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**Mutations in KIF27, GNAS and IFT140 genes are associated with VACTERL association**

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**ABSTRACT**

VACTERL association (OMIM #192350) is a rare genetic disorder involving at least three congenital malformations from multiple organ systems. VACTERL stands for vertebral defects (V), anorectal atresis (A), cardiac defects (C), trachea-oesophageal fistula with or without oesophageal atresia (TE), renal anomalies (R) and limb abnormalities (L). Until now, the aetiology of VACTERL association is unknown, particularly at the molecular level. Therefore, we aimed to profile the mutations involved in a patient with VACTERL association via whole exome sequencing (WES). An infant girl was delivered premature at 30 weeks and had 4/6 of the VACTERL malformations. Trio-WES analysis was performed in the patient and her parents. The exome data was analysed using Torrent Suite and annotated using ANNOVAR. Polymorphisms with allele frequency of >0.01 were excluded and the remaining variants were filtered based on de novo mutations, autosomal recessive, X-linked and di-genic inheritance traits.We did not detect any homozygous, compound heterozygous or X-linked mutations associated with VACTERL association in this patient. However, we identified two heterozygous mutations; KIF27 (ENST00000297814:c.3004 A > C:p.N1002H) and GNAS (ENST00000371098:c.205 C > A:p.H69N) genes that were inherited from her father and mother respectively. A de novo, IFT140 gene mutation (ENST00000426508:c.683 C > G:p.S228C) was also identified in this patient. The VACTERL phenotype seen in this patient could be due to heterozygous mutations affecting KIF27 and GNAS genes, inherited via autosomal recessive trait. In addition, IFT140 gene mutation may also be involved. All the 3 genes are known to be directly or non-directly involved in the sonic hedgehog signaling that have been implicated in VACTERL. This is the first report of the involvement of these 3 genes in association with VACTERL.