

Genetics Corner: A Consultation for Joint Limitations that Developed After Birth

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Clinical Summary:

A 13-week-old female was initially evaluated by the Pediatric Genetics service when she was admitted for progressive joint limitations that were not present at birth.

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The family history was noncontributory. She had an 8-year-old maternal half-sister and a 15-year-old paternal half-sister, who were both healthy. The parents were both in their early 30s and denied consanguinity. The prenatal history was noncontributory except for emergency surgery under general anesthesia for a maternal incarcerated umbilical hernia at 16 weeks gestation.

The baby was delivered at term by repeat C-section for low transverse presentation with normal growth parameters.

Birth weight: 3130 g (6 lb 14.4 oz)

Birth length: 49 cm (19.29")

Birth head circumference: 34 cm (13.39")

There was concern for right clubfoot at birth, which resolved without treatment. At delivery, she had a full range of motion of all joints. The parents provided a photograph showing her raising her arms above her head in the delivery room.

Decreased range of motion of all her joints was evident by 13 weeks of age. She had increased tone in her upper extremities and contractures of her lower extremities. She had hyperpigmentation on her knuckles and ankles. Her legs were positioned in a “frog-leg” posture, and she could not extend her arms above her shoulders. Brain MRI and MRS imaging were negative. Chromosome microarray analysis and a gene panel for distal arthrogryposis were negative.

The pediatric neurology service was also consulted. A neuromuscular gene panel was ordered. This was nondiagnostic, revealing variants of uncertain significance in several genes that did not match the phenotype. A nerve conduction study

(NCS) performed at three months of age showed very low motor amplitudes but normal sensory/mixed amplitudes. A needle EMG on the same date showed no spontaneous discharges or fibrillation potentials, but there were small motor unit potentials with probable early recruitment, raising concern for a myopathy. The findings ruled out anterior horn cell disease, demyelination, or motor or sensory axon loss.

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At five months, she was evaluated in the muscular dystrophy clinic for generalized weakness and hypotonia of unclear etiology. She had a reduced range of motion in all joints, particularly finger extension, elbow flexion, extension, and shoulder abduction. At ten months, she developed perianal tags, which increased in size over the ensuing months (see Figure 1).

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Figure 1.

1a Frog-leg posture at 3 mos:



1b. Hyperpigmentation over ankles and knuckles



(3 mos)



1c Progression of perianal tags:
at 10 mos and 18 mos



1d. Infiltration on right arm:
19 mos



1e. Perinasal masses and gingival nodules at 22 mos



“By 17 months of age, mitochondrial DNA test results were negative. Trio whole exome sequencing revealed a paternally inherited heterozygous pathogenic variant in *ANTXR2* (c.1073dup; p.Ala359Cysfs*13). Biallelic variants in this gene are associated with autosomal recessive hyaline fibromatosis syndrome (HFS, MIM #228600). She was initially considered an unaffected carrier of this condition because only one variant was identified. However, by 18 months, she had the classic features of hyaline fibromatosis syndrome.”

Further genetic testing was ordered, but it took several months to complete. By 17 months of age, mitochondrial DNA test results were negative. Trio whole exome sequencing revealed a paternally inherited heterozygous pathogenic variant in *ANTXR2*

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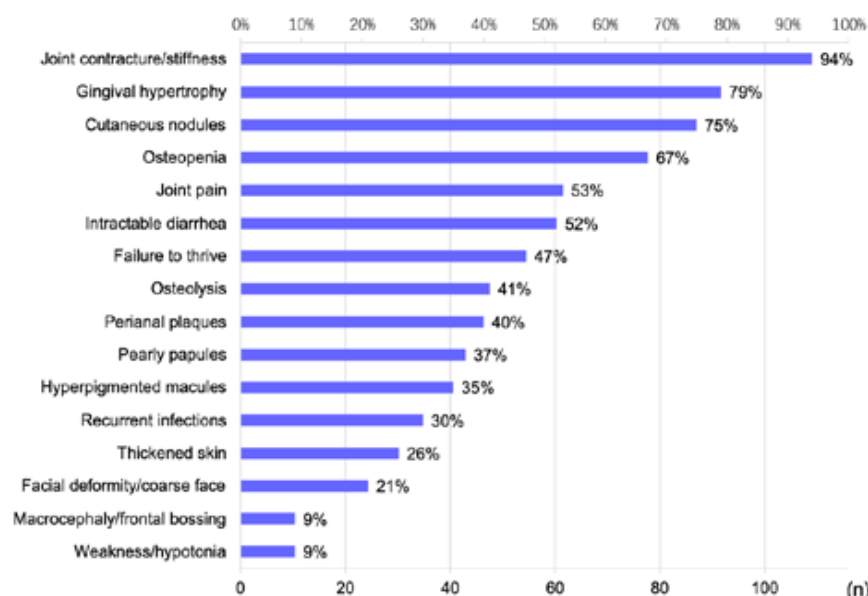
Her facial features were coarse, and her skin was shiny. Passive or active movement of her extremities was painful. Progressive joint limitations severely restricted the movement of her extremities. Perianal tags had increased in size. She developed gingival and perinasal nodules and a palpable subcutaneous infiltrate on her right arm. She had chronic diarrhea with protein-losing enteropathy. She underwent endoscopy and colonoscopy with biopsies. Histopathologic changes from these biopsies showed hyaline deposition. The diagnosis of infantile hyaline fibromatosis was confirmed on clinical and histopathologic grounds even though molecular genetic testing had failed to identify a second (maternal) pathogenic variant in *ANTXR2*. Further, genome-based testing is planned to detect this gene's cryptic maternal variant.

Her diarrhea improved with dietary changes to increase her protein intake (Pediasure with peptide). She was referred to Palliative Medicine for pain management and Dentistry for management of the gingival nodules. Immunology and Rheumatology services were consulted for long-term management recommendations.

Discussion:

Hyaline fibromatosis (HFS; MIM# 228600) is a rare **autosomal recessive** disorder of variable severity caused by pathogenic variants in the anthrax toxin receptor-2 gene (*ANTXR2*; MIM# 608041). It is named for the characteristic and widespread hyaline deposits in the papillary dermis, skeletal and cardiac muscle,

Table 1: These clinical features were reported in a large cohort of 116 patients with HFS. (Published with permission from Zhu et al. (3) <http://creativecommons.org/licenses/by-nc-nd/4.0/>)



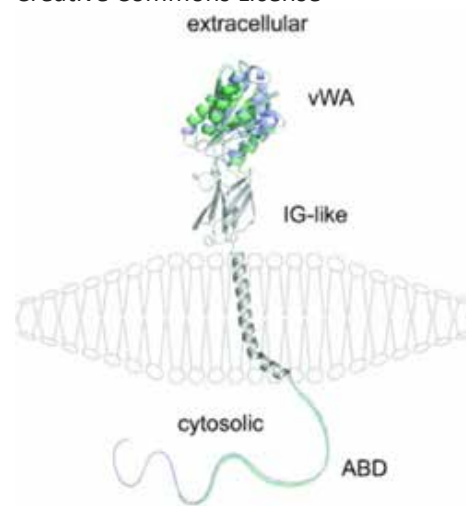
gastrointestinal tract, lymph nodes, spleen, thyroid, adrenal glands, and other tissues in affected individuals. It has also been called infantile systemic hyalinosis (ISH).

The severe form of HFS can present at birth or infancy with severe pain with movement, progressive joint contractures and severe motor disability, thickening and nodularity of the skin, and hyperpigmented macules/patches over bony prominences of the joints. Gingival hypertrophy, skin nodules, pearly papules of the face and neck, and perianal masses are common. Complications of chronic diarrhea, protein-losing enteropathy, and failure to thrive can be life-threatening. Cognitive development is normal.

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Figure 2 depicts the protein ANT XR2, showing extracellular, transmembrane, and cytoplasmic domains. Ig: Immunoglobulin, ABD: Actin-binding domain

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Prior to the gene's discovery, infantile systemic hyalinosis was the diagnostic term used for the more severe form that caused significant morbidity and mortality in early childhood. JHF for juvenile hyaline fibromatosis was used for patients with a more benign course. Now, it is known that these disorders are allelic, both caused by biallelic variants in the same gene, *ANTXR2*. Nofal et al. (1) proposed a grading system, modified by Denadai (2) that classifies HFS into grade 1 or mild (skin and/or gingival involvement), grade 2 or moderate (joint and/or bone involvement), grade 3 or severe (internal organ involvement with or without clinical manifestations such as protein-losing enteropathy and recurrent infections), and grade 4 or life-limiting (organ failure, sepsis).

A published review of clinical manifestations in 116 patients with HFS (3) is summarized in Table 1. Zhu and colleagues noted that the most common findings were joint contractures, gingival hypertrophy, cutaneous nodules, osteopenia, joint pain, and intractable diarrhea. The most common presenting symptoms in the infantile form were severe pain with movement and progressive joint contractures.

ANTXR2 codes for anthrax toxin receptor 2, a transmembrane protein with a von Willebrand A (vWA) domain, an Ig-like domain, a transmembrane domain, and a cytoplasmic tail (Figure 2). The vWA domain binds to both laminin and collagen IV and has a possible role in basement membrane matrix assembly. The long and highly conserved cytoplasmic tail domain is predicted to be largely unstructured and contain an actin-cytoskeleton interacting domain. Loss of function mutations in the gene that result in abnormal protein function can lead to extravasation of hyaline material through the basement membrane into the perivascular space, with the subsequent multisystemic clinical symptoms.

Some genotype-phenotype correlations are inferred from homozygotes (who have identical mutations in both gene copies), although they are not always consistent. Our patient's known (paternal) mutation is a recurrent frameshift in the cytoplasmic tail that generates a premature stop codon. Homozygotes with this recurrent mutation in the cytoplasmic tail are reported to have

clinical severity ranging from mild to life-limiting, with the majority having severe disease (5). In-frame and missense variants in the cytoplasmic domain were associated with a milder phenotype.

Knowing that her features developed after birth refocused the differential diagnosis on progressive disorders.

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“There is no disease-specific therapy, and treatment is symptomatic. Protein-losing enteropathy and recurrent infections can be life-limiting in the first years of life. Early surgical excision of subcutaneous nodules and gingival hypertrophy has been performed. Joint contractures may respond to intralesional steroid injections in the early stages, as well as systemic steroid therapy. Other treatments, including methotrexate and steroid use, have had limited success. Non-steroidal anti-inflammatory drugs and/or opiates can be used for pain management. Supportive care and lifelong physical rehabilitation are indicated.”

It is well known that next-generation sequencing methods may miss hard-to-detect variants, such as large insertion-deletions (indels), complex rearrangements, and small copy number variants. Gene analysis of *ANTXR2* is reported to detect ~95% of pathogenic variants by sequencing methods, whereas ~5% of variants are identified only on gene-targeted deletion/duplication analysis (6). It will be important to detect the second variant in our patient to understand better her clinical course, prognosis, and potential gene-targeted therapies in the future. This information is also necessary to provide parents with accurate recurrence risk in future offspring and offer prenatal diagnosis if desired.

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Practical Applications:

1. Document the phenotype carefully, including the age of onset of symptoms. This patient's hypotonia, pain with movement, and joint limitation were not present at birth. This ruled out all types of arthrogryposis, which is, by definition, congenital.

2. Understand that all types of genetic tests, including next-generation sequencing (NGS) based gene panels and whole exome sequencing, have limitations. NGS can miss deep intronic variants, single exon deletions, insertions, inversions, and complex gene rearrangements.
3. Consider genetic test results in the context of the patient's physical phenotype and other clinical information, such as, in this case, histopathology. When only one pathogenic variant is identified in a gene associated with an autosomal recessive disorder, the diagnosis may still be appropriate if the patient's phenotype is consistent.
 - a. When only one pathogenic variant is identified in a gene associated with an autosomal recessive disorder that DOES NOT match the patient's phenotype, it is reasonable to conclude that the patient is a heterozygous carrier for that disorder.

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