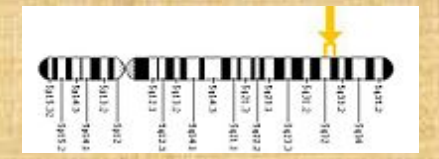
TREACHER COLLINS SYNDROME (TCS)



by Chau Vu

What is Treacher Collins syndrome?

- affects development of bones and other tissues in the face
- affects an estimated 1 in 50,000 people
- Penetrance: signs and symptoms vary greatly
- Symptoms
  - ❖ underdeveloped facial bones (cheek bones)
  - ❖ Micrognathia - a very small jaw and chin
  - ❖ cleft palate
  - ❖ underdevelopment of the facial bones may restrict an affected infant's airway →respiratory problems.
  - ❖ eyes that slant downward, sparse eyelashes, and a notch in the lower eyelids called a coloboma.
  - ❖ Additional eye abnormalities that can lead to vision loss.
  - ❖ absent, small, or unusually formed ears.
  - ❖ Defects in the middle ear cause hearing loss in about half of cases.
  - ❖ usually have normal intelligence.

What genes are related to Treacher Collins syndrome?

- Mutations in the TCOF1 gene
- 5q32-q33.1 – chromosome 5, long arm (q), between positions 32 and 33.1
- TCOF1 gene is located from base pair 149,717,427 to base pair 149,760,063 on chromosome 5.
- TCOF1 gene provides instructions for making a protein called treacle.
- precise function of this protein unknown, but researchers believe that TCOF1plays a critical role before birth in the development of bones and other tissues in the face.
- Mutations in the TCOF1 gene reduce the amount of treacle
- Loss of treachle signals cells that are important for the development of facial bones to undergo apoptosis. Abnormal cell death →specific problems with facial development.
- Treacle involved in production of ribosomal RNA (rRNA). Treacle is active in nucleolus (small region inside the nucleus where rRNA is produced). rRNA is essential for the assembly of proteins.

How do people inherit Treacher Collins syndrome?

- autosomal dominant: one copy of the altered gene in each cell is sufficient to cause the disorder
- 60 percent of cases result from new mutations in the TCOF1 gene; occur in people with no history of the disorder in their family.
- Remaining cases caused by inheritance of mutant gene from affect parent

Diagnostic Methods

- Direct sequencing of the coding and flanking intronic regions of *TCOF1*
- detects mutations in about 90%-95% of individuals

Treatment

- Tailored to the specific needs of each individual
- For newborns, tracheostomy – treat difficulties in breathing (construction of an artificial opening through the neck into the trachea)
- bone conduction amplification – treat hearing loss
- speech therapy
- Craniofacial reconstruction
- Cleft palate – repaired when individual is one to two years old

Novel diagnostics

- A novel exon in TCOF1 that, although alternatively spliced, is involved in production of treacle protein.
- Most published mutations in this gene do not conform to current mutation nomenclature guidelines. → Development of an online database of TCOF1 mutations in which all the reported mutations are renamed according to standard recommendations and in reference to the genomic and novel cDNA reference sequences (www.genoma.ib.usp.br/TCOF1_database).
- Wiley-Liss, Inc. Twenty-eight families screened for mutations in the 25 coding exons of TCOF1 and their adjacent splice junctions through SSCP and direct sequencing.
  - Mutations detected in 26 patients = highest detection rate reported so far (93%)
  - Number of known disease-causing mutations increased from 35 to 51
- Thirteen novel polymorphic alterations confirm unusually high rate of single-nucleotide polymorphisms (SNPs) within its coding region.
- identified two families with no apparent pathogenic mutation in the gene → data confirm the absence of genotype-phenotype correlation and reinforce that the apparent anticipation often observed in TCS families is due to ascertainment bias

Novel Therapy

Unfortunately, no novel therapy based on genetic knowledge