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Genetics Corner: Syndromic Etiology of Apparently Isolated Clubfeet: a Child with Loeys-Dietz Syndrome

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Clinical Summary:

A 2-year-old male with prenatally diagnosed clubfeet presented for a genetics evaluation in the Craniofacial team clinic for suspected craniosynostosis. The pregnancy history was noteworthy for the prenatal diagnosis of bilateral and isolated clubfeet in the second trimester but was otherwise noncontributory. He was born in a regional hospital at term by NSVD to a 35-year-old G2P1→2 mother. The birth weight was appropriate at ~7 lbs. There were no other postnatal complications, and he was discharged home from the regular newborn nursery with his mother. His clubfeet were treated with serial casting. He had a strabismus that had been surgically repaired. His mother noticed a bony prominence on his anterior skull in the first year of life that prompted a referral to the Craniofacial team clinic. His motor milestones were appropriate, but he had a speech delay. The family history was noncontributory.

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He was tall, at the 91st percentile for height, and slender. His physical exam was notable for scaphocephaly with a bony prominence over the anterior sagittal suture and depression over the (closed) anterior fontanel. He had dysmorphic facial features (Figure 1): hypertelorism, prominent eyes, shallow orbits, mild beaking of the nose, micrognathia, and a previously undocumented bifid uvula. Arachnodactyly was present with significant hypermobility of the joints of the hands and wrists and prominent heels. His subcutaneous tissue had a soft and doughy consistency. His skin was thin, and his veins were visible. There was moderate bruising on both shins. Loeys-Dietz syndrome was suspected based on his clinical features.

Laboratory and Imaging Studies

Molecular genetic testing detected a *de novo* likely pathogenic variant in *TGFBR2,* c.1178G>A (p.Cys393Tyr*),* confirming the diagnosis of Loeys-Dietz syndrome 2 (LDS2, OMIM 610168)(1).

An echocardiogram detected a dilated aortic root, and a pediatric cardiology consultant initiated therapy with an angiotensin II receptor antagonist, losartan (0.1 milligrams/kg/d; 0.7 mg PO bid). CT scan of the head detected pan-craniosynostoses with premature fusion of the sagittal, lambdoid, and bicoronal sutures. Flexion/extension radiographs of the cervical spine revealed atlantodental instability. Whole-body MRA and brain MRI studies will be completed prior to the planned surgical repair of his craniosynostoses.

Discussion

"Flexion/extension radiographs of the cervical spine revealed atlantodental instability. Whole-body MRA and brain MRI studies will be completed prior to the planned surgical repair of his craniosynostoses."

Congenital talipes equinovarus, or clubfoot, is a common disorder in 1-3/1000 live births. The sex ratio favors males: 2M:1F. In about 50-70% of cases, the clubfoot is an isolated anomaly (2), and the rest are considered to be complex with associated structural or genetic anomalies. Notably, the prenatal diagnosis of an isolated clubfoot is not reliable and should be confirmed with a careful examination after birth. A prenatally diagnosed isolated clubfoot is confirmed postnatally in only 70-75% of cases because 10-20% are false positives, and 5-13% are mislabeled as isolated and are, in fact, complex cases with other associated anomalies (3, 4) In our patient, the postnatal diagnosis of Loeys-Dietz syndrome type 2 provided a monogenic etiology for what was complex. However, it had previously been treated as isolated clubfeet.

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The syndromic nature of his clubfeet might have been diagnosed earlier had his associated anomalies been appreciated. Some of his other anomalies were evident in photographs that we reviewed from the newborn period (Figure 1). Interestingly, his craniosynostosis was not evident until later in infancy. However, his stra-

TABLE: Syndromes associated with clubfoot

CONDITION/SYNDROME NAME	KNOWN GENES
Arthrogryposis, distal type 3	*PIEZO2*
Barth syndrome	*TAZ*
Bruck syndrome	*PLOD2, FKBP10*
Carey-Finerman-Ziter syndrome	*MYMK*
Catel-Manzke syndrome	*TGDS*
Charcot-Marie-Tooth Disease Type 4D	*NDRG1*
Charcot-Marie-Tooth Disease, axonal type	*LMNA, GDAP1*
Diastrophic dysplasia	*SLC26A2*
Ehlers-Danlos syndrome, musculocontractural types	*CHST14, DSE*
Ehlers-Danlos syndrome, vascular type	*COL3A1*
Epileptic encephalopathy	*AARS*
Joubert syndrome	*ATXN10, TCTN2*
Larsen syndrome	*FLNB, CHST3*
Loeys-Dietz syndrome	*TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2, TGFB3*
Marfan syndrome	*FBN1*
Moebius syndrome	*PLXND1, REV3L*
Multiple epiphyseal dysplasias	*COL9A1, COL9A2, COL9A3, COMP, MATN3, SLC26A2*
Multiple synostosis syndrome	*GDF5*
Peroxisomal biogenesis disorder 7A	*PEX26*
Richeri-Costa – Pereira syndrome	*EIF4A3*
Santos syndrome	*WNT7A*
Saul-Wilson syndrome	*COG4*
Shprintzen-Goldberg craniosynostosis syndrome	*SKI*
Simpson-Golabi-Behmel syndrome	*GPC3*
TARP syndrome	*RBM20*
Van Maldergern syndrome, 2	*DCHS1, FAT4*
VISS syndrome	*IPO8*

Some of the more common causes of syndromic clubfoot are listed with their associated genes (adapted from Sadler et al., 2019)(6). Several of these syndromes are connective tissue disorders, including Ehlers-Danlos, Loeys-Dietz, Marfan, and Schprintzen-Goldberg syndromes.

bismus, joint hypermobility, arachnodactyly, and bifid uvula could have been detected with a careful physical exam in the newborn period. His strabismus was recognized early. A search of the Online Mendelian Inheritance in Man (OMIM) database (www.omim.org) using the search terms "clubfoot and bifid uvula" returns 31 entries, which include three different types of Loeys-Dietz syndrome in the first ten responses.

Loeys-Dietz syndrome (LDS) describes a group of connective tissue disorders that cause dysmorphic craniofacial features, joint instability, and significant vascular anomalies characterized by arterial tortuosity and aortic dilation, which can lead to an aortic aneurysm in childhood. The phenotype of LDS overlaps Marfan syndrome and other connective tissue disorders. Many genetic disorders that can present with clubfeet are listed (Table).

Craniofacial features of Loeys-Dietz syndrome(5) include hypertelorism (widely spaced eyes), craniosynostosis of any suture, and cleft palate/bifid uvula. Skeletal manifestations include talipes equinovarus and arachnodactyly. Approximately 15% of individuals with Loeys-Dietz syndrome have cervical spine instability, and all patients should be examined for this with flexion-extension X-rays. Joint instability manifests in clubfoot, flat feet, scoliosis, pectus anomalies, and joint hypermobility. Approximately 25 to 30% of affected individuals can also have gastrointestinal complications and severe food allergies.

There is wide clinical variability and severity in LDS. The most

Figure 1a:

Figure 1b:

Caption for Figure 1a-d: Craniofacial features of Loeys-Dietz syndrome, a) as an infant and b) at two years of age, are evident: hypertelorism, shallow orbits, mildly beaked nose, short columella, micrognathia; Note the unusual posture of the fingers as a newborn. Strabismus and mild ptosis of the left eye were present from birth, although subtle in the newborn period. His hypertelorism and unusual head shape are less evident as a newborn. c. Bilateral talipes in the newborn period d. Arachnodactyly, camptodactyly of the little fingers, and hypermobility of interphalangeal joints at age 3

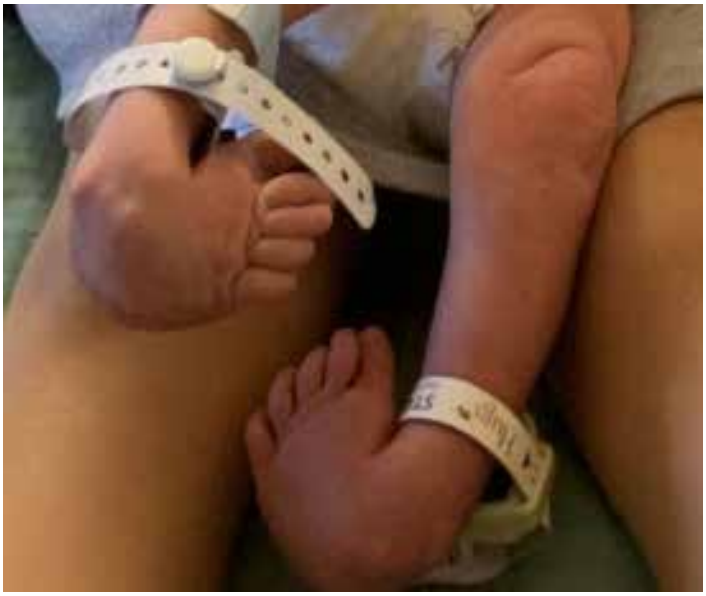

Figure 1c:

Figure 1d:

"Lowering the blood pressure, reducing the pulse pressure, and slowing the heart rate reduce morbidity and mortality."

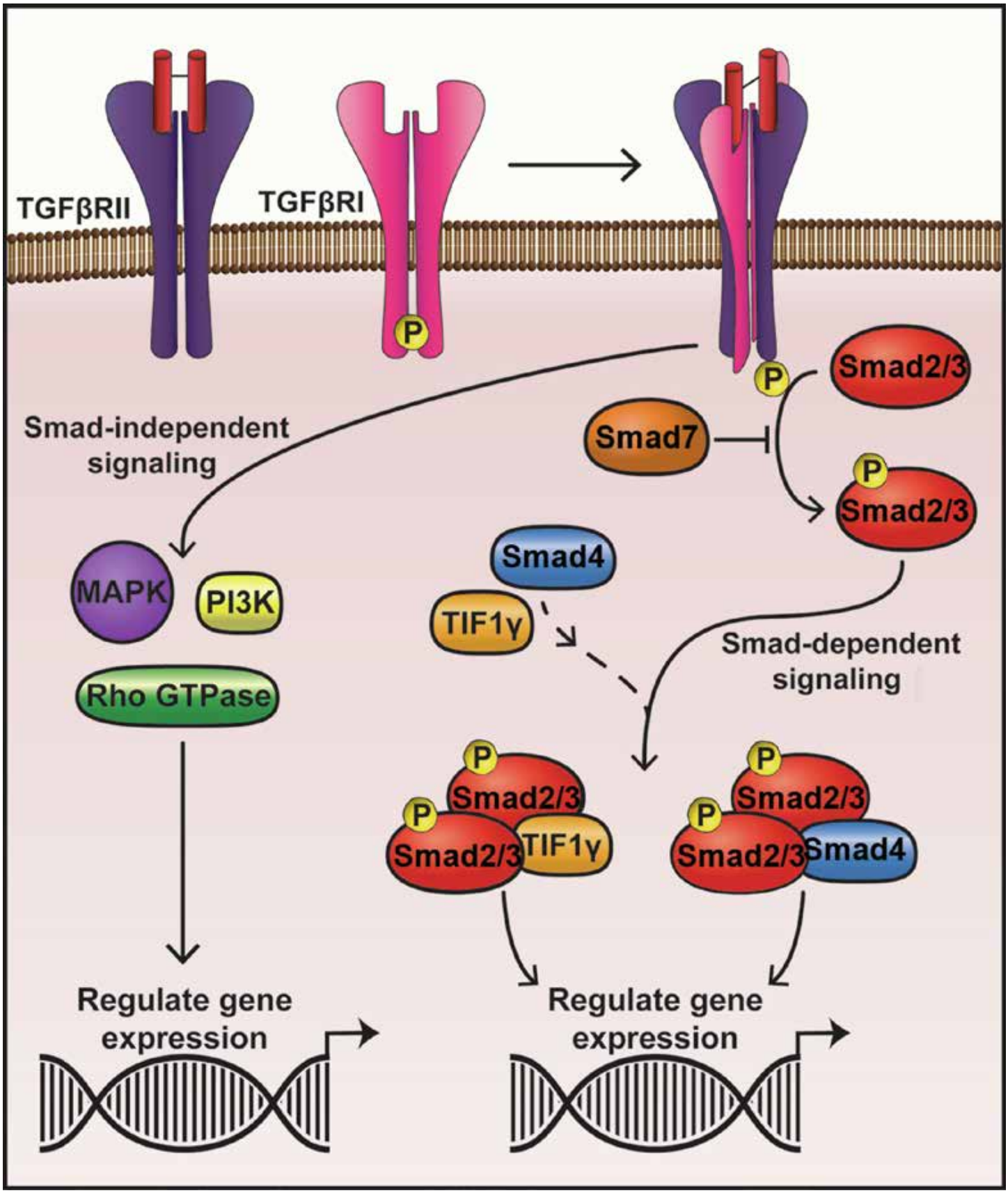

Figure 2 Diagram of TGF beta signaling pathway TGFβ signaling pathways work in a Smad-dependent or Smad-independent manner. Upon binding of active TGFβ to a TGFβRII dimer, a tetrameric receptor complex is formed with a TGFβRI dimer. This activates the kinase activity of TGFβRI and can trigger signaling either through a Smad-dependent or -independent manner. Adapted from Kelly et al. (2017)(7)

serious sequelae are arterial tortuosity, cerebral, thoracic, and abdominal arterial aneurysms, and/or dissections. Management of individuals with LDS includes surveillance with echocardiograms at least annually and annual head to pelvis CTA/MRA to assess for arterial tortuosity and aneurysms. The major morbidity and early mortality in LDS are from aortic dilatation at the sinuses of Valsalva, which predispose to aortic dissection and rupture that can occur in childhood. Mitral valve prolapse and enlargement of the proximal pulmonary artery are also seen. Individuals with LDS have a more aggressive vascular course than those with other connective tissue disorders such as Marfan syndrome. Aortic root replacement is recommended earlier in LDS than in Marfan syndrome, at 4 cm. Early diagnosis of Loeys-Dietz syndrome can change the course of the disease. Lowering the blood pressure, reducing the pulse pressure, and slowing the heart rate reduce morbidity and mortality. Beta-adrenergic blockers or angiotensin receptor blockers are the mainstay of medical treatment.

"LDS is inherited in an autosomal dominant manner but new, de novo mutations are responsible for most cases of LDS. Only 25% have an affected parent, which means negative family history is not reassuring. Heterozygous pathogenic variants in 6 known genes cause LDS."

LDS is inherited in an autosomal dominant manner but new, *de novo* mutations are responsible for most cases of LDS. Only 25% have an affected parent, which means negative family history is not reassuring. Heterozygous pathogenic variants in 6 known genes cause LDS. These genes are part of the transforming growth factor-β (TGF β) signaling pathway (Figure 2): *SMAD2* (mothers against decapentaplegic homolog 2), *SMAD3* (mothers against decapentaplegic homolog 3), *TGFB2* (TGF-β2), *TGFB3* (TGF-β3), *TGFBR1* (TGF-β receptor type I), or *TGFBR2* (TGF-β receptor type II). Variants in *TGFBR2* make up over 50% of the variants found in affected individuals (5).

Practical applications:

1. Think outside the foot. Examine every infant with clubfoot for associated anomalies to identify those with a syndromic etiology.
   a. Recall that 30% of infants with clubfoot have additional congenital anomalies.
   b. Examine affected infants for craniofacial, palatal, ocular, skeletal, joint, cardiac, or skin manifestations.
   c. Refer patients with clubfoot, whether unilateral or bilateral, for a genetic evaluation when associated anomalies are present,
2. Do not rely on a negative prenatal ultrasound to rule out associated anomalies in infants with clubfoot. A prenatal ultrasound cannot reliably detect complex or syndromic clubfoot.
3. Do not be reassured by negative family history. Many genetic disorders are caused by a *de novo* pathogenic variant in the infant.
4. Be familiar with connective tissue disorders associated with clubfeet, such as Loeys-Dietz and Marfan syndromes. These conditions are more likely to have serious cardiac vascular sequelae that can be modified by early treatment.
5. Be aware of the potential benefits of early diagnosis of syndromic clubfoot and the harms associated with later diagnosis beyond the newborn period. Losartan treatment was only begun after aortic root dilation was detected in this patient.

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