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ORIGINAL INVESTIGATION

Hennekam syndrome can be caused by *FAT4* mutations and be allelic to Van Maldergem syndrome

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Abstract The Hennekam lymphangiectasia–lymphedema syndrome is a genetically heterogeneous disorder. It can be caused by mutations in CCBE1 which are found in approximately 25 % of cases. We used homozygosity mapping and whole-exome sequencing in the original HS family with multiple affected individuals in whom no CCBE1 mutation had been detected, and identified a homozygous mutation in the FAT4 gene. Subsequent targeted mutation analysis of FAT4 in a cohort of 24 CCBE1 mutation-negative Hennekam syndrome patients identified homozygous or compound heterozygous mutations in four additional families. Mutations in FAT4 have been previously associated with Van Maldergem syndrome. Detailed clinical comparison between van Maldergem syndrome and Hennekam syndrome patients shows that there is a substantial overlap in phenotype, especially in facial appearance. We conclude that Hennekam syndrome can be caused by mutations in FAT4 and be allelic to Van Maldergem syndrome.

Introduction

Defects in lymphatic structures resulting in congenital lymphedema and lymphangiectasia are the main features of the Hennekam lymphangiectasia–lymphedema syndrome (HS) (OMIM#235510). Other characteristics include unusual facial morphology, variable intellectual disabilities and, at a low frequency, malformations (van Balkom et al. 2002). HS has been reported in 45 individuals (Alders et al. 2013). Mutations in *CCBE1*, an extracellular matrix protein essential for the development of the lymphatic vasculature, have been found responsible for the syndrome (Alders et al. 2009). However, mutations in this gene are detected only in

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a subset of patients (~25 %), indicating that the syndrome is genetically heterogeneous (Alders et al. 2013).

Here, we describe the identification of mutations in *FAT4* as a second cause for HS. Mutations in this gene have been previously reported in patients with Van Maldergem syndrome (VMS) (Van Maldergem et al. 1992; Cappello et al. 2013). VMS is characterized by intellectual disability, periventricular heterotopia, an unusual face, camptodactyly and syndactyly, small kidneys, osteoporosis and tracheal anomalies sometimes necessitating tracheostomy, and not known to be associated with lymphedema (Mansour et al. 2012). We compare clinical features of both HS and VMS and show that each of the two entities shows specific manifestations but otherwise also a substantial overlap in phenotype exists.

Results

Identification of FAT4 mutations in HS patients

Homozygosity mapping in family F1 (Fig. 1), originally described by Hennekam et al. (1989) and of Dutch descend, identified a single homozygous region on chromosome 4q28, containing *FAT4*, in all affected individuals (Supplementary table S1). Whole-exome sequencing and filtering for homozygous variants that were shared in all three affected, absent in 20 other whole exomes that served as normal controls, and with a minor allele frequency of <1 % yielded only one variant: a homozygous nucleotide substitution at position c.7123G>A in *FAT4* predicted to result in the amino acid substitution p.(Glu2375Arg). Sanger sequencing of *FAT4* in 24 additional HS patients identified biallelic mutations in four other families: a homozygous duplication of 6 nt (c.7041_7046dup) resulting in a two-aminoacid duplication p.2348_2349dupGlyThr in proband F2-1 and his affected niece (Al-Gazali et al. 2003); two homozygous missense variants, c.1423T>C (p.Phe475Leu) and c.1456G>C (Glu486Gln) in F3-1; compound heterozygous mutations c.1195delC (p.Leu399Serfs*19) and c.12851C>T (p.Ser4284Phe) in F5-1; and a homozygous splice site mutation c.7200-2A>C in F4-1 (Table 1; Fig. 1; supplementary Fig. S1). According to, at that time only existing refseq for *FAT,4* NM_015284.3, the latter mutation would be annotated as c.7200-8A>C. However, mRNA analysis in multiple tissues (Supplementary Fig. S3)

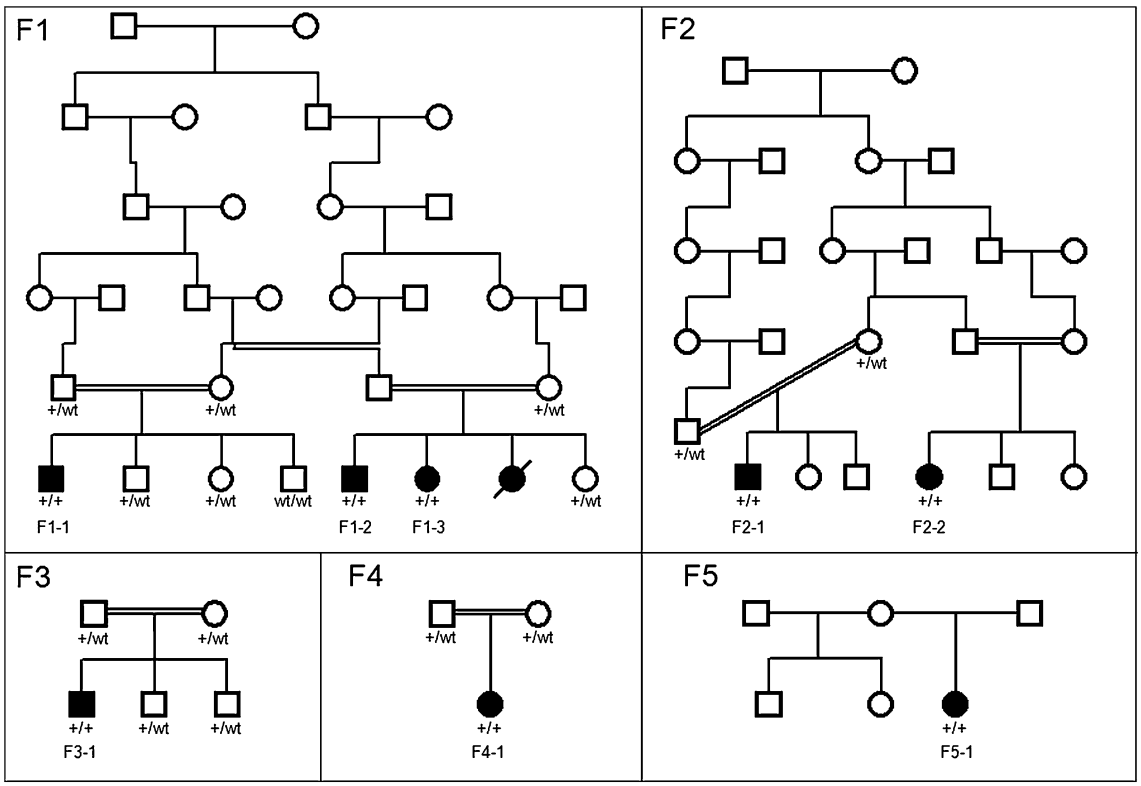

Fig. 1 Pedigrees of the families with homozygous *FAT4* mutations. Families *F1*, *F2* and *F4* have been previously described (*F1* in Hennekam et al. (1989), *F2* in Al-Gazali et al. (2003) and *F4* in Erkan et al. (1998). The *FAT4* mutation status of genotyped individuals is indicated (+/+ for homozygotes, +/wt for heterozygotes and wt/wt for mutation-negative individuals). Two-point parametric linkage analysis in the families *F1, F2, F3* and *F4* yielded a maximum additive LOD score of 3.6

Table 1 *FAT4* mutations identified in five families with Hennekam syndrome

Family	Mutation FAT4 (NM_001291303.1)		Zygosity	SIFT score	Polyphen
	cDNA level	Protein level (predicted)			
F1 (4 affected)	c.7123G>A	p.Glu2375Lys	Homozygous	Deleterious (score: 0)	Probably damaging HumDiv score 0.999 HumVar score: 0.998
F2 (2 affected)	c.7041_7046dup	p.Gly2348_Thr2349dup	Homozygous		
F3	c.1423T>C	p.Phe475Leu	Homozygous	Deleterious (score: 0)	Probably damaging HumDiv score 0.980 HumVar score: 0.958
	c.1456G>C	p.Glu486Gln	Homozygous	Deleterious (score: 0)	Probably damaging HumDiv score 0.999 HumVar score: 0.999
F4	c.7200-2A>C	splicing	Homozygous		
F5	c.1195del	p.Leu399Serfs*19	Heterozygous		
	c.12851C>T	p.Ser4284Phe	Heterozygous	Deleterious (score: 0)	Probably damaging HumDiv score 0.999 HumVar score: 0.998

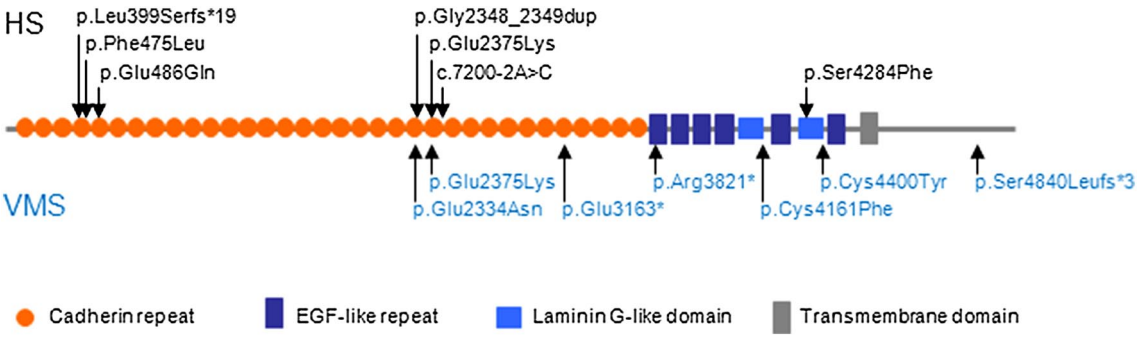

Fig. 2 FAT4 domain structure and location of FAT4 mutations in HS (*above*) and VMS (*below*). The annotation of the mutations is based on the transcript that uses the alternative upstream splice site of exon 8 (see Supplementary Fig. S3), which means that after position p.2400, the annotation is different from refseq NM_ 015284.3. We show only the annotation for all mutations according to refseq NM_001291303.1

demonstrated that splicing actually occurs 6 nt upstream of the annotated splice site of transcript NM_015284.3, placing the mutation in patient F4-1 at the invariant nucleotides of the exon 8 acceptor splice site (c.7200-2A>C) (new refseq NM_001291303.1). This mutation is predicted to result in the usage of the originally annotated (in NM_015284.3) splice site 6 nt downstream, resulting in the deletion of two aminoacids p.SerTyr2400_2401del. Unfortunately, no mRNA from this patient is available to confirm this predicted effect. All parents studied were heterozygous and all identified mutations were at evolutionary conserved aminoacid positions (Supplementary Fig. S2) and absent in control populations (dbSNP, 1000 genomes, NHBLI ESP, GoNL), except for c.12851C>T (p.Ser4284Phe), which has been found in 1/1302 alleles in the NHBLI ESP cohort. One of the mutations in *FAT4* reported as causal for VMS (together with a truncating mutation on the other allele) is identical to the mutation homozygously identified in family F1, p.(Glu2375Lys) (Cappello et al. 2013) (Fig. 2).

VMS can also be caused by mutations in the gene encoding for the ligand for *FAT4*, *DCHS1*. Therefore, we have sequenced the *DCHS1* gene in 14 HS patients in whom no molecular abnormalities had been found in *CCBE1* or *FAT4*, but no mutations were detected.

Clinical comparison HS and VMS

A comparison between the phenotype in HS and VMS shows a considerable overlap between the two entities (Table 2). Facial resemblance is remarkable (Fig. 3a, b), and in both entities cognitive impairment, decreased height, microcephaly and distal limb anomalies (camptodactyly and syndactyly) are common. Most VMS patients with a FAT4 mutation have a severe intellectual disability although milder intellectual disability does occur. In HS, the cognitive impairment is usually mild to moderate and in some individuals cognition is even normal (Alders et al. 2013). A major sign in HS is the marked lymphatic vessel dysplasia which shows edema especially evident at

Table 2 Comparison of phenotype in Hennekam syndrome and Van Maldergem syndrome

	Hennekam syndrome										Van Maldergem syndrome
	CCBE1 pos ($n = 13$)	*FAT4* pos									*FAT4*pos ($n = 7$[a])
Family		**F1**				**F2**		**F3**	**F4**	**F5**	All	
Individual		**F1-1**	**F1-2**	**F1-3**	**F1-4**	**F2-1**	**F2-2**	**F3-1**	**F4-1**	**F5-1**		
Impaired cognition[b]	9/13	+	B	++	+	–	–	B	+	B	7/9	5/5
Growth <P3	9/13	+	–	+	+	+	+	–	–	–	5/9	1/4
OFC <P3	6/13	–		+	–	–	–	–	–	–	1/8	1/4
Periventricular heterotopia[c]	0/13										nd	4/7
Hypotonia	1/13	–	–	–	–	–	–		+	–	1/8	3/5
Unusual face	13/13	+	+	+	+	+	+	+	+	+	9/9	5/5
Hypertelorism	13/13	+	+	+	+	+	+	+	+	+	9/9	5/5
Epicanthus	11/13	+	+	+	+	+	+	+	+	+	9/9	5/5
Blepharophimosis	6/13	+	+	+	+	–	–	+	+	–	6/9	3/5
Flat nasal bridge	11/13	+	+	+	+	+	+	–	+	+	8/9	7/7
Small mouth	7/13	+	–	–	–	+	+	+	+	+	6/9	4/5
Irregular dentition	12/13	+	+	+	+	+	+		+	+	8/8	3/5
Small ears, thick helices	13/13	+	+	+	+	+	+		+	+	8/8	5/5
Hearing loss	0/13	–	–	–	–	+	+	–	–	–	2/9	6/6
Tracheal anomalies	0/13	–	–	–	–	–	–	–	–	–	0/9	5/7
Camptodactyly	5/13	+	–	+	+	+	+		–	–	5/8	7/7
Syndactyly fingers/toes	4/13	–	–	–	–	+	–		+	–	2/8	6/7
Lymphedema limbs	13/13	+	+	+	+	+	+	+	+	+	9/9	1[d]/5
Lymphangiectasia gut	13/13	+	+	+	+	+	–	–	+	+	7/9	nd
Lymphangiectasia other[e]	10/13	+	+	+	+	+	–	+	+	–	7/9	nd
Cardiac malformation	2/13	–	–	–	–	–	–	–	–	–	0/9	0/5
Small kidneys	0/4	–	–		–	–	–		–	–	0/7	5/7
Osteoporosis	0/8	–	+	–	–	–	–	–	+	–	2/9	3/5

+ Feature present, – feature not present, *nd* no data available

[a] We added to existing literature a newly diagnosed pair of VMS sibs homozygous for p.Ile2334Asn in *FAT4*

[b] + Mild cognitive deficit, ++ moderate cognitive deficit, *B* borderline cognitive development

[c] No MRI data from HS patients available

[d] Pitting edema hand

[e] Lungs, pericardium, kidneys, genitalia

the distal limbs but regularly is generalized (Alders et al. 2013). Lymphedema in HS caused by *CCBE1* mutations always is present from birth on, but in HS caused by *FAT4* mutations the lymphedema can also start later in life during childhood, as is the case in patient F2-1 (Al-Gazali et al. 2003). Only in a single VMS individual pitting edema of one limb has been reported (Mansour et al. 2012). In VMS a major sign is periventricular heterotopia. This has been reported once in a HS patient (not available for further molecular studies) (Alders et al. 2013). Since there is usually no clinical reason to perform brain MRI studies in HS individuals, further MRI data are lacking. Other manifestation characteristics for VMS such as tracheal anomalies, small kidneys, and osteoporosis are very uncommon or absent in HS.

Discussion

We report here that mutations in *FAT4* are a second cause of Hennekam syndrome. Mutations in *FAT4* were identified in 5/24 families (~20 %), a rate comparable to *CCBE1* mutations in this patient group. As mutations in these two genes explain <50 % of HS cases, further heterogeneity is likely to be present. The mechanism behind *FAT4* mutations causing defects in lymphangiogenesis needs further studies. Whereas CCBE1 has been shown to be critically involved in lymphangiogenesis in zebrafish and mice (Hogan et al. 2009; Bos et al. 2011), mice deficient for *fat4* do not have signs of lymphedema (Saburi et al. 2008; Mao et al. 2011). It should be noted however that *FAT4* knockout mice die perinatally and defects in the lymphatic vasculature can

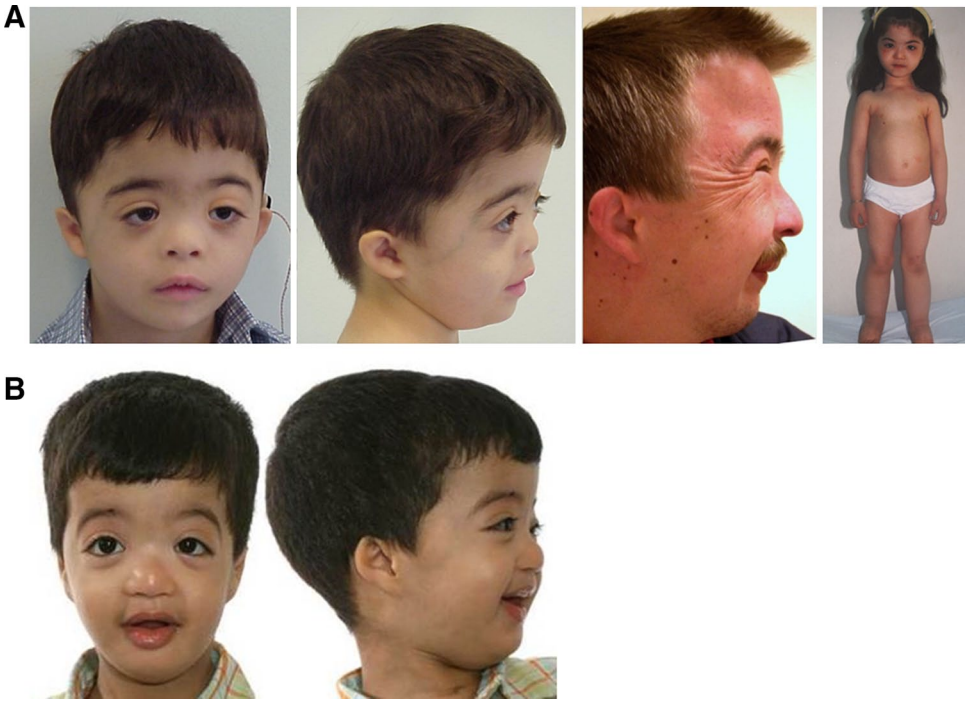

Fig. 3 Clinical features in individuals with *FAT4* mutations. **a** Individual F2-1 (front and side), F1-1, and F4-1 (total body) with Hennekam syndrome. Note flat face, hypertelorism, epicanthi, narrow palpebral fissures, and small ears. **b** Two-year-old boy with Van Maldergem syndrome and *FAT4* mutation for comparison, note strong resemblances to **a**

easily escape attention unless specifically sought for, and may only become more evident later in development. Generation of non-lethal mouse models, possibly by the use of hypomorphic alleles or conditional knockout of *fat4* expression, may offer the possibility to study the effect of *fat4* mutation on the lymphatic system in mice. Mouse *fat4* knockout models do not resemble HS and do not resemble VMS either. The renal hypoplasia present in those mice is in concordance with the small kidneys found in VMS, but no other phenotypic features of VMS are present, including periventricular heterotopia as which is a major characteristic of this entity. Only using in utero intraventricular electroporation of shRNAs, the involvement of FAT4 in neuronal proliferation and differentiation could be demonstrated (Cappello et al. 2013).

FAT4 is the mammalian orthologue of the Drosophila fat gene (*ft*), and known to act on two pathways, the Planar Cell Polarity (PCP) pathway and the Hippo signaling pathway. The involvement in the PCP pathway seems conserved in mice since *Fat4* −/− mice display several planar cell polarity phenotypes such as curved body axis and curly tails, disturbed orientation of hair cells in the cochlea, broadened spinal cord and loss of cell polarity in the renal tubular epithelium (Saburi et al. 2008). A role of FAT4 in the Hippo pathway in mice is less clear. Livers of *FAT4* mutant mice did not show any phenotypic abnormality whereas knock out of other genes in the Hippo pathway causes hepatomegaly and bile duct hamartomas. In addition, the Hippo interacting domain in Drosophila is not conserved in mammals (Bossuyt et al. 2014). In the mouse brain the increased proliferation of neuronal progenitor cells could be rescued or mimicked by repression or upregulation of Yap, a downstream effector of the Hippo pathway (Cappello et al. 2013). The exact role of FAT4 in human and the pathways involved in the phenotypic expression of mutation in VMS and HS remains to be determined. Recently, it was reported that the core PCP proteins Celsr1 and Vangl2 are critically involved in the morphogenetic process of intraluminal valve formation in lymphatic vessels (Tatin et al. 2013). At present there are not detailed reports on valve morphology in HS patients.

The identification of mutations in *FAT4* in both HS and VMS implicates FAT4 to be involved in both neuronal and lymphatic development in human. Such link is not novel and it has been hypothesized that similar mechanisms and pathways are involved for migration and differentiation of both neuronal and lymphendothelial progenitor cells. Several genes crucial for lymphangiogenesis have also been shown to play a role in brain development. For instance, PROX1 is involved in differentiation of neuronal progenitor cells (Kaltezoti et al. 2010), VEGFC and its receptor FLT4 cause proliferation of the neuronal progenitor cells (Hou et al. 2011; Le Bras et al. 2006) and ANGPT2 is involved in the radial migration of neuronal cells towards the cortical plate (Marteau et al. 2011).

Furthermore, we report here that HS and VMS can be allelic disorders, although both can also be caused by mutations in another gene. Detailed comparison of the phenotypes of HS and VMS shows a substantial overlap on one hand and features specific for each syndrome on the other

hand. Especially the facial appearance is remarkably alike, and also cognitive impairment, decreased height, microcephaly, small ears and distal limb anomalies are common in both syndromes (Fig. 3). Within the HS patient group no major phenotypic differences are noticed between patients with a *CCBE1* mutation and those with a *FAT4* mutation. Similarly, within the VMS group phenotypes cannot distinguish between *FAT4* mutation-positive patients and patients carrying mutations in the second gene causing VMS, *DCHS1*, the ligand of *FAT4*.

In HS patients no mutations were found in *DCHS1*. The number of patients tested ($n = 14$) is too low to definitely exclude *DCHS1* as a HS candidate gene, but there may be differences in *FAT4* and *DCHS1* function that explain the differences in phenotype in VMS and HS. The periventricular heterotopia seen in VMS is partially penetrant and more consistently present in patients with *DCHS1* mutations than in patients with a mutated *FAT4* gene (Cappello et al. 2013). Also, type or localization of *FAT4* mutations may play a role in explaining phenotypic variability between the two entities. The mutation p.(Glu2375Arg) was found homozygously in three affected individuals in family F1, all presenting with lymphedema and lymphangiectasias, and in combination with a truncating mutation in a patient with VMS. Differences in phenotypic expression may be due to different effects of a mutation present either in a homozygous or compound heterozygous state. Alternatively, other (epi-)genetic factors may be of influence on the phenotypic outcome of a mutation, for instance the influence on the phenotype in cystic fibrosis by the Cystic Fibrosis Modifier (Zielenski et al. 1999) and Dynactin 4 (Emond et al. 2012). Detailed phenotype–genotype comparisons (Hennekam and Biesecker 2012) may shed more light on this matter.

Methods

Homozygosity mapping

Homozgosity mapping in family F1 (F1-1, F1-2 and F1-3) was performed using the Affymetrix® Genome-Wide Human SNP Array 6.0 array. Results were analyzed using Nexus Copy Number™ software version 7 (BioDiscovery). Homozygous regions of more than 5 Mb were called (SNPRank Segmentation).

Whole-exome sequencing

Whole-exome sequencing was conducted using the SeqCap EZ Human Exome Library v3.0 (Roche NimbleGen) and a 5500 SOLiD™ instrument (Life Technologies). Samples were prepared using standard SolID 75 × 35 paired-end sequencing protocols. Alignment of sequence reads to human reference genome (hg19) was done using Lifescope 2.5.1, and variants were called using the GATK2.5 software package.

Whole-exome sequencing in three affected children in family F1 generated 195,673,578, 293,569,596 and 153,863,822 sequence reads, respectively. Coverage of targeted regions at 2×, 10× and 20× read depth (after removal of duplicate reads) was 93, 86 and 79 % for individual F1-1; 94, 89 and 84 % for individual F1-2; and 92, 85 and 75 % for individual F1-3.

Prioritization of variants identified with WES was done using the Cartagenia BENCHlab NGS software v3.0.4 (Cartagenia NV). Public databases used for determining the frequency of the identified variants in the general population were 1,000 genomes (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20110521/ALL.wgs.phase1_release_v3.20101123.snps_indels_sv.sites.vcf.gz), dbSNP137 (http://www.ncbi.nlm.nih.gov/projects/SNP) the ESP6500 dataset (http://evs.gs.washington.edu/EVS/), and the GoNL database (498 Dutch individuals, http://www.nlgenome.nl/).

Sanger sequencing of *FAT4* and *DCHS1*

Primers were designed to amplify all coding exons of *FAT4* and *DCHS1* using the Primer3 software (http://frodo.wi.mit.edu/). Amplification was performed with M13-tagged primers using HOT FIREPol™ DNA polymerase (Solys Biodyne) and a touchdown PCR program. PCR fragments were sequenced using the Bigdye kit v1.1(Applied Biosystems). Reactions were run on an ABI3700 or ABI3730XL genetic analyzer (Applied Biosystems) and sequences were analyzed using Sequence Pilot (JSI Medical systems) or CodonCode aligner (CodonCode Corporation). Variants were further characterized using Alamut version 2.3 (Interactive Biosoftware, Rouen, France).

Statistics

Two-point parametric Linkage analysis was performed by EasyLinkage Plus v5.08 package (http://sourceforge.net/projects/easylinkage/) using the Superlink v1.6 program. Pedigree was analyzed as a recessive model and LOD scores were obtained at 0.05 recombination increment steps until a recombination value of 0.45. Penetrance of disease and disease allele frequency were given 99 % and 0.001, respectively.

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