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Situs inversus totalis in a fetus with a deletion at 7q36.2 detected on microarray analysis.

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Laterality disorders are a heterogeneous group of disorders associated with maternal diseases (maternal IDDM), maternal exposures to teratogens (retinoic acid), chromosome abnormalities and single gene disorders (ZIC3 mutation). We report on a fetus with a submicroscopic deletion at 7q36.2 with right atrial isomerism (RAI). CASE: The mother was a 30y G4P1SA2L1 and the father was 35y. Both were healthy and non-consanguineous and their family history was non-contributory. They had a healthy son and daughter and had two miscarriages. MSS was negative. Detailed fetal U/S and echocardiography at 20w showed: RAI with levocardia, L-sided liver and R-sided stomach with common atrium, unbalanced AVSD, hypoplastic LV, DORV, unobstructed aorta arising anteriorly from RV, hypoplastic pulmonic valve and branched pulmonary arteries. The pulmonary veins drained into a confluence and entered the back of the common atrium slightly L- sided. The couple decided to terminate the pregnancy. The autopsy confirmed the ultrasound findings and in addition, detected trilobed L lung, asplenia and bilateral eparterial bronchi. The fetal karyotype & FISH for 22q11.2 were normal. Microarray analysis (SignatureGenomic ®) showed deletion at 7q36.2. FISH analysis showed that the father is mosaic for this deletion. CONCLUSION: Genome-wide, array-based CNV confirms the presence of the deletion, shared by affected fetus and his father. Overlapping deletions described in the Decipher database do not show the same phenotype. Based on the deleted interval in the affected fetus, all isoforms of the DPP6 gene are predicted to be haploinsufficient. Looking at the other de novo and shared CNVs, we could not identify other candidate gene directly involved in left right axis patterning. However, a de novo deletion of the KCNC3 gene was detected. Interestingly, DPP6 interacts with the potassium channels of the KV- type. Although these channels have not been described to play a role in LR patterning, several other potassium channels do play a role in LR asymmetry in model organisms. These studies propose a mechanism in which a change in potassium current at the cell membrane leading to a change in the movement of the cilia which are crucial for proper left right axis formation. Thus, the deletion of KCNC3 and DPP6 may act in an epistatic fashion, consistent with a two-hit model affecting potassium channel assembly and, subsequently, cilia movement and LR patterning.