Program Number: 805 **Poster Board Number:** C0094
Presentation Time: 1:30 PM–3:15 PM
Lack of association between primary angle-closure glaucoma susceptibility loci and the phenotypes axial length to lens thickness ratio and lens thickness to axial length factor

Rene Hoehn[1, 2], Aslihan Gerhold-Ay[3], Stefan Nickels[2], Thomas Muenzel[4], Karl J. Lackner[5], Manfred Beutel[6], Tanja Zeller[7, 8], Philipp S. Wild[9, 10], Norbert Pfeiffer[2], Harald Binder[3]. [1]Ophthalmology, Inselspital Bern, Bern, Switzerland; [2]Ophthalmology, University Medical Center Mainz, Mainz, Germany; [3]Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center Mainz, Mainz, Germany; [4]Center for Cardiology, University Medical Center Mainz, Mainz, Germany; [5]Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz, Mainz, Germany; [6]Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Mainz, Mainz, Germany; [7]Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany; [8]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; [9]Preventive Cardiology and Preventive Medicine / Center for Cardiology and Center of Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany; [10]German Center for Cardiovascular Research (DZHK), Partner site RhineMain, Mainz, Germany.

Purpose: The genetic background in the development of primary angle closure glaucoma (PACG) is still inconsistent and little is known in European populations. This study investigated the genetic overlap between the biometric risk predictors of PACG axial length to lens thickness ratio (ALR) or the lens thickness to axial length factor (LAF) and known genetic variants associated with PACG.
Methods: Within the Gutenberg Health Study (GHS), a genome-wide association study for ALR and LAF was conducted in two cohorts (GHS 1, n = 1725 and GHS 2, n = 832) of Caucasian individuals (age range, 40 - 79) with a subsequent meta-analysis of both cohorts. The GHS is a population-based prospective, observational single center study in the Rhine-Main-Region in mid-western Germany. Axial length (AL) and lens thickness (LT) were measured using optical low-coherence reflectometry (Lenstar LS 900). Any pseudophakic or aphakic eye was excluded from analysis. The ALR was calculated by dividing AL by LT and the LAF by dividing LT by AL x 10. The average of both eyes or the value of the remaining eye were used for association analysis.
Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 and genotyped data were imputed with MACH/Minimac to the 1000 Genomes reference panel (phase 1, March 2012). Genome-wide association was tested by a linear regression model, adjusting for age and sex (ProbABEL 0.4.5 software). Finally, a meta-analysis based on the effect and standard error of both single analyzed cohorts (GHS 1 and GHS 2) was performed using the METAL software.
Results: None of the known SNPs to be associated with PACG (rs1015213, rs3753841, rs11024102, rs1401999, rs4656461, rs1900004, rs17576 or rs2250880) showed an association with ALR or LAF (p>0.05 for all listed SNPs). However, we identified novel SNPs of borderline significance associated with ALR and LAF. Results of the ALR exhibited systematically lower p-values than for the LAF.
Conclusions: While ALR and LAF are clinical useful risk predictors for PACG, they showed no strong genetic overlap with genetic variants previously associated with PACG, but these clinical-based endophenotype might help to improve our genetic insight. However, our results emphasize that the knowledge of the genetic background of PACG is still limited.

Program Number: 806 **Poster Board Number:** C0095
Presentation Time: 1:30 PM–3:15 PM
Genome wide linkage scan of primary angle-closure glaucoma and its endophenotypes

Sancy Low[1], Pia Ostergaard[2], Naushin Waseem[1], Jonathan Ruddle[4], Mingguang He[3, 4], Heather Cordell[5], Shomi Bhattacharya[1], David F. Garway-Heath[1], Peng T. Khaw[1], Paul J. Foster[1]. [1]NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, United Kingdom; [2]Medical Genetics Unit, St. George's University of London, London, United Kingdom; [3]Sun Yat-sen University, Zhongshan Ophthalmic Centre, Guangzhou, China; [4]Department of Ophthalmology, Centre for Eye Research Australia, University of Melbourne, Melbourne, VIC, Australia; [5]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom.

Purpose: To investigate genetic mechanisms influencing risk of primary angle closure disease (PAC) and related endophenotypes.
Methods: 155 British probands (17 PACS/ 76 PAC/ 62 PACG) and 363 relatives were examined. Subjects with two or more quadrants of iridotrabecular contact on darkroom gonioscopy were considered affected (n=311). Measurements from anterior segment optical coherence tomography (Visante, Zeiss) and axial biometry (IOLMaster, Zeiss) were used for QTL linkage analyses. ASOCT parameters that were not available on Visante software were analysed with the Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China). Linear regression models were used to normalize values for angle opening distance (AOD), trabecular iris space area (TISA), angle recess area (ARA), anterior chamber area, volume and width (ACA, ACV, ACW) and maximum iris thickness (ITmax). Anterior chamber depth (ACD) and lens vault (LV) were adjusted on age and sex, and axial length (AL) adjusted on sex (SPSS v19). Genotyping was performed on 432 subjects from 63 families (Illumina, Infinium® assay). Selected markers (9,761 SNPs) were exported from BeadStudio software (Illumina) and entered into MERLIN and MINX (Michigan, USA) for binary trait and QTL linkage analyses.
Results: There were 54 families with multiple affected individuals. Presumed autosomal dominance was observed in 80% of the families (n=43). Parametric binary trait linkage with a rare disease model and autosomal dominant inheritance showed a maximum LOD score of 1.1 (non-significant). Non-parametric linkage of QTLs showed a number of suggestive regions but no region reached statistical significance of 3.6. Z-scores >2.0 were found for ACD on chromosomes 2p23 and 7q22. AL and ITmax were found together on chromosome 10p14 (Z: 1.2 to 1.5) and chromosome 13q31 (Z: 1.4 to 1.6). Chromosome 10q23 was found for AL, LV and ACW (Z: 1.2 to 1.7); ITMax and ACW were found in a 20cM region on chromosome 5q33-35 (Z: 2.4 both).
Conclusions: While no single locus was found to show statistically significant linkage to angle closure or its endophenotypes, there were 6 chromosomal regions of interest. Shorter ACD and AL, thicker ITMax and LV and smaller ACW were the endophenotypic characteristics most commonly shared within these families. Further

work to elucidate the molecular mechanisms of angle closure is required.

Program Number: 807 **Poster Board Number:** C0096
Presentation Time: 1:30 PM–3:15 PM
Investigation of PACG associated genetic variants in persons with early stages of angle closure disease

Eranga N. Vithana[1, 2], Monisha E. Nongpiur[1, 2], Baskaran Mani[1, 2], Chiea-Chuen Khor[3, 1], Ching-Yu Cheng[1, 2], John Allen[2], Tien Yin Wong[4, 1], Tin Aung[4, 1]. [1]Singapore Eye Research Institute, Singapore, Singapore; [2]Duke-NUS Graduate Medical School, Singapore, Singapore; [3]Genome Institute Singapore, Singapore, Singapore; [4]Singapore National Eye Center, Singapore, Singapore.

Purpose: Primary angle closure glaucoma (PACG) is classified into three stages: primary angle closure suspects (PACS), primary angle closure (PAC) and PACG. The reasons for disease progression from the early stages of the disease to blindness from PACG is yet unknown. We identified significant association at three genetic loci for PACG; rs11024102 at *PLEKHA7,* rs3753841 at *COL11A1* and rs1015213 at *PCMTD1-ST18* on chromosome 8q (Vithana et al, Nature Genetics, 2012). Recently two additional PACG associated loci were dentifed: one within the *NUCB2* gene (338 Gln→Glu (rs757081), $P = 1.30$ x 10^{-10}, OR = 1.14) and another within *PXDNL* (833 Ser→Asn (rs11985241), $P = 2.39$ x 10^{-9}, OR= 0.87 (Aung T et al ARVO Meeting Abstracts May 6, 2015. 4383). Here we aimed to investigate whether these PACG associated genetic variants, are also associated with PACS.
Methods: We collected a total of 1200 PACS and 943 controls from Singapore of Chinese ethnicity. PACS cases had bilaterally narrow drainage angles with inability to visualize the pigmented posterior trabecular meshwork in primary gaze for >180 degrees on gonioscopy but normal intraocular pressure (IOP) and optic discs. Control individuals were those with IOP ≤ 21 mm Hg with open angles and normal optic discs. The 5 SNPs were genotyped in cases and controls by Taqman assays. The association between SNP genotypes and PACS status was measured using logistic regression. A p-value of 0.01 was set to account for the testing of 5 genetic loci using a Bonferroni correction.
Results: Only 2 of the 5 SNPs investigated showed experimentally significant associations with PACS, after adjustment for age and sex. The top associated SNPs were rs1015213 [T] at *PCMTD1-ST18* (OR=) 2.26, p = 0.004) and rs757081 [G] in *NUCB2* (OR=1.22, P= 0.008). However, no significant associations were noted for SNPs rs3753841 (OR 1.13, p = 0.15), rs11985241 (OR=0.86, p = 0.087) and rs11024102 (OR 1.05, p = 0.53) in our Chinese PACS subjects, despite these SNPs showing significant association (p < 0.05) with a similar sized cohort (N=980) of Chinese PACG subjects.
Conclusions: In our study, the PACG associated SNPs rs1015213 and rs757081 were significantly associated with PACS, the earliest stage in the angle closure glaucoma disease course. Evaluation of the genetic biomarkers may help in early recognition of subjects at risk for development of PACG.

Program Number: 808 **Poster Board Number:** C0097
Presentation Time: 1:30 PM–3:15 PM
Identification of two Single Nucleotide Polymorphisms in SRBD1 Gene Associated to Glaucoma in several Dog Breeds

Pierre F. Isard[1], Kissaou T. Tchedre[2], Valerie Tsobnang[2], Marielle Mentek[1], Thomas Dulaurent[1], Pascale Quignon[3], Tetsushi Omori[2], Mouad Lamrani[2]. [1]Ophthalmology, CHVSM, Saint-Martin Bellevue, France; [2]Diagnositic, Menicon Co Ltd, Geneve, Switzerland; [3]Genetique, CNRS/Rennes 1 University, Rennes, France.

Purpose: Glaucoma is a serious eye disease that often leads to blindness. Glaucoma is often described as a degenerative optic neuropathy that is associated with elevated intraocular pressure. Primary glaucoma is a hereditary disease that affects both human and canines. But the genetic mutations association with glaucoma is not fully investigated.
Methods: Previously, we have shown a specific association of two single nucleotide polymorphisms (SNPs) with glaucoma in Shiba-Inus and Shih-Tzus. In this study, we screened polymorphisms within SRBD1 and CYP1B1 genes that have been shown to be associated with Glaucoma in several dog breeds. 77 healthy dogs and 135 cases dogs were recruited from the Centre Hospitalier Veterinaire Saint-Martin (France), and from the REOVVA member (European Network in Veterinary Ophthalmology and Vision in Animals). All Dogs were clinically evaluated before taking blood samples for direct sequencing Analysis.
Results: Two new SNPs (rs9172407 and rs22115601) within SRBD1 gene were significantly associated with glaucoma in within and across Dog breeds data analysis. In Across breed analysis both rs9172407 (Chi-Square test: P<4.26E-09; Odd Ratio: 3.567), and rs22115601 (Chi-Square test: P<0.00116827; Odd Ratio: 2.041) within SRBD1 gene showed a significant association with glaucoma. Both SNPS were also significantly associated with glaucoma in Within Dog breeds analysis in Golden Retriever: rs9172407 (Chi-Square test: P<0.003; Odd Ratio: 7.33) and rs22115601 (Chi-Square test: P<0.0162; Odd Ratio: 4.95), French bulldog rs9172407 (Chi-Square test: P<0.00177; Odd Ratio: 10.28) and rs22115601 (Chi-Square test: P<0.026; Odd Ratio: 3.6). In Eurasier Dog, SNP: rs9172407 (Chi-Square test: P<1.62E-12; Odd Ratio: 11) was significantly associated with glaucoma. There were no significant associations between the CYP1B1 polymorphisms and glaucoma in across and within Dog breeds.
Conclusions: As previously shown, *SRBD1* may be a common susceptibility gene for glaucoma in dogs. The results of this study further confirm that SRBD1 is an important gene in dog glaucoma pathophysiology. Using direct sequencing these two identified SNPs combined with the previously identified SNPs can be used in genetic testing for Glaucoma development prediction in several Dog breeds. The results of this study show for the first time a strong association of SNPs in several dog breed.