Familial atrial septal defect: a unique family with Holt-Oram syndrome

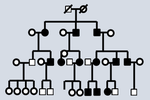
Background

- ASD can occur in families, though rarely
- The genes *GATA4, NKX2.5, TBX5* are associated with monogenic familial ASD
- Congenital heart disease (CHD) is a heterogenic disease and CHD genes have overlapping phenotypes
- Most commonly familial ASD is an autosomal dominant inherited disease
- ASD can occur in syndromic disorders

Aim

- To map the phenotype of a family with ASD
- To identify the disease causing variant in this family

Methods



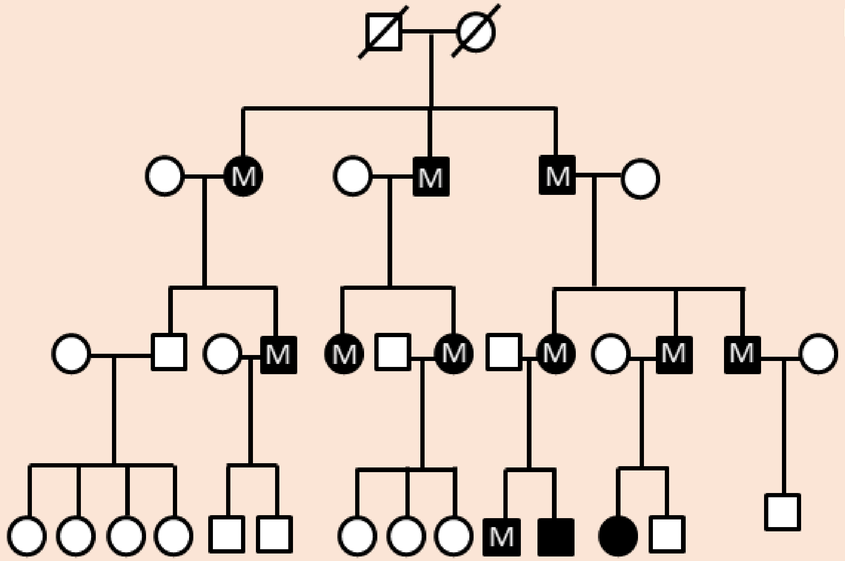
We identified a unique family with ASD
We investigated with Holter monitoring, x-ray of upper extremities, and clinical examination.

Collected blood samples and performed exomesequencing

Filtering for very rare gene variants, classification of variant using ACMG guidelines

Results

Pedigree



Genotype

- Novel missense variant in TBX5
- p.Phe232Leu
- Autosomal dominant pattern

Phenotype

- ASD/VSD
- Bradycardia
- Pacemaker need
- Atrial fibrillation or flutter
- Small hands
- Abnormal scaphoid bone on x-ray

Holt-Oram syndrome

- Abnormalities of upper limbs
- Congenital heart defect
- Arrhythmias
- TBX5 variants

Conclusion

- Evaluation of family history of congenital heart disease is important to discover syndromes with a genetic cause
- Holt-Oram Syndrome may be underdiagnosed in familial ASD because of subtle malformations of upper limbs

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