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Overgrowth syndromes

CATSHL syndrome

CATSHL syndrome (MIM 610474) received this name as an acronym for its main features: campodactyly, tall stature, scoliosis and sensorineural hearing loss. Microcephaly and developmental delay can also occur. It is caused by the inactivation of \textit{FGFR3} gene, a well-
known bone growth inhibitor, and its inheritance has been described as autosomal dominant in two families and as autosomal recessive in one family\textsuperscript{1-3}.

**Congenital contractural arachnodactyly**

Also known as Beals syndrome, congenital contractural arachnodactyly (CCA; MIM 121050) shares a similar phenotype with Marfan syndrome, including kyphoscoliosis, arachnodactyly and marfanoid habitus. However, patients with CCA rarely have *ectopia lentis* and, when aortic root dilation is present, it is usually mild and not progressive\textsuperscript{4}. Newborns show a folded upper helix of the external ear and large joint contractures, mainly in knees and elbows. It is caused by mutations in *FBN2* gene with autosomal dominant inheritance\textsuperscript{5}.

**Simpson-Golabi-Behmel syndrome**

Simpson-Golabi-Behmel syndrome (MIM 312870) has as major characteristics macrosomia, macrocephaly, coarse face, organomegaly, muscular hypotonia and supernumerary nipples. Cardiac defects, dental malocclusion and polydactyly can also occur\textsuperscript{6, 7}. As seen in Beckwith-Wiedemann syndrome, these patients have a high risk of developing embryonal tumors like Wilms tumor, especially in childhood. This syndrome is caused by mutations in *GPC3* gene that are inherited in a recessive X-linked manner. Female carriers may exhibit only mild characteristics such as tall stature and supernumerary nipples due to non-randomic X chromosome inactivation\textsuperscript{7}. A severe and often lethal presentation, referred as Simpson-Golabi-Behmel type 2 syndrome (MIM 300209), has also been described in a few patients, with fetal hydrops and respiratory problems\textsuperscript{8}.

**Weaver syndrome**

Patients with Weaver syndrome (MIM 277590) present with increased birth length, macrocephaly, intellectual disabilities and dysmorphic face – broad forehead, retrognathia, round face, hypertelorism and almond-shaped palpebral fissures. Campodactyly, advanced bone age and low-pitched cry are often present\textsuperscript{9}. The main differential diagnosis is Sotos syndrome.
due to phenotypic superposition. Weaver syndrome is caused by mutations in $EZH2$ gene and cases are mostly sporadic, with some families exhibiting an autosomal dominant inheritance. Cancer predisposition is a concern since somatic mutations in $EZH2$ gene have been identified in hematological malignancies. However, in a cohort of 48 $EZH2$ positive Weaver patients only two were identified with cancer so far – one patient with lymphoma and another with acute lymphoblastic leukemia and neuroblastoma\(^ {10}\).

**Epiphyseal chondrodysplasia, Miura type**

Epiphyseal chondrodysplasia, Miura type (MIM 615923) is an overgrowth syndrome in which skeletal features, such as big toes, arachnodactyly, marfanoid habitus and scoliosis, are present since birth\(^ {11-13}\). Adult height is markedly increased, reaching around 4 or more SDS above average. Bone resorption and formation markers are elevated and BMD is normal, but it can be overestimated because of tall stature\(^ {12, 13}\). No cardiac or renal malformations have been described. It is an autosomal dominant disorder caused by overexpression of genes in CNP/NPR2 pathway, which acts in the growth plate. Chromosomic translocations causing transcriptional upregulation of $NPPC$ gene as well as gain-of-function point mutations in $NPR2$ gene have been described as the etiology in those patients\(^ {11-14}\).

**Lujan-Fryns syndrome**

Lujan-Fryns syndrome (MIM 309520) is a X-linked recessive disease that presents with marfanoid habitus (evident after puberty), intellectual disability, long and narrow face, crowded teeth, macrocephaly, hyperextensibility of digits and dysgenesis of corpus callosum\(^ {15}\). It is caused by a mutation in $MED12$ gene, which is part of a mediator complex that facilitates transcription and has been linked to Wnt/β-catenin and sonic hedgehog pathways\(^ {16}\).

**Sclerosteosis**

Affected individuals with sclerosteosis (MIM 269500) present with tall stature, mandibular overgrowth since childhood, conductive hearing loss, facial palsy, syndactyly of
second and third fingers and hyperostosis and sclerosis of tubular bones, which are less prone to fracture. Sudden death due to intracranial hypertension can occur. It is an autosomal recessive condition more frequent in South Africa, caused by an inactivating variant in \textit{SOST} gene. This gene encodes sclerostin, known to suppress bone formation through the inhibition of Wnt-1 signaling.

**Bannayan-Riley-Ruvalcaba syndrome**

Bannayan-Riley-Ruvalcaba syndrome (MIM 153480) has as major findings hamartomas, macrocephaly and speckled penis in males. It is also associated with benign thyroid disease, joint laxity, frontal bossing, scoliosis and seizures. Overgrowth is present since birth, but there is a decrease in growth velocity during childhood, leading to a normal adult stature. It is caused by the inactivation of \textit{PTEN} gene transmitted in an autosomal dominant manner. As a PTEN hamartoma tumor syndrome, cancer surveillance is advisable, especially for thyroid, breast and endometrial cancers. It shows clinical overlap with Cowden syndrome (MIM 158350) and affected members in the same family can have either Cowden or Bannayan-Riley-Ruvalcaba phenotypes, suggesting that both syndromes are variable phenotypic expressions of the same disorder.

**Sotos syndrome 2 and 3**

Patients with Sotos syndrome 2 (MIM 614753), also known as Malan syndrome, are large for gestational age and have macrocephaly, long and narrow face, \textit{pectus excavatum}, strabismus and intellectual impairment. It is caused by autosomal dominant mutations in \textit{NFIX} gene. \textit{NFIX} gene is also implicated in Marshall-Smith syndrome, which comprises an accelerated bone maturation, failure to thrive, blue sclerae and early death due to respiratory problems, mostly by airway obstruction. Mutations leading to Marshall-Smith syndrome are in different regions of \textit{NFIX} gene in relation to mutations causing Sotos syndrome 2 and those syndromes are clinically distinct entities.
Sotos syndrome 3 (MIM 617169) has been described in two siblings from a consanguineous marriage and only one of them had height in the percentile 90th, while the other had it in the percentile 25th. Both had macrocephaly and facial characteristics resembling Sotos syndrome (pointed chin, long face), but no abnormalities in other organs. A mutation in \textit{APC2} gene, responsible for neuronal migration and part of a downstream pathway for \textit{NSD1} active only in nervous system, was identified\textsuperscript{23}. 
References

type natriuretic peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation. *Hum Mutat* 2007 **28** 724-731.


