**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**

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**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.

**Commercial Relationships: Sancy Low**, None; **Pia Ostergaard**, None; **Naushin Waseem**, None; **Jonathan Ruddle**, None; **Mingguang He**, None; **Heather Cordell**, None; **Shomi Bhattacharya**, None; **David F. Garway-Heath**, None; **Peng T. Khaw**; **Paul J. Foster**, None

**Support:** Fight for Sight (UK, ref 1956), Richard Desmond Charitable Trust, International Glaucoma Association (UK), NIHR BRC2_009 at Moorfields and UCL