From Heterotaxy to VACTERL-H syndrome - The clinical variability of ZIC3-related disorders

S. Keating[3], H. Y. B. Chung[1,2], L. Shaffer[4], D. Chitayat[1,2] 1) Department of Pediatrics, Division of Clinical and Metabolic Genetics, Hospital for Sick Children,Toronto, Ontario, Canada; 2) The Prenatal Diagnosis and Medical Genetics Program, Mount Sinai Hospital, Toronto, Ontario, Canada; 3) Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; 4) Signature Genomic Laboratories, Spokane, Washington, USA.

BACKGROUND: The ZIC3 gene functions as a transcription factor in early stages of left-right body axis formation. Mutations in ZIC3 gene cause a variety of clinical manifestations including isolated congenital heart disease (CHD), heterotaxy & other midline CNS, urogenital & hindgut malformations. We report a four generation family with X-linked heterotaxy associated with a deletion of the ZIC3 gene at Xq26.3. METHODS AND RESULTS: The proband was a 31y G2P1 woman of Italian descent and her husband was 33y and of the same descent. The couple was healthy, non-consanguineous and had a 3y daughter with a small VSD. The family history revealed a 4 generation pedigree consistent with X-linked pattern of multiple congenital anomalies. The maternal grandmother had a brother and two sons who were born with imperforate anus, developed cyanosis and died shortly after birth. Autopsy on an affected maternal uncle showed normal situs, hydrocephalus, vertebral abnormalities and anal atresia, which was compatible with VACTERL-H. His karyotype was 46, XY. The couple was seen during their 2nd pregnancy. Fetal ultrasound at 19w showed a male fetus and the stomach was not well visualized. A subsequent ultrasound at 23w revealed abnormal cardiac anatomy, bilateral enlarged kidneys, right-sided stomach, and polyhydramnios. Fetal echocardiography showed DORV, left atrial isomerism, interrupted IVC, unbalanced AVSD, and hypoplastic left ventricle. The pregnancy was terminated at 23.5w and the autopsy showed in addition imperforate anus. The karyotype was 46,XY. Oligoarray (SignatureChipOS) detected a 1.4Mb deletion in Xq26.3 including the ZIC3 gene. FISH analysis revealed that the proband, her daughter, sister, mother and grandmother were all carriers of this deletion. Echocardiography done on them showed no cardiac abnormalities and abdominal ultrasounds were normal. CONCLUSION: VACTERL-H is a genetically heterogeneous condition and some of the X-linked cases were found to be caused by a mutation in the FANCB gene associated with Fanconi anemia B. However, early reports pointed out there is higher incidence of rotational CHD, lung lobation defects and spleen anomalies in patients with VACTERL-H when compared to VACTERL, suggesting a potential linkage between VACTERL-H and the left-right patterning defects in embryogenesis. Our report support the suggestion that some of the cases with VACTERL-H syndrome may be caused by a mutation in the ZIC3 gene.