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Biallelic deletions of the Waardenburg II syndrome gene, *SOX10*, cause a recognizable arthrogryposis syndrome

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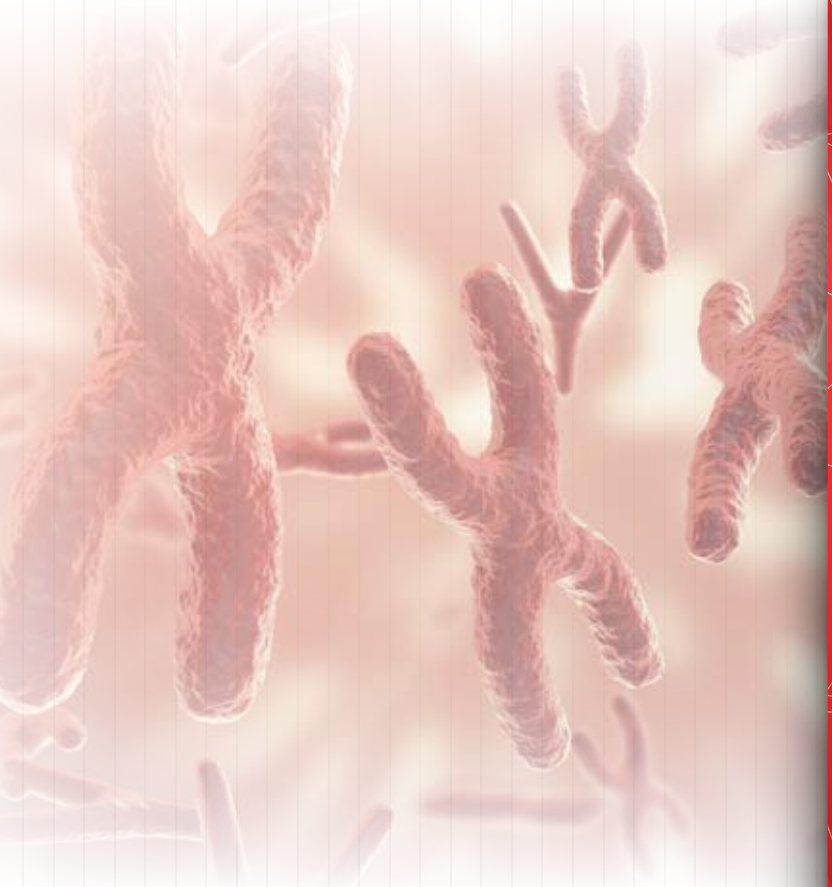

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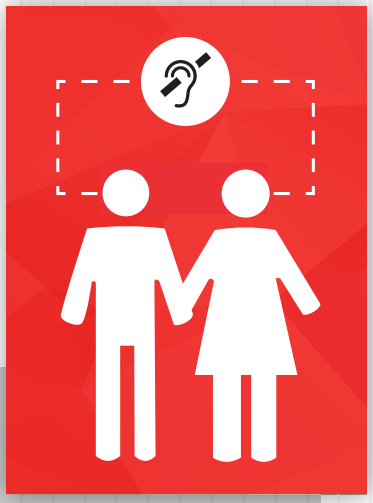
Assortative mating



For cultural reasons, some hereditary disorders such as deafness or short stature, lead affected individuals to interact with other affected individuals.

Waardenburg syndromes are dominant among autosomal disorders causing hearing loss

This leads to the occurrence of biallelic variants in genes that cause Waardenburg syndromes when two affected individuals mate

Waardenburg genes

Waardenburg I syndrome

Associated with homozygous and compound heterozygous variants of ***PAX3***

Biallelic variants cause:

- **Musculoskeletal anomalies**
- **Hypopigmentation**
- **Hearing loss**
- **Dystopia canthorum**

Waardenburg II and IV syndromes

Associated with biallelic deletions in ***SOX10***

Waardenburg II syndrome

Associated with compound heterozygous variants in ***MITF***

Symptoms reported in two unrelated children include:

- **Colobomatous microphthalmia**
- **Macroencephaly**
- **Deafness**
- **Osteopetrosis**
- **Hypopigmentation**

Case Report

Researchers described biallelic deletions in SOX10 in a stillborn fetus whose parents both have Waardenburg syndrome

Mother

- African American
- 24 years old
- Waardenburg II syndrome

Father

- African American
- 21 years old
- Waardenburg symptoms and family history of Waardenburg syndrome

Fetus

Stillborn at 32 weeks

- White hair
- Dystopia canthorum
- Cleft palate
- Four-limb pterygia
- Absence of palmar and plantar creases

Previous pregnancies from same parents

Male infant born with iris heterochromia, deafness and ADHD

Female fetus stillborn at 31 weeks with Waardenburg symptoms including white hair, broad nasal root, small low set ears, micrognathia and muscle hypoplasia

Genetic sequencing

Whole exome sequencing showed no variants in **PAX3, SOX10, MITF, EDN3, EDNRB** and **SNA12**

Two deletions in **SOX10** found by genomic array and quantitative PCR

Microarray analysis performed using CytoScan XON assay (6.85m probes on platform with emphasis on exonic coverage of the RefSeq genes)

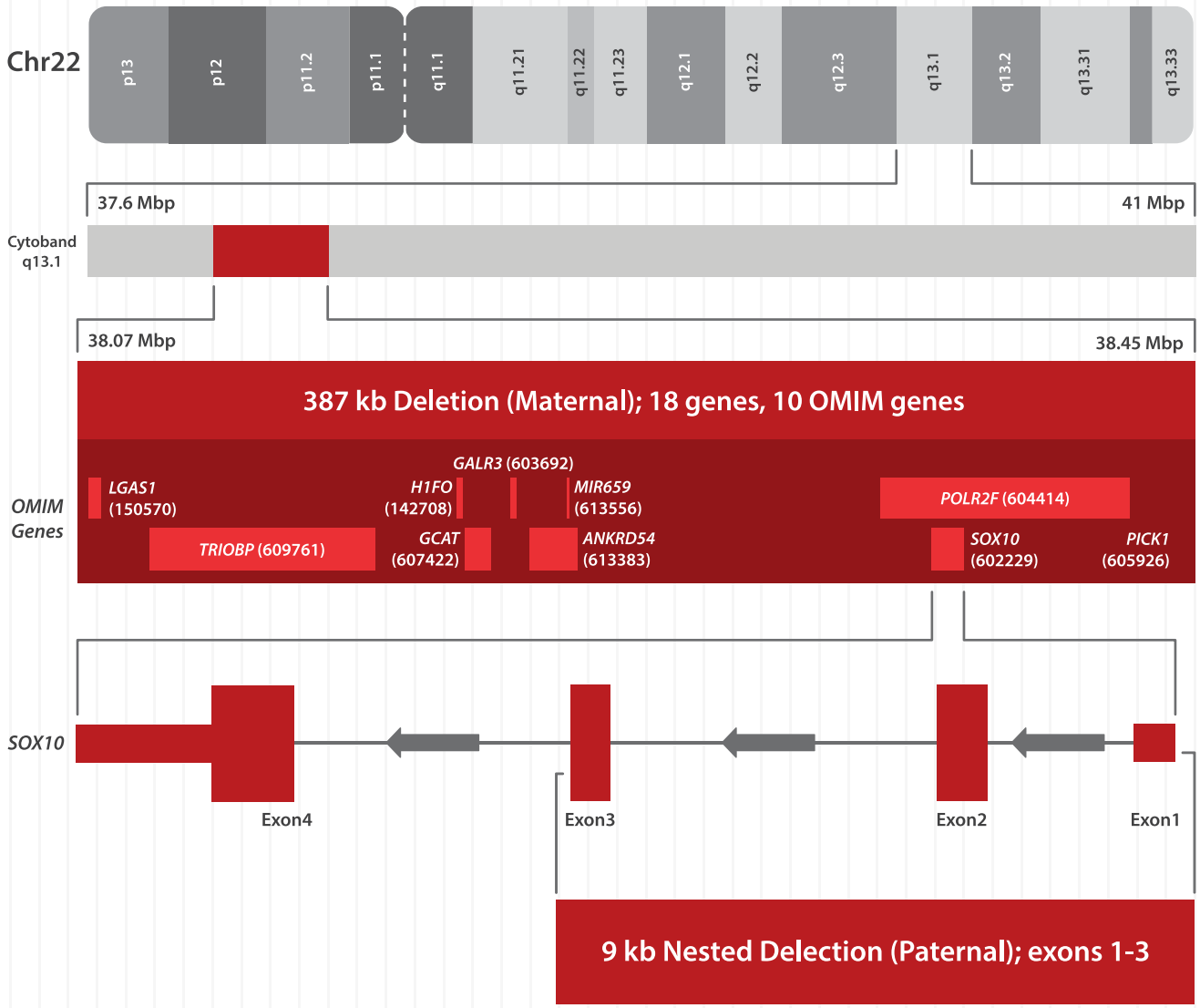


FIGURE:- Location and size of maternal deletion in 22q13.1 and nested paternal deletion within the SOX10 gene [Color figure can be viewed at wileyonlinelibrary.com]

Observations

It is not known whether biallelic deletions, nonsense or frameshift variants would cause a more severe fetal phenotype as all cases of PAX3 alterations have been missense variants.

MITF is in the same pathway as PAX3 and SOX10, but biallelic sequence variants of MITF cause a very different phenotype (macroencephaly, microphthalmia, dense bones).

The microarray test commonly used as a first-line diagnostic text does not cover all protein-coding pathogenic alterations.

Whole exome sequencing showed no variants in PAX3, SOX10,MITF, EDN3, EDNRB, and SNAI2. However, two deletions in SOX10 were found by genomic microarray and quantitative PCR (qPCR).

The novel array platform with 6.85m probes across the genome is better at identifying copy number alterations in the coding regions and 5'-untranslated regions of all genes.

Hypothesis

Researchers anticipated that biallelic sequence variants of SOX10 would result in similar pathogenic symptoms and observed that double heterozygosity for two different Waardenburg genes had not been reported

Defining reproductive risk

Researchers anticipated that biallelic sequence variants of SOX10 would result in similar pathogenic symptoms and observed that double heterozygosity for two different Waardenburg genes had not been reported

Parents may not be aware of the risk of babies with multiple and potentially lethal anomalies

Microarray analysis and sequencing of Waardenburg-associated genes may be required to identify couples at risk of complex birth defects

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