Novel presentation of dextrocardia in TGIF1-related holoprosencephaly

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BACKGROUND

Holoprosencephaly (HPE) is a structural anomaly of the brain that arises from either failed or incomplete forebrain division during the third to fourth week of gestation. There are several types, with alobar HPE being the most severe as there is a monoventricle and no interhemispheric fissure. Single-gene causes of HPE have been linked to TGF β/Nodal signaling, which establishes the **left-right patterning in early embryogenesis**. Haploinsufficiency of one such gene, ***TGIF1*** (Transforming Growth Factor-Beta-Induced Factor), a co-repressor that limits transcriptional response to TGFβ signaling, leads to dominant **holoprosencephaly-4** (OMIM: 142946). Laterality defects, however, have not been associated thus far with *TGIF1* loss of function.

Here, we present a case of severe alobar holoprosencephaly in the presence of a laterality defect, mirror-image dextrocardia, in which a heterozygous pathogenic frameshift variant in *TGIF1* was identified.

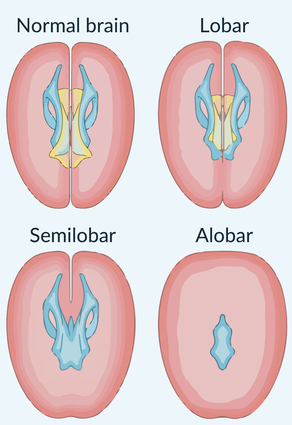
CASE PRESENTATION

The male proband, born to a G2P2 mother, presented on fetal ultrasound (US) with **holoprosencephaly** and dextrocardia. Post-delivery, the patient developed seizures and upon head US was found to have alobar holoprosencephaly. Cardiac imaging revealed mirror-image dextrocardia, small muscular ventricular septal defects, and an interrupted inferior vena cava.

Historically, ***TGIF1*** has been associated with isolated HPE without dextrocardia, or other laterality defects. In this case, our patient presents with ***both***.

What is the genetic basis of HPE?

HOLOPROSENCEPHALY (HPE)[1]



4 genes, *SHH, ZIC2, SIX3, and TGIF1* account for 25% of HPE, Mercier et al.

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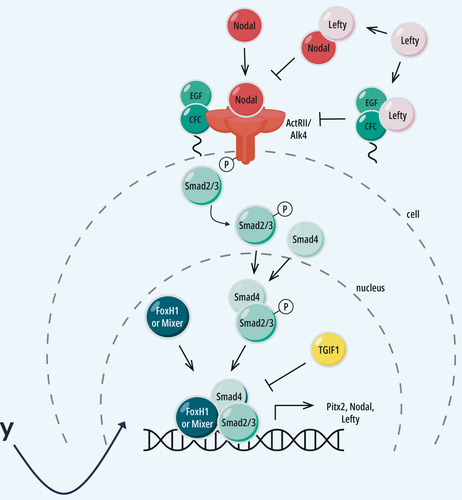
One of these genes, *TGIF1*, encodes Transforming Growth Factor-Beta-Induced Factor, a regulator of **nodal signaling, which establishes laterality during embryogenesis.**

NODAL SIGNALING[2]



Defects in **Nodal signaling genes** have been associated with **holoprosencephaly and dextrocardia**, including ***NODAL***, ***CFC1***, and ***GDF1***. Other genes have been implicated in each finding separately including *SHH*, *ZIC2*, *SIX3*, and *TGIF1* which are associated with isolated HPE. These HPE genes are key regulators of highly conserved signaling pathways including Notch, Nodal, Hedgehog, Wnt, and transforming growth factor-beta 1 (TGFβ-1), which are involved in forming the left-right axis.

What phenotypes are associated with altered Nodal signaling in mammals?

Component	Species	Cardiovascular phenotype	Other phenotypes	PMID
NODAL	Human	Dextrocardia, d-TGA, DORV, VSD, ASD, l-TGA, DILV, PA, TOF	Asplenia, bilateral trilobed lungs, hydronephrosis, HPE, intestinal malrotation	19064609, 19553149
	Mouse	l-TGA, VSD	Heterotaxy, asplenia, isomerisms, HPE, cyclopia, disrupted endoderm and mesoderm specification, defective A-P axis	7924997, 11418863, 18773491, 11311163
CRYPTIC	Human	Dextrocardia, TGA, d-TGA, PA, VSD, ASD, TOF, DORV	Heterotaxy, isomerisms, polysplenia, asplenia	11062482, 18538293, 11799476
	Mouse	l-TGA, ASD	Heterotaxy, r-isomerism of the lung, hyposplenia	10574770
CRIPTO	Human	TOF, VSD, ASD	HPE	18538293, 12073012, 19853938
	Mouse	None	HPE, disrupted mesoderm specification, defective A-P axis	9790191, 16291788
SMAD2	Human	Dextrocardia, d-TGA, DORV, ASD	Heterotaxy, asplenia, HPE	18538293, 23665959
TGF-βR2	Mouse	TGA, DORV, dextrocardia, levocardia, VSD, ASD, arch artery defects	R-isomerism of the lung, axial skeleton abnormalities	9242489
FOXH1	Human	VSD, TGA, TOF	HPE	18538293, 19525021
	Mouse	None	Defective elongation of the primitive streak, defective A-P axis	11358868

d-TGA = Dextro-Transposition of the Great Arteries, DORV = Double Outlet Right Ventricle, VSD = Ventricular Septal Defect, ASD = Atrial Septal Defect, l-TGA = Levo-Transposition of the Great Arteries, DILV = Double Inlet Left Ventricle, PA = Pulmonary Atresia, TOF = Tetralogy of Fallot

DYSMORPHIC FEATURES were found to include microcephaly, orofacial cleft, hypotelorism, shallow orbits, upslanting palpebral fissures, depressed nasal bridge, wide nasal base, and near arrhinia with singular naris, high-riding testes and microphallus.

CHROMOSOMAL MICROARRAY AND ANEUPLOIDY FISH were used to rule out chromosomal aneuploidies and copy-number variations, which are causative in 25-50% of HPE cases. CMA and FISH were non-diagnostic.

PROBAND WHOLE-EXOME SEQUENCING ANALYSIS on a blood sample revealed a heterozygous frameshift variant in the *TGIF1* gene, **NM_003244.3:c.257del, p.(F86Sfs*13)**, which has been previously reported in a case of isolated alobar HPE inherited from an unaffected mother.

CONCLUSIONS

Here, we present a proband with laterality defects in addition to HPE, who was found to have a pathogenic *TGIF1* frameshift variant. Historically, *TGIF1* has been associated with isolated HPE without dextrocardia or other laterality defects. This is an important finding to **expand the phenotypic spectrum of TGIF-related holoprosencephaly-4** and to provide evidence for the potential impact of ***TGIF1* loss of function on TGFβ/Nodal signaling**.

References

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