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Genome-wide linkage and association analysis of primary open-angle glaucoma endophenotypes in the Norfolk Island isolate

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Purpose: Primary open-angle glaucoma (POAG) refers to a group of heterogeneous diseases involving optic nerve damage. Two well-established risk factors for POAG are elevated intraocular pressure (IOP) and a thinner central corneal thickness (CCT). These endophenotypes exhibit a high degree of heritability across populations. Large-scale genome-wide association studies (GWASs) of outbred populations have robustly implicated several susceptibility gene variants for both IOP and CCT. Despite this progress, a substantial amount of genetic variance remains unexplained. Population-specific variants that might be rare in outbred populations may also influence POAG endophenotypes. The Norfolk Island population is a founder-effect genetic isolate that has been well characterized for POAG endophenotypes. This population is therefore a suitable candidate for mapping new variants that influence these complex traits.
Methods: Three hundred and thirty participants from the Norfolk Island Eye Study (NIES) core pedigree provided DNA. Ocular measurements of CCT and IOP were also taken for analysis. Heritability analyses and genome-wide linkage analyses of short tandem repeats (STRs) were conducted using SOLAR. Pedigree-based GWASs of single-nucleotide polymorphisms (SNPs) were performed using the GenABEL software.
Results: CCT was the most heritable endophenotype in this cohort ($h^2 = 0.77$, $p = 6\times10^{-6}$), while IOP showed a heritability of 0.39 ($p = 0.008$). A genome-wide linkage analysis of these POAG phenotypes identified a maximum logarithm of the odds (LOD) score of 1.9 for CCT on chromosome 20 ($p = 0.0016$) and 1.3 for IOP on chromosome 15 ($p = 0.0072$). The GWAS results revealed a study-wise significant association for IOP at rs790357, which is located within *DLG2* on chr11q14.1 ($p = 1.02\times10^{-7}$). *DLG2* is involved in neuronal signaling and development, and while it has not previously been associated with IOP, it has been associated with myopia. An analysis of 12 known SNPs for IOP showed that rs12419342 in *RAPSN* on chromosome 11 was nominally associated in Norfolk Island (NI; $p = 0.0021$). For CCT, an analysis of 26 known SNPs showed rs9938149 in *BANP-ZNF469* on chromosome 16 was nominally associated in NI ($p = 0.002$).
Conclusions: These study results indicate that CCT and IOP exhibit a substantial degree of heritability in the NI pedigree, indicating a genetic component. A genome-wide linkage analysis of POAG endophenotypes did not reveal any major effect loci, but the GWASs did implicate several known loci, as well as a potential new locus in DLG2, suggesting a role for neuronal signaling in development in IOP and perhaps POAG. These results also highlight the need to target rarer variants via whole genome sequencing in this genetic isolate.

Glaucoma refers to a group of heterogeneous diseases causing optic nerve fiber damage. Primary open-angle glaucoma (POAG) is the most common type of glaucoma in most populations. Elevated intraocular pressure (IOP), defined as >22 mmHg, is a principal risk factor for POAG and can cause optic nerve damage [1]. Heritability estimates (h2) for IOP range from 0.29 to 0.67 [1].

Genome-wide association studies (GWASs) have been successful in mapping genetic variants for IOP. On a large scale, a GWAS meta-analysis was performed on 18 cohorts comprising 35,296 individuals. This study showed robust associations among 12 different single-nucleotide polymorphisms (SNPs) representing nine different genes/loci. Notably, four of these genes (*TMCO1*, *CAV7*, *ABCA1*, and *GAS7*) were also associated with POAG, highlighting the key role of this endophenotype in end-stage ocular disease [2].

Linkage mapping of genes for IOP identified seven regions of interest on chromosomes 2, 5, 6, 7, 12, 15, and 19 [3]. Chromosomes 6 and 13 were implicated in another IOP linkage study [4]. Evidence for the linkage of a maximum IOP has been mapped to chromosome 10 near region 10p15-p14, which is near another locus involved in up to 17% of low-tension glaucoma pedigrees [5]. Chromosome 2p15-p16.3

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is implicated in IOP [6], while 2cen-q13 is found in normal-tension glaucoma, with onset at over 50 years; chromosome 7q35-q36 has also been found to be associated with IOP [7].

A thinner central corneal thickness (CCT) is also a risk factor for POAG and has been shown to have high heritability across populations (0.65–0.95) [1]. A large GWAS of >20,000 individuals confirmed the previously identified 10 different loci and revealed the presence of 16 new loci associated with CCT [8]. Of particular interest is the *FNDC3B* gene on chromosome 3, which was also associated with POAG in this study and with IOP in the GWAS of Hysi et al. [2]. This suggests that variants of the *FNDC3B* gene may be conferring a pleiotropic effect on POAG endophenotypes and end-stage clinical diseases.

Despite this progress, a substantial amount of genetic variance remains unexplained. Population-specific variants that might be rare in outbred populations may also influence POAG endophenotypes. Founder-effect genetic isolates may offer some advantages for gene mapping because of such features as reduced genetic heterogeneity and an extensive familial structure. Linkage and association analyses of ocular phenotypes in a Dutch population isolate revealed new linkage regions for optic disc morphology at 20p13 (*SIRPA* and *RNF24*/*PANK2* loci) and 2q33-q34 (*IGFBP2* locus). In addition, significant and suggestive GWAS signals at the previously identified *RERE*, *LRP1B*, *CDC7*, *TGFBR3*, and *ATOH7* loci were replicated in this isolate [9].

The Norfolk Island (NI) population, located off the east coast of Australia, is a genetic isolate with well-defined familial lineages dating back 12 generations to the originating founders, 12 Tahitian women and six European men. As part of the Norfolk Island Eye Study (NIES), the prevalence of chronic ocular diseases has previously been reported [10]. In general, the prevalence of blindness and visual impairment was observed to be lower than that in mainland Australia. However, the prevalence of glaucoma was higher in NI at 6% compared to 3% in mainland Australia [10]. Differences between NI pedigree and non-pedigree groups were observed for several POAG risk factor traits, suggesting a possible genetic influence some traits [11]. In an effort to understand better the genetic basis of POAG, we focused on two primary risk factor phenotypes—elevated IOP and a thinner CCT—by conducting heritability, genome-wide linkage and association studies of a large core pedigree from the NI isolate.

METHODS

Subjects and phenotyping: The study sample consisted of 330 participants from the NIES. These individuals belong to a single large NI pedigree of 6,537 members dating back to the original Bounty mutineers and Tahitian founders. Pedigree construction and characteristics have been well described in previous papers [12-14]. All participants underwent a full eye examination as part of the NIES, which was designed to investigate the genetics and epidemiology of ocular disease traits in this population. Comprehensive ocular measurements for IOP and CCT were taken (see [11] for details).

Genotyping: Genotypes for all 330 individuals were obtained for 400 microsatellite (STR) markers with an average heterozygosity level of 76% spaced at 10cM. Chromosomal marker maps were obtained from the Marshfield Centre for Medical Genetics. Cytobands for markers were obtained from the University of California Santa Cruz (UCSC) Genome Browser.

Individuals were also genotyped for a genome-wide panel of SNPs using Illumina Infinium High Density (HD) Human610-Quad BeadChip version 1, according to the manufacturer's instructions. Samples were scanned on the Illumina Bead Array 500GX Reader. Raw data were obtained using the Illumina Bead Scan image data acquisition software (version 2.3.0.13). Raw data from the Illumina data files were then SNP genotyped in R using the CRLMM package [15]. Genotype data then underwent initial quality control routines using PLINK [16]. SNPs were filtered based on a minor allele frequency of >0.01, a call rate of >0.95, and a Hardy–Weinberg equilibrium testing p value of $>10^{-5}$. After this initial quality control, 590,603 SNPs were exported from PLINK and imported into the CRAN package GenABEL [17]. Further filtering (including Mendelian inheritance violations and sex-checking based on available X and Y markers) in GenABEL led to the reduction of the SNP set to a total of ~480,000; this included the removal of both X and Y chromosome SNPs after gender checking, as well as the removal of mitochondrial and XY SNPs.

Statistical analyses: Heritability analyses were conducted using a variance components-based methodology implemented in the Sequential Oligonucleotide Linkage Analysis Routines (SOLAR) version 4.0.6 software package [18]. Heritability estimates (h^2) were calculated as the ratio of the trait variance explained by additive polygenic effects to the total phenotypic variance of the trait [19]. The applied polygenic model assumes an infinite number of genetic factors, each with a small additive effect contributing to the trait variance. Estimates were screened for covariate effects of sex, age, age*sex, age^2, age^2*sex, height, ultraviolet autofluorescence, glaucoma status, visual acuity pinhole, sphere, cylinder, axis, kvalue-v, kvalue axis, CCT, ACD, IOP, pterygium, eye color, visual acuity, axial length, outdoors, and kvalue-h. Glaucoma was treated as a continuous variable

using "EnableDiscrete 0" to circumvent convergence errors due to discrete trait modeling in SOLAR. Covariates with p values less than or equal to 0.10 were retained in the final model. SOLAR requires kurtosis to be <0.8 and a standard deviation of <0.5 to proceed with the analysis. The SOLAR bivariate analysis was used to calculate genotypic, environmental, and phenotypic correlations between metrics. Genome-wide linkage mapping of adjusted eye metric traits was conducted with SOLAR using a multipoint analysis.

A pedigree-based GWAS analysis of all heritable endophenotypes was batched using custom R scripts in GenABEL [17]. A correction was made for the relatedness and admixture inherent in the NI population using the polygenic model with age and sex interactions, as well as the genetic structure—the top two genomic principal components of the complete SNP set, as calculated by KING [20]. For an association analysis, the mmscore function implemented in GenABEL was used. This function represents a mixed-model approximation analysis of the association between a trait and genetic polymorphism(s) and it is specifically designed for association testing in samples of related individuals. This allows for per-SNP association testing using a mixed-model polygenic approach. After adjusting for linkage disequilibrium (LD) among SNPs using M_{eff} [21], the study-wide significance was set at $p = 1.84\times10^{-7}$. This significance threshold has been used in previous GWAS publications of NI [22,23]. GWAS Manhattan plots were generated for each trait association using a custom modified version of the GenABEL *plot.scan.gwaa* function (for all Manhattan plots, see Supplemental Material).

Previous studies of CVD risk have determined the current trimmed pedigree structure and size had >80% power to detect the heritability of phenotypes whose variation is partially attributable to additive genetic effects and to detect major effect loci via linkages and associations as that are statistically significant at accepted thresholds [24,25]. Evidence that the major effect loci exist for complex quantitative traits in this NI pedigree has also been published [22,23].

RESULTS

Heritability analyses showed that CCT was the most heritable trait, with an unadjusted h^2 of 0.85 ($p = 1.5\times10^{-6}$). Adjusted heritability for CCT decreased to $h^2 = 0.77$ ($p = 5.7\times10^{-6}$), with the inclusion of IOP, pterygium, and sphere as significant covariates. The adjusted IOP heritability was 0.39 (p = 0.008) with significant covariates anterior chamber depth (ACD) and ultraviolet autofluorescence, a biomarker for sun exposure accounting for 1% of the trait variation. Overall, the heritability values for CCT and IOP in the NI population fell within the range of heritability estimates among worldwide populations [1]. Importantly, these results indicate a substantial influence of genetic factors on these traits in the NI pedigree.

A genome-wide linkage and association analysis was performed on the core NI pedigree to identify loci for CCT and IOP. Table 1 summarizes logarithm of the odds (LOD) scores for the traits adjusted for significant covariates. There were no statistically significant linkage peaks (i.e., LOD ≥ 3). The highest linkage peak was for CCT on chromosome 20 (LOD = 1.9, p = 0.0016). Table 2 summarizes the GWAS results. For IOP, there was a statistically significant association at rs790357 located in *DLG2* on chromosome 11q14.1 (odds ratio [OR] = 1.70, $p = 1.02\times10^{-7}$). This top-ranking SNP was part of a cluster of seven SNPs forming an LD block spanning a 16.6-kb region ($P_{all} < p = 1.00\times10^{-6}$). There were also several suggestive hits on chromosomes 10 and 20 for IOP. For CCT, there were no association peaks that met the genome-wide level of statistical significance, but there were several suggestive hits, with the most significant being for rs13095933 on chromosome 3 ($p = 2.86\times10^{-6}$). We also examined the previously associated index SNPs for IOP (n = 12) and CCT (n = 26), as reported in the large-scale GWASs of Hysi et al. (2014) and Lu et al. (2013), respectively [2,8]. These results showed that for IOP, only one SNP—rs12419342 in *RAPSN* on chromosome 11—was statistically significant at the nominal level (p = 0.0021). For CCT, the only statistically significant SNP was rs9938149 in *BANP-ZNF469* on chromosome 16 (p = 0.002).

DISCUSSION

Herein, we examined the genetic isolate of NI and performed heritability and genome-wide linkage and association studies of phenotypes associated with POAG, CCT, and IOP. Overall, the heritability estimates were consistent with previous values, and the indicated genetic factors influence these traits. A linkage analysis for IOP showed that the highest LOD Score occurred on chromosome 15 (LOD 1.3), where a peak was also found in the Beaver Dam Eye Study [4]. Linkage results for CCT did not overlap any previously published peaks. Although a previous study indicated a linkage to chromosome 3 for IOP [7], in this study, chromosome 3 was associated with CCT.

A GWAS of ocular endophenotypes in this study identified a statistically significant association at a SNP representing a 16.6-kb locus harboring the Disks large homolog 2 (*DLG2*) gene. DLG2, also known as channel-associated protein of synapse-110 (chapsyn-110) or postsynaptic density protein 93 (PSD-93), is involved in neuronal signaling and

Table 1. Summary of genome-wide linkage results of POAG endophenotypes in the Norfolk pedigree.

Endophenotype	Loci	Chr.	Map Distance (cM)	LOD score >1*	P value
IOP	3	15	116	1.3	0.0072
		22	51	1.1	0.012
		8	60	1.2	0.0094
CCT	5	20	15	1.9	0.0016
		11	40–58	1.7	0.0026
		14	59	1.2	0.0094
		4	102	1.3	0.0072
		3	55	1.4	0.0056

IOP: intraocular pressure, CCT: central corneal thickness.* Results adjusted for age and sex

development. Specifically, the protein forms a heterodimer with a related family member that may interact at postsynaptic sites to form a multimeric scaffold for the clustering of receptors, ion channels, and associated signaling proteins. DLG2 is expressed in many neuronal and immunological tissues and the retina [26]. *DLG2* variants have not previously been associated with IOP or POAG. However, a GWAS performed by Kiefer et al. identified a significant and replicated association of a *DLG2* SNP (rs2155413) and myopia in a large cohort of >400,000 individuals [26]. Myopia is associated with intra-ocular pressure and is a risk factor for POAG [26].

Our GWAS also revealed several suggestive minor effect peaks in the NI population that may represent new loci requiring replication. Surprisingly, association testing of the known SNPs for IOP and CCT did not indicate confirmation in NI for most loci. This may reflect the modest sample size of NI, a different genetic architecture for these traits in NI, or both. In addition, the fact that CCT does not exhibit a major effect locus indicates it is of a greater than expected complexity (e.g., genetic heterogeneity) in the NI isolate.

This study indicates that the POAG endophenotypes CCT and IOP exhibit a substantial degree of heritability in the NI pedigree, indicating a genetic component. A genome-wide linkage analysis of these traits did not reveal any major effect loci, but a GWAS did implicate several known loci, as well as a potential new locus in *DLG2*, suggesting a role for neuronal signaling and development in IOP and perhaps POAG. Given the substantial degree of heritability, further genetic studies are warranted, and future endeavors implementing approaches such as whole genome sequencing may help identify important, rare, or private variants of these ocular traits.

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Table 2. Summary of GWAS results for POAG endophenotypes in the Norfolk pedigree.

Endophenotype	Loci*	Chr.	Top SNP	Position	Allele	β	P value
IOP	3	11	rs790357	83,620,940	T	0.60	1.02E-07
		10	rs10761970	67,160,860	T	−0.36	8.38E-06
		20	rs2285142	40,978,940	C	0.40	5.34E-06
CCT	4	1	rs856077	158,969,075	C	0.43	4.15E-06
		3	rs1164313	144,339,407	T	1.48	5.31E-06
		3	rs13095933	148,408,108	G	0.44	2.86E-06
		3	rs344002	156,455,269	T	−0.87	5.15E-06

IOP=Intra-ocular pressure, CCT=Central corneal thickness,*Loci=a cluster of >3 directly adjacent SNPs yielding a p value <1E-05

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