Feelings Matter to Muscles and Joints

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Background

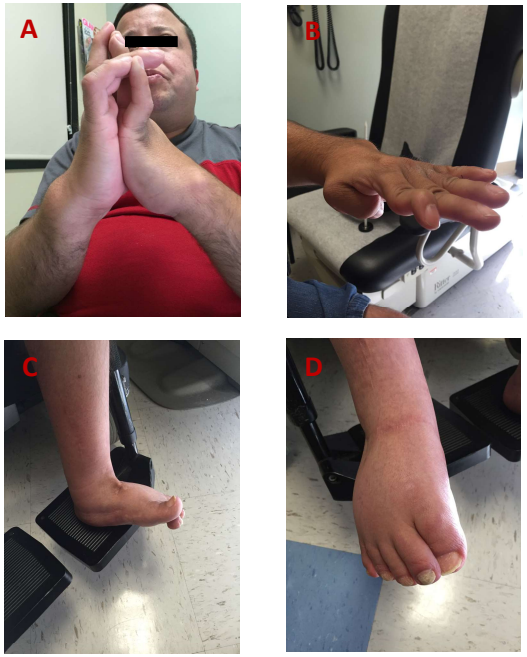
PIEZO2 is a widely expressed stretch-gated ion channel recently shown to mediate human mechanosensation. A consistent and unique clinical phenotype with selective sensory deficits, early progressive scoliosis in the absence of muscle weakness as well as systemic manifestations of transient respiratory distress and feeding difficulty in the newborn period, impaired gastrointestinal transit and bladder function has been described in a small cohort of young patients.

Design and Methods

Review of history per medical records, Magnetic Resonance Imaging (MRI) of the brain and the right thigh, in a single case of clinically documented UCMD. MRI of the brain used at 3.0 Tesla, multiplanar and multisequence, pre and post contrast with 10 ml of gadolinium injection. Study of the femur was without contrast. 3D image postprocessing was performed on a dedicated workstation and images were used for interpretation and reporting.

Results

A 42 year-old adopted Hispanic man was born with bilateral club feet, hip dysplasia, hand and forearm malformations. He developed progressive scoliosis in childhood and never achieved independent ambulation with permanent use of a power wheelchair as of age 12. He carried an initial diagnosis of muscular dystrophy. Next generation panel-based sequencing had revealed a polymorphism in *COL6A3* while research based whole exome sequencing identified a homozygous truncating mutation in *PIEZO2* (c.2004delG;p.Glu688*). Physical exam revealed distal hyperlaxity, small feet, a short lower segment and fused scoliosis. Strength was normal and out of proportion with his disability, reflexes were absent. Highly selective sensory deficits were found and were consistent with the previously described *PIEZO2* loss of function phenotype, including a striking loss of joint proprioception, vibratory sense and glabrous skin touch discrimination. Additional Investigations including a CK, MRI of the brain and thigh muscles were unremarkable. Muscle biopsy showed mild, non-specific myopathic changes.



Figures A) Significant finger flexion contractures, most prominent in B) left thumb. C, D) Small feet and decreased bulk of distal muscles of the lower extremities.

Additioanl photos pending

Discussion

There are different anatomical classes of somatosensory neurons with distinct selectivity for mechanical stimuli.[1, 2] Proprioception is considered to be essential for posture and controlled movement.[3]

Piezo channels are non-selective cation channels. There are two Piezo genes in mammals, *PIEZO1* and *PIEZO2*.[4] Both genes are strongly expressed in the urinary bladder and lung, *PIEZO1* is expressed in kidney and skin, and *PIEZO2* is specifically expressed in dorsal root ganglia[5] and in Merkel cells in the skin.[6] *PIEZO2* is required to transduce the mechanical forces at the sensory afferent terminals in humans. Despite major deficits in discriminative touch perception and loss of proprioception that noticeably affect movement control and posture, patients have been able to perform complex movements by relying on compensatory inputs, such as vision. Other forms of somatosensation, including pain from high-threshold mechanical stimuli and the touch responses evoked by gentle stroking on hairy skin, remain intact.[7] In mice, homozygous inactivation of *PIEZO2* is associated with perinatal death, but humans can survive without this channel. Study of human subjects born with hip dysplasia suggest a function for *PIEZO2* in utero in humans, as well.[7] Patients can present arthrogryposis, muscle atrophy and other features resembling other disorders. Prior to diagnosis, our patient had MRI findings in his thighs suggestive of a collagen-VI-related myopathies. These consist on the presence of a rim of abnormal signal at the periphery of each muscle and relative sparing of the central part of the vasti muscles, which are the most affected muscles groups.[8, 9]

PIEZO2 may have a direct role in skeletal development. Alternatively, loss of *PIEZO2* function may result in prenatal impairment of proprioception, which thus cause abnormal joint positioning and may be the primary cause of arthrogryposis, hip dysplasia, and progressive scoliosis. [7]

Conclusion

The *PIEZO2*-loss of function phenotype is highly specific and clinically recognizable, yet it can evade identification in older patients who were misdiagnosed as having a muscular dystrophy in the pre-genetic era. The identification of an older adult patient furthers our understanding of this distinct phenotype. Its diagnosis and careful phenotyping allow for the development and implementation of rehabilitative measures aimed at recruiting intact sensory modalities in order to compensate for specific deficits and optimize function.

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