DAND5: A newly-recognized cause of autosomal recessive laterality disorders

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בית החולים לילדים
אדמונד ולילי ספרא

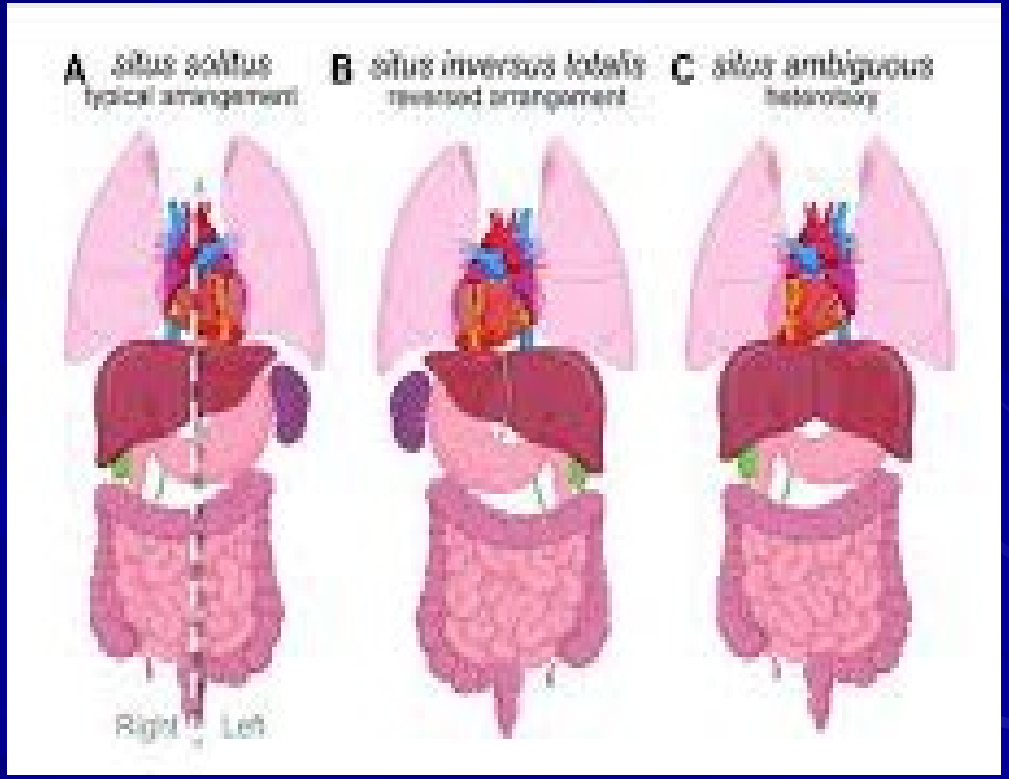
שיבא
תל השומר

Laterality Disorders- Background:

- Congenital heart disease-

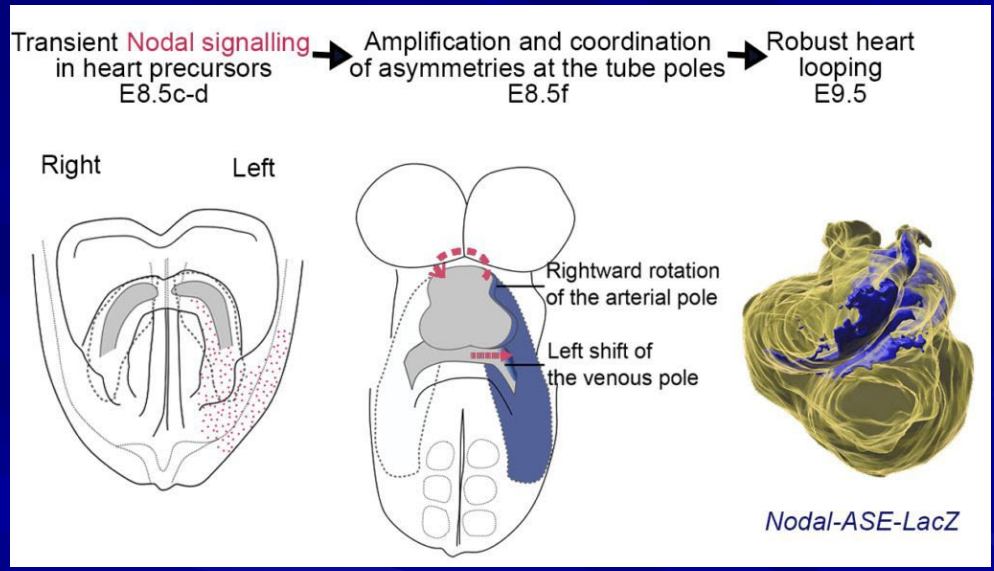
most common congenital malformation, ~ 1% of births

- Laterality disorders- ~ 1% of total CHD cases
- Isolated/ multisystemic manifestations
- More than 25 genes have been implicated in all modes of inheritance.



Laterality Disorders- Pathogenesis:

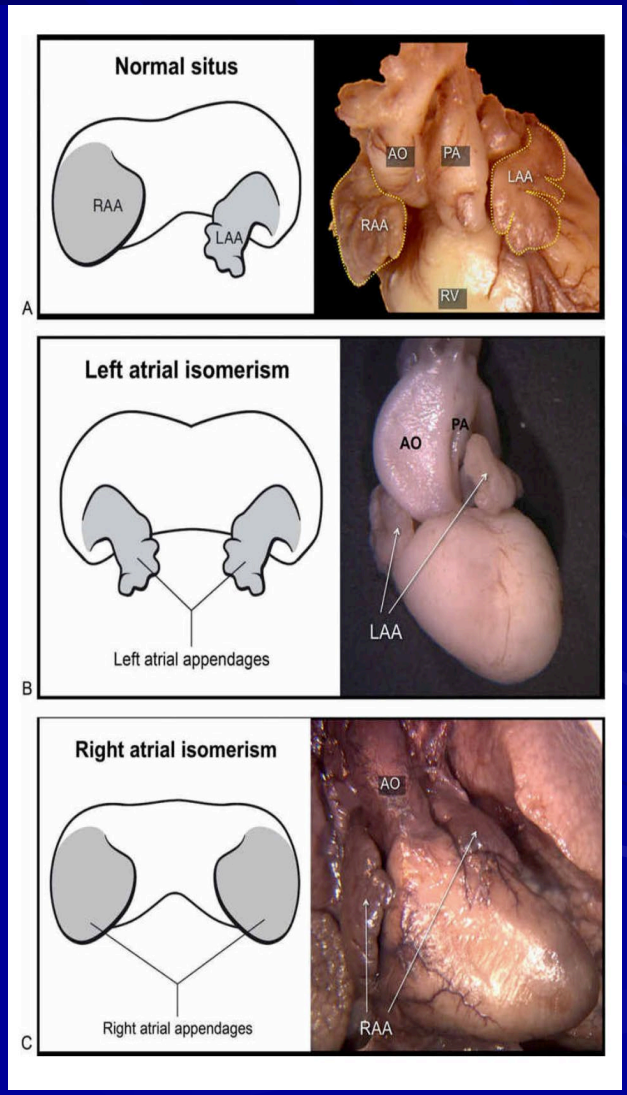
- First asymmetry in morphogenesis occurs with rightward heart looping (embryonic days 22-23)
- Involves multiple signaling molecules, of the TGF-β superfamily
  - Differential activation of Nodal on the left
  - BMP signaling on the right
  - Additional cell signaling pathways: Shh, FGF, Notch



From: *Desgrange et al., 2020 – Summary of the role of Nodal signalling in heart looping.*

Laterality Disorders- Pathogenesis:

- **Situs inversus totalis-** 3–9% accompanied by CHD
- **Situs Ambiguous- Heterotaxy**
  - **Right atrial isomerism**
    - Two morphologic Rt atria often w' single ventricle, AVSD, TGA and APVD
    - Rt bronchial isomerism and asplenia
  - **Left atrial isomerism**
    - Two morphologic Lt atria often w' ASD or AVSD.
    - Absence of SA/AV node-> risk for CAVB
    - Lt bronchial isomerism and polysplenia
  - > 20% of cases, variable rearrangements



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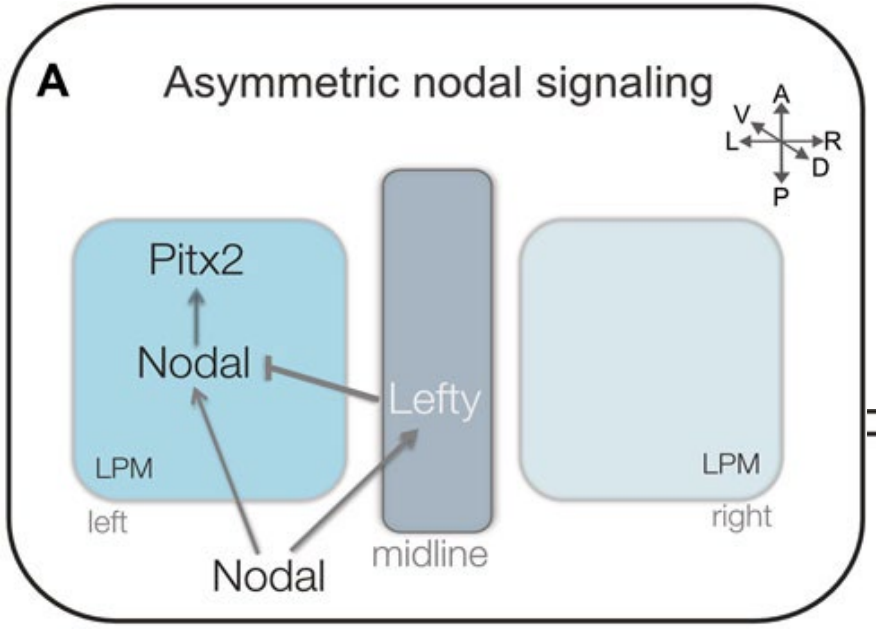
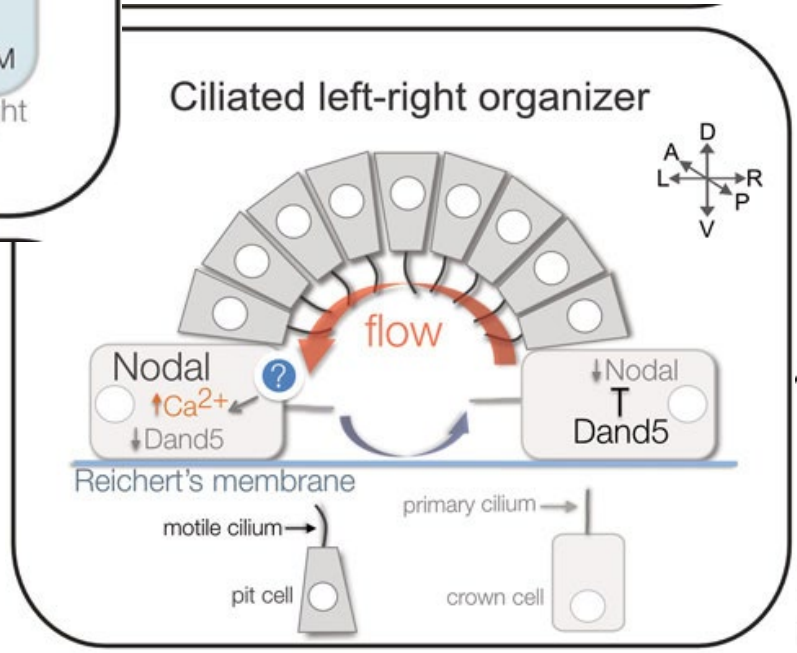
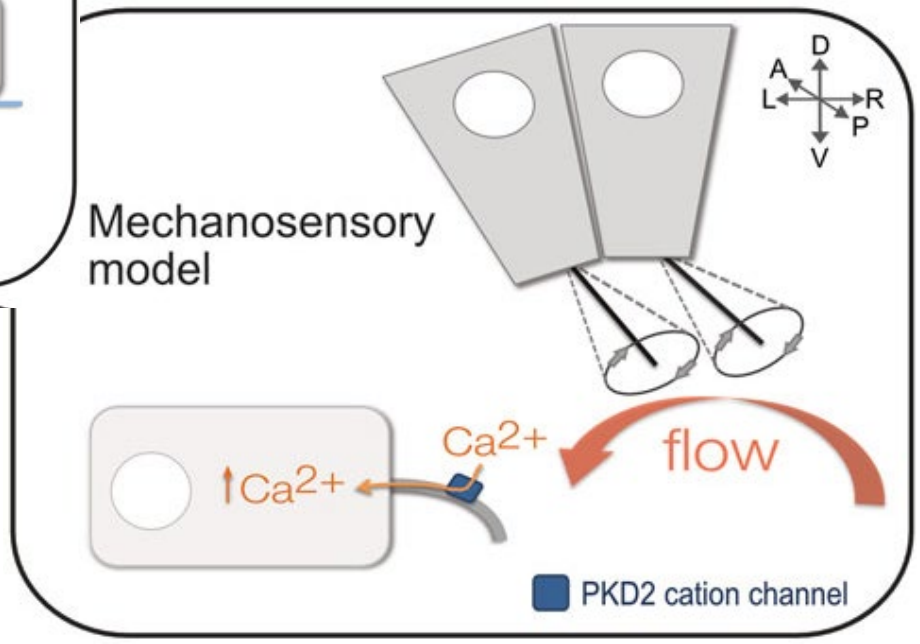
Understanding laterality disorders and the left-right organizer: Insights from zebrafish





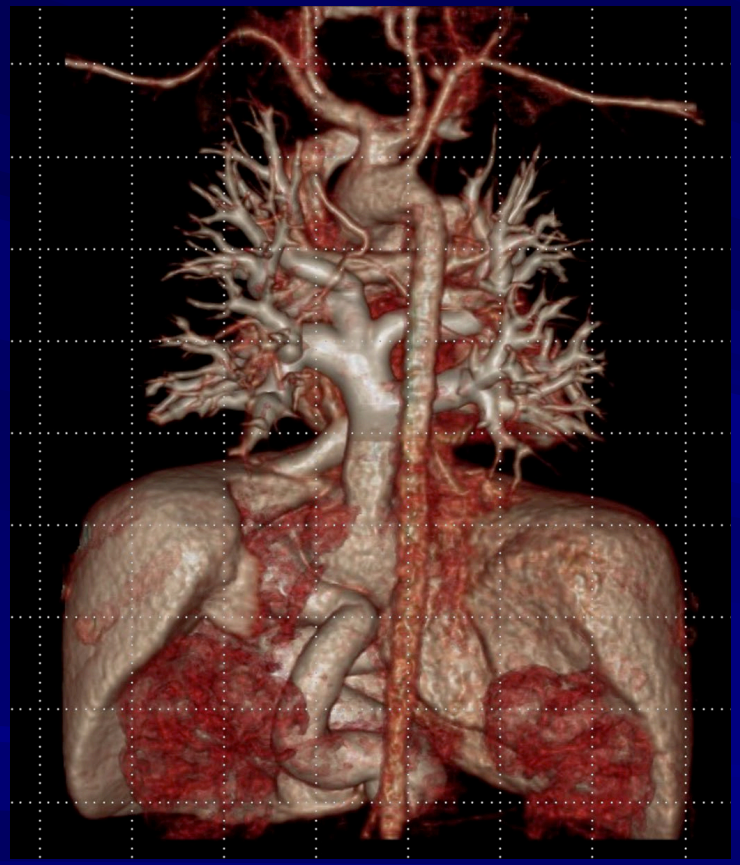


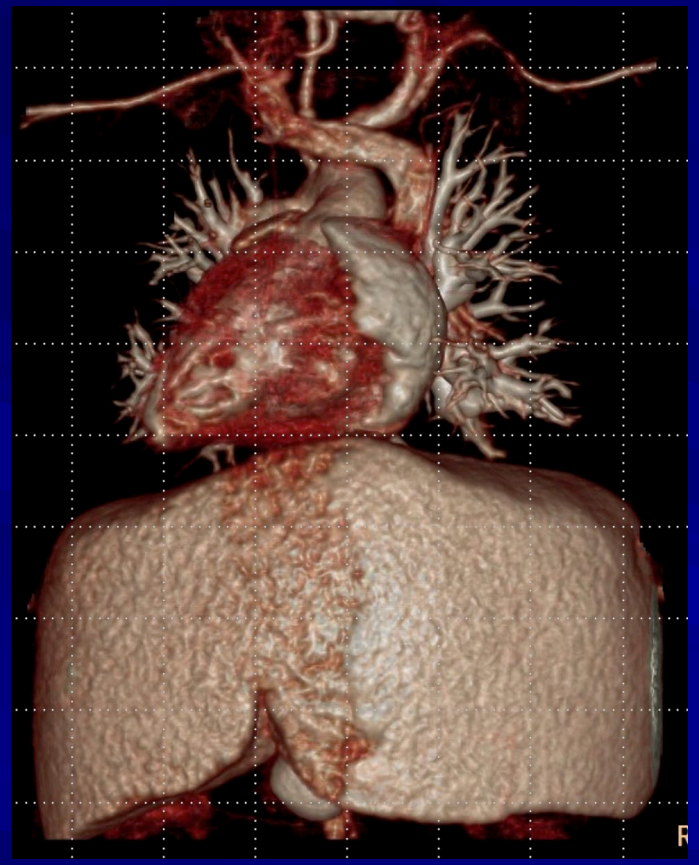
From:

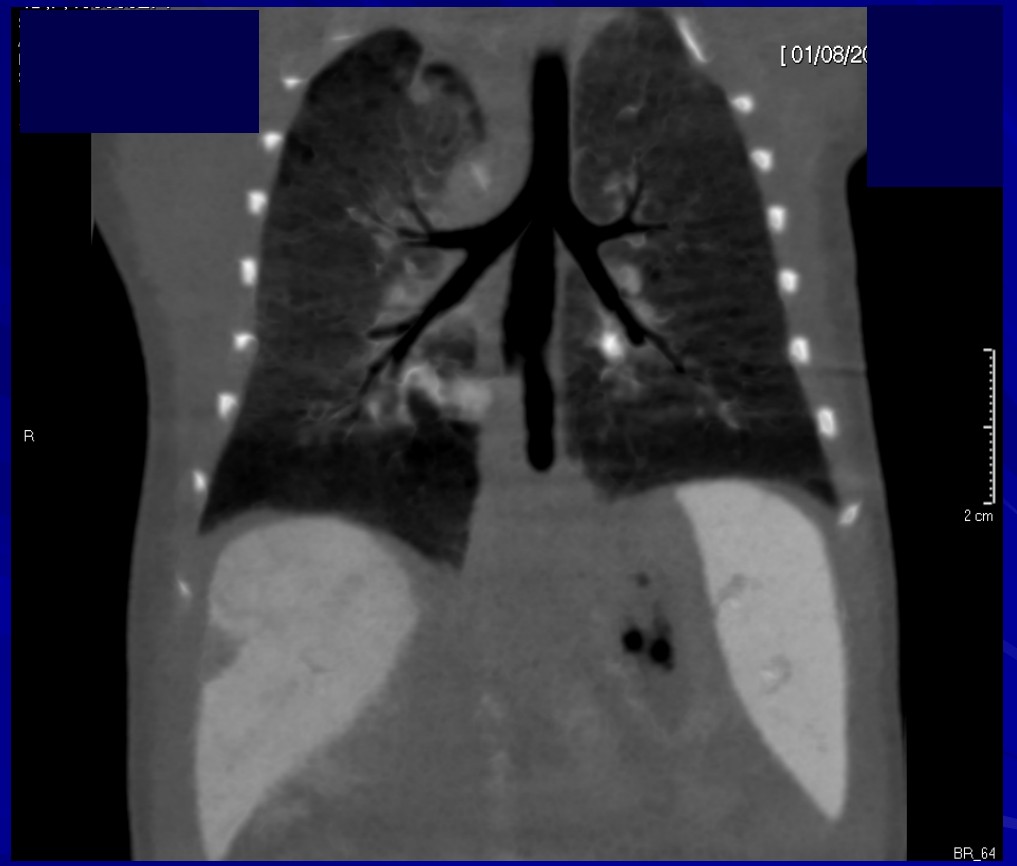
Forrest K, Barricella AC, Pohar SA, Hinman AM, Amack JD. Understanding laterality disorders and the left-right organizer: Insights from zebrafish. Front Cell Dev Biol. 2022 Dec. PMID: 36619867

Case Presentation -Patient 1:

- A 2 day old female referred to our hospital due to dextrocardia with a complex CHD
- Prenatal history uneventful
- Born term, AGA, cyanosis surrounding feeds
- Upon arrival: saturation 50% RA, tachycardia 180 and tachypnea 100, treated with Prostin
- Echo: situs inversus, unbalanced AV canal, infradiaphragmatic TAPVR, PA, asplenia
- Underwent atrial septectomy, SANO conduit, TAPVR repair



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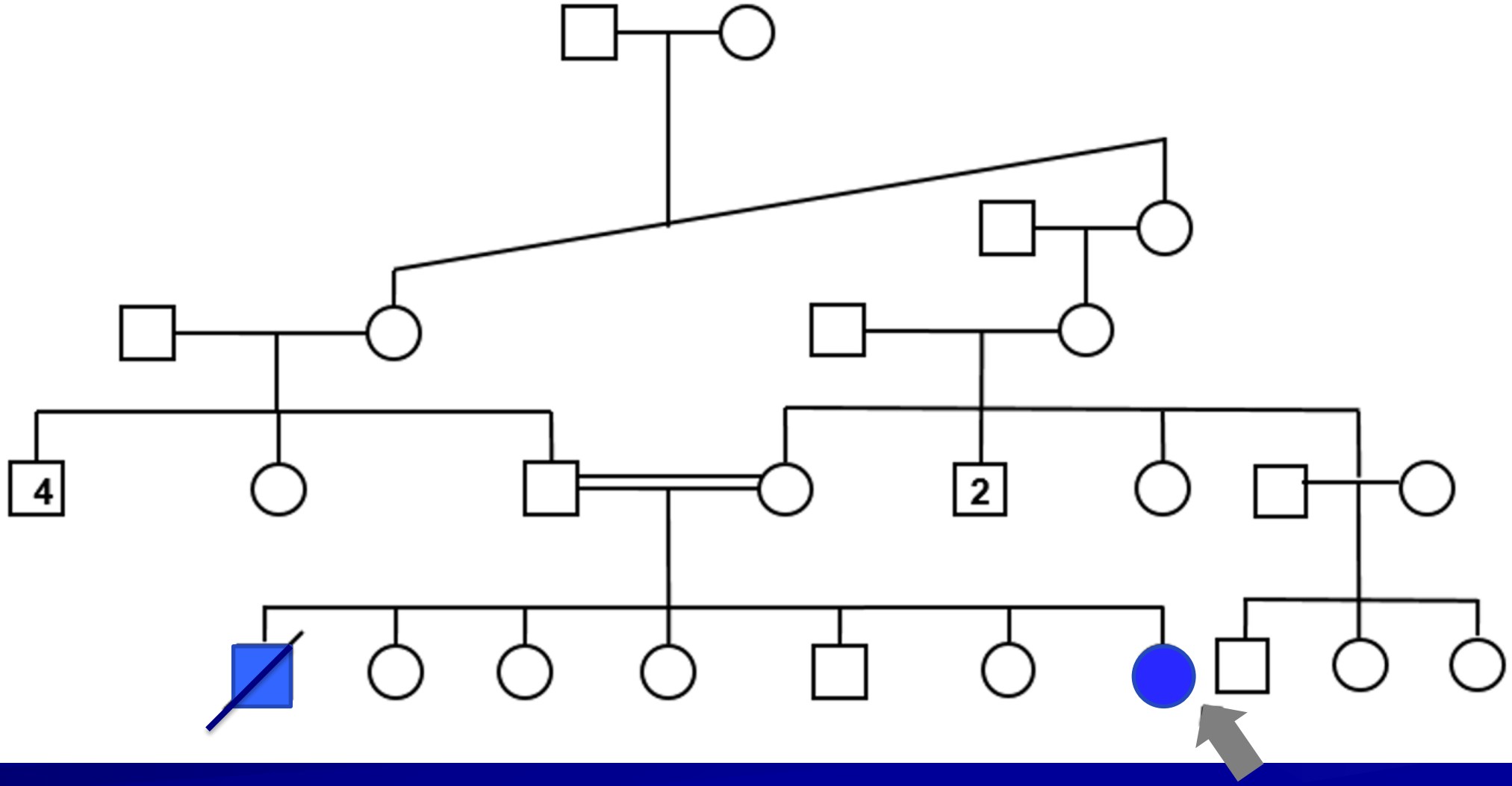
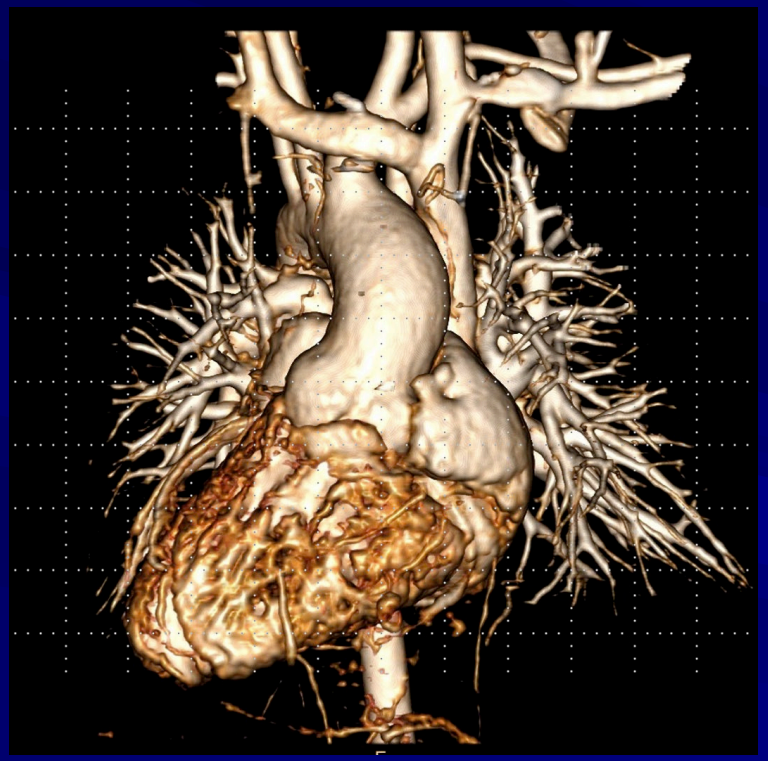
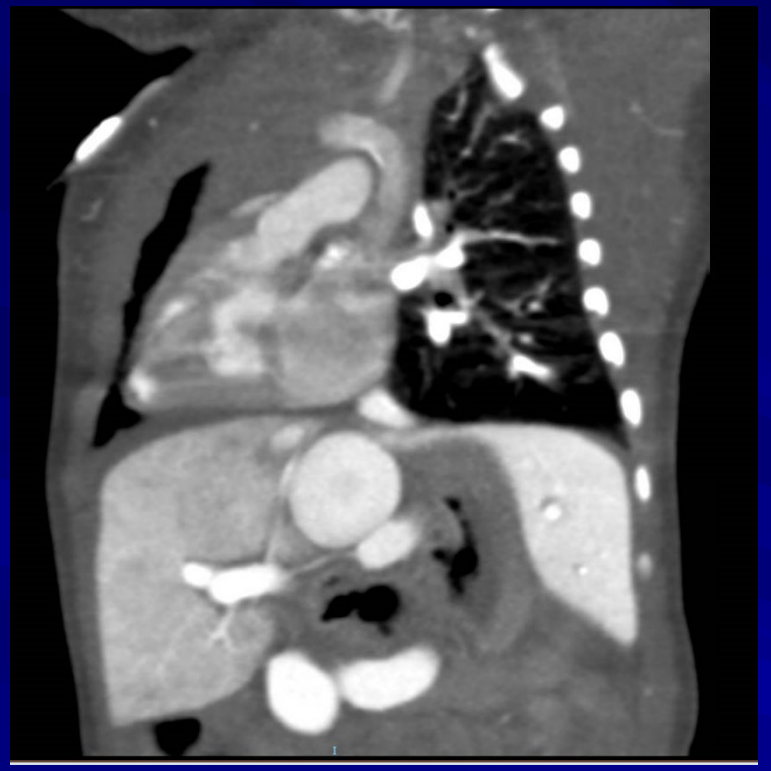
Family 1 Pedigree:

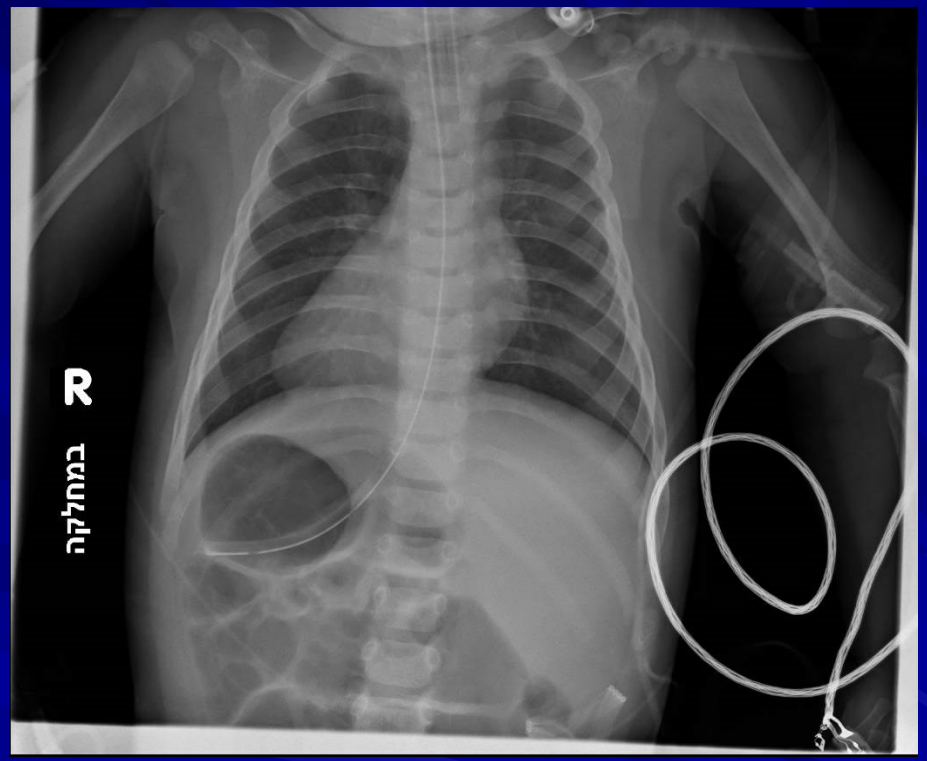


Case Presentation -Patient 2:

- A 4 months old male referred d/t dextrocardia with complex CHD
- Prenatal history uneventful
- Born term, AGA, readmitted at 5 days due to cyanosis
- Echo (Gaza)- Dextrocardia, hypoplastic LT ventricle, PA, VSD treated with Deralin
- Upon arrival: saturation 40% RA, ventilated
- Echo/ CTA- dextrocardia, atrial situs inversus, TOF, PA, non confluent pul. arteries, MAPCAS,abdominal situs inversus
- Underwent BT shunt & unifocalization of MAPCAS



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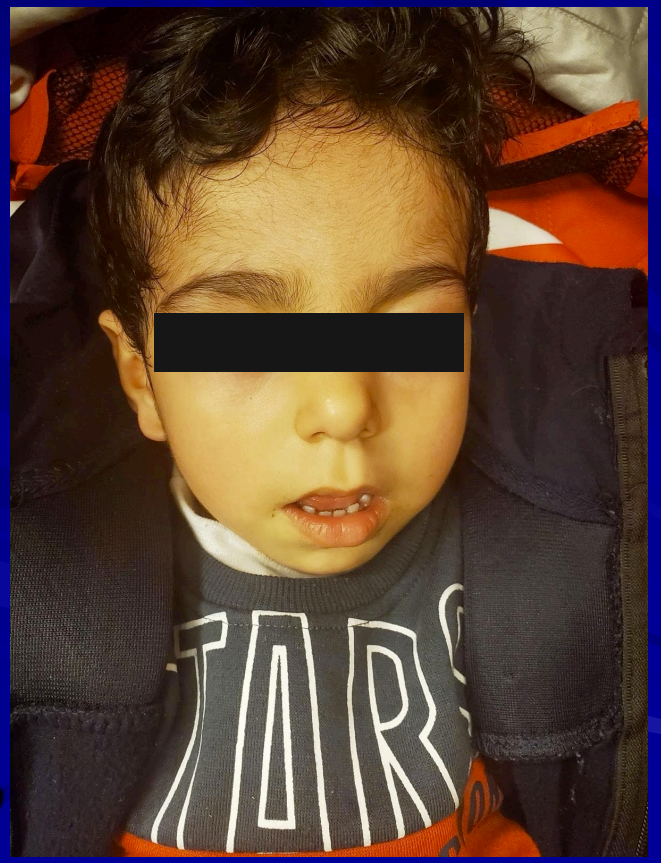
Case Presentation -Patient 2, cont'd:

- Follow up reveals global developmental delay and failiure to gain weight
- Physical examination:
  - Microcephaly, -3SD
  - Weight, - 2.5 SD
  - Height- + 1.SD
- Dysmorphic facial features synophrys, long phyltrum, thin upper lip, retrognathia, high arched palate



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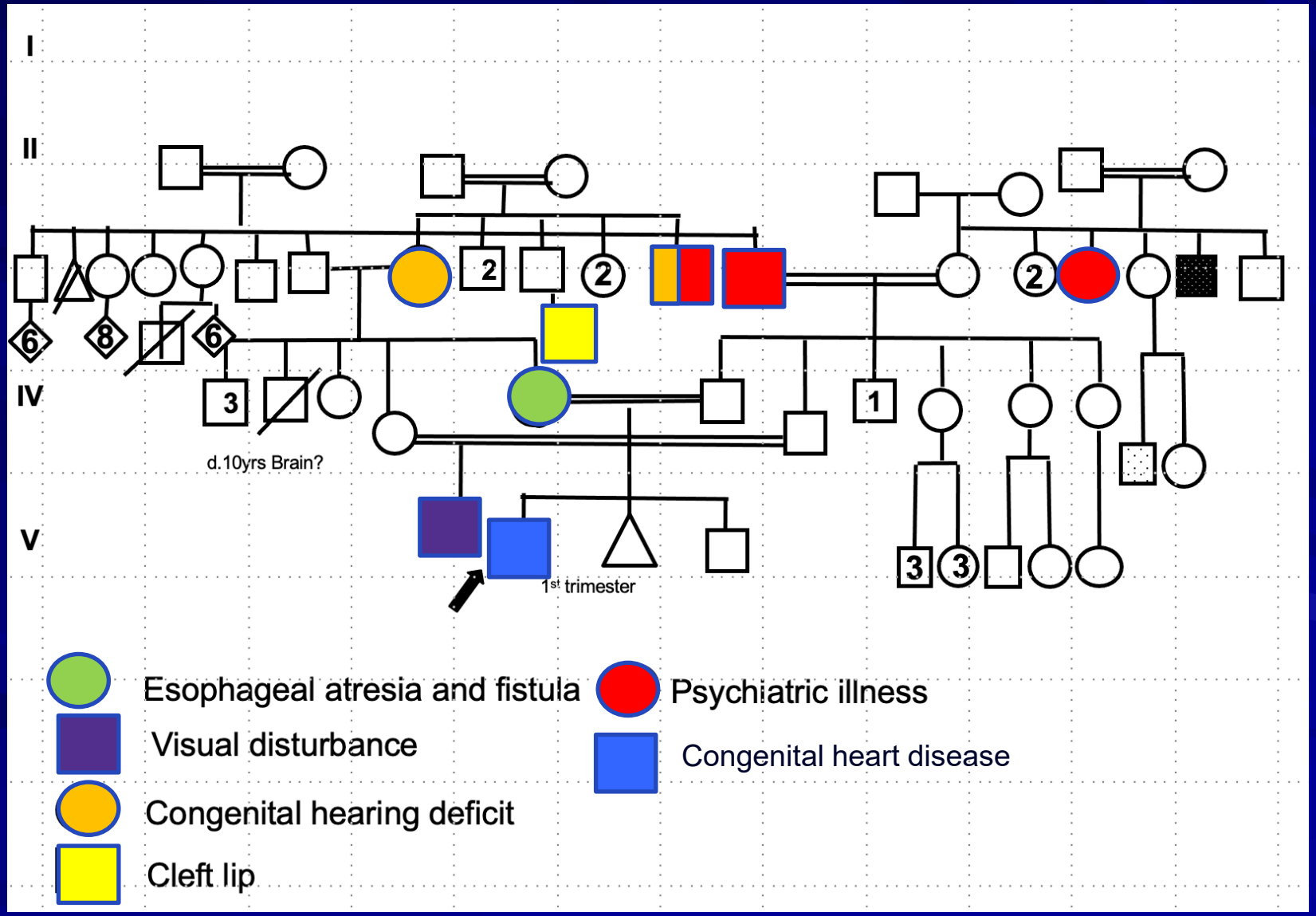



DIAGNOSIS

Exome sequencing:

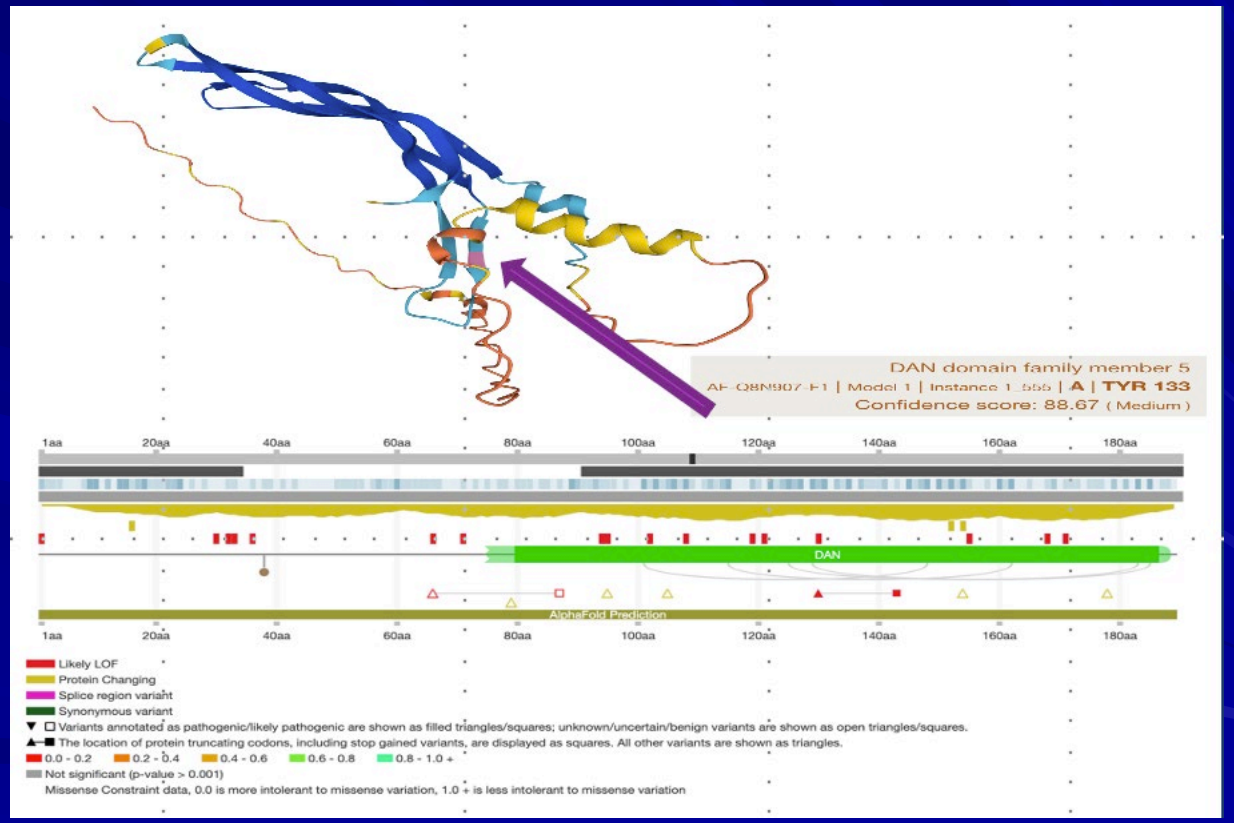
- Homozygous *DAND5* variant shared by both patients:

NM_152654.2: c.396_397dup, p.Tyr133SerfsTer11 exon 2/2

- Predicted to cause early termination of translation of RNA to protein, leading to a truncated protein predicted to undergo nonsense mediated decay

DAND5- DAN DOMAIN FAMILY, MEMBER 5

- Encodes for a member of the Cerberus-related DAN protein family
- Involved in regulating organogenesis, body patterning, and tissue differentiation.
- In mouse, this protein has been shown to bind Nodal and to inhibit the Nodal signaling pathway which patterns left/right body asymmetry.



Cristo *et al. BMC Medical Genetics* (2017) 18:77
DOI 10.1186/s12881-017-0444-1

RESEARCH ARTICLE

Functional stu
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Fernando Cristo[1,2,3,4], José M. Iná
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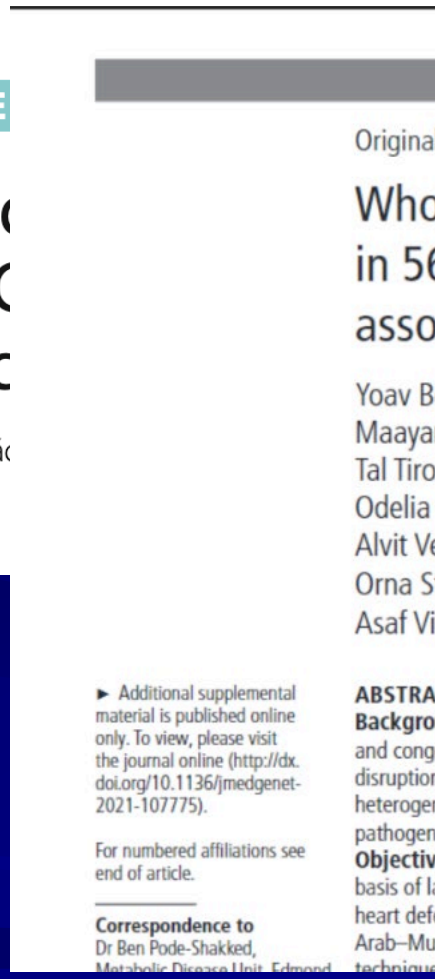
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COLD SPRING HARBOR
Molecular Case Studies

RAPID COMMUNICATION

A novel biallelic loss-of-function variant in *DAND5* causes heterotaxy syndrome

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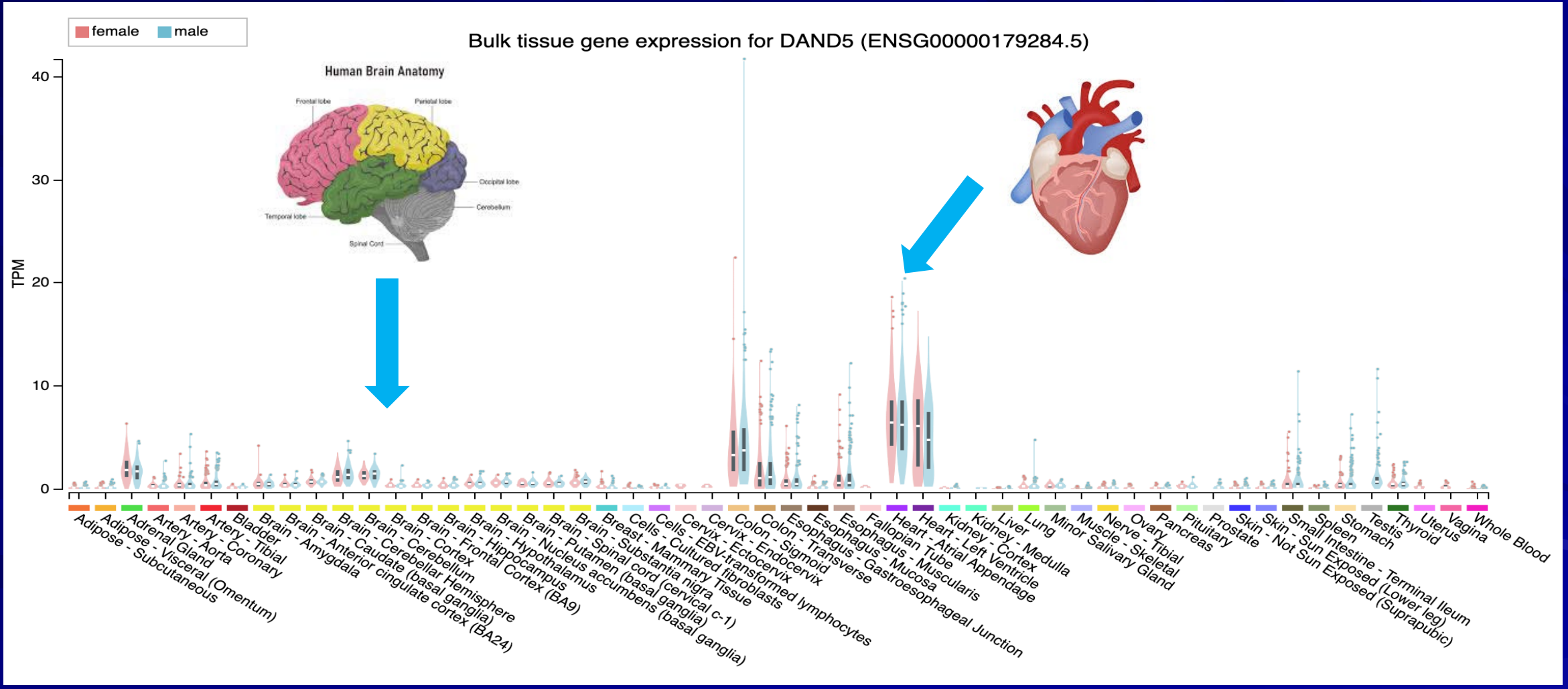
Abstract The majority of heterotaxy cases do not obtain a molecular diagnosis, although pathogenic variants in more than 50 genes are known to cause heterotaxy. A heterozygous missense variant in *DAND5*, a nodal inhibitor, which functions in early development for establishment of right–left patterning, has been implicated in heterotaxy. Recently, the first case was reported of a *DAND5* biallelic loss-of-function (LoF) variant in an individual with heterotaxy. Here, we describe a second unrelated individual with heterotaxy syndrome and a homozygous frameshift variant in *DAND5* (NM_152654.2:c.197del [p.Leu66ArgfsTer22]). Using an in vitro assay, we demonstrate that the *DAND5* c.197del variant is unable to inhibit nodal signaling when compared with the wild-type expression construct. This work strengthens the genetic and functional evidence for biallelic LoF variants in *DAND5* causing an autosomal recessive heterotaxy syndrome.

Bulk Tissue Gene Expression for DAND5



Conclusions:

- DAND5 has been suggested as a candidate gene in heterotaxia and CHD in the heterozygous state (
- Our findings confirm the association of *DAND5* variants and laterality-related CHD in biallelic state among two families.
- Our report, along with a previous report of associated GDD in an affected male may suggest a role of the gene in neuro-developmental processes.
- Further studies are required to decipher the full spectrum of *DAND5* disorders.

ד"ר יואב בולקיאר

ד"ר בן פודה-שקד

- קרדיולוגיה ילדים דר׳ כץ ודר׳ תירוש והצוות
- מעבדה ביואינפורמטית - דר׳ בראל וצוותה
- מחלקת ילדים ב׳- פרופ׳ ויונטה והצוות
- מעבדה מטבולית- פרופ׳ אניקסטר ודר׳ שלווה והצוות
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- המכון למחלות נדירות- פרופ׳ אניק רוטשילד, שלי לב הוכברג, בר גולדברג והצוות

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