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FSHD type 2 and Bosma arhinia microphthalmia syndrome

Two faces of the same mutation

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Abstract

Objective

To determine whether congenital arhinia/Bosma arhinia microphthalmia syndrome (BAMS) and facioscapulohumeral muscular dystrophy type 2 (FSHD2), 2 seemingly unrelated disorders both caused by heterozygous pathogenic missense variants in the *SMCHD1* gene, might represent different ends of a broad single phenotypic spectrum associated with SMCHD1 dysfunction.

Methods

We examined and/or interviewed 14 patients with FSHD2 and 4 unaffected family members with N-terminal *SMCHD1* pathogenic missense variants to identify BAMS subphenotypes.

Results

None of the patients with FSHD2 or family members demonstrated any congenital defects or dysmorphic features commonly found in patients with BAMS. One patient became anosmic after nasal surgery and one patient was hyposmic; one man was infertile (unknown cause) but reported normal pubertal development.

Conclusion

These data suggest that arhinia/BAMS and FSHD2 do not represent one phenotypic spectrum and that *SMCHD1* pathogenic variants by themselves are insufficient to cause either of the 2 disorders. More likely, both arhinia/BAMS and FSHD2 are caused by complex oligogenic or multifactorial mechanisms that only partially overlap at the level of *SMCHD1*.

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Glossary

ATPase = adenosine triphosphatase; **BAMS** = Bosma arhinia microphthalmia syndrome; **FSHD** = facioscapulohumeral muscular dystrophy; **SMCHD1** = structural maintenance of chromosomes flexible hinge domain containing 1.

Identical pathogenic variants in the "structural maintenance of chromosomes flexible hinge domain containing 1" (*SMCHD1*) gene are associated with 2 seemingly unrelated disorders: facioscapulohumeral muscular dystrophy type 2 (FSHD2),[1] a rare form of adult-onset muscular dystrophy, and arhinia, a severe congenital malformation often accompanied by reproductive and ocular defects, a triad called Bosma arhinia microphthalmia syndrome (BAMS).[2–4]

FSHD2 has a complex etiology that involves *SMCHD1* (18p11.32) and the D4Z4 macrosatellite repeat array (4q35).[1] Loss of SMCHD1 repressive activity leads to partial relaxation of the D4Z4 chromatin structure and derepression of the normally suppressed *DUX4* retrogene in the D4Z4 unit. Only specific 4q35 haplotypes provide a polyadenylation signal (*DUX4*PAS) that stabilizes the DUX4 messenger RNA, permitting translation of the myotoxic DUX4 protein.[1,5] Contraction of the D4Z4 repeat array to 1–10 units can also relax the D4Z4 locus and derepress DUX4 expression; this is the mechanism underlying the more common form of FSHD called FSHD type 1 (FSHD1).[5]

In contrast to FSHD2, where missense and loss-of-function variants are distributed along the entire *SMCHD1* locus, in patients with BAMS, the variants are all missense and clustered within or immediately downstream of the adenosine triphosphatase (ATPase) domain.[2,3] While D4Z4 hypomethylation akin to FSHD2 in patients with BAMS suggests a loss-of-function mechanism,[2] a gain-of-function mode of action has also been proposed.[3]

To date, only one patient with both arhinia and FSHD2 and one multiplex family with both conditions have been reported.[2] There has yet to be a systematic investigation of BAMS-associated features in patients with FSHD2. Therefore, we performed phenotypic and genotypic studies in patients with FSHD2 and their family members with pathogenic missense variants in the N-terminal region of *SMCHD1* to identify potential areas of overlap.

Methods

Patients

We identified 23 patients with FSHD with heterozygous pathogenic missense variants near the ATPase domain of *SMCHD1* in the FSHD genetic database in the Department of Human Genetics of the Leiden University Medical Center. Family members of one patient were recruited through a cohort study (FSHD-FOCUS study) by the Department of Neurology of the Radboud University Medical Center, Nijmegen. Another 10 sporadic cases were recruited for participation by referring clinicians from the United States, France, United Kingdom, and the Netherlands.

Genetic testing

DNA was extracted from blood samples and analyzed for D4Z4 repeat size and chromosome 4q and 10q haplotypes, as described previously,[6] and for *SMCHD1* pathogenic variants by Sanger sequencing.[1] CpG methylation at the D4Z4 repeat was determined by Southern blot and the methylation-sensitive restriction enzyme FseI. Detailed protocols are freely available from the Fields Center website (urmc.rochester.edu/fields-center). The Delta1 score, a measure of the degree of D4Z4 hypomethylation, was calculated as described previously.[7] The Delta1 threshold for FSHD-associated *SMCHD1* pathogenic variants lies below −21%.

Clinical assessment

All participants were interviewed regarding nasal and olfactory abnormalities, pubertal development, fertility, eye anatomy and vision, history of maxillofacial surgery, and presence of cleft lip/palate. Photographs were available for 10 participants, which were independently assessed by 3 clinicians.

In addition, 10 members of one family with FSHD were examined in person for (subtle) signs of arhinia or associated comorbidities by a clinical geneticist (M.K.) who was blinded to mutation status. Olfactory function was assessed using the Sniffin' Sticks Screening Test (Burghart Medizintechnik, GmbH, Wedel, Germany), which assigns a sex- and age-adjusted olfactory score. One family member was examined using Skype.

Standard protocol approvals, registrations, and patient consents

This study was conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Participants were consented under a protocol approved by the local ethics committee of the Radboud University Medical Center, Nijmegen.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Genetic results

In the large Euro-Caucasian family with FSHD, 8 family members carried a pathogenic missense variant in *SMCHD1* (c.320T>C; p.Leu107Pro) (figures 1 and 2, table 1). Of note,

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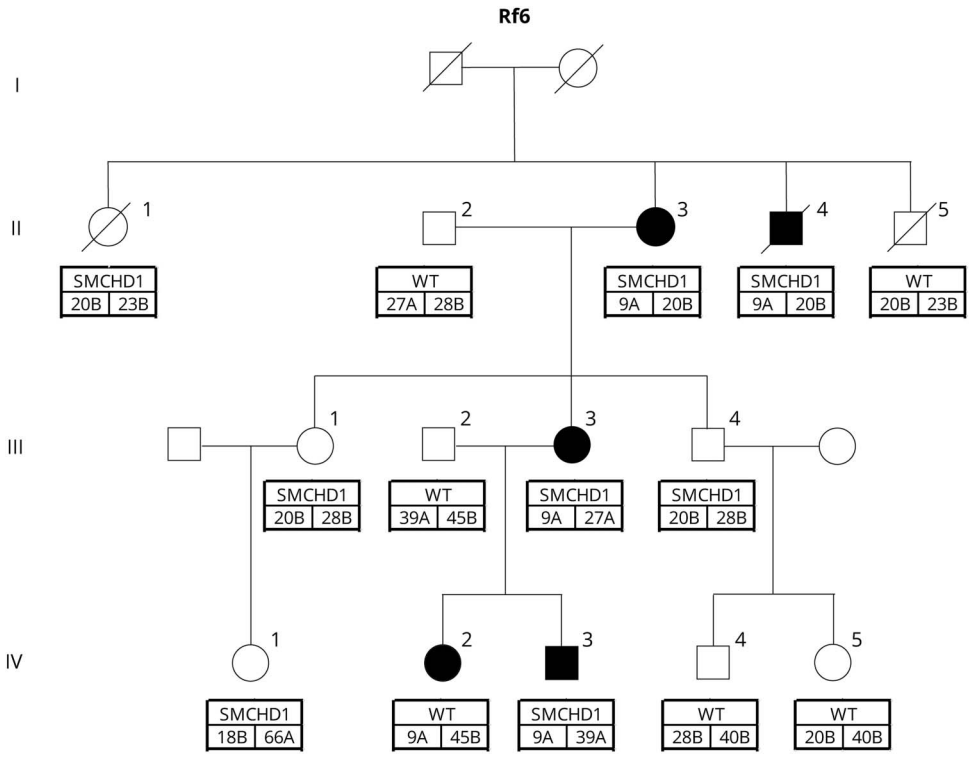
Figure 1 Pedigree for FSHD2 multiplex family with pathogenic variant (p.L107P) in *SMCHD1*

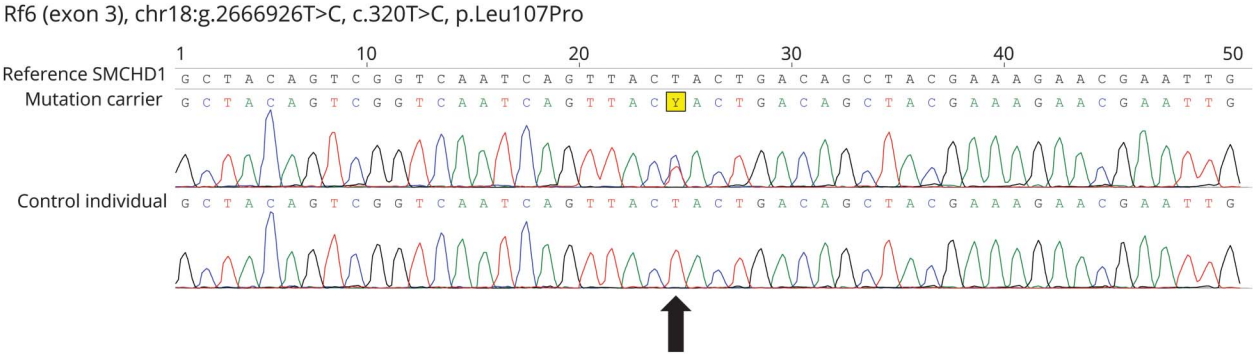


Shaded symbols represent family members meeting clinical criteria for FSHD2. Genetic information is listed below each family member: top box is mutation status (*SMCHD1* variant present or WT [wild type]); lower boxes indicate the 4q35 haplotype (A or B) and D4Z4 repeat length (units) for each allele. FSHD2 = facioscapulohumeral muscular dystrophy type 2.

this pathogenic variant was previously reported in an unrelated, African American female with BAMS.[2] All pathogenic variant carriers showed profound hypomethylation at the D4Z4 locus on chromosome 4q with Delta1 scores below −26%.[7] The 5 affected individuals had the FSHD-permissive, 4qA haplotype that contains the somatic *DUX4* PAS.[6] In addition, 4 of them had a D4Z4 repeat array of 9 units, compatible with an additional molecular diagnosis of FSHD1,[5] but also found in 1% to 2% of the Caucasian control population.[8–10] The 3 unaffected individuals were homozygous for the 4qB haplotype, which is not FSHD-permissive because of the absence of a somatic *DUX4* PAS. One family member who tested negative for the *SMCHD1* pathogenic variant did carry a 9-unit repeat on a 4qA haplotype. Her Delta1 score was −9%.

We identified 23 other sporadic FSHD2 patients in the FSHD genetic database with a pathogenic missense variant in close proximity to or identical to those previously identified in patients with arhinia or BAMS,[2,3] (Shaw, unpublished

Figure 2 Sequence track of the *SMCHD1* pathogenic variant in the family with FSHD2 and in a control sample



The position of the variant in exon 3 is indicated above the sequence traces and is highlighted in yellow. The genomic position is based on reference genome hg19 and the transcript and protein position on accession number NM015295 and NP056110, respectively. FSHD2 = facioscapulohumeral muscular dystrophy type 2.

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Table 1 Genetic characteristics of family members with FSHD

			4q35 locus				*SMCHD1* variant and D4Z4 methylation			
ID, figure 1	Sex	Age, y	4q_1 units	4q_1 haplotype	4q_2 units	4q_2 haplotype	FseI methylation, %	Delta1 methylation, %	*SMCHD1*	At risk of FSHD
II-1	F	Deceased	20	4B163	23	4B163	**3**	**−42**	+/−	No
II-2	M	80	27	4A161	28	4B163	58	12	+/+	No
II-3	F	75	9	4A161	20	4B163	**4**	**−33**	+/−	FSHD1 + 2
II-4	M	Deceased	9	4A161	20	4B163	NA	NA	+/−	FSHD1 + 2
II-5	M	Deceased	20	4B163	23	4B163	**25**	**−16**	+/+	No
III-1	F	52	20	4B163	28	4B163	**11**	**−34**	+/−	No
III-2	M	61	39	4A161	45	4B168	NA	NA	+/+	No
III-3	F	51	9	4A161	27	4A161	**6**	**−35**	+/−	FSHD1 + 2
III-4	M	47	20	4B163	28	4B163	**7**	**−39**	+/−	No
IV-1	F	21	18	4B163	66	4A161	**22**	**−29**	+/−	No
IV-2	F	18	9	4A161	45	4B168	36	−9	+/+	FSHD1
IV-3	M	16	9	4A161	39	4A161	**16**	**−26**	+/−	FSHD1 + 2
IV-4	M	19	28	4B163	40	4B168	52	6	+/+	No
IV-5	F	14	20	4B163	40	4B168	47	3	+/+	No

Abbreviations: FSHD = facioscapulohumeral muscular dystrophy; ID = identification; NA = not available.
4q_1 and 4q_2 represent the 2 alleles on chromosome 4q35. IDs correspond to those in the pedigree (figure 1).
Bold font signifies D4Z4 hypomethylation.

observation). All patients with FSHD2 had a permissive haplotype and D4Z4 hypomethylation (table 2). Seventeen of the 20 pathogenic variants in these patients with FSHD2 involved the same *SMCHD1* exon as in patients with arhinia and 3 pathogenic variants were identical to those found in patients with arhinia (figure 3). We also identified one family with a heterozygous 3–base pair deletion in exon 6 (c.729_731delCTT; p.Phe244del) resulting in the deletion of a single amino acid just 2 positions downstream of an amino acid affected in patients with BAMS.

Clinical characteristics

In the large FSHD family, 6 individuals with an N-terminal *SMCHD1* pathogenic missense variant were examined (individuals II:1 and II:4 were deceased at the time of the study). None of them had microphthalmia, congenital cataracts, coloboma, nasolacrimal duct atresia, midface hypoplasia, or cleft lip/palate (table 3). Several family members had narrow nares and/or hypoplastic alae nasi (rounded prominence of nostril) but these features did not segregate with the *SMCHD1* pathogenic variant, suggesting they were unrelated, familial traits. One family member with FSHD1 and 2 (II-3) developed anosmia shortly after surgery for a deviated nasal septum. A second affected patient with both FSHD1 and 2 (III-3) was hyposmic (Sniffin' Sticks Screening Test result below the 10th percentile). All family members who were questioned reported normal pubertal timing and denied infertility.

Four family members had symptoms of FSHD: the 2 older individuals (50 years and older) displayed severe muscle weakness and were wheelchair-dependent, whereas the 2 younger individuals had facial weakness, an early sign of FSHD. Three of them had both FSHD1 and 2, and one of the younger individuals had only FSHD1.

The 10 sporadic FSHD2 patients who were phenotyped did not have physical features consistent with arhinia/BAMS (table 4). One male reported normal pubertal development but had infertility of unknown etiology. He denied other signs of hypogonadism such as cryptorchidism or micropenis and had never required testosterone replacement. Photographs of this patient revealed no signs of a craniofacial defect.

Discussion

We assessed patients with FSHD who had pathogenic missense variants in the N-terminal region of *SMCHD1*, which were recently shown to cause arhinia/BAMS, to determine whether FSHD2 and BAMS might represent the opposite ends of one broad, phenotypic spectrum or if each condition is caused by SMCHD1 dysfunction in the presence of a genetic background unique to each condition. Only one patient with arhinia has been identified thus far who meets clinical and genetic criteria for FSHD2,[2] and until now, patients with FSHD2 had never been specifically assessed for BAMS-like features.

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Table 2 Genetic characteristics of patients with FSHD2

ID, figure 3	Sex	4q35 locus				*SMCHD1* variant and D4Z4 methylation					
		4q_1 units	4q_1 haplotype	4q_2 units	4q_2 haplotype	FseI methylation, %	Delta1 methylation, %	*SMCHD1* cDNA (NM_015295.2)	*SMCHD1* variant (NP_056110.2)	Position relative to known BAMS mutation	Exon
2		See table 1				See table 1		c.320T>C	p.Leu107Pro	Identical to p.Leu107Pro	3
7	M	13	A	33	B	12	−28	c.580C>T	p.Leu194Phe	23 aa distal to p.Phe171Val	5
8	M	11	A	39	B	5	−33	c.610A>G	p.Lys204Glu	33 aa distal to p.Phe171Val	5
10a	M	No genotype data (no DNA)				3	NA	c.729_731delCTT	p.Phe244del	2 aa distal to p.Ala242Gly	6
10b	F	No genotype data (no DNA)				NA	NA	c.729_731delCTT	p.Phe244del	2 aa distal to p.Ala242Gly	6
10c	M	No genotype data (no DNA)				NA	NA	c.729_731delCTT	p.Phe244del	2 aa distal to p.Ala242Gly	6
12	F	13	A	NA	NA	5	NA	c.848A>G	p.Tyr283Cys	41 aa distal to p.Ala242Gly	7
14	M	17	A	47	A	9	−41	c.1058A>G	p.Tyr353Cys	5 aa distal to p.His348Arg	9
15	F	14	A	15	A	1	−37	c.1273G>A	p.Gly425Arg	5 aa distal to p.Asp420Val	10
18	M	11	A	35	B	7	−29	c.1474T>C	p.Cys492Arg	19 aa distal to p.Glu473Gln	12
19	F	17	A	18	A	11	−31	c.1556T>C	p.Phe519Ser	1 aa distal to p.Lys518Glu	12

Abbreviations: BAMS = Bosma arhinia microphthalmia syndrome; cDNA = complementary DNA; FSHD = facioscapulohumeral muscular dystrophy; ID = identification; NA = not available.
4q_1 and 4q_2 represent the 2 alleles on chromosome 4q35. IDs correspond to the mutation number in figure 3.

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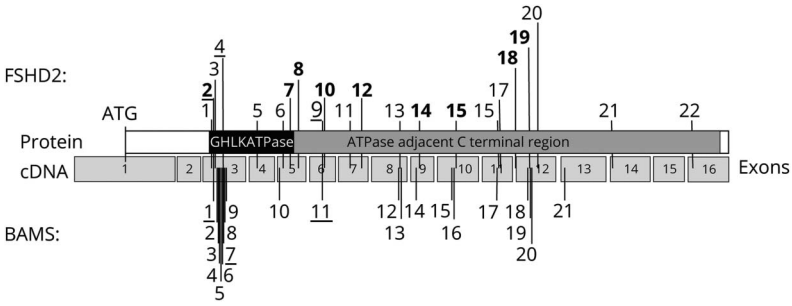
Figure 3 Schematic of pathogenic missense variants in the N-terminal region of *SMCHD1* associated with FSHD2 and/or arhinia/BAMS



FSHD2:

1. *p.N104S*	9. *p.A242T*	17. *p.R479P*
2. p.L107P	**10. p.F244del**	**18. p.C492R**
3. *p.A110T*	11. *p.H263D*	**19. p.F519S**
4. *p.G137E*	**12. p.Y283C**	20. *p.T527M*
5. *p.D150H*	13. *p.R344Q*	21. *p.V615D*
6. *p.M189V*	**14. p.Y353C**	22. *pP690S*
7. p.L194F	**15. p.G425R**	23. *p.L748P*
8. p.K204E	16. *p.G478E*	

BAMS:

1. *p.L107P*	8. *p.N139H*	15. *p.Q400L*
2. *p.M129K*	9. *p.L141F*	16. *p.D420V*
3. *p.A134S*	10. *p.F171V*	17. *p.E473Q*
4. *p.S135C*	11. *p.A242G*	18. *p.K518E*
5. *p.S135N*	12. *p.W342S*	19. *p.T523K*
6. *p.E136G*	13. *p.Q345R*	20. *p.N524S*
7. *p.G137E*	14. *p.H348R*	21. *p.R552Q*

SMCHD1 (exon 1–48)	aa 1–2,005
GHKL ATPase domain (exon 3–5)	aa 111–365
ATPase adjacent C terminal region (exon 5–16)	aa 365–702

Pathogenic variants in the FSHD2 cohort in the current study are in bold (table 2), and the pathogenic variants that have been implicated in both FSHD2 and BAMS are underlined. ATPase = adenosine triphosphatase; BAMS = Bosma arhinia microphthalmia syndrome; cDNA = complementary DNA; FSHD2 = facioscapulohumeral muscular dystrophy type 2.

Detailed examination of a large FSHD family with an *SMCHD1* pathogenic variant identical to one found in patients with BAMS did not uncover any congenital defects or dysmorphic features commonly found in patients with BAMS. We identified one patient in this family who developed cataracts in her 70s and lost olfaction after nasal surgery. These findings are unlikely to be related to BAMS as cataracts are very common with aging secondary to cumulative photooxidative insults (e.g., ultraviolet B) and she did not have congenital anosmia as occurs in patients with BAMS; rather, she lost olfactory function after nasal surgery, which is a recognized, albeit rare, potential side effect of septoplasty.[11,12] We also observed several family members with nasal hypoplasia. The power of our combined genetic and phenotypic approach, however, allowed us to confidently classify this phenotype as a familial rather than SMCHD1-related trait as it did not segregate with the *SMCHD1* pathogenic variant.

All other patients with FSHD2 included in this study reported normal olfaction, no craniofacial or ocular abnormalities, and normal pubertal development, and those of reproductive age were fertile with the exception of one male patient with infertility of unknown cause. Thus, we find no evidence for phenotypic overlap in FSHD2 and BAMS patients.

The phenotyping protocol for this study was intentionally simple and noninvasive in design such that all study procedures could be performed by patients from afar. Although we performed detailed, structured interviews to collect phenotypic data on the sporadic cases, it is possible that patients were not fully aware of any subtle BAMS-associated features. Future studies will be required to confirm our findings in a larger number of patients with FSHD using more sophisticated tools, such brain imaging, to assess the integrity of the olfactory bulbs and tracts, dilated eye examinations, and reproductive hormone testing.

Our data support the hypothesis that arhinia/BAMS and FSHD2 represent 2 distinct oligogenic disorders. In both conditions, SMCHD1 dysfunction appears to be necessary but not sufficient to cause disease. In FSHD2, a permissive 4q35 haplotype is one known requirement, but the variability in muscle weakness that is seen among family members with the same *SMCHD1* pathogenic variant (and D4Z4 repeat size) suggests that there are other genetic or environmental modifiers yet to be discovered. Incomplete penetrance of *SMCHD1* variants in the form of nasal hypoplasia or isolated anosmia has also been observed in multiplex arhinia/BAMS families.[2] Modifier genes have not been identified in arhinia, but SMCHD1 binding partners and/or downstream targets are rational candidates. Thus, in the extremely rare chance that a patient has an N-terminal *SMCHD1* pathogenic variant and meets the genetic requirements unique to arhinia/BAMS and to FSHD2, he or she can demonstrate both conditions.

Pathogenic variants in the N-terminal region of *SMCHD1* have a critical role in the pathogenesis of both FSHD2 and arhinia/BAMS. The complete absence of phenotypic overlap between these 2 disorders, however, suggests that these variants are, by themselves, insufficient to cause either disorder. The current study instead supports an oligogenic or multifactorial disease mechanism for both FSHD2 and arhinia/BAMS.

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Table 3 Clinical findings in FSHD family with a pathogenic *SMCHD1* variant

ID, figure 1	Sex	Age, y	*SMCHD1* variant	Signs of FSHD	Interview and assessment of dysmorphic features	Pubertal development	Sniffin' Sticks Test	Other
II-1	F	Deceased	+/−	NA (not at risk)	NA	NA	NA	
II-2	M	80	+/+	NA (not at risk)	NA	nl; fertile	NA	
II-3	F	75	+/−	Severe FSHD, wheelchair-bound	Narrow nares; high nasal bridge; hypoplastic alae nasi; bilateral cataracts at age 73 y; dystopia canthorum; elongated philtrum	nl; fertile	Anosmia	Anosmia after nasal septum surgery
II-4	M	Deceased	+/−	Severe FSHD, wheelchair-bound	NA	NA	NA	
II-5	M	Deceased	+/+	NA (not at risk)	Narrow nares; hypoplastic alae nasi	nl	NA	Assessment using photographs
III-1	F	52	+/−	nl (not at risk)	Hypoplastic alae nasi; unilateral epicanthal fold; glasses (−0.25 and −4.25)	nl; fertile	NA	Assessment using Skype
III-3	F	51	+/−	Severe FSHD, able to walk a few steps with support	Narrow nares and nose; high nasal bridge; hypoplastic and asymmetrical alae nasi; micrognathia	nl; fertile	Hyposmia	
III-4	M	47	+/−	nl (not at risk)	High nasal bridge; asymmetrical alae nasi; long philtrum	nl; fertile	Normosmia	
IV-1	F	21	+/−	nl (not at risk)	Asymmetrical alae nasi	nl	Normosmia	
IV-2	F	18	+/+	Mild facial weakness	Tendency to hypertelorism; short philtrum	nl	Normosmia	
IV-3	M	16	+/−	Facial weakness	Coarse facial features; thick and asymmetrical alae nasi; strabism; tendency to hypertelorism; retrognathia	nl	Normosmia	Mild learning disability
IV-4	M	19	+/+	nl (not at risk)	None	nl	Normosmia	
IV-5	F	14	+/+	nl (not at risk)	Midline raphe	nl	Normosmia	

Abbreviations: FSHD = facioscapulohumeral muscular dystrophy; ID = identification; NA = not available; nl = normal.
IDs correspond to those in the pedigree (figure 1).

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Table 4 Clinical findings in sporadic FSHD2 patients as determined by interview and photographs

		BAMS-associated phenotypes										
ID, figure 3	Sex	Smell	Nasal abnormalities	Nasal surgery	Open nostrils	Vision	Eye anatomical abnormalities	Tear production	Pubertal development	Fertility	Cleft lip/palate	Photographs
7	M	nl	No	No	Yes	nl	No	nl	nl	nl	No	NA
8	M	nl	No	Adenoid removal	Yes	Glasses	No	nl	nl	nl	No	NA
10a	M	nl	No	No	Yes	Astigmatism, hypermetropy	No	nl	nl	nl	No	NA
10b	F	nl	No	No	Yes	nl	No	nl	nl	nl	No	NA
10c	M	nl	No	No	Yes	nl	No	nl	nl	nl	No	NA
12	F	nl	No	No	Yes	nl	No	nl	NA	NA	No	NA
14	M	nl	Difficulty clearing secretions	No	Yes	Glasses	No	Decreased (Schirmer test score 4)	Decreased body hair	Infertile	No	No abnormalities
15	F	nl	No	No	Yes	nl	No	nl	nl	nl	No	NA
18	M	nl	No	No	Yes	nl	No	nl	nl	nl	No	NA
19	F	nl	No	No	Yes	Glasses	No	nl	nl	nl	No	No abnormalities

Abbreviations: BAMS = Bosma arhinia microphthalmia syndrome; FSHD2 = facioscapulohumeral muscular dystrophy type 2; ID = identification; NA = not available; nl = normal.
IDs correspond to the mutation number in figure 3.

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Author contributions

K.M., R.J.L.F.L., B.G.M.v.E., C.G.C.H., N.D.S., and S.M.v.d.M.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and tables/figures. M.K.: acquisition of data, analysis and interpretation of data, drafting of tables/figures, revision of the manuscript. P.J.v.d.V., M.L.v.d.B., U.A.B., J.M.G., A.E.L., H.B., S.A.M., K.J., T.E., A.T., V.S., S.K.G., S.S., R.T., S.J.T., and N.C.V.: acquisition of data, analysis and interpretation of data, revision of the manuscript. B.G.M.v.E., N.D.S., and S.M.v.d.M.: obtained funding for the study.

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