

# Mutations in SPATA13/ASEF2 Cause Primary Angle Closure Glaucoma

Naushin H Waseem (1) , Sancy Low (2,3,4) , Amna Z Shah (3) , Deepa Avisetti (5) , Pia Ostergaard (6) , Michael Simpson (7) , Katarzyna A Niemiec (5) , Belen Martin-Martin (8) , Hebah Aldehlawi (5) , Saima Usman (5) , Pak Sang Lee (1,2,3) , Anthony P Khawaja (1,2,3) , Jonathan B Ruddle (9) , Ameet Shah (10) , Ege Sackey (6) , Alexander Day (2) , Yuzhen Jiang (2) , Geoff Swinfield (11) , Ananth Viswanathan (1,2,3) , Giovanna Alfano (3) , Christina Chakarova (3) , Heather J Cordell (12) , David F Garway-Heath (1,2,3) , Peng T Khaw (1,2,3) , Shomi S Bhattacharya (1,3) , Ahmad Waseem (5) , Paul J Foster (1,2,3)

1 NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, United Kingdom.

2 Moorfields Eye Hospital NHS Foundation Trust, City Road, London, United Kingdom.

3 UCL Institute of Ophthalmology, Bath Street, London, United Kingdom.

4 Department of Ophthalmology, St. Thomas' Hospital, Westminster Bridge Road, London, United Kingdom.

5 Centre for Oral Immunobiology and Regenerative Medicine, Institute of Dentistry, Queen Mary University of London, London, United Kingdom.

6 Medical Genetics Unit, St. George's University of London, Cranmer Terrace, London, United Kingdom.

7 Genetics and Molecular Medicine, King's College London, Great Maze Pond, London, United Kingdom.

8 Blizard Advanced Light Microscopy, Blizard Institute, Queen Mary University of London, London, United Kingdom.

9 Department of Ophthalmology, University of Melbourne, Victoria, Australia.

10 Department of Ophthalmology, Royal Free Hospital NHS Foundation Trust, Pond Street, London, United Kingdom.

11 Society of Genealogists, Goswell Road, London, United Kingdom.

12 Institute of Genetic Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom.

Current estimates suggest 50% of glaucoma blindness worldwide is caused by primary angle-closure glaucoma (PACG) but the causative gene is not known. We used genetic linkage and whole genome sequencing to identify Spermatogenesis Associated Protein 13, SPATA13 (NM\_001166271; NP\_001159743, SPATA13 isoform I) , also known as ASEF2 (Adenomatous polyposis coli-stimulated guanine nucleotide exchange factor 2) , as the causal gene for PACG in a large seven-generation white British family showing variable expression and incomplete penetrance. The 9 bp deletion, c.1432\_1440del; p.478\_480del was present in all affected individuals with angle-closure disease. We show ubiquitous expression of this transcript in cell lines derived from human tissues and in iris, retina, retinal pigment and ciliary epithelia, cornea and lens. We also identified eight additional mutations in SPATA13 in a cohort of 189 unrelated PACS/PAC/PACG samples. This gene encodes a 1277 residue protein which localises to the nucleus with partial co-localisation with nuclear speckles. In cells undergoing mitosis SPATA13 isoform I becomes part of the kinetochore complex co-localising with two kinetochore markers, polo like kinase 1 (PLK-1) and centrosome-associated protein E (CENP-E) . The 9 bp deletion reported in this study increases the RAC1-dependent guanine nucleotide exchange factors (GEF) activity. The increase in GEF activity was also observed in three other variants identified in this study. Taken together, our data suggest that SPATA13 is involved in the regulation of mitosis and the mutations dysregulate GEF activity affecting homeostasis in tissues where it is highly expressed, influencing PACG pathogenesis.

