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50 Years Ago in *The Journal of Pediatrics*

Clinical and Genetic Delineation of Saethre–Chotzen Syndrome

Bartsocas CS, Weber AL, Crawford JD Acrocephalosyndactyly type III: Chotzen's syndrome. J Pediatr 1970; 77:267-72.

Bartsocas et al described a 3-generation family in which affected individuals had craniofacial abnormalities including acrocephaly, craniosynostosis, shallow orbits, ptosis, hypertelorism, nasal septal deviation, and minor ear anomalies. Some affected individuals had seizures, cognitive impairment, and short stature. Limb anomalies included partial syndactyly of the second and third fingers and toes, radioulnar synostosis, and transverse palmar creases. This pattern of clinical features was similar to a family described by Chotzen in 1932 with acrocephaly, hypertelorism, downslanting palpebral fissures, and syndactyly. McKusick referred to this condition as "acrocephalosyndactyly, type III"[1] and included patients reported by Saethre. These patients had acrocephaly with minimal ptosis, incurving of the second and fifth fingers and syndactyly. An autosomal-dominant mode of inheritance with variable expression was observed in affected families.

Further delineation of Saethre–Chotzen syndrome included features of brachycephaly with coronal craniosynostosis, limb anomalies, facial asymmetry, and maxillary hypoplasia. A low frontal hairline, ptosis, strabismus, prominent ear crus, low set posteriorly rotated small ears, cleft palate, conductive deafness, enlarged parietal foramina, malocclusion, and enamel hypoplasia are observed less frequently. Most affected individuals have normal intellect.

Subsequent molecular studies identified missense, nonsense, insertions, and whole gene deletion mutations in the phylogenetically conserved *TWIST* gene, which encodes a transcription factor localized to chromosome 7p21 in patients with Saethre–Chotzen syndrome.[2] The *TWIST* gene has a DNA binding and helix-loop-helix motif and likely exerts its action through induction of tissues and cytokine expression through the nuclear factor-$\kappa\beta$ signaling pathway. Haploinsufficiency of *TWIST* is a likely genetic mechanism for Saethre-Chotzen syndrome.

A similar but genetically distinct condition, Muenke coronal synostosis syndrome, characterized by unilateral or bilateral coronal synostosis, sensorineural hearing loss, brachydactyly, and cognitive impairment, is associated with a single recurrent Pro250Arg mutation in exon 7 of the *FGFR3* gene.

Philip F. Giampietro, MD, PhD
Division of Medical Genetics
Rutgers Robert Wood Johnson Medical School
New Brunswick, New Jersey

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