

Ethical considerations on Genome Wide Association Studies (GWAS) of mental disorders in the Greenlandic population

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The Greenlandic population has historically been small and isolated and can be characterized as a founder population. This means that the population can be traced back to a relative few founders, and that the genetic homogeneity is much higher than in populations where interbreeding with other populations occur more frequently. This was documented in a study by Moltke et al. who found no indication of higher inbreeding rates. [Moltke 2015]

This makes the population highly suited for genetic analyses of genetic variants associated with disease, and in a study linking specific genetic variants with Diabetes 2, a strong association was found in the Greenlandic population. [Moltke 2014].

Mental disorders are known generally known to have a high degree of heritability when comparing the concordance rates in monozygotic and dizygotic twins. [Sullivan 2003]

Over the last years, large scale GWAS have found more than one hundred genetic loci associated with Schizophrenia. [Ripke 2014] This has led to the discovery of a gene variant associated with Schizophrenia. [Sekar 2016]

However the genome wide associated loci still explain very little of the heritability found in the twin studies [Sullivan 2003], and a general problem is the very large sample sizes required to confirm the associations.

All newborns born in Denmark and Greenland are tested for rare diseases by a dried blood spot sample, and the samples are kept in The Danish Neonatal Screening Biobank.

Permissions have been obtained to link retrieve these test for patients later diagnosed with mental disorders according to the national patient registries and genotype these individuals.

However according to a statement from the Greenlandic Ministry of Health [Departementet for Sundhed 2010], there is a discrepancy between the low prevalence of psychiatric diagnoses relative to the Danish population and the high occurrence of suicide attempts, suicides, substance abuse, sequelae after sexual assaults and neglect of care, reported by schools, social services and health services.

It is especially emphasized that the child and adolescent psychiatry is limited by the the absence of full time doctors and school visits.

Geographical challenges are obvious and for this reason, the most straight forward approach is to either include patients through national patient registries or patients currently being treated at Dronning Ingrid Hospital (DIH) in Nuuk.

Identification of cases through national patient registries

Although the registries may not capture all patients suffering for mental illness, there is a chance this might be sufficient to detect new genome-wide significant associations. A large benefit is obviously that this does not require any further recruitment of patients.

To protect the patients, current permissions from the Danish National Committee on Health Research Ethics, does not allow for contacting patients for further assessment such as further blood samples or neuroimaging.

Sampling at clinical facility

Recruiting patients already diagnosed with mental disorders at DIH is also being considered. This will however require that patients are willing to participate and have a genetic test done.

Besides this approach may identify a very selected group of patients that could be biased by geography, socioeconomic stratification, disease severity and genetics, since the only psychiatric facility is located in the capital.

As also stated in the statement from the Greenlandic Ministry of Health, psychiatric health among adolescents are of special concern and believed to be under diagnosed thus the recruitment of patients already being followed at DIH may will not enable elucidate the mental health of greenlandic patients in general.

Depending on the study design of choice, the study could be either cross-sectional examining in or out patients in a given time period of time or longitudinal if medical records are included.

Future possibilities: Recruitment of new patients outside DIH

The recruitment of patients not already followed by professionals, would require a large effort and would raise other ethical concerns. It would require cooperation with psychiatrist in the diagnostic process and would to some degree give rise to a morale obligation to provide treatment and care if new cases were identified.

Possible benefits for patients

Patients with schizophrenia show great heterogeneity in symptoms, prognosis and treatment respons in the Western populations, and treatment is often based on trying out different medications until a satisfying respons is obtained.

It can be hypothesized that the greater homogeneity of genetics among Greenlanders would lead to fewer genes being associated to the disease and that this eventually could help in establng a narrower and more effective treatment strategy.

Ethical perspective on performing genetic tests on patients:

Genotyping - the method that has primarily been used in population genetics so far, only asses a small proportion of the DNA, and thus does not have the issues of random findings associated with whole genome sequencing.

With the current knowledge, no genes have been associated to treatment respons in mental illnesses, and even overall genetic risk predicts only a fraction of the overall risk of mental illness. Therefore future concerns about whether patients should be informed about the results are not of concern at the moment.

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