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HERITABILITY AND GENOME-WIDE LINKAGE ANALYSIS OF MIGRAINE IN THE GENETIC ISOLATE OF NORFOLK ISLAND

Hannah C Cox[1], **Rod A Lea**[1], **Claire Bellis**[2], **Dale R Nyholt**[3], **Thomas D Dyer**[2], **Larisa M. Haupt**[1], **Jac Charlesworth**[2], **Elizabeth Matovinovic**[1], **John Blangero**[2], and **Lyn R Griffiths**[1]

[1]Genomics Research Centre, Griffith Health Institute, Gold Coast Campus, Griffith University, Queensland 4222, Australia

[2]Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio 78227, USA

[3]Neurogenetics Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland 4029, Australia

Abstract

Migraine is a common neurovascular disorder with a complex envirogenomic aetiology. In an effort to identify migraine susceptibility genes, we conducted a study of the isolated population of Norfolk Island, Australia. A large portion of the permanent inhabitants of Norfolk Island are descended from 18th Century English sailors involved in the infamous mutiny on the Bounty and their Polynesian consorts.

In total, 600 subjects were recruited including a large pedigree of 377 individuals with lineage to the founders. All individuals were phenotyped for migraine using International Classification of Headache Disorders-II criterion. All subjects were genotyped for a genome-wide panel of microsatellite markers. Genotype and phenotype data for the pedigree was analyzed using heritability and linkage methods implemented in the program SOLAR. Follow-up association analysis was performed using the CLUMP program.

A total of 154 migraine cases (25%) were identified indicating the Norfolk Island population is high-risk for migraine. Heritability estimation of the 377-member pedigree indicated a significant genetic component for migraine (h^2=0.53, P=0.016). Linkage analysis showed peaks on chromosome 13q33.1 (P=0.003) and chromosome 9q22.32 (P=0.008). Association analysis of the key microsatellites in the remaining 223 unrelated Norfolk Island individuals showed evidence of association, which strengthen support for the linkage findings (P≤0.05).

In conclusion, a genome-wide linkage analysis and follow-up association analysis of migraine in the genetic isolate of Norfolk Island provided evidence for migraine susceptibility loci on chromosomes 9q22.22 and 13q33.1.

Corresponding Author, Professor Lyn Griffiths, Genomics Research Centre, Griffith Health Institute, Griffith University, Gold Coast Campus, Queensland 4222, Australia: Telephone: +61 7 5552 8664, l.griffiths@griffith.edu.au.

Keywords

Migraine; gene; linkage; heritability; association

1.1 INTRODUCTION

Migraine is a common episodic neurological disorder with an annual prevalence of 5.6% in males and 17.1% in females in the United States of America (Lipton et al., 2007). Clinical diagnosis is established using International Classification of Headache Disorders-II (ICHD-II) criterion, which recognises 2 forms of migraine: migraine with aura (MA) and migraine without aura (MO) (ICHD-II, 2004). These two types of migraine are differentiated by the presence or absence of aura, a reversible focal neurological symptom preceding or accompanying the headache phase of an attack. Individuals may experience MA, MO or a combination of both forms of migraine with varying frequency throughout life. The headache is thought to be caused by activation of the trigeminovascular system and the aura by spreading depression, a slow propagating wave of neuronal and glial depolarization that spreads across the cortex (Goadsby et al., 2009; Hadjikhani et al., 2001).

Migraine is a complex, multifactorial disorder for which the aetiology is not fully understood. The disorder displays strong familial aggregation, with first degree relatives of MO and MA probands having an increased relative risk of developing the disorder compared to the general population (Cologno et al. 2003; Stewart et al. 2006; Stewart et al. 1997). Recent population based twin studies report heritability estimates to range from 0.34 to 0.57 (Mulder et al. 2003; Svensson et al. 2003).

The complex nature of migraine is evident from international pedigree studies that have so far reported linkage regions on chromosome 1q31 (Lea et al. 2002), 4q21 (Björnsson et al. 2003), 4q24 (Wessman et al. 2002), 4q28 (Anttila et al. 2006), 5q21 (Nyholt et al. 2005), 6p12.2-p21.1 (Carlsson et al. 2002), 10q22-23 (Anttila et al. 2008), 10q25.3 (Lafreniere et al., 2010), 11q24 (Cader et al. 2003), 14q21.2-q22.3 (Soragna et al. 2003), 15q11-q13 (Russo et al. 2005), 17p13 (Anttila et al. 2006), 18q12 (Anttila et al. 2006) and 19p13 (Jones et al. 2001; Nyholt et al. 1998b) and Xq24-28 (Nyholt et al. 2000; Nyholt et al. 1998a).

Pedigree studies conducted to date have made significant contributions to understanding the complex aetiology of migraine. This study aimed to validate existing and/or discover new migraine susceptibility loci by conducting heritability and genome-wide linkage analyses in a large affected pedigree from the geographically isolated population of Norfolk Island.

2.1 MATERIALS AND METHODS

2.1.1 Sample Ascertainment

Data collection procedures have been previously described in a demographic investigation of CVD risk phenotypes (Bellis et al., 2005), with the study protocol approved by Griffith University Human Research Ethics Committee prior to commencement. All subjects provided a signed, informed consent prior to participation. In brief, subjects were ascertained based on permanent resident status (not selected on phenotypes of interest), to ensure sampling of individuals from the same genealogical background. Phenotypic data and biological specimens were obtained from 600 subjects (261 males, 339 females) with a mean age of 50.8 years (standard deviation of 16.4 years). All biological samples were from venous blood. Genealogical data was obtained via questionnaire, and municipal and historical records.

2.1.2 Phenotyping

Migraine was diagnosed in accordance with current ICHD-II using interviews with a migraine questionnaire and followed up by qualified migraine diagnostician (ICHD-II, 2004). Under the hypothesis of a common major gene, all individuals diagnosed with subtypes MA and/or MO were grouped together and phenotyped as being affected with migraine.

2.1.3 Pedigree Reconstruction and Validation

Norfolk Island census data indicate a large portion of the permanent residents are of Pitcairn descent (Matthews, 2001). These individuals are related through a 6,379-member, 10-generation genealogy founded by Isle of Man *Bounty* Mutineers and their Tahitian consorts in 1790. At the commencement of the Norfolk Island Health Study in 2000, it was hypothesised the ascertained subjects (n = 600) resided within the last five generations of the genealogy. All 600 participants were genotyped for 400 genome wide microsatellite markers to validate relationship status of all individuals in the sample population using identity-by-descent matricies (Bellis et al., 2008). PREST analysis produced an inferred pedigree structure of 6,537, which was inflated from 6,379 because of the coding of missing parents.

The size and complexity of the original genealogical structure (N=6,537) and large volume of missing data prohibited direct use in variance component linkage analysis (Bellis et al., 2008). Hence, the pedigree was split (N=1,078) using a peeling algorithm in the pedigree database management system PEDSYS (Southwest Foundation for Biomedical Research, San Antonio, Texas, USA) to facilitate analysis (Dyke, 1996). This 1,078 member pedigree has been previously employed in genome-wide screens of cardiovascular risk traits (Bellis et al., 2008). A total of 377 (171 males, 206 females) of the 600 participants are related through this multigenerational pedigree and included in the linkage analysis.

2.1.4 Genotyping

The genome screen included 400 highly polymorphic autosomal microsatellites markers genotyped across all 600 participants. Markers had an average spacing of 10cM throughout the human genome. All PCRs were performed under standard conditions using fluorescently labelled primer pairs. Markers were organised into multi-plex panels and electrophoresed on a 3730 DNA Analyzer (Applied Biosystems). Data was analysed using Applied Biosystems Genescan version 3.1 and Genotyper version 2.1 software. Sex-averaged chromosomal maps were obtained from the Marshfield Centre for Medical Genetics (http://research.marshfieldclinic.org/genetics). Pedigree structure validation, elimination of typing errors and estimation of multipoint identity-by-descent allele sharing matrices have been described (Bellis et al., 2008).

2.1.5 Statistical Analyses

Heritability (h^2) was estimated as the ratio of the trait variance that is explained by additive polygenic effects to total phenotypic variance of the trait (Göring et al., 2001) using the Sequential Oligonucleotide Linkage Analysis Routines (SOLAR) v4.0.6 software package (Texas Biomedical Research Institute, San Antonio, Texas, USA). The polygenic model applied assumes an infinite number of genetic factors with a small additive effect contributing to the trait variance. Estimates were screened for the covariate effects of age, age-squared, sex and their interactions to allow for differential symptom prevalence in males and females and adjust for the variable age of onset. Covariates with p-values less than or equal to 0.05 were retained in the final model. Heritability was measured on a scale ranging from 0 to 1. A value of 0 indicates the phenotype is completely controlled by non-genetic (environmental) factors. As the score approaches 1 the genetic component increases.

Linkage was tested throughout the genome using multipoint variance component analysis. This method localises QTLs for dichotomous traits by assuming the trait has a latent liability threshold with an underlying multivariate normal distribution (Duggirala et al., 1997). All heritability estimations and linkage analyses utilize maximum likelihood, variance component methods implemented in the SOLAR v4.0.6 software package (Almasy and Blangero, 1998). Like parametric LOD scores, under the null hypothesis of no linkage, the variance component LOD score is distributed as an equal mixture of a chi-square random variable at point mass of 0 and a degree of freedom of 1 (Blangero et al., 2001). As a result, point-wise P-values can be estimated for each LOD score value using the method described by Nyholt et al. (2000) (Nyholt, 2000). A SOLAR LOD score of 3.0, 2.1, 1.2 and 0.59 equate to pointwise P values of 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, and 0.05, respectively. Previous studies of CVD risk determined the current trimmed pedigree structure had good power to detect the heritability of phenotypes whose variation is partially attributable to additive genetics and to detect loci for such phenotypes (Bellis et al., 2007).

2.1.6 Validation Cohort

Important findings were further assessed in 223 unrelated Norfolk Island Health Study participants (90 males; 133 females) included in the initial genome wide scan but genetically unrelated to the core pedigree. This unrelated sub-population included 58 migraineurs (41MA; 17MO). Allelic association was tested at polymorphic loci implicated in the pedigree genome wide linkage scan using the program CLUMP (Sham and Curtis, 1995). CLUMP performs chi-squared tests for allelic association employing an empirical Monte Carlo test of significance that does not require correction for multiple alleles at a highly polymorphic locus. A total of four 'chi-squared' test statistics are generated for each marker analysed. Three of these tests combine rare alleles present in a marker data set by collapsing adjacent columns before performing the chi-squared test.

3.1 RESULTS

This study aimed to define the genetic basis of migraine within an extended pedigree from the isolated population of Norfolk Island whose origins date to the infamous 'mutiny on the *Bounty*'. We identified a total of 154 (25.7%) migraine cases in the full cohort and a total of 96 (25.5%) migraine cases in 377-member core pedigree (Table 1). These pedigree individuals were integrated into subsequent heritability and linkage analyses. A heritability of 0.53 was estimated for migraine (P=0.016). The high prevalence and heritability of migraine in this pedigree imply its suitability for mapping susceptibility loci via linkage analysis.

The maximum LOD score obtained in our study was 1.60 (point-wise P=0.003) on chromosome 13q33.1 nearest marker D13S158 (102cM). The 1-LOD-unit support interval around the linkage peak on chromosome 13q was approximately 26cM long, extending between markers D13S265 and D13S1265. Potential evidence of linkage (LOD>1.2) was also detected for migraine on chromosome 9q22.32 (100cM) nearest marker D9S287 with a LOD score of 1.26 (point-wise P=0.008). Additional linkage peaks were identified on chromosome 2, 4, 10 and 12 exceeding the threshold for nominal significance (LOD≥0.59; point wise P≤0.05). Results are detailed in Table 2.

3.1.2 Replication Cohort

Genome-wide genotype data was available for all 600 Norfolk Island participants to establish pedigree membership. Of these individuals, 223 individuals were genetically unrelated to the core pedigree and therefore suitable for assessing the validity of the linkage results. From the genome scan of the pedigree, two microsatellites D9S287 and D13S158

provided some evidence for linkage with migraine. These two markers were tested in the unrelated sub-population using the program CLUMP. Using this method, both D9S287 and D13S173 provided evidence for association with migraine (Table 3). D9S287 was significant with an empirical P-value of 0.04 for the CLUMP T3 test. In the region surrounding D13S158, microsatellite D13S173 was significant for the CLUMP T1, T2 and T3 tests with empirical P-values of, 0.05, 0.01 and 0.05, respectively.

4.1 DISCUSSION

The Norfolk population isolate is a unique island community. It is of particular interest for gene mapping as the current population structure includes a very large multigenerational pedigree derived from 17 founding individuals, as well as cultural and geographical isolation leading to reduced genetic and environmental diversity. The current investigation assessed migraine using autosomal genome wide STR data in an effort to identify susceptibility loci. A high prevalence of migraine was observed – twice that compared to most outbred populations (25% v 12%). Variance components methods showed a migraine heritability of 0.53 using the 377-member core Norfolk pedigree. This is consistent with population-based twin studies, which estimate heritability for migraine to vary from 0.34 to 0.57 (Honkasalo et al., 1995; Larsson et al., 1995; Mulder et al., 2003; Svensson et al., 2003; Ziegler et al., 1998). Although the present study did not analyse migraine subtypes, heritability estimates of 0.65 are reported for MA (Ulrich et al., 1999) and 0.61 for MO (Gervil et al., 1999) \ for population-based twin studies.

After detecting a significant genetic component, linkage to the migraine phenotype was tested across the autosomes. A region of potential interest was detected on chromosome 9q22.32, residing near a familial occipitotemporal lobe epilepsy and combined MA locus on chromosome 9q21-q22 (MIM 611631) (Deprez et al., 2007). Near the linkage peak detected in the Norfolk pedigree resides the gabba-aminobutyric acid-B receptor type 2 (*GABBR2*; MIM607340) gene on chromosome 9q22.1. This gene is a receptor for the major inhibitory neurotransmitter in the brain, gabba-aminobutyric acid (GABA). GABA type B receptors are a family of g-protein coupled receptors widely expressed in the peripheral and central nervous system that inhibit or depress synaptic transmission via second messenger coupling (Kornau, 2006). Common variants in the *GABBR2* have been positively associated with mesial temporal lobe epilepsy (Wanga et al., 2008). The 9q22.32 linkage peak supports the findings of the Deprez et al. (2007) study and may be of further interest considering the potential gene candidate, *GABBR2* located in close proximity to the 9q22.32 locus. In addition to the chromosome 9q22.32 locus, a linkage peak of potential interest also occurred on chromosome 13q (LOD=1.60; point-wise p=0.003). The 1-LOD-support interval spanned 13q33.1 to 13q33.3. The peak marker D13S158, is within 10cM of a locus linked previously to migraine symptom phenotype, pulsation (LOD=3.31; p=0.00005) in a large Dutch cohort (Ligthart et al., 2008). Interestingly, other neurological disorders display linkage and association to chromosome 13q32-34. A bipolar locus is reported at 13q32-q33 (Badner and Gershon, 2002) and the 13q-related schizophrenia susceptibility locus (SCZD7; MIM603176) at 13q34 (Chumakov et al., 2002). Both bipolar disorder and schizophrenia display association with variants in the D-amino acid oxidase activator gene located at 13q34 (*DAOA*; MIM607408) (Chumakov et al., 2002; Hattori et al., 2003). *DAOA* encodes a protein that is expressed in the human brain and is involved in degrading D-serine, a potent activator of N-methyl-D-aspartate-type glutamate receptor (*NMDAR2D*; MIM602717) (Chumakov et al., 2002). Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system. Disruption of normal glutamate homeostasis is hypothesized to contribute to the pathogenesis of a range of neurological disorders, including migraine (Vikelis and Mitsikostas, 2007). Given current knowledge of the chromosome 13q32-34

locus in bipolar disorder and schizophrenia, as well as the close proximity of the potential gene candidate *DAOA*, further assessment of this region in terms of migraine is warranted.

Upon further assessment, evidence of validation was detected for the chromosome 9 peak marker and chromosome 13 markers in a subpopulation of 223 genetically unrelated individuals. Positive allelic association in non-pedigree members strengthens the linkage signals and suggests further studies are warranted using this unique Island population. Aside from the overlap of chromosome 9 and 13 regions with some neurological phenotypes and the presence of a gene candidate under each peak, no replication (LOD≥0.59; point wise P≤0.05) of previously known migraine loci was observed.

5.1 Conclusion

This study performed hertitability and linkage analysis of migraine in an extended pedigree from the Norfolk Island isolate. We identified a high prevalence and heritability of migraine in this pedigree. Peak linkage signals occurred on chromosomes 9q22.22 and 13q33.1. Focussing on these regions, nominal evidence of validation was detected in an unrelated sub-population also from Norfolk Island. These linkage peaks overlap with regions reported for familial occipitotemporal lobe epilepsy and combined MA, migraine trait symptom ‘pulsation’ and bipolar disorder. On-going recruitment of pedigree members, analysis of additional markers from dense SNP arrays and analysis in outbred populations may strengthen and refine these results.

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Abbreviations

SOLAR	Sequential Oligonucleotide Linkage Analysis Routines
MA	Migraine with aura
MO	Migraine without aura
ICHD II	International Classification of Headache Disorders II
PDSYS	Pedigree Database Management System
QTL	Qualitative Trait Loci
GABR2	Gabba-Aminobutyric Acid-B Type 2
DAOA	D-Aminoacid oxidase activator gene

Highlights

- This study investigated migraine in a unique Norfolk Island founder effect population
- Migraine prevalence in this population was determined to be 25%
- A significant genetic component of 0.53 was shown for migraine in the core pedigree
- A microsatellite genome scan identified novel linkage peaks on 13q33.1 and 9q22.32
- Association analysis in unrelateds supported these linkage findings

Table 1

Migraine Characteristics in the Norfolk Island Cohort and Pedigree

	Entire Cohort (N=600)	Pedigree (N=377)
Total Migraine	154	96
Average Age in Years (SD)	49.01 (16.31)	46.41 (16.48)
Female Migraine	113	71
Average Age in Years (SD)	49.90 (15.68)	49.74 (16.76)
Male Migraine	41	25
Average Age in Years (SD)	46.56 (17.92)	42.14 (15.71)
MA*	105	64
MO	49	32

*Individuals experiencing both types of migraine were classified as MA

Table 2

Multipoint genome wide results exceeding the nominal threshold for linkage (P≤0.05)

Chromo-some	LOD Score	Point wise P-value	Position (cM)	Nearest Marker	Marker Position (cM)
2	0.9188	0.02	69	D2S2259	68.38
4	1.0068	0.016	173	D4S1539	172.85
9	1.2603	0.008	100	D9S287	100.82
10	0.9674	0.017	20	D10S189	20.36
12	0.7655	0.03	146	D12S324	151.13
13	1.6001	0.003	102	D13S158	100.73

Table 3

CLUMP tests of allelic association for microsatellites on chromosome 9 and 13

Marker	Location (cM)	Migraine Allele Count	Control Allele Count	T1 χ^2	P*	T2 χ^2	P*	T3 χ^2	P*	T4 χ^2	P*
D9S287	100.73	116	330	8.71	0.48	**8.31**	**0.04**	4.78	0.08	4.78	0.41
D13S173	106.26	114	328	**15.32**	**0.05**	**13.90**	**0.01**	**7.07**	**0.04**	7.86	0.13

*Empirical P-values using 10,000 Monte Carlo simulations; Empirical P-values ≤ 0.05 are in bold