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Biallelic mutation of *FBXL7* suggests a novel form of Hennekam syndrome

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Abstract

Hennekam lymphangiectasia-lymphedema syndrome is an autosomal recessive disorder characterized by congenital lymphedema, intestinal lymphangiectasia, facial dysmorphism, and variable intellectual disability. Known disease genes include *CCBE1*, *FAT4*, and *ADAMTS3*. In a patient with clinically-diagnosed Hennekam syndrome but without mutations or copy-number changes in the three known disease genes, we identified a homozygous single-exon deletion affecting *FBXL7*. Specifically, exon 3, which encodes the F-box domain and several leucine-rich repeats of FBXL7, is eliminated. Our analyses of databases representing >100,000 control individuals failed to identify biallelic loss-of-function variants in *FBXL7*. Published studies in *Drosophila* indicate Fbxl7 interacts with Fat, of which human FAT4 is an ortholog, and mutation

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Disclosure Declaration

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of either gene yields similar morphological consequences. These data suggest that *FBXL7* may be the fourth gene for Hennekam syndrome, acting via a shared pathway with *FAT4*.

Keywords

Hennekam syndrome; *FBXL7*; congenital lymphedema; *MiR-887*; lymphatic dysplasia

Introduction

Hennekam lymphangiectasia-lymphedema syndrome (HKLLS) is an autosomal recessive condition involving defective lymphatics. Major features include lymphedema, lymphangiectasia, facial dysmorphism, and intellectual disability [Van Balkom et al., 2002]. Lymphedema (soft-tissue swelling from compromised lymphatic flow) may be congenital or infantile and primarily affects the lower extremities, genitals, and face. Lymphangiectasia (dilation of lymphatic ducts) primarily affects the intestines and can cause protein-losing enteropathy. Facial dysmorphisms include a flat face, hypertelorism, epicanthal folds, a broad and depressed nasal bridge, a small mouth, and low-set ears with a narrow canal. Intellectual disability is inconsistent. Other features can include dental anomalies and hearing loss.

Biallelic variants in three genes are known to cause Hennekam syndrome: *CCBE1*, *FAT4*, and *ADAMTS3* (OMIM #235510, 616006, and 618154). CCBE1 and ADAMTS3 affect VEGFC/VEGFR3 signaling, a known pathway directing lymphangiogenesis [Brouillard et al., 2017; Le Guen et al., 2014]). FAT4 impacts endothelial cell polarity and is necessary for normal lymphatic valve formation in mice [Pujol et al., 2017]. Here, we describe a patient with features of Hennekam syndrome, but without a previously observed pathogenic variant in one of the three known Hennekam syndrome genes. We identified a homozygous deletion in *FBXL7*, predicted to eliminate a key domain of FBXL7. Population genetic evidence supports *FBXL7*'s candidacy as a novel disease gene, and published animal data implicate FBXL7 in a shared pathway with FAT4. Thus, we propose *FBXL7* may be the fourth Hennekam syndrome gene.

Methods

Human subjects research

Subjects were enrolled under Boston Children's Hospital IRB-approved protocol #10-02-0053. Experimental work at Massachusetts General Hospital (MGH) were performed under IRB-approved protocol #2013P000323.

Clinical genetic testing

Clinical sequencing and copy-number analysis of known lymphedema genes was performed by Fulgent Genetics (https://www.fulgentgenetics.com; CNVs ≥ 2 exons were reported). Clinical microarray analysis (copy-number and SNP analysis) was performed by Baylor Genetics (https://www.bcm.edu/research/medical-genetics-labs/) using the CMA-HR+SNP V11.2 platform.

Deletion breakpoint PCR

Long-range PCR was performed using 100ng DNA, 1.25µl (0.625µl if multiplexed) of each 10µM F and R primer, 1X Mg^{+2}-free LA PCR Buffer II (TaKaRa), 2.5mM $MgCl_2$, 400µM each dNTP, 1.5U TaKaRa LA Taq, and water to 25µl. Thermocycler conditions were 94°C x 1'; 30 cycles of 94°C x 30" and 68°C x 7' or 15'; and 72°C x 10'. Short-range PCR utilized 50ng DNA, 1.25µl of each 10µM F and R primer, 12.5µl 2X PCR Master Mix (Promega), and water to 25µl. Thermocycler conditions were 95°C x 2'; 40 cycles of 95°C x 30", 57°C x 30", and 72°C x 3'; and 72°C x 5'. Primers are listed in Table S1. PCR products were gel-extracted or treated with ExoSAP-IT (Thermo-Fisher), then Sanger sequenced by the MGH DNA Core.

Droplet digital PCR (ddPCR)

ddPCR reactions consisted of 1X ddPCR Supermix for Probes without dUTP (Bio-Rad), 1X HEX control assay targeting the *RPP30* gene (Bio-Rad; Assay ID dHsaCP2500350), 1X FAM TaqMan (Thermo-Fisher) assay targeting each of the four exons of *FBXL7* (Table S2), 2.5U MseI restriction enzyme (NEB), 50ng DNA, and water to 20µl. PCR parameters were: 95°C x 10', 40 cycles of 94°C x 30" and 57°C x 1', 98°C x 10', then 4°C hold. Droplets were made using the Automated Droplet Generator, read on the QX200 Droplet Reader, and analyzed with QuantaSoft (all Bio-Rad). Positive droplet thresholds were set via a no-DNA control.

Results

Clinical description

The subject is a two-year-old Turkish boy with no noteworthy family medical history or known consanguinity. He was the product of an uncomplicated, term, IVF pregnancy with normal prenatal ultrasounds. Shortly after birth he was noted to have facial swelling and scrotal edema. He spent one week in the birth hospital over which time the swelling spontaneously resolved. An echocardiogram and renal ultrasound were both normal by report. At 3 months he developed bilateral foot swelling. Lymphedema was confirmed by scintigraphy. Foot and lower leg edema persist to the present, and he wears compression stockings daily.

Upper endoscopy was reportedly non-diagnostic. Neither capsule endoscopy nor MR lymphangiography has been done. Nonetheless, it is suspected he has intestinal lymphangiectasia causing mild protein-losing enteropathy, as he is intermittently hypoalbuminemic. For example, after a brief episode of vomiting and diarrhea at 27 months he had low serum albumin (1.8 g/dL) and total protein (3.4 g/dL); these labs normalized after his symptoms resolved. Serum IgG was also low at 27 months (172 mg/dL), and stool alpha-1-antitrypsin was high (0.83 mg/g). He is maintained on a low-fat diet supplemented with medium-chain triglyceride oil.

Physical exam at 29 months demonstrated a well-nourished child with mildly prominent forehead, down-slanting palpebral fissures, marked bilateral epicanthal folds (surgically corrected at age 30 months), apparent telecanthus and hypertelorism, a broad and depressed

nasal bridge, thickened nasal alae, and bilateral microtia with absent helices and narrow auditory canals. Distichiasis was not observed. His philtrum was short, and his mouth was downturned. He had delayed eruption of some primary teeth and hypodontia with small, conical teeth. The palate was normally arched with a single midline uvula. There was tonsillar hypertrophy. The neck had normal length with no webbing. He had mild pectus excavatum. Heart, lung, and abdominal exams were normal. He had a bifid scrotum. He had fifth finger clinodactyly bilaterally, present since birth and treated with stretches and splinting. There was no kyphosis or scoliosis. He had bilateral edema of his feet and lower legs. Skin and hair were normal. Neurological exam was normal. Development was normal by exam and by history.

Otoscopy confirmed narrow auditory canals precluding assessment of the tympanic membranes. Temporal bone CT displayed abnormal canals, middle, and inner ears including ossicular ankylosis, abnormally shaped ossicles, a stenotic and thickened oval window, and a soft tissue mass in the left middle ear – possibly a dermoid. Audiogram revealed mild-to-moderate conductive hearing loss, and hearing aids were prescribed at age 28 months.

Clinical molecular testing

The subject's clinical features suggested Hennekam lymphangiectasia-lymphedema syndrome (HKLLS). Thus, clinical sequencing and copy-number analysis of the three known HKLLS genes (*CCBE1*, *FAT4*, and *ADAMTS3*) as well as *FOXC2* (gene for lymphedema distichiasis, OMIM #153400), *GJC2* (gene for lymphatic malformation 3, OMIM #613480), and *KIF11* (gene for microcephaly with or without chorioretinopathy, lymphedema, or mental retardation, OMIM #148760) did not reveal any pathogenic variants. A chromosomal microarray revealed regions of homozygosity on several chromosomes totaling 150 Mb. These regions contain two known lymphedema genes (*ADAMTS3* and *FOXC2*), both of which were mutation negative, and *ALB*, which does not fit the phenotype (Table S3).

Within the region of AOH at 5p15.2p13.3 (Fig. S1), the microarray identified a homozygous deletion estimated to span at least 7 kb based on available probe density and encompassing part of the *FBXL7* gene and a micro-RNA, *MIR-887* (Fig. 1a). Two heterozygous duplications in non-disease regions were also identified (0.091 Mb dup at 3p22.2 and 0.935 Mb dup at Xq21.1) (Table S4).

Characterization of the FBXL7 deletion

Deletion breakpoints were mapped via an initial long-range PCR (Fig. S2) followed by standard PCR (Fig. 1c) and Sanger sequencing (Fig. S3). This confirmed a 28,705 bp homozygous deletion completely eliminating exon 3 (out of four total exons) of *FBXL7* as well as *MIR-887* (Fig. 1b). Each parent was heterozygous by PCR and droplet digital PCR (Fig. 1c-d). This deletion has not previously been identified in healthy (Database of Genomic Variants, gnomAD-SV) or diseased (ClinVar, ClinGen, DECIPHER) individuals.

FBXL7 exon 3 is constitutive (https://gtexportal.org/home/gene/FBXL7). Removal of this exon eliminates codons 43-246 of the canonical *FBXL7* transcript (CCDS54833.1). This predicted in-frame but extensive deletion would remove the entire F-box domain

(AAs 111-157) and three of eleven C-terminal leucine-rich repeat (LRR) domains (AAs 170-463) of FBXL7 (http://www.uniprot.org/uniprot/Q9UJT9) (Fig 1e). RNA/protein were not available from the subject.

Assessing the potential of FBXL7 and MIR-887 as novel disease genes

FBXL7 is not a known Mendelian disease gene in humans (OMIM) nor animals (OMIA). No biallelic LoF variants in *FBXL7* were found among 117,856 healthy individuals (gnomAD) nor among multiple cohorts of all-comers referred for genetic testing including the Matchmaker exchange (Table S5). Heterozygous loss of function (LoF) alleles appear tolerated (pLI=0.31; http://gnomad.broadinstitute.org/gene/ENSG00000183580) but rare (5/>200,000 alleles).

FBXL7 is expressed in various tissues in human (https://gtexportal.org/home/gene/FBXL7) and mouse (https://www.ebi.ac.uk/gxa/home), however lymphatic endothelium is not represented in these databases. At least some homozygous *Fbxl7*$^{tm1a(EUCOMM)Wtsi}$ mice display cornea-lens/fusion and small lateral ventricles (https://www.mousephenotype.org); a lymphatic phenotype has not been specifically assessed. In *Drosophila*, *Fbxl7* is expressed embryonically and in multiple adult tissues, with roles in protein ubiquitination and development (http://flybase.org/reports/FBgn0038385.html). In *Drosophila*, *Fblx7* interacts with *Ft*, an ortholog of human *FAT4* [Bosch et al., 2014; Rodrigues-Campos and Thompson 2014].

MIR-887 is not a known disease gene. Its function is unknown and it is not conserved even among mammals (Fig. 1f). No Hennekam syndrome genes are among its predicted targets (http://www.targetscan.org/cgi-bin/targetscan/vert_71/targetscan.cgi?species=Human&mir_nc=miR-887-3p).

Discussion

We present a two-year-old male with lymphedema, protein losing enteropathy, dental anomalies, camptodactyly, microtia, small auditory canals, conductive hearing loss, middle ear anomalies, bifid scrotum, and facial dysmorphic features including hypertelorism, telecanthus, epicanthal folds, downslanting palpebral fissures, broad and depressed nasal bridge, and thickened nasal alae. His features suggest Hennekam lymphangiectasia-lymphedema syndrome (HKLLS), an autosomal recessive syndrome characterized by generalized lymphatic dysplasia affecting various organs including the intestinal tract, pericardium, and limbs. Protein loss can lead to hypoalbuminemia and hypogammaglobulinemia. Additional features of the disorder include conductive hearing loss with middle ear anomalies, camptodactyly, cognitive impairment, and facial features including flat midface, flat nasal bridge, hypertelorism, epicanthal folds, small mouth, tooth anomalies, and small ears.

Biallelic mutations in three genes are currently known to cause HKLLS: *CCBE1*, *FAT4*, and *ADAMTS3* (Table 1). These genes were sequenced and assessed for copy-number variation in this subject, which revealed no mutations. Thus, we hypothesized that the subject may have mutations in an as yet undescribed HKLLS gene. We identified a homozygous, single-

exon, predicted in-frame deletion of *FBXL7* exon 3. This deletion is predicted to eliminate several domains of FBXL7. *FBXL7* has not previously been associated with a Mendelian disease in humans. A predicted micro-RNA, *MIR-887*, is also eliminated by this deletion. As this micro-RNA is not conserved even among mammals, we posited that it was less likely to be the causative gene for this individual's disease.

FBXL7 is a protein of 491 amino acids (minor isoform 444 amino acids). As its full name (F-box and leucine-rich repeat protein 7) suggests, it contains both an F-box domain – a 42-48 amino acid domain that allows binding to SKP1 (S-phase kinase-associated protein 1) – as well as 11 leucine-rich repeats at its C-terminal end [Jin et al., 2004]. F-box proteins are subunits of E3 ubiquitin ligases called SCFs (for SKP1, cullin, F-box proteins) [Coon et al., 2012]. SCF engage in phosphorylation-dependent ubiquitination of proteins.

One of the roles of FBXL7 occurs via its interaction with Aurora A (AURKA), an Aurora kinase family member with a pro-mitotic effect on spindle formation and chromosome segregation [Coon et al., 2012]. As a part of a SCF, FBXL7 limits the abundance of Aurora A during mitosis by polyubiquitinating it, leading to its degradation and therefore negatively regulating cell cycle progression. FBXL7 and Aurora A also have opposing roles on the anti-apoptotic protein survivin: Whereas expression of AURKA drives expression of survivin, the FBXL7 E3 ubiquitin ligase binds, ubiquitinates, and leads to the destruction of survivin [Kamran et al., 2017; Liu et al., 2015].

In *Drosophila*, Fbxl7 regulates the Daschsous-Fat-Dachs (Ds-Ft-D) system, a pathway with roles in establishing planar cell polarity to guide proximodistal patterning, and organ size and shape via the Hippo pathway [Bosch et al., 2014; Rodrigues-Campos and Thompson 2014] (Fig. 1g). Fbxl7 binds via its leucine-rich repeats to the intracellular domain of the transmembrane protocadherin Fat, and the two colocalize to the proximo-apical part of wing disc cells [Bosch et al., 2014]. Clones containing mutations of either gene exhibit competitive overgrowth, and Fbxl7- and Ft-deficient flies have similar alterations in wing morphology (reviewed in [Bosch et al., 2014]). A loss of either Fbxl7 or of Fat allows Dachs and Ds to spread beyond its usual disto-apical location, suggesting that the presence of Fat and Fbxl7 on the proximal side of the cell restricted Dachs and Ds to the distal side, potentially via Fbxl7-facilitated ubiquitination of Dachs, contributing to cellular polarity [Bosch et al., 2014; Rodrigues-Campos and Thompson 2014].

These data are intriguing given that *FAT4*, a human ortholog of *Drosophila* Fat, is the gene for HKLLS2. Furthermore, *FAT4* and *DCHS1*, a human ortholog of *Drosophila* Ds, are both disease genes for Van Maldergem syndrome, a disorder without lymphedema but with similar facial and other features to Hennekam syndrome. Mouse mutants of *Fat4* or *Dchs1* display normal lymphatic vessel patterning, but aberrant lymphatic valve morphology via aberrant polarization of valve endothelial cells [Pujol et al., 2017], so this may be the anatomic cause of lymphedema in *FBXL7*-related Hennekam syndrome as well. In our subject, the loss of three of 11 leucine-rich repeats of FBXL7 may impair binding to FAT4, and the complete loss of the F-box domain may impair its role in ubiquitination.

In conclusion, we describe a subject with a clinical diagnosis of Hennekam syndrome but without pathogenic variants in the known disease genes. We identified a homozygous deletion in *FBXL7*, predicted to affect key domains of FBXL7. Drawing on population genetic evidence and published animal data, we propose *FBXL7* may be the fourth Hennekam syndrome gene, acting in a shared pathway with a known Hennekam syndrome gene, *FAT4*. This will need to be confirmed by study of future subjects and animal or *in vitro* modelling. Our patient did not have developmental delay, so perhaps this is not a feature of this new Hennekam subtype. Biallelic LoF variants in *FBXL7* appear to be quite rare. This may be a consequence of low carrier frequency, but could also suggest that prenatal lethal lymphedema is a disease feature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement

Data sharing is not applicable to this article as all relevant research data are contained within the published article and its supplement.

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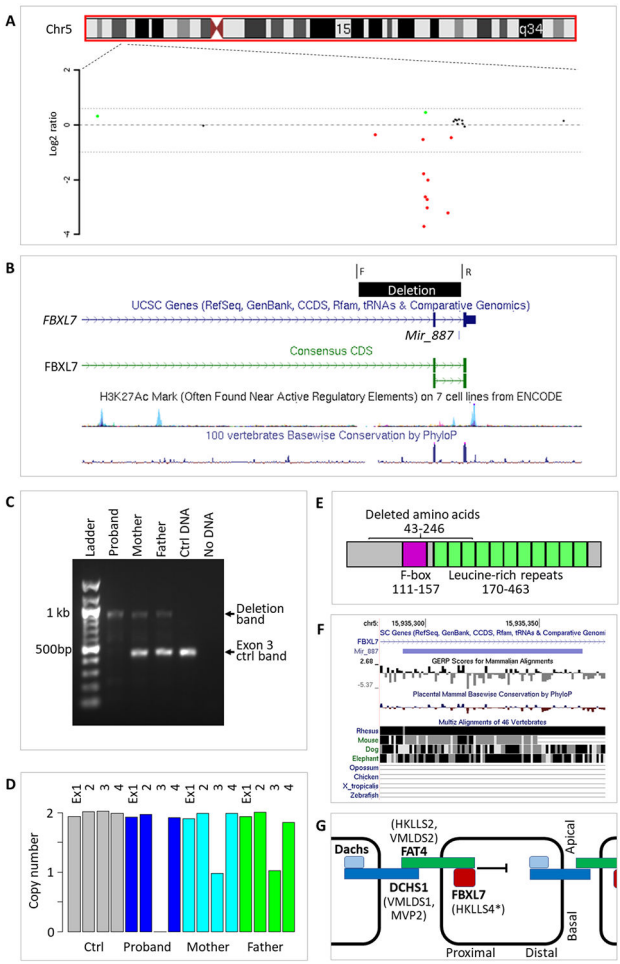

Figure 1. Homozygous deletion affecting *FBXL7* and *MIR-887*.

a. Microarray data demonstrating a homozygous deletion at 5p15.1. **b-c.** The deletion (black bar) was mapped by breakpoint PCR using primers F and R, demonstrating that it eliminates exon 3 of 4 of *FBXL7* as well as *MIR-887*. The *FBXL7* gene (blue) gives rise to two predicted protein variants (green; (top=canonical; bottom=alternative). **d**. Droplet digital PCR of each *FBXL7* exon confirmed that exon 3 is homozygously deleted in the proband and heterozygously deleted in each parent. **e.** Diagram of FBXL7 protein showing known domains (https://www.uniprot.org/uniprot/Q9UJT9). The predicted in-frame deletion of exon 3 would eliminate an extensive part of the protein including the F-box domain, two full leucine-rich repeats (LRRs), and one partial LRR. **f.** *MIR-887* is only partially conserved throughout mammals and not conserved throughout vertebrates. **g.** The Dachs-Fat-Daschsous pathway, modeled from [Bosch et al., 2014; Rodrigues-Campos and Thompson 2014], with human orthologs and their associated syndromes superimposed. This demonstrates that FBXL7 shares a common pathway with another Hennekam Lymphangiectasia-Lymphedema syndrome (HKLLS) gene, with two genes for the phenotypically related Van Maldergem syndrome (VMLDS), and with mitral valve prolapse 2 (MVP2). Dachs does not have a clear human ortholog. *, proposed.

Table 1.

Hennekam syndrome subtypes.

AR, autosomal recessive. †Proposed.

Hennekam syndrome subtype	OMIM	Gene	Chr	Inheritance	Gene OMIM
HKLLS1	#235510	*CCBE1*	18q21.32	AR	*612753
HKLLS2	#616006	*FAT4*	4q28.1	AR	*612411
HKLLS3	#618154	*ADAMTS3*	4q13.3	AR	*605011
HKLLS4† (Current report)	None	*FBXL7*	5p15.1	AR	*605656