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Review Article

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The Role of Mutations on Genes ASXL3, FOXP1, IFT140, MAGEL2 in C Syndrome

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Abstract

Syndrome C, also known as Opitz Trigoncephaly Syndrome (OTCS), is a complex disease defined by a wide range of clinical features and abnormalities. In 1969, John Marius Opitz, a German-American medical geneticist, was treating two siblings, a brother and a sister.

Keywords: C Syndrome, Genetic Mutations, ASXL3, FOXP1, IFT140 & MAGEL2 genes.

Generalities of C syndrome

Syndrome C, also known as Opitz Trigoncephaly Syndrome (OTCS), is a complex disease defined by a wide range of clinical features and abnormalities. The disease may be initially diagnosed in children and later diagnosed with a specific genetic condition. Children with C syndrome are born with a deformity in which the head is abnormal due to premature fusion of the skull bones, a pointed forehead, a wide nose bridge with a short nose, vertical folds in the inner corners of the eyes, and an abnormal palate. Deeply grooved, ear abnormalities, strabismus, bent or fixed joints, and loose skin appear. Inability to grow and learn is also common in this syndrome. These signs and symptoms can vary significantly from patient to patient [1].

Clinical Signs and Symptoms of C Syndrome

OTCS is a heterogeneous disorder, meaning it has no single cause. Mutations in multiple and distinct genes, gene combinations, and chromosomal abnormalities may be the main cause of this disease [1].

In 1969, John Marius Opitz, a German-American medical geneticist, was treating two siblings, a brother and a sister. He noted similar features: a triangular head, bad facial disability, and severe mental retardation. The syndrome was originally called "Syndrome C of Multiple Congenital Anomalies," where "C" meant the family name. It was later renamed Syndrome C, Opitz C Syndrome, or Opitz Trigonocephaly Syndrome [1].

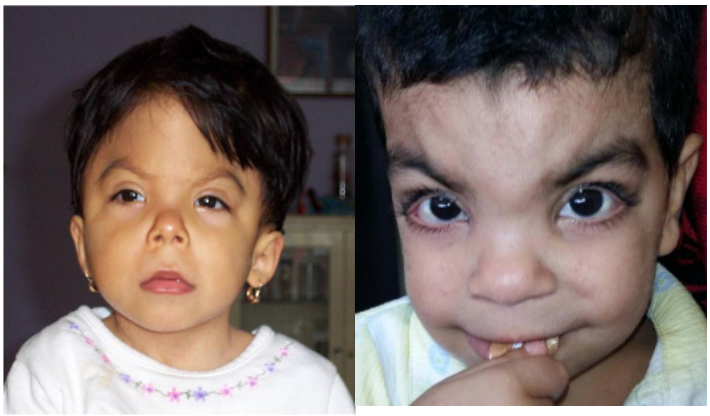

Figure 1: Images of children with C syndrome with distinct facial features [1].

One of the most important features of OTCS is the position in which the skull is triangular. This is due to premature closure of the bones (triangular sutures or prominent tropical sutures due to premature fusion). Patients with this disorder also have a distinct face in which there is a broad bridge of the nose with a short nose, vertical folds in the inner corners of the eye (epicanthosus) and paralysis of the facial muscles (facial paralysis). These children may have external ear abnormalities, strabismus, a thin upper lip, a smooth vertical groove between the base of the nose and the border of the upper lip (filtrum), a small jaw (micrognatia), a short

neck, and loose skin. Additional features can include abnormalities of the breast (sternum), fingers and / or toes (syndactyly), short limbs, heart, pancreas, kidney and lung abnormalities, and inability of one or both testicles to move into the scrotum (cryptorchidism [1, 2].

Nutritional problems may be due to cleft palate in the mouth and deformed teeth. Additional features include loss of muscle tone and joints in arms that are bent or dislocated in a fixed position [1, 2].

Affected children may have abnormalities and seizures in the central nervous system. Developmental delays (motor, mental, or general) and speech delays are common, and children with C syndrome have a mental disability that varies from mild to severe [1, 2].

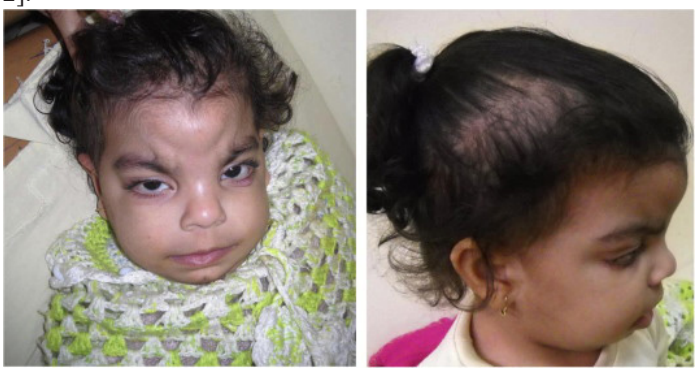

Figure 2: Images of children with C syndrome [1].

Etiology of C Syndrome

There is no common genetic cause for OTCS. Recent research has shown that changes (mutations) in specific genes can be associated with the following conditions: MAGEL2, FOXP1, IFT140 and ASXL3 [1, 3].

Until recently, OTCS was thought to follow the pattern of autosomal recessive inheritance. However, it is now believed that this disorder occurs as a result of autosomal dominant inheritance or gonadal mosaic. Mosaicism is a condition in which a person has cells that are genetically different from each other [1, 3].

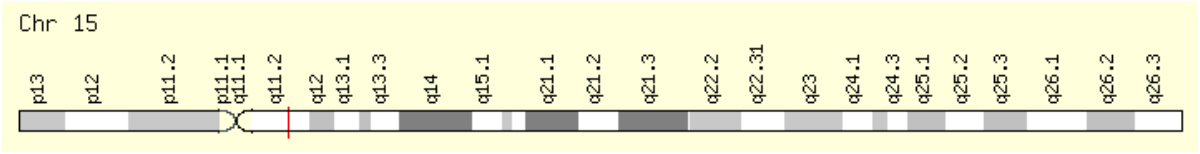

Figure 3: Schematic of chromosome 15 where the MAGEL2 gene is located in the long arm of this chromosome as 15q11.2 [1].

Dominant genetic disorders occur when only one copy of the altered gene is needed to cause a particular disease. The altered gene can be inherited from the affected parents or it can be the result of a new mutation in the infected person. The risk of transmitting the altered gene from the parents to the offspring for each pregnancy is 50%. The risk is the same for men and women [1, 4].

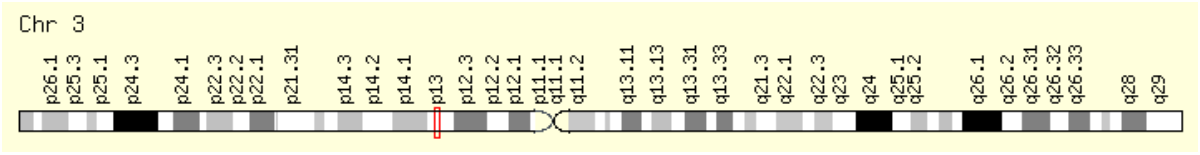

Figure 4: Schematic of chromosome 3 where the FOXP1 gene is located in the short arm of this chromosome as 3p13 [1].

Frequency of C Syndrome

Only about 60 patients with OTCS have been reported in the world medical literature. OTCS is a very rare disease that seems to affect men and women equally. Its prevalence is between 1 / 800,000 and 1 / 1,000,000 [1, 5].

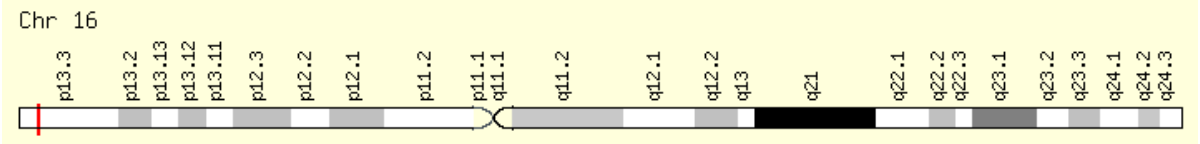

Figure 5: Schematic of chromosome 16 where the IFT140 gene is located in the short arm of this chromosome as 16p13.3 [1].

Disorders Associated with C Syndrome

The symptoms of the following disease may be similar to those of OTCS. A comparison may be useful for the differential diagnosis of this syndrome:

Boring-Opitz syndrome (BOS) is a rare multiple anomaly syndrome that affects the growth and development of organ systems. People with BOS often have severe growth limitations and are therefore very small. They may have nutritional problems, facial features, and a red or pink birthmark (nevus flammeus) on the forehead or eyelids. People may also have seizures, heart abnormalities, and a "BOS status" in which the elbows are bent and the wrists are angled. Additional abnormalities may include below-average head size (microcephaly), visible bumps on the forehead (ridge), cleft lip and / or palate, eye abnormalities, recurrent infections, and sleep apnea (apnea). Sleep), as well as sleep problems. Children with BOS may have varying degrees of learning, but these are usually severe and most children do not learn to speak or walk. BOS is caused by mutations in the ASXL1, ASXL2 and KLHL7 genes [1, 6].

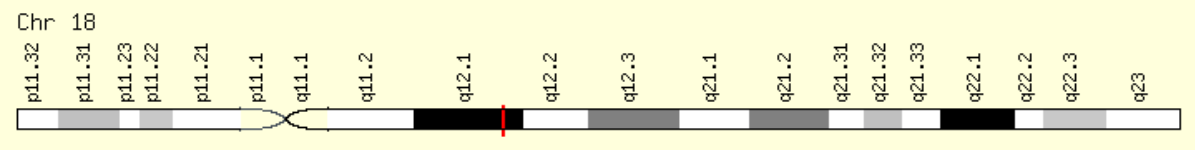

Figure 6: Schematic of chromosome 18 where the ASXL3 gene is located in the long arm of this chromosome as 18q12.1 [1].

Diagnosis of C Syndrome

OTCS is a clinical diagnosis based on the features mentioned earlier. Because multiple genes (and chromosomal abnormalities) may be associated with this condition, exome sequencing (WES) can be used to identify the underlying molecular cause in some patients who have been clinically diagnosed with the condition., used [1, 7].

Treatment Routes for C Syndrome

There is no specific treatment for OTCS, but some symptoms can be treated. When trigonecephaly is severe, surgery may be performed to reduce pressure on the brain and improve the appearance of the face. Other surgeries may be indicated for heart and other abnormalities. Supportive therapies such as speech therapy and interdisciplinary rehabilitation may be helpful in some patients. Genetic counseling is also recommended for patients and their families [1, 7].

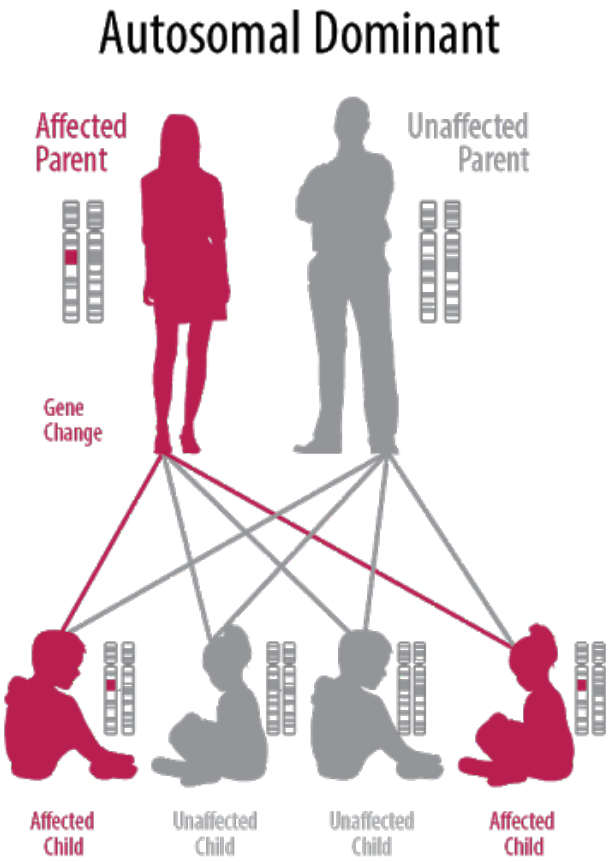

Figure 7: Schematic of the dominant autosomal inherited pattern that C syndrome follows [1].

Discussion and Conclusion

C syndrome is a rare multiple congenital anomaly/intellectual disability syndrome characterized by trigonocephaly and metopic suture synostosis, dysmorphic facial features, short neck, skeletal anomalies, and variable intellectual disability. C Syndrome is a genetically heterogeneous disease and its mode of inheritance is under debate. Autosomal dominant, autosomal recessive, and germline mosaicism as well as sporadic (de novo mutations) have been suggested. At least some cases were found to be associated with mutations in the CD96 Antigen (CD96) gene, which has been mapped to chromosome 3q13.1-q13.2. Few cases may be attributed to mutations in the MAGE-like 2 (Melanoma Antigen-like 2; MAGEL2) gene on chromosome 15q11.2. There is no specific treatment for OTCS, but some symptoms can be treated. When trigonecephaly is severe, surgery may be performed to reduce pressure on the brain and improve the appearance of the face [1-7].

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