Search for Susceptibility Loci on Selected Chromosomes in Patients with Mental Disorders from the Faroe Islands

Leitan eftir ílegumøguleikum á útvaldum kromosomum hjá føroyskum sjúklingum við sinnisligum sjúkum

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Úrtak

Kring allan heim verður roynt at koma nærri møguligum ílegum, sum kunnu hava týdning fyri eitt nú sinnisligar sjúkur. Tey seinastu árini hevur áhugin serstakliga vent sær ímóti kanningum millum fólk í útjaðaraøkjum, har frávik í ílegum kunnu vera í færri útgávum og tí lættari at finna. Í hesum føri er kanningarøkið Føroyar.

Sum liður í heildarkanning við atliti at íleguøki, sum hevur við tvípólasjúku, skisofreni og panikksjúku at gera, kunnu vit her vísa á úrslit, ið peika á nøkur øki, sum eru verd at kanna nærri (sí talvu 1).

Kanningin hevur allar góðkenningar og er ikki handilslig. Men kemur ein inn at eini ítøkiligari ílegu, verður spurningurin, um hetta skal almannakunngerast beinanvegin fyri at sleppa undan einkarrætti, ella tvørturímóti.

Abstract

Around the world, scientists are trying to identify chromosomal regions that possibly contain genes involved in mental disorders. To some extent, genetically isolated populations are used for such studies, based on the assumption that locus heterogeneity is lower in isolated populations. A reduction in genetic and environmental heterogeneity may increase the likelihood of detecting a disease-bearing locus. For the search of susceptibility genes, we have chosen the Faroe Islands, which, both historically and geographically, seems ideal for such genetic studies.

A full genome screening was performed, searching for areas that could be of interest in relation to bipolar illness, schizophrenia, and panic disorder. From the ongoing screening, our results point to some areas of the genome that are of interest for further studies, Table 1.

This study has been accepted on legal and ethical terms. However, if an illness-related gene locus is identified, patenting versus publishing issues will need to be resolved.

Introduction

Although genetic factors have considerable influence in mental disorders, so far no candidate genes associated with a specific disorder have been located. Many of the genes that cause Mendelian diseases have been identified by traditional genetic methods. These traditional methods, although effective, have not been as successful when complex diseases, such as mental disorders, have been investigated.

The search is complicated by the fact that the aetiology of most complex diseases is unknown. In addition, a complex disease is likely the result of perhaps more than one gene, each exerting its effect of unknown strength to contribute to the manifestation of the disease. With the emergence of strong, genetic and statistical methods, new strategies are evolving. In recent years, much interest has turned towards isolated populations, which, with their presumed genetic and environmental homogeneity, might fulfil the requirements for Linkage Disequilibrium (LD) mapping. Shared, haplotype-based analyses have been used in several studies in recent years (de la Chapelle, 1993; Te Meerman and van der Meulen, 1997; van Houwen *et al.*, 1994). The method has also been tried in the Faroe Islands in the North Atlantic, which has a bottleneck population (Wang, 1996; Wang *et al.*, 1998; Ewald *et al.*, 1999b; Tygstrup *et al.*, 1999; á Steig *et al.*, 1999). The population in the Faroe Islands remained around 4,000 for several hundred years, with periods with population bottlenecks, and has recently undergone a ten-fold increase, mainly due to reproduction. These conditions may give rise to the so-called "founder effect", where a disease-bearing chromosome is introduced at some point in time into this homogeneous genetic pool, and the disease locus is subsequently passed down though the generations to a number of present-day relatives. These relatives will share a relatively large chromosomal segment around the disease locus.

Material and Methods

Method

A population-based method is used in a search for Linkage Disequilibrium (LD) within a "founder population". Under conditions of LD, the location of the disease locus is inferred from association between marker and disease loci, inherited identically by descent (IBD) from a founding ancestor. By selecting cases that are related 5-12 generations ago, a low rate of recombinative fragmentation of the genome is obtained. As the flanking region around an IBD inherited disease locus is relatively large following 10 generations, it is possible to perform a genome-wide scan with a moderate number of polymorphic markers. In the present study, the distance between the markers is approximately 7-10 cM, resulting in a total coverage of the genome with approximately 500 markers.

Clinical Material

Well-documented cases of patients with psychiatric disorders (autism, bipolar affective disorder, schizophrenia, panic disorder, and alcoholism) from the Faroe Islands, where local psychiatry was established in 1968 (Joensen and Wang, 1983),

were interviewed by experienced psychiatrists using a brief version of the Present State Examination (Wing *et al.*, 1990). On the basis of the interview, a clinical narrative was made for each patient. Final diagnosis was made by consensus as a best estimate by a psychiatrist who independently had reviewed the clinical narrative and if necessary other relevant material.

The diagnoses were made in accordance with the ICD-10 Diagnostic Criteria for Research (WHO, 1996). Groups of ten to twenty patients with each disorder, according to ICD-10, were included in the study.

Twenty-five control families, unscreened for psychiatric disorders, were collected from the same sub-region of the Faroe Islands.

Genealogical Assessment

Cases related six to ten generations ago were sought in order to obtain a reasonable size of shared chromosomal segment around putative disease genes. A genealogical search of church and civic records of births, marriages, and deaths was made for each patient. Lineage was traced back as far as possible in order to determine if the patients were related. The shortest possible distance between any pair of the patients' parents was established. Excellent church records exist from around 1700, while civic records exist from even earlier. In our studies, all patients from each group were related back to the middle of the 17th century, five to eleven generations ago.

Statistical Analyses

For each microsatellite marker, allele and segment frequencies were computed and compared between the cases and controls. Comparisons of haplotypes or alleles between cases and controls were tested by chi-square analyses or Fisher's exact test. Statistical calculations were performed by CLUMP (Sham, 1998). Generally, a significant difference is obtained by a p-value of 0.05 or less, indicating a probability of 0.05 or less for an arbitrary difference. However, in genetics some authors argue for more strict criteria, such as a p-value of 0.01 or less.

Results

In the ongoing genome screening, we do see interesting regions, *i.e.* regions with increased haplotype sharing among cases when compared to controls.

Bipolar Affective Disorder

For bipolar affective disorder, we have results that support a previous reported finding in two Costa Rican pedigrees (Freimer *et al.*, 1996). Several markers seem to point to the area distally on 18q, possibly related to bipolar disorder (Table 1). These results have been published previously (Ewald *et al.*, 1997; Wang *et al.*, 1998; Ewald *et al.*, 1999b; Nyegaard *et al.*, 1999). Recently, a new, interesting area has been found on chromosome 10q26 (Ewald *et al.*, 1999a; 2000), Table 1.

Schizophrenia

Studies related to schizophrenia have been described in posters at the World Congress on Psychiatric Genetics in 1999 and 2000. Studies on chromosome 22 could not con-

firm an interesting area, related to the DiGeorge syndrome and Velocardiofacial syndrome, but did show an interesting area more distally on 22q13 (Mors *et al.*, 1999; 2000), Table 1.

Panic Disorder

For panic disorder, results have been described in 1998, 1999, and 2000 (Degn *et al.*, 1998; Wang *et al.*, 1999; 2000). Our data could not support the previously reported association between panic disorder and the cholecystokinin genes on chromosomal regions 3pter-p21 and 11p15,4 (Degn *et al.*, 1998). Instead, our preliminary data point towards an interesting area on chromosome 21q22 (Wang *et al.*, 2000), Table 1.

Table 1. *Areas of possible interest, so far identified.* Øki higartil funnin, sum kunnu hava týdning.

Disorder	Chromosome area
Bipolar affective disorder	18q23
	10q26
Schizophrenia	22q13
Panic disorder	21q22

Discussion

When mapping complex diseases, the choice of population is a critical factor. A genetically simplified isolate is probably more useful than a diverse continental population (Editorial, 1998; Wright *et al.*, 1999). A basic requirement for LD mapping is a homogenous population, thus, isolated population regions were sought. The suitability of some of these isolated populations is at present being questioned (Arnason *et al.*, 2000; Eaves *et al.*, 2000) and, more theoretically, the whole idea has been disputed on the grounds that the study models are inadequate for diseases that are probably multifactoral (Edwards, 1999). However, the findings of a high degree of homogeneity for cystic fibrosis and benign, recurrent intrahepatic cholestasis in the Faroe Islands (Tygstrup *et al.*, 1999; á Steig, 1999) could be taken as an indication that the Faroe Islands might meet the criteria of homogeneity.

In our genome screening, although not finished, we do see moderate numbers of candidate regions. In a totally out-bred population, the useful levels of LD will rarely extend beyond 3 kb (Kruglyak, 1999) and no regions of LD would be expected with the marker density used in the present study. On the other hand, a small population size may tend to increase LD by genetic drift and, in addition, the process might be enhanced by population stratification into small, inbred communities (Wright *et al.*, 1999). The result would be many regions with LD. Whether the regions detected in this study are false positives caused by stratification, or true, disease-bearing, identical-by-descent segments is not yet clear, but the small amount of detected regions does signal a low degree of stratification.

With a common forefather 10-12 generations ago, the possible size of a common haplotype among persons with a disease would require about 500 markers to ensure its capture. However, the availability and order of the markers could make some areas too long, with the result of missing the

possible disease-related area (van der Meulen and Meerman, 1997).

So far, interesting areas, but no genes have been identified. The area around 18q23, in bipolar affective disorder, looks especially promising, as another group has reported this area previously in a different population (Freimer *et al.*, 1996).

The study presented here is non-commercial. However, if one or more areas prove to be the focus of a search for a possible disease-related gene, the question will arise as to whether or not this finding is to be patented or published. Publishing will preclude patenting. In an ever more commercialised area of research, the latter course may be challenged (Rifkin, 1998). At present, there is no Faroese legislation on these matters.

Ethics

The study has been accepted by the Faroese Board for Ethics in Medical Research and the Faroese Board for Registration. The study is non-commercial and funded by public and private grants.

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