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**Digenic Inheritance of Heterozygous FANCA and BRCA2 mutations in a VACTERL-H patient**

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**ABSTRACT**

VACTERL-hydrocephalus (VACTERL-H) is a subtype of VACTERL association, which is clinically diagnosed based on the presence of 3 or more congenital anomalies affecting the vertebrae, anus, heart, trachea, oesophagus, kidneys or limbs. VACTERL-H is an autosomal recessive or X-linked genetic disease and accounts for about 5% of all VACTERL cases. We performed whole exome sequencing analysis of a 2-year-old Malaysian boy with VACTERL-H and his unaffected parents. The exome data were analysed using Torrent Suite version 5.0.4 and annotated using ANNOVAR. Polymorphisms with allele frequency > 0.01 were excluded (1000 Genomes Project, 6500 NHLBI exomes, maximum population frequency) and the remaining variants were filtered based on de novo mutations and autosomal recessive, X-linked and digenic inheritance traits. We did not detect any homozygous, compound heterozygous or X-linked mutations associated with VACTERL-H. However, we found that the patient harboured heterozygous mutations in BRCA2 (c.C7052G:p.A2351G) and FANCA (c.C397T:p.H133Y), which were inherited from his father and mother, respectively, suggesting digenic inheritance in this VACTERL-H patient. The candidate mutations were confirmed by Sanger sequencing. We have discovered the possibility that VACTERL-H is heritable through a digenic inheritance and that combined heterozygous mutations of FANCA and BRCA2 might be the cause of VACTERL-H in our patient. As FANCA and BRCA2 are linked to Fanconi anaemia (FA), clinical follow-up of the patient is crucial for determining the risk for FA and for managing the patient in future.