523 Genetic epidemiology used to identify risk factors for eye disease
Thursday, May 07, 2015 12:00 PM–1:45 PM
1CD Mile High Blrm  Paper Session
Program #/Board # Range: 5814–5819
Organizing Section: Clinical/Epidemiologic Research

Program Number: 5814
Presentation Time: 12:00 PM–12:15 PM

Heterogeneous environmental effects on myopia in parents and their children
—The Guangzhou Twin Eye Study
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Purpose: Phenotypic correlation between parents and offspring has been commonly used to estimate the heritability assuming the parents and offspring share the same environment. However, it is well known that prevalence of myopia has been increasing considerably in recent decades suggesting heterogeneity on myogenic environmental factors. Recently, we develop a new genetic modeling to decompose the common environmental effects into heterogeneous environmental effect. In this analysis, we attempt to use this model to estimate the heterogeneous environmental effects and their contribution to parent-offspring phenotypic variation using the data from a twin study.

Methods: Twins aged 7-21 years old and their parents were enrolled from Guangzhou Twin Eye Study. Spherical equivalent (SE) and corneal curvature (CC) was measured by auto-refraction while axial length (AL) was measured by optical partial coherence interferometry (IOLMaster) in both twins and their parents. ACDE-H model using PROC MIXED in SAS was used to estimate the proportion of parent-offspring variation that explained by heterogeneous environmental effects across generations.

Results: A total of 927 pairs of twins and their parents were available for analysis. Heterogeneous environmental effects between parents and offspring explained about 9.6% of SE variation, and 17.1% of AL variation between parents and offspring. However, this estimation was not statistically significant for CC variation.

Conclusions: In this parent-offspring twin study, the heterogeneous on environmental effects explain a significant amount of parent-offspring variation on the progressive traits relevant to myopia such as SE and AL but not on the trait that remains unchanged with myopia such as CC.

Commercial Relationships: Xiaohu Ding, None

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Genome-wide association study of nuclear cataract finds suggestive association with a common variant in TRPM3
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Purpose: The aim of this study was to identify common genetic variants and genes associated with nuclear cataract in a Caucasian population using genome-wide approaches. A recent genome wide association study (GWAS) meta-analysis identified two loci associated with age-related nuclear cataract in Asian populations. Further genetic loci remain to be found, given twin studies suggest a heritability of 48%.

Methods: Nuclear cataract was measured in 2265 twins (age ≥ 50) from the TwinsUK registry from Scheimpflug lens images, graded using an objective densitometry-based system. Genotypes were obtained using Illumina platforms (610K and 317K) and later imputed against the HapMapII panel. Next generation sequencing data was available for a subset of 940 individuals. Common genetic variants were analysed using a score-test-based analysis implemented in MERLIN, accounting for age, sex and family structure. All genes in close proximity to GWAS variants associated with nuclear cataract (n=63) were included for gene-centred association analysis using the sequencing data. In this case, the association between genes and nuclear cataract was tested using a rare variants burden test implemented in SKAT, adjusting for age and sex.

Results: The most associated variant in our GWAS was rs9792446 (p=1.0e-7) in the second intron of the TRPM3 gene which encodes for a calcium channel. In mice, Trpm3 was found to be highly expressed in lens. A missense mutation in TRPM3 was recently reported to cause congenital cataract with high tension glaucoma. In addition, twelve other loci showed suggestive association with nuclear cataract (p<1.0e-5). We nominally replicated the association with CRYAA found previously in the Asian study (p=0.01 at rs870137). Analysis of rare variants using the burden test found 9 out of 63 genes to be associated with nuclear cataract (p<0.05). The most significantly associated gene was CALHM1 (p=0.001) which also encodes for a calcium channel.

Conclusions: Our results identify suggestive association between common TRPM3 variants as well as several other loci and nuclear cataract. We also found some evidence for an effect of rare variants in the CALHM1 gene on nuclear cataract. Ongoing replication studies will clarify the role of TRPM3 in age-related nuclear cataract, and larger samples will provide more power to discover further genetic associations.

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A Genome-Wide Association Study of Age-Related Cortical Cataract and Its Progression Identifies Novel Genes
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Purpose: Age-related cortical cataract is a common progressive disorder in the elderly. Despite importance of gene discovery for age-related cortical cataract, large-scale genome-wide association (GWA) studies have never been conducted.

Methods: We performed meta-analysis of GWA studies in Age Related Eye Disease Study (AREDS) and Blue Mountains Eye Study (BMES) with baseline measures of cortical lens opacity and annual change over time as a quantitative trait, using 3,364 unrelated subjects. Promising genes containing at least one GWA marker with P<10^-4 were further evaluated in single marker or gene-based
replication using a cross-sectional measurement of cortical lens opacity from the Framingham Heart Study (FHS).

**Results:** Genome-wide significant associations (p<5x10^-8) were detected for baseline risk in **BCL11A**, near **STAP2**, and in **NBPF22P** (best SNP, rs79657645 in **STAP2**; meta-analysis p=1.3x10^-10). Markers influencing the rate of progression were genome-wide significant near **LINC00536**, in **FGFR2**, and in **THBD** (best SNP, rs1649201 in **FGFR2**; p=7.6x10^-10); **FGFR2** is necessary for lens cell differentiation and cell survival. Among the top ranked genes in discovery, single marker tests in **BCL11A**, **ITGA8**, **RAB31**, **STAP2**, **FGFR2**, **CNTN5**, and **THBD** were significant with different markers (p<10^-8) in replication. Meta-analysis of discovery and replication sets in gene-based tests revealed that **BCL11A**, **ITGA8**, **STAP2**, **FGFR2**, and **THBD** were genome-wide significant (gene-based p<10^-5), while **RAB31**, **CNTN5**, and **FGFR2** were significant after multiple testing correction (gene-based p<8x10^-5). Two additional genes, **KLHL8** and **TMEM161B** were also significant in gene-based tests with p<8x10^-4. A bioinformatic survey found **ITGA8**, **FGFR2**, and **CNTN5** to play roles in axon guidance pathway, wherein **EPHA2**, a known gene for cortical cataract, is involved.

**Conclusions:** We discovered novel genome-wide significant genes for age-related cortical cataract enriched in axon guidance pathway.

**Commercial Relationships:** Jin Wang, None; Emily Chew, None; Sudha Iyengar, None; Joan Bailey-Wilson, None; Robert Igo, None; Gyungah Jun, None; Christopher Hammond, None; Cornelia van Duijn, None; Rene Hoehn, None; Ching-Yu Cheng, None; Paul Mitchell, None; Emily Y. Chew, None; Jie Jin Wang, None; Sudha K. Iyengar, None

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**Presentation Time:** 12:45 PM–1:00 PM

**Gene by gene interaction analyses identifies evidence of epistasis and new candidate genes that influence intraocular pressure in the general population**

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**Purpose:** Genome-wide association studies (GWAS) have identified several loci determining intraocular pressure (IOP), many of which were also associated with susceptibility to primary open angle glaucoma. However, these variants collectively only explain a small proportion of the expected genetic effects for IOP. Epistatic interaction between genetic loci is one of the proposed hypotheses to explain missing heritability. The purpose of this study is to assess the importance of gene-gene epistatic interactions relating to IOP in population-based studies.

**Methods:** GWAS data from 15 cohorts involving about 28,000 subjects from the International Glaucoma Genetic Consortium (IGGCC) were included in this study. A total of 12 single nucleotide polymorphism (SNPs) from the seven loci most strongly associated with IOP identified in the previous GWAS were selected a priori. Pairwise epistatic interactions between these 12 SNPs and all other SNPs in the HapMap2 dataset were assessed by calculating the statistical interaction term using linear regression models for each cohort independently. These terms were then combined by means of a fixed-effect inverse variance meta-analysis. The threshold of significance was set at 4.1 x 10^-4.

**Results:** Several associations met the adjusted genome-wide significance threshold (alpha=4.1E-09). The strongest associations were observed between rs10258482 (within the CAV1 gene) and SNPs within or in immediate proximity to the TOX2 (p=2.5E-11), TBC1D1 (p=2.2E-10), TNKS (2.8E-10) and NRXN3 (p=7.8E-10) genes. Previous works suggest that the last three genes are involved in fat metabolism and were associated with body mass and obesity. SNPs located on chromosome 4 showed moderate eQTL effects over the TBC1D1 (p=0.007) gene, but also had eQTL effects of similar magnitude over other adjacent genes.

**Conclusions:** This work has identified statistically significant associations of synergistic interaction between SNPs and IOP and illustrates the importance of using other approaches than study of linear associations of common variants for traits of interest, to include other potential sources of heritability. These results suggest that multi-locus effects are important and may need to be investigated more thoroughly in the future.

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**Heritability of anterior segment optical coherence tomography parameters in the Indian Family Angle Closure Evaluation**

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**Purpose:** We previously reported a very high sibling recurrence risk of angle-closure (AC) in a South Indian population. In the current study, we report on the heritability (h²) of quantitative parameters measured using anterior segment optical coherence tomography (ASOCT) in 631 individuals in 305 sibships in the Indian Family Angle Closure Evaluation.

**Methods:** AC (i.e., either AC suspects, primary angle closure or primary angle closure glaucoma) and open-angle control (OA) probands and their siblings were examined at the Aravind Eye Hospital glaucoma specialty clinic in Pondicherry, India. All participants received a complete eye examination and full glaucoma workup. ASOCT (Zeiss Visante) was performed on both eyes under ambient light and dark illumination. AC biometric parameters were estimated using automated image analysis software. These included AC width (ACW); AC depth (ACD); AC area; angle-opening distances (AOD); angle recess area (ARA), trabecular-iris spacing (TISA); iris area (IA); iris thickness (IT); maximum iris thickness, iris volume; and iris concavity. Means or first principal components (PC1) of parameters measured at multiple locations and illuminations (e.g., AOD, TISA, etc.) were used as derived traits in the analyses. H² estimates were obtained for each derived trait using generalized estimating equations and computing the residual within-sibship correlation matrix after adjusting for age and sex.

**Results:** PC1 explained 47% (IA) to 73% (TISA, AOD) of the variance of AC parameters. H² of AC parameters ranged from 48% (ACD) to >80% (AOD, ARA, TISA, IT). ACD had a lower (pseudo) h² in AC sibships (2%, NS) compared to OA sibships (40%).

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Iridolenticular contact (IC) parameters had relatively low $h^2$ (14-30%) although PC1 for IC explained less than 35% of their variances. 

Conclusions: Our results show that AS biometric parameters measured with ASOCT are highly heritable in a South Indian population. Interestingly, ACD—a measure often used as a clinical predictor of AC glaucoma development—was uncorrelated in AC siblings. Though numerous measures were taken at different anatomical locations and illumination conditions, one principal component was generally sufficient to capture >50% of the variability of these parameters, simplifying their clinical interpretation and utility.

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Family history is a risk factor for severe stages of angles closure in a South Indian population

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Purpose: To determine if more severe stages of angle closure, defined as primary angle closure or primary angle closure glaucoma (PAC/PACG), are more prevalent amongst siblings of PAC/PACG patients as compared to siblings of primary angle closure suspects (PACS).

Methods: Design: Cross-sectional clinical study
Participants: A total of 596 South Indian proband-sibling pairs, including 422 probands with diagnosis of PACS and 174 with a diagnosis of PAC/PACG.

Methods: A masked grader evaluated probands and siblings by gonioscopy, applanation tonometry, slit lamp biomicroscopy and optic nerve evaluation in order to define the angle closure phenotype. Probands were recruited from one of 2 groups based on the phenotype of the more severely affected eye: (1) PACS, or (2) PAC/PACG. One sibling of each proband was then examined and classified into one of 3 groups: open angles (OA), PACS, or PAC/PACG. Multivariable logistic regression models were used to estimate the odds of PAC/PACG in siblings of PAC/PACG probands as compared to siblings of PACS probands.

Results: Across both sibling groups, 387 individuals (64.9%) had OA, 172 (28.9%) had PACS and 37 (6.2%) had PAC/PACG. There was no significant difference in the prevalence of any angle closure (PACS, PAC or PACG) among PACS siblings (35.3%) and PAC/PACG siblings (34.1%) (p=0.8). However, PAC/PACG was more prevalent among siblings of PAC/PACG probands as compared to siblings of PACS probands (9.7% vs 4.7% respectively; p=0.02). In multivariable models adjusting for proband and sibling age and gender, the odds of PAC/PACG was 2.1 times greater in PAC/PACG siblings as compared to PACS siblings (95% CI=1.1 to 4.3; p=0.03). PAC/PACG siblings were noted to have a significantly higher intraocular pressure as compared to PACS siblings, (β=+0.85 mmHg, 95% CI 0.22-1.48; p=0.008) but did not demonstrate higher cup/disc ratios (p=0.74) or more frequent peripheral anterior synechiae (PAS) (p=0.96).

Conclusions: Siblings of South Indian PAC/PACG probands have a greater than two times greater odds of a more severe stage of angle closure than siblings of probands with PACS, suggesting there may be different sets of genetic risk factors that determine whether iridotrabecular contact is tolerated, or whether it progresses towards PAS formation, elevated intraocular pressure and/or glaucomatous damage.

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