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Abstract Topic:- Clinical Genetics

Abstract Title:- Decoding the genetic Insights of Neonatal-Onset of Primary Congenital Glaucoma through whole exome sequencing

Presenting author name & Institute :- Rahila Sardar**,** Vgenomics India Private Limited

Co-authors name:- Julie Pegu, Suneeta Dubey, Ria Ratna, Anil Tiwari, Abha Gour, Preeti Gupta Lal

Co-authors institute:-Dr Shroffs Charity Eye Hospital, Vgenomics India Private Limited

Aims:-Primary congenital glaucoma (PCG) is a rare but serious disease that presents in children as early as birth and as late as 3 years of age with an incidence of 1 in 1,250-1,10,000 people affected. PCG is caused by mutations in genes that are potentially involved in eye development when the child is still in the womb, particularly in the formation of the drainage channels of the eye. Mutations in several genes have been implicated to cause PCG. Of these genes, CYP1B1 is the most common. Other genes that are known to be associated with PCG include LTBP2, MYOC, FOXC1 and TEK. There are still other genes that are yet to be identified since only potentially 13-25% of PCG cases have mutations in these known genes.

Methods:- Whole exome sequencing was conducted to discover novel mutations in a cohort of 28 patients who had congenital glaucoma. This cohort underwent clinical diagnosis, phenotyping and sampling at Glaucoma department, Genetics Department, Eicher Shroff Centre for Stem Cell Research, and Cornea Department of Dr. Shroff's Charity Eye New Delhi India. Presenting complain for most patients was enlarged, whitened eyes since birth. Photophobia was observed in both eyes without any associated watering or discharge. Most of the children had enlarged corneal with elevated intraocular pressure. All patients underwent trabeculotomy with Trabeculectomy in both eyes. Optical penetrating keratoplasty (OPK)was done after a minimum period of 3 months following the Trab with Trab surgery. Some of the children were from consanguineous marriages.

Results:- A range of 17-44K Single nucleotide polymorphisms (SNP) were detected with majority of them benign as expected. In the 5 genes known to be associated with PCG a range of 33-91 variations were detected in this cohort of 28 patients. 9 out of the 28 patients had variations in CYP1B1 gene with SNP rs4646433 at the 3'UTR common in most of the patients. Out of 5 known reported genes, TEK gene is found to harbor multiple SNPs in all the 28 patients with rs682632 being common in all, currently reported as VUS. This SNP leads to a change in glutamine to proline at position 346 and has been reported in PCG by others however, the impact of this mutation on the pathogenicity is not yet known. Additionally, new SNPs with high pathogenicity scores were present in 15 out of 28 patients in the glycogen phosphorylase muscle associated (PYGM) and 14 out of 28 patients in the PPARGC1 and ESRR Induced Regulator Muscle1 (PERM1) genes, that have not yet been reported.

Conclusions:- Many known SNPs have been verified in this cohort of Indian PCG patients. Interestingly novel genes having variants with high pathogenicity scores have been identified in the present study that can be significant in clinical implications for the development of appropriate disease-monitoring/treatmentplan. This work is the first step towards identifying causative mutations tailored towards Indian population and development of a diagnostic panel. However, validation of these findings in a larger, more diverse cohort is required before comprehensive genetic testing can be offered.

Keywords:- Genomics, Whole exome Sequencing, Primary Congenital Glaucoma, Personalized Treatment