Tara Gallo

DEN 2311/D246

December 6, 2015

**Greig Syndrome**

Greig cephalopolysyndactyly syndrome (GCPS) is a rare genetic disorder present at birth involving physical abnormalities of the fingers and toes and the craniofacial area. In most cases, GCPS is inherited as an autosomal dominant trait but the phenotype may range from mild to severe in affected individuals. Dominant genetic disorders occur when only a single copy of an abnormal gene is present. People with this condition typically have supernumerary fingers or toes, or an abnormally wide thumb or big toe. The skin between the fingers and toes may also be fused. Craniofacial malformations associated with this disease include an abnormally broad nasal bridge, frontal bossing, macrocephaly, and ocular hypertelorism. Rarely, more serious medical problems are involved which include seizures, developmental decay, and intellectual disability.

The GLI3 gene provides instructions for making a protein that controls gene expression, which is a process that regulates whether genes are turned on or off, in particular cells. By interacting with certain genes at specific times during development, the GLI3 protein plays a role in the normal shaping of many organs and tissues before birth. According to the Genetics Home Reference, different genetic changes involving the GLI3 can also be the cause of Greig cephalopolysyndactyly syndrome. In some cases, the condition results from a chromosomal abnormality, such as a large deletion or rearrangement of genetic material. In others, a mutation in the GLI3 gene itself is responsible for the disorder. Each of these genetic changes prevents one copy of the gene in each cell from producing any functional protein. It remains unclear how a reduced amount of this protein disrupts early development and causes the characteristic features of Greig cephalopolysyndactyly syndrome. It is very difficult to detect the true frequency of GCPS in the general population. According to the National Organization for Rare Diseases (NORD), GCPS affects males and females equally. There have been over 200 patients reported in medical history with this disorder. However, because some affected individuals may express fewer symptoms, they may never be diagnosed with the disorder. It is impossible to determine the incidence of a disorder for which there are no reliable clinical criteria and molecular diagnostics are not yet in wide use. As the disorder blends in a phenotypic continuum with non-syndromic polydactyly, it may be much more prevalent than it seems.

GCPS is usually diagnosed at birth based upon a thorough clinical evaluation and specialized imaging procedures including X-rays and computed tomography (CT) scanning. NORD states that in pregnancies at 50% risk, GCPS may be detected before birth by observing the presence of extra digits and enlarged skull during ultrasound imaging. Prior to the diagnostic testing, two conditions must be considered. First, the presence of developmental delay, intellectual disability and history of recurrent pregnancy losses in the parent of the individual should be evaluated. Once the clinical features consistent with GCPS are confirmed through X-rays and CT scans, individuals without significant developmental delay or intellectual disability should have genetic testing through sequence analysis. This will detect benign deletion. On the other hand, if development delay or intellectual disabilities are present, he or she should have either comparative genomic hybridization to detect possible copy numbers changes in GL13. Another prenatal testing method available is analyzing the fetal cells. X-rays and CT scanning can also be used to reveal the extent of bone fusion in severe occurrences of osseous syndactyly.

Treatment of the disorder is symptomatic, with plastic or orthopedic surgery indicated for significant limb malformations. The prognosis for typically affected patients is excellent. There may be a slight increase in the incidence of developmental delay or cognitive impairment. Patients with large deletions that include GLI3 may have a worse prognosis. Generally, the patients are healthy and have a normal lifespan. Surgical treatment of polysyndactyly should be considered, and in many cases leads to excellent outcomes. Proper developmental assessment and early intervention should be offered to any patient manifesting developmental delay.

**Sources**

1. "Greig Cephalopolysyndactyly Syndrome." *Genetics Home Reference*. Web. 6 Dec. 2015.
2. "Greig Cephalopolysyndactyly Syndrome - NORD (National Organization for Rare Disorders)." *NORD (National Organization for Rare Disorders)*. Web. 6 Dec. 2015.
3. "The Greig Cephalopolysyndactyly Syndrome." *Orphanet Journal of Rare Diseases*. Leslie G Biesecker. Web. 6 Dec. 2015.