Diagnosis implications of the whole genome sequencing in a large Lebanese family with hyaline fibromatosis syndrome

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Abstract

Background: Hyaline fibromatosis syndrome (HFS) is a recently introduced alternative term for two disorders that were previously known as juvenile hyaline fibromatosis (JHF) and infantile systemic hyalinosis (ISH). These two variants are secondary to mutations in the anthrax toxin receptor 2 gene (ANTXR2) located on chromosome 4q21. The main clinical features of both entities include papular and/or nodular skin lesions, gingival hyperplasia, joint contractures and osteolytic bone lesions that appear in the first few years of life, and the syndrome typically progresses with the appearance of new lesions.

Methods: We describe five Lebanese patients from one family, aged between 28 and 58 years, and presenting with nodular and papular skin lesions, gingival hyperplasia, joint contractures and bone lesions. Because of the particular clinical features and the absence of a clinical diagnosis, Whole Genome Sequencing (WGS) was carried out on DNA samples from the proband and his parents.

Results: A mutation in ANTXR2 (p. Gly116Val) that yielded a diagnosis of HFS was noted.

Conclusions: The main goal of this paper is to add to the knowledge related to the clinical and radiographic aspects of HFS in adulthood and to show the importance of Next-Generation Sequencing (NGS) techniques in resolving such puzzling cases.

Keywords: Juvenile hyaline fibromatosis, Infantile systemic hyalinosis, Hyaline fibromatosis syndrome, Whole genome sequencing, Anthrax toxin receptor 2 gene

Background

Juvenile hyaline fibromatosis (JHF, OMIM # 228600) is a rare inherited autosomal recessive disorder [1] that was first described by McMurray as Molluscom fibrosum [2]. Clinically, it is characterized by skin lesions (nodules and/or pearly papules); gingival hyperplasia; joint contracture; abnormal growth of hyalinized fibrous tissues of the head, neck and extremities; and bone lesions [3]. Affected individuals are usually asymptomatic at birth, the onset of clinical signs occurs between 3 months and 4 years of age [4, 5], and these signs increase in severity with age [6, 7]. Most people with JHF survive until the fourth decade of life [8].

Infantile systemic hyalinosis (ISH, OMIM # 236490), another rarer disorder, shares many similarities with JHF [9, 10]. It is characterized by a more severe presentation than JHF and has an early onset (first weeks or months of life) and symptoms that include failure to thrive, short stature, diffuse thickening of the skin, hyperpigmented plaques over the joints, visceral involvement, persistent diarrhea and recurrent infections, and death usually occurs within the first 2 years of life [11–13].

Deleterious mutations of Anthrax toxin receptor 2 gene, (ANTXR2; OMIM # 608041) have been shown to cause both JHF and ISH [14–16]. The presence of a significant overlap at the molecular, histological and clinical levels between JHF and ISH have led to the adoption by Nofal et al. of an unifying taxonomy of “hyaline fibromatosis syndrome or HFS”, signifying that both entities represent...
the same disorder but with different degrees of severity [10, 17]. ANTXR2 encodes a 55 kDa type I transmembrane (TM) protein which comprises an extracellular N-terminal von Willebrand A (vWA) domain, followed by an immunoglobulin-like domain (Ig-like), a TM domain and a cytosolic tail [18, 19]. This protein is responsible for binding laminin and collagen IV via the vWA domain and the consequent plays a role in basement membrane matrix assembly and endothelial cell morphogenesis [15]. The Ig-like domain contains two disulfide bonds that are essential for proper ANTXR2 localization in the endoplasmic reticulum [18]. The cytosolic tail contains multiple sites for posttranslational modifications such as palmitoylation [20], phosphorylation and ubiquitination [21].

Genotype-phenotype correlation studies have suggested that the mutational spectrum might explain the wide phenotypic variability. Milder phenotypes are associated with in-frame and missense mutations within the cytoplasmic domain, whereas the more severe forms are caused by missense and truncating mutations in the vWA domain and at least one insertion/deletion mutation causing a translational frameshift. However, this correlation is not always constant, thus indicating that modifier genes and/or environmental elements can be involved [15, 22].

Approximately 150 cases of HFS have been reported in the literature [23]. Most of them were diagnosed in early childhood [24], but only a few cases were investigated in adults; the oldest patient was 51 years old [25].

In this paper, we report a large Lebanese family with five HFS patients aged between 28 and 58 years. The oldest patient (58 years) is described here. The aim of this report is to augment the findings related to the clinical, radiographic and differential diagnosis of HFS.

**Methods**

**Clinical report**

We identified one Lebanese Shiite family with three branches from a small village in North Lebanon (Fig. 1). All five patients were born to healthy consanguineous couples. The pregnancies were not followed medically but were reported to be without complications. For all
patients, the skin eruptions and gingival enlargement were first noticed at the age of 6 months, and the nodules continued to gradually increase in number and size.

At the time of physical examination, patient VI-3 was 42 years old, patient VI-4 was 36 years old, patient VI-5 was 30 years old, patient VI-10 was 28 years old and patient V-15 was 58 years old. Patients VI-3, VI-4, VI-10 and V-15 presented with an important postural deformity, and had been in wheelchairs since they were 10 years old, whereas patient VI-5 had a severe retardation of physical growth and development that caused movement difficulty.

The patients were thin with underdeveloped musculatures. Cognitive development, hearing and eyesight were noted to be normal in all patients.

Each patient was found to have recurrent, painless, variable-sized nodules over the scalp, ear, lobules, postauricular folds, forehead, nose, upper lip, shoulder, elbows, thorax, chest, back, fingers, perianal area, knee and feet. Small, pearly papules were limited to the chin and paranasal folds. The nose and ears were deformed and bulbous, secondary to numerous tumors. All patients had severe gingival hypertrophy covering the teeth completely. Patients VI-10 and V-15 had flexion contractures of the elbows, and fingers and hips and knees, which resulted in a frog leg position (Fig. 2).

Swellings and deformities in the feet, especially in the terminal phalanges of the toes, were also noted. The toenails were thickened.

Hematological and biochemical investigations were within normal limits. Only, patient VI-3 reported having persistent diarrhea since the age of 2 years. The clinical features of the present cases and of ISH and JHF, on the basis of the work of Urbina et al.[10] are shown in Table 1.

A skeletal X-ray of patient VI-10 showed subcutaneous soft tissue calcifications in the pinna of both ears and in the parietal region of the scalp, radial bone bowing, thoraco-lumbar scoliosis with paravertebral calcifications at T10, T11 and T12 levels, deformity of the iliac bones, thinned pubic rami, severe narrowing of the hip joints, acetabular protrusion, erosion of joint spaces, coxofemoral ankylosis, thinned fibula, amyotrophy and cutaneous calcifications (Fig. 3).

The patients refused biopsies of their lesions.

DNA extraction and Whole Genome Sequencing (WGS)
Genomic DNA was extracted from peripheral blood samples by standard salt-precipitation methods [26]. Whole genome sequencing was carried out on the DNA of patient VI-4 and his parents with a HiSeq 2500 sequencer (Illumina, San Diego, CA, USA) at Sidra Medical and Research Center - Qatar. Genomic libraries were generated from 1 μg of genomic DNA using an Illumina TruSeq DNA PCR-Free Sample Preparation Kit. Genomic DNA was sheared using a Covaris system.
Fig. 3 X-rays of patient VI-10 showing (a) radial bone bowing and thin diaphyses, (b) deformity of the iliac bones, thinned pubic rami, severe narrowing of the hip joints, acetabular protrusion, erosion of joint spaces, coxo-femoral ankylosis, thinned fibula, amyotrophy and cutaneous calcifications, (c) thoraco-lumbar scoliosis with paravertebral calcifications at T10, T11 and T12 levels and (d) subcutaneous soft tissue calcifications in the pinna of both ears and in the parietal region of the scalp.
Isolated DNA fragment ends were blunt-ended, A-tailed and ligated with sequencing adaptors with index sequences. Excess adapters and enzymes were removed using AMPure beads (Beckman Coulter Genomics, Danvers, MA, USA). Indexed libraries were size-selected to the 350 bp range using bead-based capture, and the concentration of amplifiable fragments was determined by qPCR, relative to sequencing libraries with a known concentration. Normalized libraries were clustered on a c-BOT machine, and 125 bp paired-end sequencing was performed on the HiSeq 2500 system.

**WGS data analyses**

Raw data were mapped to the human genome reference, build 19 (http://www.broadinstitute.org/ftp/pub/seq/references/Homo_sapiens_assembly19.fasta), using BWA aligner [27] version 0.7.7-r441, and variant calling was performed using GATK [28] version 3.3.2. Rare variant analysis was performed using the xbrowse tool (https://xbrowse.broadinstitute.org/). For the trio, the model of inheritance “autosomal recessive” was selected, with the severity of the variant effect set to ‘moderate to high impact’ (Nonsense, essential splice sites, missense frameshift and in frame), call quality as high (genotype quality > 20 and allele balance ratio > 25%) and allele frequency < 1% in 1000 genomes and The Exome Aggregation Consortium (ExAC) v0.3 datasets. The functional consequences of amino acid substitutions were predicted using various tools [29–32].

**Sanger sequencing**

Genomic sequence of ANTXR2 (NM_058172.5) was obtained from UCSC Genomic Browser on Human. Primers used for PCR amplification were designed using Primer3 software (http://frodo.wi.mit.edu) to amplify the region surrounding the mutation detected by WGS in exon 4. PCR reactions were performed using Taq DNA polymerase (Invitrogen Life Technologies, Carlsbad, CA, USA). PCR fragments were run on 1% agarose gel. The fragments were purified using «SIGMA-ALDRICH™» kit and then sequenced using the Big Dye_Terminator v 1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). Sequence reaction was purified on Sephadex G50 (Amersham Pharmacia Biotech, Foster City, CA) and then loaded into an ABI 3100 system after the addition of Hidi formamide. Electropherograms were analyzed using Sequence Analysis Software version 5.2 (Applied Biosystems) and then aligned with the reference sequences using ChromasPro v1.7.6.1 (Technelysium, Queensland, Australia).

**Results**

WGS identified 2 mutations in ANTXR2 (NM_058172.5: c.347G > T) and in zinc finger protein 618 (ZNF618) (NM_133374.2: c.832G > T). The ANTXR2 mutation results in a substitution of glycine by valine, and the zinc finger protein 618 (ZNF618) mutation leads to a premature stop codon. Both had damaging effects, according to the majority of the effect predictors tested (Table 2). Sanger sequencing confirmed the segregation of the c.347G > T mutation in ANTXR2 with the disease within the family (Fig. 1). The mutation was homozygous in the affected patients, heterozygous in the parents and heterozygous or not found in the unaffected siblings in this family.

**Discussion**

Here, we report five adult patients from a consanguineous Lebanese family, who presented with nodular skin lesions, gingival hyperplasia, joint contractures and bone lesions. By WGS, we identified 2 mutations: a mutation in ZNF618 (c.832G > T) and a mutation in ANTXR2 (c.347G > T).

ZNF618, also known as KIAA1952 or NEDD10, is a protein-coding gene located on chromosome 9q32 and is implicated in transcriptional regulation. Association studies have demonstrated that ZNF618 may be involved in the occurrence of cleft lip [33], high blood pressure [34], kidney diseases [35] and, in women, in brachial-ankle pulse wave velocity and arterial stiffness [36, 37]. On the basis of these clinical characteristics, we excluded this gene as a candidate gene.

ANTXR2, also called the capillary morphogenesis protein gene-2 (CMG2) is located on chromosome 4q21.

**Table 2** Variants identified with the WGS analysis while running an autosomal recessive model using xbrowse. Damaging effects of these mutations according to three softwares predictors was tested

| Gene      | Position | Function | Software prediction                  |
|-----------|----------|----------|--------------------------------------|
| ANTXR2    | Chr4:80977117 G > T | Missense c.347G > T p. Gly116Val | Polyphen score: 0.99 Polyphen prediction: probably damaging Sift score: 0 Sift prediction: damaging Mutation taster prediction: disease causing Mutation taster score: 0.99 |
| ZNF618    | Chr9:116794951 G > T | Missense c.832G > T p. Glu278* |
and is implicated in basement membrane matrix and cell morphogenesis [15]. Mutations of this gene have been found to be responsible for HFS. After reviewing the clinical features of our patients, we considered ANTXR2 to be a candidate gene responsible for the phenotype of the patients studied here.

A clinical diagnosis of HFS was missed because of the advanced age and status of the patients, the stage of the disease, the severity of the clinical manifestations, and incomplete knowledge of the syndrome's pathogenesis. The patients reported here had undergone multiple surgeries in infancy for the resection of cutaneous nodules, but long-term regression was unlikely, and the tumors continued to increase in size and number. Their parents stopped treating the lesions, and no follow-up was performed for economic reasons. Biopsies were refused by the patients for many reasons, including pain and the absence of treatment. WGS allowed us to diagnose the disease, assess the genotype-phenotype correlations and offer genetic counseling and prenatal diagnosis to the people of the village.

Classification of HFS
HFS and inherited systemic hyalinosis represent the same disorder, comprising two variants with severe (ISH) and mild (JHF) forms of the disease.

Gilaberte et al. [6] have proposed 2 major and 3 minor diagnostic criteria for JHF. The major criteria are cutaneous lesions (including nodules, tumors and plaques) and gingival enlargement. The minor criteria include joint contractures, osteolytic lesions and/or cortical erosions, and a family history of JHF. In fact, the presence of persistent diarrhea, hyperpigmented plaques, growth retardation and death within the first 2 years of life are more consistent with ISH. The severity and progression of HFS vary among patients, and hence it is difficult to classify a patient into a single class because many cases of JHF are incorrectly identified as ISH, or vice versa and mutations in the same gene underlie both syndromes. Indeed, Bedford et al. [38] have described a severe form of JHF, with persistent or repeated episodes of diarrhea and death occurring in early infancy after several infections yet with no subcutaneous nodules. Hata-mochi et al. [39] have reported a 6-year-old girl who was diagnosed with a severe form of JHF and presented with confluent papules and nodules, recurrent respiratory tract infections and chronic diarrhea since birth. Dhingra et al. [40] have reported a 3-year-old girl who presented with recurrent episodes of diarrhea and was diagnosed as having a case of JHF. ISH patients with atypical prolonged survival have also been reported [41]. Kawasaki et al. [42] have reported an elderly woman with JHF who died from aspiration pneumonia. For these reasons, we prefer to classify our patients as having HFS, which includes both disorders, as proposed by Nofal et al. [17].

In contrast, Nofal et al. [17] have classified HFS into three grades according to the severity of organ involvement: G1: mild, G2: moderate and G3: severe. On the basis of this gradation, the mild type presents with only skin involvement and gingival hypertrophy, the moderate type shows additional joint contractures and bone lesions, and the severe type has manifestations resulting from organ involvement, such as persistent diarrhea and recurrent pulmonary infections. Denadai et al. [22] have added a new lethal grade (G4) for patients with organ failure and/or septicemia. In the family studied here, patients VI-4, VI-5, VI-10 and V-15 can be classified as JHF grade 2 and patient VI-3 as ISH grade 3, thus demonstrating the difficulty of clearly differentiating these subclasses.

Prevalence
HFS is a rare genetic disorder, but it has been documented in families of different ethnic backgrounds on several continents [11]. The life expectancy of patients with HFS syndrome varies from early death in childhood to normal survivorship. The oldest known patient (58 years) is reported here.

Diagnosis
The diagnosis of this syndrome is based on the clinical features and/or the presence of a molecular diagnosis.

Clinical diagnosis
The clinical features associated with HFS syndrome consist of multiple subcutaneous skin nodules/papules, gingival hypertrophy and joint contractures and may be accompanied by systemic symptoms.

The specific pathogenesis of HFS also remains unclear, but some authors have suggested that it results from an abnormality in type IV or VI (α1, α2 and α3 chains) collagen [3, 43] or defective glycosaminoglycan formation [44, 45].

Skeletal radiographs in adults
To our knowledge, 33 cases of HFS have been reported in adults, of which 14 with X-ray findings. In 13 of these 14 cases, joint contractures, osteolytic destruction of the skull, of the large joints, of the long bones and of the extremities, triangular carpal bones and an isolated cortical erosion of mandibular bone and calcifications in the subcutaneous tumors were noted [4, 8, 16, 22, 25, 42, 46–52]. In one patient, no calcifications or bone involvement were noted on radiography [53].

Magnetic resonance imaging (MRI) of HFS lesions has rarely been described in adults and shows a hypointense, central, radiating scar and heterogeneous signal...
intensity. After the administration of a gadolinium contrast medium, the lesion showed diffuse enhancement, with the exception of the central scar and discrete enhancement of subcutaneous masses in contrasted phases [8, 51, 53].

Computed tomography (CT) of the head has demonstrated a normal aspect [51] or an abnormal buccal-lingual expansion with lingual cortical erosion [46], calcifications within the subcutaneous tumors, and a soft tissue mass extending from the hard palate into the nasal cavity and maxillary sinus [42]. Enhanced CT has revealed dye uptake in the submandibular and cervical lymph nodes bilaterally [42]. Brain CT has shown small ischemic regions in the right periventricular aspect, mild brain atrophy and extracranial tumor masses in the soft tissues of the right peritumoral and occipital aspects [47].

**Histopathology** The histopathologic features of this disease include a normal epidermis with few inflammatory cells in the dermis and minor pigmentary incontinence. Deposits of an amorphous, homogeneous and eosinophilic, hyaline substance (periodic acid-Schiff positive), can be found in the papillary and reticular dermis, accompanied by a proliferation of spindle cells without atypia [10, 22].

Electron microscopic studies have shown stromal deposits of a fibrillogranular material focally displaying a banding pattern similar to that of type VI collagen and fibroblasts with prominent Golgi complexes, dilated endoplasmic reticulum, multi vesicular bodies and vesicles filled with a fibrillogranular material [3, 10, 43]. Calciospherules, defined as calcium-containing lamellar body have been described in JHF by Ko and Barr in 2003 [54].

**Intestinal biopsy and imaging** The results of biopsy cases from patients with gastrointestinal signs include villous atrophy, edema, lymphangiectasia and hyalinosis. Rapid transit time has been described in real-time upper-gastrointestinal imaging investigations [55].

**Immune system deficit** Deficits of the humoral and cellular branches of the immune system have been observed [56].

**Laboratory studies** Laboratory examination may demonstrate a normal [22, 42, 57, 58] or abnormal aspect, such as an elevation of the Erythrocyte Sedimentation Rate (ESR) [47, 51, 59], thrombocytosis [60], mild anemia [4, 47, 51], or an elevation of serum albumin [61] or alkaline phosphatase [62].

**Molecular diagnosis**

ANTXR2 is the only gene in which pathogenic variants are known to cause HFS. Mutations of this gene disrupt the formation of basement membranes. This disruption may allow the hyaline material to leak from plasma components through the basement membrane into the perivascular space, thus explaining the histological features of HFS [15].

As shown in Table 3, 41 different ANTXR2 mutations have been described. Yan et al. [63] have reported that three frameshift mutations (c.1073-1074insC, c.1073-1074insCC and c.1074delT) represent approximately 60% of all pathogenic alleles. The incidence of insertions and deletions at positions 1073–1074 is probably due to its proximity to a low-complexity, GC-rich region encoding a stretch of proline residues that may constitute a vulnerable site for errors during DNA replication. The mutation p. Gly116Val identified in all patients in this study has previously been reported by Tümer et al. [64] in an 11-month-old Turkish girl with HFS. This mutation is located in the vWA domain and may damage ligand binding, not plasma membrane targeting, thus causing a severe manifestation of HFS. A comparison between the clinical signs of the patients in this study and the girl with the same mutation shows some differences: the girl presented with short stature and gingival hypertrophy and developed recurrent infections. She did not present with any visceral involvement. X-ray images did not show any osteolytic lesions [64]. These differences may be explained by the differences in age, and/or environmental factors.

**Mode of inheritance and genetic counseling**

An autosomal recessive mode of inheritance has been established for HFS. Therefore, the risk for a parental carrier to have an affected offspring is 25%.

**Treatment and follow-up**

Currently, only symptomatic treatments for HFS are available. Early surgical excision of the lesions is recommended for functional and cosmetic improvement [9, 52]. However, the lesions may recur and new lesions may appear [4, 52, 65, 66]. Intraläsional steroid injections have been suggested because they can reduce the size of early lesions [9]. Capsulotomy, physiotherapy, treatment with cortisone and adrenocorticotropic (ACTH) have found modest success in the treatment of joint contractures [67]. Radiotherapy is not effective [10, 68]. Oral D-penicillamine may improve joint mobility and flexibility [65, 69]. Nonsteroidal anti-inflammatory drugs and opiates may be used to control pain and improve the quality of life [9, 70]. Gingival hyperplasia requires special dental care and many dental consultations to promote strict oral hygiene [71]. Gingivectomy may
| Mutation | Location | Domain | Protein | Hom/Het | Phenotype/grading system | Ethnicity | Reference |
|----------|----------|--------|---------|---------|--------------------------|-----------|-----------|
| 1) c.2 T > G | Exon 1 | Signal peptide | p.M1R | Hom | ISH/3 | Dominican Republican | Antaya et al. [75] |
| 2) c.116G > T | Exon 1 | vWFA | p.C39F | Het | ISH/2 (patient 1) | N.D. | Deuquet et al. [18] |
| 3) c.134 T > C | Exon 1 | vWFA | p.L45P | Hom | ISH/3 (family R) | Bedouin | Hanks et al. [19] |
| 4) c.148G > A | Exon 1 | vWFA | p.D50N | Hom | ISH/4 | Saudi | Mohamed et al. [81] |
| 5) c.225-4G > A | Intron 2 | vWFA | Presumed splice defect | Hom | ISH/3 | Indian | Fong et al. [76] |
| 6) c.277_278insATTATT | Exon 3 | vWFA | p.L93YfsX14 | Hom | ISH/3 | Indian | Koonuru and Venugopal [77] |
| 7) c.304_305insA | Exon 4 | vWFA | p.I102VfsX12 | Het | ISH/3 | Chinese | Huang et al. [79] |
| 8) c.314G > A | Exon 4 | vWFA | p.G105D | Hom | JHF/3 (family JHF1) | Turkish | Dowling et al. [14] |
| 9) c.347G > T | Exon 4 | vWFA | p.G116V | Hom | ISH/3 | Turkish | Tümer et al. [64] |
| 10) c.353C > A | Exon 4 | vWFA | p.T118K | Hom | ISH/4 | Mexican | Lindvall et al. [80] |
| 11) c.487-2A > G | Intron 5 | vWFA | p.A163Q185del; p.A163K164del | Het | ISH/3 (Patient 5) | Brazilian | Denadai et al. [22] |
| 12) c.495_496insA | Exon 6 | vWFA | p.S166IfsX7 | Hom | ISH/3 (family N and O) | Moroccan and Pakistani | Hanks et al. [13] |
| 13) c.566 T > C | Exon 7 | vWFA | p.I189T | Hom | ISH/3 (family H) | Swiss | Dowling et al. [14] |
| 14) c.652 T > C | Exon 8 | vWFA | p.C218R | Hom | ISH/3 (family K) | European/Swiss | Hanks et al. [13] |
| 15) c.658G > T | Exon 8 | vWFA | p.E220X | Hom | ISH/3 (family ISH1) | Fijian | Hanks et al. [13] |
| 16) c.697 + 1dupG | Intron 8 | Ig-like domain | G232insG | Het | ISH/3 (family I) | Turkish | Dowling et al. [14] |
| 17) c.697 + 1 G > A | Intron 8 | Ig-like domain | Presumed splice defect | Het | ISH/3 (family ISH1) | N.D. | Deuquet et al. [19] |
| 18) c.796 + 2 T > C | Intron 9 | Ig-like domain | Presumed splice defect | Het | JHF/2 (family E) | European | Hanks et al. [13] |
| 19) c.857_945del | Exon 11 | Ig-like domain | p.E289DfsX22 | Hom | ISH/4 | Omani | Al Sinani et al. [81] |
| 20) c.876_877insCA | Exon 11 | Ig-like domain | p.D292VinsQ | Hom | ISH/2 (family G) | East Turkish | Hanks et al. [13] |
| 21) c.926G > T | Exon 11 | Ig-like domain | p.V310T | Het | ISH/2 (patient 2) | N.D. | Deuquet et al. [18] |
| 22) c.946-2A > G | Intron 11 | Ig-like domain | Presumed splice defect | Hom | ISH/4 (patient 1) | Iranian | Youssefian et al. [82] |
| #  | Description | Exon | Domain | Presumed Deletion | Hom | ISH? | N.D. | Source |
|----|-------------|------|--------|-------------------|-----|------|------|--------|
| 23) | N.D. | 11/12 | Ig-like domain-Transmembrane | | Hom | JHF/1 (family JHF2) | African American | Dowling et al. [14] |
| 24) | c.986 T > G | 12 | Transmembrane | p.L329R | Het | ISH/2 (family ISH2) | Swiss | Dowling et al. [14] |
| 25) | c.1073_1074insC | 13 | Cytoplasmic | p.A359Cfs*13 | Het | ISH/3 | N.D. | Rahvar et al. [83] |
| 26) | c.1073_1074insC | 13 | Cytoplasmic | p.A359Cfs*13 | Het | ISH/3 (family M)* | Puerto Rican + African American | Hanks et al. [15] |
| 27) | c.1073_1074insCC | 13 | Cytoplasmic | p.A359Lfs*51 | Het | ISH/3 (family L) | European/Swiss | Hanks et al. [15] |
| 28) | c.1074delT | 13 | Cytoplasmic | p.A359Hfs*50 | Het | ISH/2 (patient 2 and 5) | Brazilian | Denadai et al. [22] |
| 29) | c.1075insT | 13 | Cytoplasmic | p.A359Vfs*13 | Het | ISH/7 | N.D. | Deuquet et al. [19] |
| 30) | c.1086 + 1G > A | Intron13 | Cytoplasmic | p.V394Ifsa6 | Hom | JHF/2 (families C and F) | Turkish/European | Hanks et al. [15] |
| # | Mutation | Location | Type | Grade | Country | Reference |
|---|----------|----------|------|-------|---------|-----------|
| 31 | c.1087_1706del | Intron 13-17 | Cytoplasmic | Presumed deletion | Hom | ISH/4 (patient 2) | Mexican | Shieh et al. [84] |
| 32 | c.1142A > G | Exon 14 | Cytoplasmic | p.Y381C | Hom | JHF/1 (family D) | Moroccan | Hanks et al. [15] |
| 33 | c.1150C > T | Exon 14 | Cytoplasmic | p.R384X | Het | ISH/3 (family I) | European/Canadian | Hanks et al. [15] |
| 34 | c.1156G > T | Exon 14 | Cytoplasmic | p.V386F | Hom | JHF/2 | Turkish | Hanks et al. [72] |
| 35 | c.1179G > A | Exon 14 | Cytoplasmic | p.E383_E393del | Hom | JHF/2 (families A and B) | Indian | Hanks et al. [15] |
| 36 | c.1179 + 5G > T | Intron 14 | Cytoplasmic | Presumed splice defect | Hom | ISH/3 | Chinese | Wang et al. [89] |
| 37 | c.1179 + 5G > T | Intron 14 | Cytoplasmic | Presumed splice defect | Hom | JHF/2 (family H) | Turkish | Hanks et al. [15] |
| 38 | c.1180_1428del | Intron 14-16 | Cytoplasmic | p.V394_E476del | Het | ISH/3 (patient 2) ISH/2 (patient 3) | Brazilian | Denadai et al. [22] |
| 39 | c.1181T > C | Exon 14 | Cytoplasmic | p.V394A | Het | ISH/3 | Japanese | Hatamochi et al. [39] |
| 40 | c.1294C > T | Exon 15 | Cytoplasmic | p.R432X | Het | ISH/3 (patient 3) | Mexican | Shieh et al. [84] |
| 41 | c.1340delC | Exon 15 | Cytoplasmic | p.P447Qfs*13 | Hom | JHF/2 (family 2) | Egyptian | El-Kamah et al. [87] |

*Homozygous for mutation, Het heterozygous for mutation, N.D. not determined

*Grading system according to classification of Nofal et al. and Denadai et al. [17, 22]

*Compound heterozygote with only 1 mutation found

**This is presumed since patient DNA could not be amplified for this region of the gene
improve the quality of oral hygiene and nourishment by improving mastication and preventing gingival blood loss [72, 73]. Ablative laser surgery may be a reasonable choice and may be useful, at least as an adjunctive treatment [74]. In context of genetic therapies for this debilitating disorder, Dequ et al. [18] have revealed that proteasome inhibitors may be potential therapeutic drugs for HFS patients with mutations in the ectodomain of ANTXR2.

Conclusions

We report a Lebanese family with five adult patients with HFS. WGS showed an ability to establish a diagnosis in such puzzling cases in which the clinical signs are atypical or very severe for the classical phenotype. HFS is still a poorly understood disease with a severity that ranges from being lethal during early childhood to chronic at a later age. More studies to find an effective treatment are essential. An accurate diagnosis of the disease requires an exhaustive analysis of the radiologic and histopathological clinical findings, and genetic studies are required for family planning and counseling.

Abbreviations

ACTH: Adrenocorticotropic; ANTXR2: Anthrax toxin receptor 2 gene; CMG2: Capillary morphogenesis protein gene-2; CT: Computed tomography; ESR: Erythrocyte Sedimentation Rate; EAC: Exome Aggregation Consortium; HFS: Hyaline fibromatosis syndrome; Ig-like: Immunoglobulin–like domain; iSH: Infantile systemic hyalinosis; JHF: Juvenile hyaline fibromatosis; MRI: Magnetic resonance imaging; NGS: Next-Generation-Sequencing; TM: Transmembrane; vWA: von Willebrand A; WGS: Whole Genome Sequencing; ZNF618: Zinc finger protein 618

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We express our deepest gratitude and sympathy to the family for their full participation and any accompanying images. The patients were not able to sign by themselves due to the presence of variable-sized nodules over the fingers. Only patient V-15 signed the consent using a stick.

Ethics approval and consent to participate

This study was granted approval from the Saint Joseph University of Beirut Committee on Clinical Investigation and conformed to the tenets of the Declaration of Helsinki. Approval for the study, publication of photographs and informed written consent were obtained from legally authorized patient representatives.

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