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CLINICAL REPORT

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Clinical aspects of Hyaline Fibromatosis Syndrome and identification of a novel mutation

Bettina Härter[1] | **Francesco Benedicenti**[2] | **Daniela Karall**[3] | **Ekkehard Lausch**[4] | **Gisela Schweigmann**[5] | **Franco Stanzial**[2] | **Andrea Superti-Furga**[6] | **Sabine Scholl-Bürgi**[3]

[1]Division of Pediatric Surgery, Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Innsbruck Medical University, Innsbruck, Austria

[2]Clinical Genetics Service and South Tyrol Coordination Center for Rare Diseases, Department of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy

[3]Department of Pediatrics I, Innsbruck Medical University, Innsbruck, Austria

[4]Pediatric Genetics Section, Department of Pediatrics, University of Freiburg, Freiburg, Germany

[5]Department of Radiology, Innsbruck Medical University, Innsbruck, Austria

[6]Division of Genetic Medicine, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

Correspondence
Bettina Härter, Division of Pediatric Surgery, Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria.
Email: Bettina.Haerter@i-med.ac.at

Abstract

Background: Hyaline fibromatosis syndrome is an autosomal recessive disease caused by mutations in *ANTXR2* which leads to loss of function of the transmembrane protein anthrax toxin receptor 2. It is distinguished by characteristic skin lesions, gingival hyperplasia, joint and bone disease, and systemic involvement.

Methods: Based on the case of an 11-year-old female patient with typical features of hyaline fibromatosis syndrome and the underlying pathogenic compound heterozygote variants in *ANTXR2* we discuss the genetic and clinical aspects of hyaline fibromatosis syndrome.

Results: The novel mutation in *ANTXR2* (c.1223T>C, p.Leu408Pro variant) seems to allow for a protracted course of the disease.

Conclusion: Our findings add to the phenotypic, genetic, and biochemical spectrum of hyaline fibromatosis syndrome.

KEYWORDS

ANTXR2, *CMG2*, Hyaline Fibromatosis Syndrome, infantile systemic hyalinosis, juvenile hyaline fibromatosis

1 | INTRODUCTION

The term hyaline fibromatosis syndrome (HFS), first introduced by Nofal et al. (2009), subsumes two variants of the same progressive, disfiguring, and disabling disease, the juvenile hyaline fibromatosis (JHF) and the infantile systemic hyalinosis (ISH).

HFS is a rare autosomal recessive disease without ethnic predilection caused by loss-of-function mutations in anthrax toxin receptor 2 gene (*ANTXR2)* (MIM #608041), also called capillary morphogenesis gene 2 (*CMG2)* at 4q21 (Dowling et al., 2003). It is expressed in all tissues except the brain and encodes a 55 kDa type I transmembrane protein, the anthrax toxin receptor 2 (ANTXR2). ANTXR2 consists of an extracellular N-terminal von Willebrand factor type A domain (vWA) followed by an Ig-like domain, a single transmembrane helix and a cytosolic tail (Deuquet, Lausch, Superti-Furga, & Goot, 2012). The exact cellular role of the protein is poorly

understood. As suggested by the name, the disease is characterized by the accumulation of hyaline amorphous deposits in the skin and other organs of patients (Shieh et al., 2006; Tzellos et al., 2009; Urbina, Sazunic, & Murray, 2004). These noncancerous tissue proliferations are the most outstanding external hallmarks of the patients. They usually present characteristic skin lesions, gingival hyperplasia, joint and bone disease, and systemic involvement. The skin lesions may be disfiguring. Two types of skin lesions are usually present. Pink pearly papules and plaques are commonly located on the chin, nasolabial folds, forehead, ears, back of the neck, and perianal region whereas large subcutaneous tumors are found on the scalp and less frequently on the trunk, extremities, and eyelids. Gingival hyperplasia is a common finding that may interfere with feeding and may result in poor oral hygiene, infection, and dental caries. Painful flexion contractures, particularly of the large joints result in severe limitation of mobility. Bone involvement may present in the form of osteoporosis, fractures, and osteolytic lesions of the long bones (Nofal et al., 2009).

Disease severity is variable. It was demonstrated that JHF and ISH are allelic conditions (Hanks et al., 2003). ISH (MIM #236490) is the more severe form, whose patients have very early onset even at birth, infiltration of the small intestine and colon, the most common form of systemic involvement, leading to malabsorption and protein-losing enteropathy with diarrhea, failure to thrive, growth failure and an increased susceptibility to infection. This condition leads to early death (Lindvall et al., 2008). Other organs that may be affected include the heart, trachea, esophagus, stomach, spleen, adrenal glands, thyroid, lymph nodes, and skeletal muscle (Shin et al., 2004). Less commonly reported features of ISH include the reduction of fetal movements, rigidity of the spine, joint swelling, saddle nose deformity, and sunken eyes (Lindvall et al., 2008). Afflicted individuals for the milder form, JHF (MIM#228600), reach adulthood even though highly incapacitated by the cutaneous tumors (Deuquet et al., 2009). Molecular results have confirmed that ISH and JHF are not distinct disorders but form a continuous phenotypic spectrum determined at least partially by the combination of specific *ANTXR2* gene mutations (Deuquet et al., 2011, 2012). Also, improvements in therapeutic approaches allow today for the survival of even severely affected patients. After a first "inflammatory" phase in the first 2 years of life, surviving patients enter a more chronic, stable form of the disease characterized by stiffening of the joints and development of the benign but disfiguring tumors (personal observation). As ANTXR2 is expressed in all tissues but the brain, there is no CNS involvement in either condition, and development is unaffected (Deuquet et al., 2012; Stucki et al., 2001).

2 | METHODS

We collected clinical information by review of medical records. We evaluated history, clinical manifestations, histopathologic, radiologic and laboratory findings, nuclear medicine imaging, and therapy data of a today 11-year-old female patient. Data were reviewed from birth until April 2015. For mutation analysis, genomic DNA was extracted from peripheral blood leucocytes, and the exons of CMG2/ANTXR2 were amplified individually and sequenced in both directions using the Sanger technique and capillary sequencing. The sequences obtained were analyzed using the ANTXR2-201 transcript, ENST00000307333.7 (www.ensembl.org) as reference.

2.1 | Editorial policies and ethical considerations

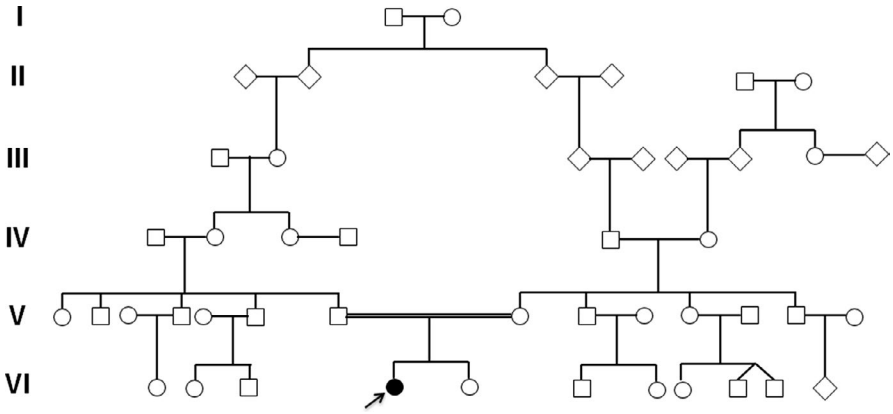
Written informed consent for retrospective data collection, molecular studies, and manuscript submission for review and possible publication was obtained from the parents, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

3 | RESULTS

A today 11-year-old female patient was full-term born at normal birth weight (2,850 g, 10th-25th percentile), length (49 cm, 10th-25th percentile), and occipito-frontal circumference (34.5 cm, 25th-50th percentile) as the first child of healthy parents from a valley in the Alps in South Tyrol. The parents are third cousins (Figure 1). Pregnancy followed a normal course except for immediate prenatal oligohydramnios and two times of antibiotic therapy of the mother due to sinusitis.

Since the first week of life decreased and painful motility of the upper extremities were recognized. Radiological subperiosteal hematomas on both upper arms were conspicuous. Progressively painful flexion contractures of the large joints of the upper and lower limb (shoulders, elbows, wrists, hips, knees, and ankles) appeared (Figure 2). Under the administration of gabapentin the painful symptoms alleviated partially. Since the fourth month of life pink to dark red papules presented in increasing number and size on the nasolabial folds, at the columella, on the auricles, and in the perianal region. Gingival hyperplasia occurred since the 15th month of life (Figure 2). The patient showed motoric but no psychomental developmental delay. MR imaging of the brain, echocardiography, abdomen sonography and ophthalmic examination with funduscopy revealed normal results. The patient didn't show any signs of enteropathy or have recurrent infections. With advancing age microsomia, reduced gross strength, muscle, and connective tissue hypotrophy, distinct impairment of gross motor skills, lesser also of fine motor skills appeared and led to increasing motoric developmental

FIGURE 1 Pedigree



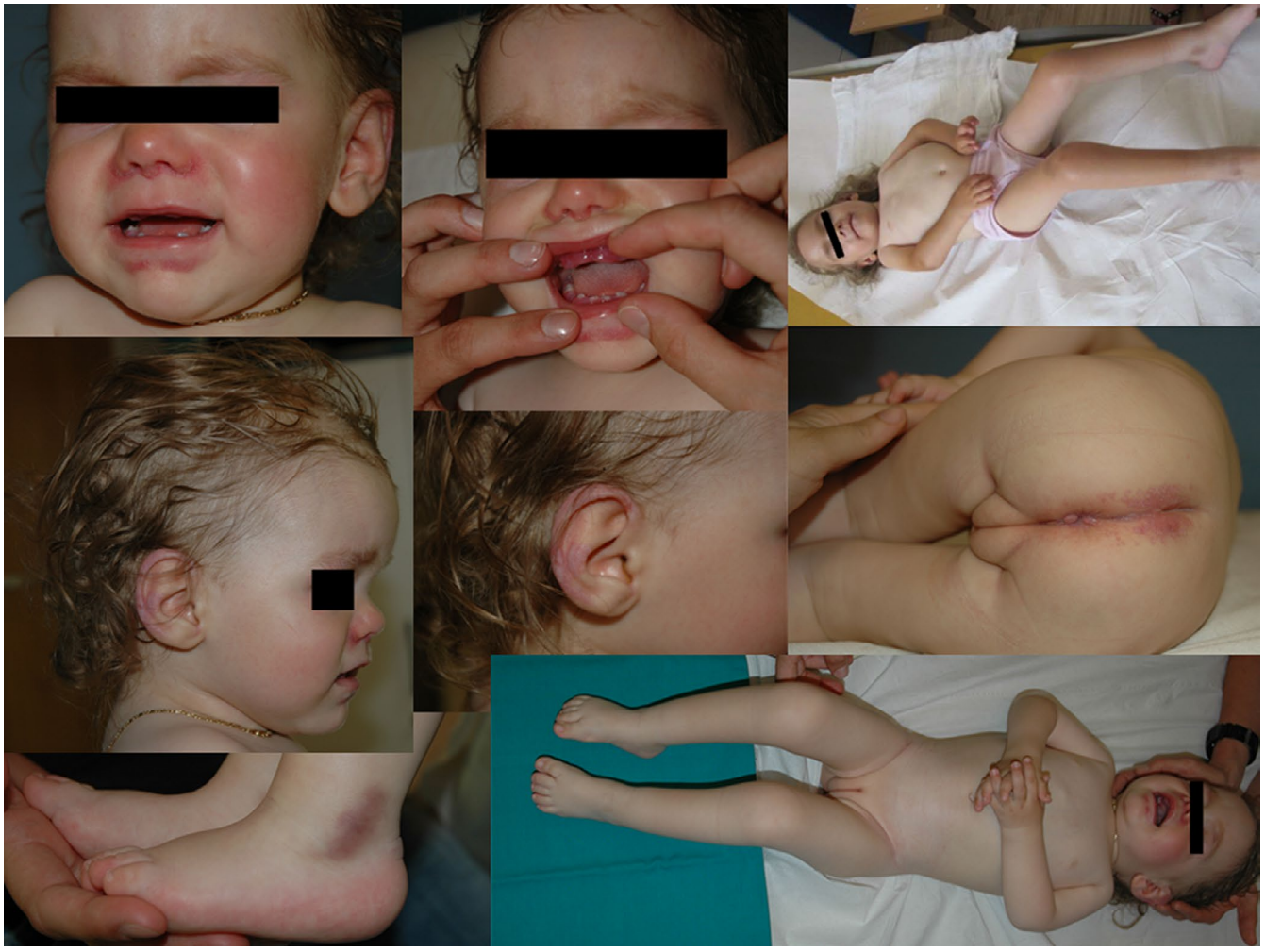


FIGURE 2 Phenotype of the patient with *ANTXR2* mutation. Flexion contractures of hips, knees, shoulders, and elbows. Pink pearly papules and plaques on the nasolabial folds, at the columella, on the lower lip, on the auricle, and in the perianal region. Gingival hyperplasia. Microsomia, muscle and connective tissue hypotrophy, barrel-shaped thorax. Out-bulged front and depressed nasal bridge. Hyperpigmented macules over the lateral malleolus

delay. The patient's thorax was barrel-shaped. The front was out-bulged and the nasal bridge depressed. Livid-red macules were seen over the lateral malleolus on both sides (Figure 2). Over the course of time, hyaline papules were surgically removed several times retroauricular and one time perianal, subcutaneous tumors were surgically removed parietal left and gluteal right. Five times gingival hyperplasia was resected. Histopathologic examination of the removed tissue showed deposits of intensive eosinophil hyaline material. Laboratory findings were unremarkable. Since the age of

7 years, the patient complains of hip pain, especially on the left side. Conventional X-ray of the pelvis showed considerable osteopenia and osteolysis of the acetabula and femoral heads leading to deformation of the hips (Figure 3). MRI of the hips showed multiple confluent hyaline masses in the hip joints and secondary strictly localized erosions of the femoral necks, femoral heads, and acetabula (Figure 4). Densitometry revealed a mean bone density of 0.288 g/cm^2 in the lumbar spine which is distinct below the norm (Figure 5). Therapy consists of pain management with gabapentin, naproxen, and omeprazole. Twice weekly the patient gets physiotherapy, her mother performs several times a day passive mobilization and at night the patient wears lower leg splints to prevent contractures.

At the age of 2 years, genetic studies were done to confirm the clinical diagnosis. In the patient, a known pathogenic variant was found, c.1074delT (p.Ala359His*fs**50), predicting a frameshift and premature stop codon; as well as a hitherto unreported variant, c.1223T>C (p.Leu408Pro) predicting an amino acid substitution in the cytoplasmic tail of the CMG2 protein. Parental analysis showed that each parent was heterozygous for one variant only, confirming compound heterozygosity in the proband.

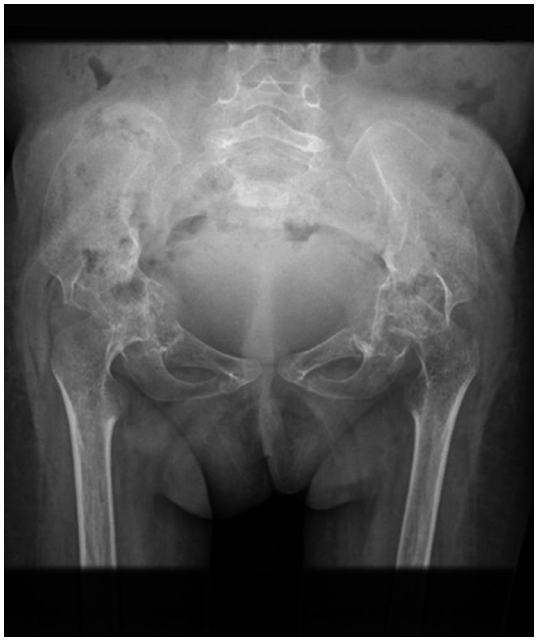


FIGURE 3 Conventional X-ray of the pelvis: Considerable osteopenia and osteolysis of the acetabula and femoral heads leading to deformation of the hip joints

4 | DISCUSSION

More than 150 cases of HFS have been reported and some 34 different mutations, predominantly in exons and spread from exon 1 to exon 15, have been identified. Although most mutations have been identified only once, there is a mutational hotspot in exon 13 (positions 1,074–1,077) at which insertion of one or two bases and deletion of one base have been repeatedly reported (c.1073 1074insC, c.1073 1074insCC (insCC) c.1074delT (delT)). Interestingly, as our patient, some 40% of the reported patients are compound heterozygous, indicating that *ANTXR2* mutations may not be extremely rare. These patients generally carry one allele with a modification at the exon 13 hotspot and one allele with a missense or non-sense mutation (Deuquet et al., 2012; Yan et al., 2013). Mutations lead to HFS by loss of function of ANTXR2 through mRNA degradation or defects in protein folding (Yan et al., 2013). The exact pathophysiology by which mutations in *ANTRX2* result in the phenotype of HFS is unknown. In a recently published study it was shown that ANTRX2 may be a receptor for collagen VI and mediates its transport to lysosomes for degradation and that thus, loss of ANTRX2 function causes accumulation of collagen VI in the extracellular matrix,

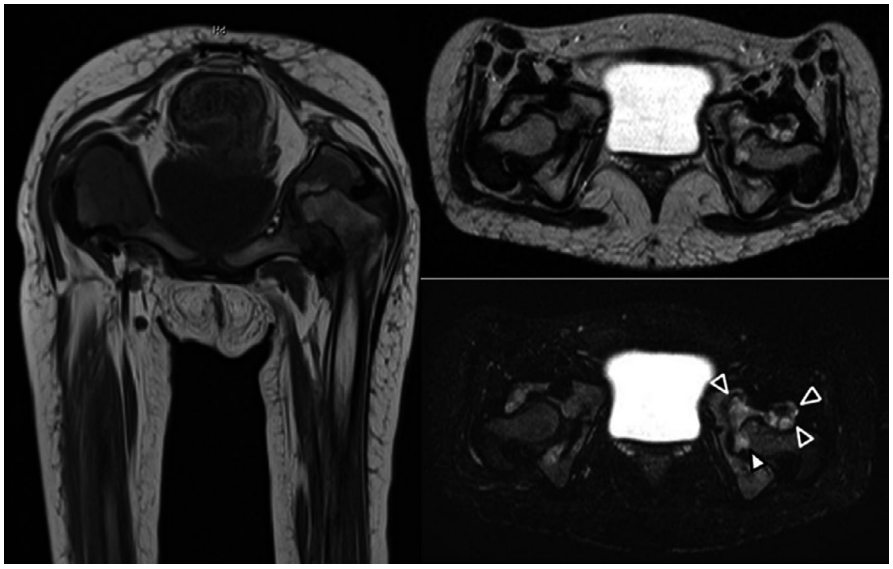


FIGURE 4 MRI of the hips: Multiple confluent hyaline masses in the joint space of the hip (black arrowhead) with erosion of the femoral head (white arrowhead)

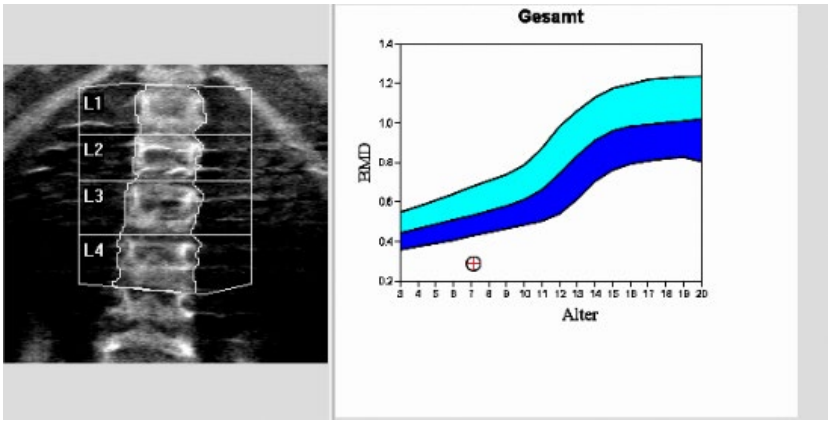


FIGURE 5 Densitometry of the lumbar spine: mean bone density of 0.288 g/cm^2 (by courtesy of Department of Nuclear Medicine, Innsbruck)

which with time may lead to tissue disruption and disease (Bürgi et al., 2017). Preliminary genotype-phenotype analyses suggest that abrogation of binding by the vWA domain results in severe disease, whereas in-frame mutations affecting the cytoplasmic domain result in a milder phenotype (Hanks et al., 2003).

No therapy has yet been discovered that can cure or halt the progression of HFS. Thus treatment is symptomatic. Important is an adequate analgetic therapy with nonsteroidal anti-inflammatory drugs, gabapentin, and opiates. As in the present case, osteoporosis, and osteolysis may cause pain. These symptoms could additionally be treated with bisphosphonates. Regular physiotherapy should be carried out to maintain the range of motion and to prevent contractures. Treatment of skin papules and subcutaneous nodules consists of surgical excision. It is better when this is performed early because lesions may become very large and ulcerated, causing the patient immense discomfort (El-Maaytah et al., 2010). Surgical excision may be definitive as in the present patient's scalp and right buttock. However, as in the patient's ear, local recurrence is common. The use of intralesional steroids in the treatment of subcutaneous nodules has been suggested, although has not yet been proven to be effective (Urbina et al., 2004). Capsulotomy of joint contractures has shown a temporary beneficial effect. Radiotherapy is ineffective (Urbina et al., 2004). Symptomatic treatment of oral lesions may include partial or radical gingivectomy and repeated as appropriate. The extraction of mobile and carious teeth is advised. Frequent visits for periodontal treatment and maintenance of good oral hygiene are important factors in decreasing the growth rate of the gingivae in patients with HFS (El-Maaytah et al., 2010). As loss of ANTRX2 function is causative for HFS future studies analyzing the normal function of the ANTRX2 protein are crucial to explore specific treatment modalities and to develop compounds that compensate for the lack of ANTRX2 function.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The need for approval was waived the local ethical committees as data were collected retrospectively and reported anonymously. The patients' legal guardian provided informed consent to participate.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients' legal guardian for publication of this case report and any accompanying images.

ACKNOWLEDGMENTS

We are very grateful to the patient and her parents for accepting to publish the findings and for their collaborative attitude.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

BH contributed to the clinical and histopathological characterization of the patient and wrote the manuscript with SSB and with input from all coauthors. FB contributed to the clinical and genetic characterization of the patient. DK contributed to the clinical and histopathological characterization of the patient. EL did the mutation analysis. GS conducted the radiological examinations and findings. FS contributed to the clinical and genetic characterization of the patient. ASF contributed to the mutation analysis and critically revised the manuscript for important intellectual content. SSB contributed to the clinical and histopathological characterization of the patient, coordinated the clinical work and wrote the manuscript with BH and with input from all coauthors.

ORCID

Bettina Härter https://orcid.org/0000-0002-1216-4227

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