increased risk of suicide in schizophrenia patients with linkage to chromosome 13q

Malherbe PJ\textsuperscript{a}, Karayiorgou M\textsuperscript{b}, Ehlers R\textsuperscript{c}, Roos JL\textsuperscript{a}

\textsuperscript{a}Department of Psychiatry, University of Pretoria, South Africa
\textsuperscript{b}Neurogenetics Laboratory, Department of Psychiatry, University of Columbia, New York
\textsuperscript{c}Department of Statistics, University of Pretoria, South Africa

\textbf{Highlights}

• Patients with linkage to chromosome 13q are 4.16 times more likely to be diagnosed with schizoaffective disorder.

• The correlation between suicidality and a diagnosis of schizoaffective disorder was significant.

• The odds ratio for completed suicide was higher for patients with linkage to chromosome 13q.

* Corresponding author:

Pierre J Malherbe

pierre@drpjmalherbe.com

+27 12 993 2768
Abstract

We link schizophrenia in families from the genetically isolated South African Afrikaner population to chromosome 13q ($n = 51$), 1p ($n = 23$) and combined 13q & 1p ($n = 18$). Patients with linkages to chromosome 13q were 4.16 times more likely to meet diagnostic criteria for schizoaffective disorder compared to patients with linkage to 1p. A third of patients with linkage to both 13q & 1p met diagnostic criteria for SAD. There was a significant positive relationship between suicidality and a diagnosis of schizoaffective disorder. Identifying linkage to chromosome 13q may be informative in identifying suicide risk early and prevent morbidity and mortality in schizophrenia patients.

Keywords: schizoaffective disorder, linkage to chromosome 13q, suicide

1. Introduction

Linkage analysis, a standard approach for identifying the location of genes that cause genetic disease, (Cui, et al., 2010) has the advantage of detecting genes of moderate to major effect. Linkage studies in schizophrenia (SCZ) have yielded positive findings in various regions of the genome, with a confusing mixture of replication and non-replication. (Sullivan, 2005)

A 9-cM genome wide scan performed on 143 families from the genetically isolated Afrikaner population from South Africa (Karayiorgou, et al., 2004) identified linkage to chromosome 13q ($n = 51$), 1p ($n = 23$) and combined 13q & 1p ($n = 18$) following both non-parametric and parametric linkage analysis. (Abecasis, et al., 2004)
Increasing the genomic coverage to better define linkage regions, we identified 13q32–34 locus as the most robustly linked in this population. (Rodriguez-Murillo, et al., 2014)

We investigate the phenotypic characteristics -- including diagnosis, suicidality, medication- and substance use -- of patients grouped according to linkage.

2. Methods

Phenotypic data obtained at recruitment were available for all subjects who showed linkage in the initial analyses. (Abecasis, et al., 2004) At recruitment each subject underwent a Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger, et al., 1994) and a blood sample was obtained.

92 subjects were assigned to 3 linkage groups: chromosome 13q (n = 51), 1p (n = 23) and combined 13q & 1p (n = 18). Subjects were re-contacted 15 years later for a follow-up clinical- and DIGS interview. Where patients were untraceable or deceased, hospital records were reviewed. Family- and care giver information was collected where possible. A data capturing tool was completed from this information, which included: Sociodemographic data; DSM 5 diagnosis; age at onset of illness; suicidality (including previous suicide attempts and completed suicide); comorbid conditions and substance use; and psychopharmacological treatment including ECT and clozapine use. Diagnostic adjustments were done based on the longitudinal course of the illness.
A psychological autopsy report was compiled for all patients who committed suicide. (Heila, et al., 1997)

We evaluated associations between diagnosis and (i) substance use, (ii) medication, (iii) chromosome linkage and (iv) suicidality by fitting multilevel models for binary data using the GLIMMIX procedure in SAS. A two-level hierarchical structure considering individuals at level 1 and families at level 2 took the dependency between individuals within families into account.

Ethical approval was obtained from the Ethics Committee of the Faculty of Health Sciences at the University of Pretoria.

3. Results

3.1 Follow-up recruitment

Participants who could be contacted at follow-up agreed to participate. The recall rate was 39.2% (13q), 52.1% (1p) and 38.9% (13q + 1p) -- figures that can be expected after 15 years. Additional clinical- and other follow-up information were available for patients who were lost to follow up. The DIGS information at recruitment was available.

3.2 Follow-up diagnostic adjustments

Minimal diagnostic adjustments were made.
In the 13q & 1p group one SAD case was changed to SCZ, and one substance induced psychotic disorder was changed to SCZ, after evaluating the longitudinal course of illness.

3.3 Demographic details
The gender distribution among patients with linkage to chromosome 13q was found to be 15 (29%) female and 36 (71%) male; with linkage to chromosome 1p, 11 (48%) female and 12 (52%) male; and with linkage to chromosome 13q & 1p, 8 (44%) female and 10 (56%) male. The median age of onset of illness was 21 for 13q patients, 22 years for 1p patients and 20 years for 13q & 1p patients.

3.4 Substance use
There was no significant relationship between diagnosis and substance abuse ($p = 0.5735$ from GLIMMIX).

3.5 Medication use
There was no significant relationship between genetic linkage and medication, when comparing antipsychotic monotherapy to combination therapy.

Subjects with SAD were more likely to use combination therapy ($p = 0.0156$ from GLIMMIX).
3.6 Diagnosis

There was a significant relationship between genetic linkage across the three groups and diagnosis. SAD diagnosis was 4.16 (95% CI:(1.07,30.17)) times more likely in patients with a 13q genetic linkage compared to 1p linkage ($p = 0.0416$).

3.7 Suicidality

Suicidality and diagnosis were significantly related ($p = 0.0397$ from GLIMMIX). Fifty-two percent of SAD patients had a history of suicide attempts compared to 24.1% of SCZ patients. Patients with a genetic linkage to 13q were 1.87 times more likely than those with linkage to 1p to have completed suicide (non-significant).

A multilevel model considering the relationship between suicidality (response variable) and both diagnosis and chromosome linkage (predictor variables) was also fitted. Because of the small sample size moderate significant results ($0.05 < p$-value $< 0.10$) were also considered in this model with two predictors. Diagnosis was a moderately significant predictor of suicidality ($p = 0.0539$), whilst chromosome linkage was not significant ($p = 0.5181$). SAD patients were estimated to be 3.73 (90% CI:(1.27,10.94)) times more likely to display suicidality than patients diagnosed with SCZ when keeping chromosome linkage constant.

Risk factors for suicidality in SAD and SCZ were found to be similar to those found by Potkin et al. (Potkin, et al., 2003) at psychological autopsy e.g., male, substance abuse, previous attempts and comorbid cluster B personality traits.
4. Discussion

Our research shows that patients with a 13q genetic linkage are 4.16 times more likely to be diagnosed with SAD compared to patients with a 1p genetic linkage.

More SAD patients had a history of suicidality compared to those with SCZ. SAD patients tend to have a higher suicide rate than schizophrenia patients. (Radomsky, et al., 1999) More completed suicides were found in patients with 13q linkage than those with 1p linkage. SAD represents a challenge for psychiatric nosology. (Jager, et al., 2011) Our findings suggest a category of schizoaffective illness in which the genetic variants that influence susceptibility are easier to identify than are those that confer specific risk to bipolar disorder or schizophrenia alone.

SCZ and SAD patients with linkage to chromosome 13q have prominent suicidal ideation and suicide may be the final outcome. Linkage analysis can identify these patients early in the course of their illness, decreasing morbidity and mortality.

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