SMCHD1 mutation spectrum for facioscapulohumeral muscular dystrophy type 2 (FSHD2) and *Bosma arhinia* microphthalmia syndrome (BAMS) reveals disease-specific localization of variants in the ATPase domain

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Supplementary Materials and Methods

Genetic analysis of D4Z4 repeats

Determination of the D4Z4 repeat size and allelic background was performed by Southern blotting and hybridization with probes p13E-11, 4qA and 4qB as described previously. Hybridization conditions slightly vary between the different laboratories. In our laboratory hybridization with probe p13E-11 was performed in a buffer with 10% Dextran sulphate, 1M NaCl, 50 mM Tris-HCl, pH 7.5, 1% SDS and 250ug/ml Salmon sperm DNA at 65°C. 4qA and 4qB hybridizations were done in a phosphate buffer with 10% polyethylene glycol 6000.[1]

Methylation at D4Z4 was determined either by Southern blotting at the FseI site in D4Z4 or by bisulphite conversion and PCR at the DR1 site.[2] For Southern blotting based methylation analysis with probe p13E-11 we used the hybridization buffer with 10% Dextran sulphate (see before). Calculations of repeat size corrected methylation compared to controls (delta1) and SMCHD1 pathogenic variant carriers (delta2) were done as described previously.[3]

SMCHD1 sequencing and variant prediction

SMCHD1 variants were identified by Sanger sequencing or by whole exome or whole genome sequencing (WES/WGS) followed by confirmation using Sanger sequencing. All variants identified in FSHD2, BAMS and controls have been submitted to the Leiden Open Variation Database (LOVD, www.lovd.nl). The putative effects of the SMCHD1 variants were investigated through prediction algorithms using Alamut Visual v.2.4.2 (Interactive Biosoftware, https://www.interactive-biosoftware.com/alamut-visual/) or Variant Effect Predictor (VEP) in Ensemble (https://www.ensembl.org/info/docs/tools/vep/index.html). This includes SIFT (Sorting Intolerant from Tolerant, http://sift.jcvi.org), Polyphen2 (http://genetics.bwh.harvard.edu/pph2/) and Align GVGD (Grantham Variation and Grantham Deviation, http://agvgd.hci.utah.edu/about.php). Splicing predictions were done in Alamut.

Statistical analysis

The FseI methylation level, delta1 and delta2 methylation score (in Supplementary figure 2) were compared using the unpaired t-test in Graphpad Prism 7. For the comparisons shown in Supplementary table 4, we used a Pearson chi-square test with Yates' continuity correction in R 3.3.2. For the visualization, the R packages ggplot2 and trackViewer from R/Bioconductor were used.[4]

Supplementary Tables

nr	publication	identified variants	new variants
1	Lemmers et al., 2012 (PMID: 23143600)[8]	15	15
2	Sacconi et al., 2013 (PMID: 24075187)[13]	3	3
3	Mitsuhashi et al., 2013 (PMID: 24128691)[10]	1	1
4	Winston et al., 2015 (PMID: 24755953)[15]	1	1
5	Lemmers et al., 2015 (PMID: 25256356)[3]	51	36
6	Larsen et al., 2015 (PMID: 25370034)[7]	11	11
7	Smith et al., 2015 (poster ASHG 2015)	8	8
8	Lemmers et al., 2015 (PMID: 25820463)[9]	2	2
9	Boogaard et al., 2016 (PMID: 25782668)[14]	5	5
10	Hamanaka et al., 2016 (PMID: 27061275)[6]	11	11
11	Gaillard et al., 2016 (PMID: 27634379)[5]	1	1
12	Nguyen et al., 2017 (PMID: 28744936)[12]	1	1
13	Mul et al., 2018 (PMID: 29980640)[11]	23	6
		Total	101

Supplementary table 1

Chronological overview of 101 published SMCHD1 variants involved in FSHD2.[3, 5-15] Third column shows all variants described in the publication. Some variants were described in consecutive publications and overlap. In the last column we only mention the non-overlapping variants.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
				SMCHD1	SMCHD1	SMCHD1								EXAC (Minor Allele Frequency)				Ensemble	Alamut				Total (1+2+3)	
ID	Family	Nr	M/F	cDNA (NM_015295.2)	gene (hg19 (GRCh37.p5)	protein (NP_056110.2)	type	ORF	position	FseI	delta1	delta2	dbSNP	AFR	EUR	EAS	SAS	PolyPhen (1)	SIFT(2)	AGVGD (3)	GV	GD	Prediction	Publication
F1	Rf871	1	M	c.101G>C	g.2656175G>C	R34P	M	P-ORF	exon 1	11	-37	-3						probably_damaging(0.969)	Deleterious(0)	C0	241	40	2	
F2	LOVD12	1		c.311A>G	g.2666917A>G	N104S	M	P-ORF	exon 3	NA	NA	NA	rs375795924	1,13E-04	7,99E-05	8,38E-04	0	benign(0)	Tolerated(0.13)	C0	223	0	0	ASHG conference 2015 (Smith, 2015)
F3	Rf6	30	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	3	-35	-6	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F4	LOVD11	1	M	c.328G>A	g.2666934G>A	A110T	M	P-ORF	exon 3	NA	NA	NA						possibly_damaging(0.863)	Deleterious(0.01)	C0	27	37	2	PMID25370034 (Larsen, 2014)
F5	Rf866	1	M	c.410G>A	g.2667016G>A	G137E	M	P-ORF	exon 3	22	-21	10	rs1057519644					probably_damaging(0.989)	Deleterious(0.01)	C0	79	30	2	PMID: 25256356 (Lemmers, HMG 2015)
F6	LOVD21	1		c.448G>C	g.2673303G>C	D150H	M	P-ORF	exon 4	NA	NA	NA						probably_damaging(1)	Deleterious(0)	C65	0	81	3	ASHG conference 2015 (Smith, 2015)
F7	Rf1685	1	M	c.562G>A	g.2674068G>A	G188R	M	P-ORF	exon 5	6	NA	NA						probably_damaging(1)	Deleterious(0)	C65	0	125	3	
F8	LOVD23	1		c.565A>G	g.2674071A>G	M189V	M	P-ORF	exon 5	NA	NA	NA						probably_damaging(0.977)	Deleterious(0)	C15	0	21	2	ASHG conference 2015 (Smith, 2015)
F9	Rf1142	1	M	c.580C>T	g.2674086C>T	L194F	M	P-ORF	exon 5	12	-28	2						probably_damaging(0.999)	Deleterious(0)	C15	0	22	2	PMID: 25256356 (Lemmers, HMG 2015)
F10	Rf677	1	M	c.610A>G	g.2674116A>G	K204E	M	P-ORF	exon 5	6	-32	-4	rs1184311800					possibly_damaging(0.851)	Deleterious(0)	C55	0	57	3	PMID: 29980640 (Mul, 2018)
F11	IW1	2	M	c.724G>A	g.2688477G>A	A242T	M	P-ORF	exon 6	14	NA	NA						probably_damaging(0.999)	Deleterious(0)	C55	0	58	3	PMID: 29980640 (Mul, 2018)
F12	Rf1247	1	F	c.787C>G	g.2688659C>G	H263D	M	P-ORF	exon7	4	-34	-5						probably_damaging(0.998)	Deleterious(0)	C65	0	81	3	PMID: 25256356 (Lemmers, HMG 2015)
F13	Rf2542	1	M	c.790G>A	g.2688662G>A	E264K	M	P-ORF	exon7	6	-33	-4						probably_damaging(0.996)	Deleterious(0)	C55	0	57	3	
F14	LOVD36	1	M	c.848A>G	g.2688720A>G	Y283C	M	P-ORF	exon 7	4	NA	NA	rs886041921					probably_damaging(0.996)	Deleterious(0)	C55	22	192	3	PMID: 27061275 (Hamanaka, 2016)
F15	Rf2484	2	F	c.848A>G	g.2688720A>G	Y283C	M	P-ORF	exon 7	5	-37	-6	rs886041921					probably_damaging(0.996)	Deleterious(0)	C55	22	192	3	
F16	IW20	1	M	c.1031G>A	g.2694682G>A	R344Q	M	P-ORF	exon 9	24	NA	NA	rs370983669	4,11E-04	3,02E-05	0	0	benign(0.031)	Deleterious(0)	C35	0	43	2	PMID: 29980640 (Mul, 2018)
F17	Rf742	1	M	c.1058A>G	g.2697047A>G	Y353C	M	P-ORF	exon 9	9	-41	-6						probably_damaging(0.997)	Deleterious(0)	C65	0	194	3	PMID: 23143600 (Lemmers, 2010)
F18	Rf959	3	M	c.1058A>G	g.2697047A>G	Y353C	M	P-ORF	exon 9	12	NA	NA						probably_damaging(0.997)	Deleterious(0)	C65	0	194	3	PMID: 25256356 (Lemmers, HMG 2015)
F19	Rf1196	1	F	c.1273G>A	g.2697970G>A	G425R	M	P-ORF	exon 10	1	-37	-8						probably_damaging(0.925)	Deleterious(0)	C65	0	125	3	PMID: 25256356 (Lemmers, HMG 2015)
F20	IW35	1	M	c.1273G>A	g.2697970G>A	G425R	M	P-ORF	exon 10	17	NA	NA						probably_damaging(0.925)	Deleterious(0)	C65	0	125	3	
F21	IW39	1	M	c.1282C>T	g.2697979C>T	R428C	M	P-ORF	exon 10	14	NA	NA						probably_damaging(0.996)	deleterious(0)	C65	0	179	3	
F22	LOVD1	1	M	c.1433G>A	g.2700627G>A	G478E	M	P-ORF	exon 11	12	NA	NA						benign(0.142)	Deleterious(0)	C65	0	98	2	PMID25370034 (Larsen, 2014)
F23	Rf739	1	M	c.1436G>C	g.2700630G>C	R479P	M	P-ORF	exon 11	10	-32	-1						probably_damaging(0.997)	Deleterious(0)	C65	0	103	3	PMID: 23143600 (Lemmers, 2010)
F24	Rf2377	1	M	c.1436G>T	g.2700630G>T	R479L	M	P-ORF	exon 11	13	-31	1						probably_damaging(0.995)	Deleterious(0)	C65	0	102	3	PMID: 28744936 (Nguyen, 2017)
F25	Rf2456	1	M	c.1436G>A	g.2700630G>A	R479Q	M	P-ORF	exon 11	2	-48	-13						probably_damaging(0.992)	Deleterious(0)	C35	0	43	3	
F26	Rf300	1	M	c.1474T>C	g.2700743T>C	C492R	M	P-ORF	exon 12	7	-29	-2						probably_damaging(0.996)	Deleterious(0)	C65	0	180	3	PMID: 23143600 (Lemmers, 2010)
F27	Rf1729	1	F	c.1556T>C	g.2700825T>C	F519S	M	P-ORF	exon 12	11	-31	-1						probably_damaging(0.994)	Deleterious(0)	C65	0	155	3	PMID: 29980640 (Mul, 2018)
F28	Rf1021	1	M	c.1580C>T	g.2700849C>T	T527M	M	P-ORF	exon 12	18	-25	6	rs397518422					probably_damaging(0.992)	Deleterious(0)	C0	78	52	2	PMID: 24075187 (Sacconi, 2013)
F29	IW31	1	M	c.1652A>G	g.2703694A>G	Q551R	M	P-ORF	exon 13	15	NA	NA						probably_damaging(0.968)	Deleterious(0.03)	C0	53	5	2	
F30	Rf2572	1	M	c.1786T>G	g.2703828T>G	W596G	M	P-ORF	exon 13	10	-21	3						probably_damaging(0.994)	Deleterious(0)	C65	0	184	3	
F31	LOVD5	1	F	c.1844T>A	g.2705693T>A	V615D	M	P-ORF	exon 14	17	NA	NA						probably_damaging(0.996)	Deleterious(0)	C65	0	152	3	PMID25370034 (Larsen, 2014)
F32	IW8	1	F	c.1865C>T	g.2705714C>T	P622L	M	P-ORF	exon 14	8	NA	NA						probably_damaging(0.997)	Deleterious(0)	C65	0	98	3	
F33	IW11	1	F	c.1921G>T	g.2705770G>T	V641L	M	P-ORF	exon 14	16	NA	NA	rs377559548	0	1,51E-05	0	0	benign(0.079)	Deleterious(0.03)	C0	29	5	1	
F34	Rf399	3	F	c.2068C>T	g.2707565C>T	P690S	M	P-ORF	exon 16	7	-28	-1	rs397514623					probably_damaging(0.996)	Deleterious(0)	C65	0	73	3	PMID: 23143600 (Lemmers, 2010)
F35	Rf917	1	M	c.2243T>C	g.2707901T>C	L748P	M	P-ORF	exon 17	11	-36	-3						possibly_damaging(0.905)	Deleterious(0)	C45	14	87	3	PMID: 25256356 (Lemmers, HMG 2015)
F36	Rf1857	1		c.2321A>G	g.2718216A>G	Y774C	M	P-ORF	exon 18	6	NA	NA						probably_damaging(0.921)	Deleterious(0.01)	C25	102	155	3	
F37	Rf676	1	F	c.2545G>A	g.2722603G>A	D849N	M	P-ORF	exon 20	5	-37	-6						probably_damaging(0.996)	Deleterious(0)	C15	0	23	2	PMID: 23143600 (Lemmers, 2010)
F38	Rf1432	1	F	c.2768T>C	g.2726517T>C	L923P	M	P-ORF	exon 22	5	NA	NA						probably_damaging(0.942)	Deleterious(0)	C0	112	53	2	
F39	Rf1492	1	M	c.2933T>A	g.2729292T>A	L978H	M	P-ORF	exon 24	14	-28	3						probably_damaging(0.998)	Deleterious(0)	C0	235	89	2	
F40	Rf385	101	M	c.2941T>G	g.2729300T>G	Y981D	M	P-ORF	exon 24	21	-24	8						benign(0.158)	Deleterious(0)	C35	56	140	2	PMID: 27153398 (Boogaard, 2016)
F41	LOVD17	1		c.3187G>C	g.2732401G>C	G1063R	M	P-ORF	exon 25	NA	NA	NA						probably_damaging(0.999)	Deleterious(0)	C65	0	125	3	ASHG conference 2015 (Smith, 2015)
F42	LOVD20	1		c.3323T>C	g.2738441T>C	L1108P	M	P-ORF	exon 26	NA	NA	NA						possibly_damaging(0.888)	Deleterious(0.05)	C15	106	80	2	ASHG conference 2015 (Smith, 2015)
F43	IW3	1	M	c.3340G>A	g.2738458G>A	V1114I	M	P-ORF	exon 26	10	NA	NA	rs778206654	0	1,13E-04	0	5,80E-04	probably_damaging(0.956)	Deleterious(0)	C25	0	29	3	
F44	Rf1659	1	F	c.3811G>T	g.2747529G>T	V1271L	M	P-ORF	exon 30	18	NA	NA						benign(0.087)	Deleterious(0)	C25	0	31	2	
F45	Rf1430	1	F	c.3899T>A	g.2747617T>A	I1300K	M	P-ORF	exon 30	13	NA	NA	rs764012354	0	2,43E-05	0	0	probably_damaging(0.986)	Deleterious(0)	C35	29	91	3	
F46	LOVD7	1	F	c.4388A>C	g.2760691A>C	Q1463P	M	P-ORF	exon 35	13	NA	NA						probably_damaging(0.969)	Deleterious(0)	C65	0	75	3	PMID25370034 (Larsen, 2014)
F47	Rf1126	204	F	c.4404G>A	g.2760707G>A	M1468I	M	P-ORF	exon 35	13	-29	1						benign(0)	Tolerated(0.64)	C0	163	0	0	PMID: 25256356 (Lemmers, HMG 2015)
F48	LOVD8	1	M	c.4454C>T	g.2762122C>T	P1485L	M	P-ORF	exon 36	18	NA	NA						probably_damaging(0.996)	Deleterious(0)	C15	99	94	2	PMID25370034 (Larsen, 2014)
F49	Rf683	1	F	c.4661T>C	g.2763729T>C	F1554S	M	P-ORF	exon 37	11	-27	1						possibly_damaging(0.477)	Deleterious(0)	C65	0	155	3	PMID: 23143600 (Lemmers, 2010)
F50	Rf1853	1	M	c.5249A>G	g.2775805A>G	D1750G	M	P-ORF	exon 42	5	-27	-2						probably_damaging(0.999)	Deleterious(0)	C65	0	94	3	
F51	IW23	1	M	c.5249A>T	g.2775805A>T	D1750V	M	P-ORF	exon 42	12	NA	NA						probably_damaging(0.999)	Deleterious(0)	C65	0	152	3	
F52	IW6	1	M	c.5537A>G	g.2778227A>G	Y1846C	M	P-ORF	exon 44	11	NA	NA						probably_damaging(0.998)	Deleterious(0)	C65	0	194	3	
F53	Rf385	102	F	c.5596C>G	g.2784496C>G	R1866G	M	P-ORF	exon 45	10	-31	-1						probably_damaging(0.995)	Deleterious(0)	C65	0	125	3	PMID: 27153398 (Boogaard, 2016)
F54	Rf1807	1	M	c.5597G>A	g.2784497G>A	R1866Q	M	P-ORF	exon 45	14	-28	3	rs886044586					probably_damaging(0.992)	Deleterious(0)	C35	0	43	3	
F55	Rf975	201	F	c.24del	g.2656098del		D	D-ORF	exon 1	15	-38	-1												PMID: 25256356 (Lemmers, HMG 2015)
F56	IW10	1	F	c.173_174insCT	g.2656247_2656248insCT		D	D-ORF	exon 1	19	NA	NA												
F57	Rf743	1	M	c.182_183dup	g.2656256_2656257dup		D	D-ORF	exon 1	14	-30	2												
F58	Rf1472	1	M	c.182_183dup	g.2656256_2656257dup		D	D-ORF	exon 1	15	NA	NA												
F59	Rf1817	1		c.201_210delACCTGAAGAA	g.2666169delACCTGAAGAA		D	D-ORF	exon 2	6	NA	NA												
F60	Rf1101	2	F	c.582dupT	g.2674088dup		D	D-ORF	exon 5	16	-29	4												PMID: 25256356 (Lemmers, HMG 2015)
F61	IW7	1	M	c.687_690delTAGTinsG	g.2688440_2688443_delinsG		D	P-ORF	exon 6	5	NA	NA												
F62	Rf1819	1		c.728_730delTCT	g.2688481delTCT		D	P-ORF	exon 6	3	NA	NA												PMID: 29980640 (Mul, 2018)
F63	LOVD27	1	M	c.823_825del	g.2688695_2688697del		D	P-ORF	exon 7	11	NA	NA												PMID: 24128691 (Mitsuhashi, 2013)
F64	Rf2259	1	F	c.975_976delAG	g.2694626_2694627del		D	D-ORF	exon 8	14	-31	1												
F65	Rf2359	2	F	c.1036_1039del	g.2694687_2694690del		D	D-ORF	exon 8	11	NA	NA												
F66	LOVD30	1	F	c.1205_1268del	g.2697902_2697965del		D	D-ORF	exon 10	11	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F67	Rf1033	1	F	c.1302_1306delTGATA	g.2697999_2698003del		D	D-ORF	exon 10	24	-25	9	rs387907319											PMID: 23143600 (Lemmers, 2010)
F68	Rf2282	1	M	c.1490_1492delAGA	g.2700759_2700761delAGA		D	P-ORF	exon 12	8	-37	-5	rs886043345											
F69	Rf393	203	M	c.1608del	g.2700875del		D	D-ORF	exon 12	19	-31	4												PMID: 23143600 (Lemmers, 2010)
F70	IW26	1	F	c.1672_1673delGA	g.2703714_2703715delGA		D	D-ORF	exon 13	10	NA	NA												
F71	Rf1637	2	M	c.2088_2138del	g.2707585_2707635del		D	D-ORF	exon 16	10	-34	-2												
F72	Rf1469	1	M	c.2129dup	g.2707626dup		D	D-ORF	exon 16	5	NA	NA												
F73	IW25	1	F	c.2142dupT	g.2707639dupT		D	D-ORF	exon 16	6	NA	NA												
F74	LOVD14	1		c.2335dupA	g.2718230dup		D	D-ORF	exon 18	NA	NA	NA												ASHG conference 2015 (Smith, 2015)
F75	Rf1666	1	F	c.2468delC	g.2722526delC		D	D-ORF	exon 20	11	-34	-2												
F76	Rf1823	1		c.2523_2525delTAA	g.2722580delTAA		D	P-ORF	exon 20	6	NA	NA												
F77	Rf909	206	F	c.2665dupA	g.2724958dup		D	D-ORF	exon 21	9	-23	2												PMID: 25256356 (Lemmers, HMG 2015)
F78	LOVD37	1	F	c.3073_3075del	g.2732287_2732289del		D	P-ORF	exon 25	16	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F79	IW32	1	M	c.3197delT	g.2732411delT		D	D-ORF	exon 25	20	NA	NA												
F80	Rf1199	1	M	c.3238_3239delGA	g.2732452_2732453del		D	D-ORF	exon 25	9	NA	NA	rs886043182											PMID: 25256356 (Lemmers, HMG 2015)
F81	Rf941	1	M	c.3527_3529delinsTGC	g.2740713_2740715delinsTGC		D	P-ORF	exon 28	7	-29	-2												PMID: 25256356 (Lemmers, HMG 2015)
F82	LOVD38	1	M	c.4118_4132del	g.2750458_2750472del		D	P-ORF	exon 32	8	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F83	Rf753	1	M	c.4457_4462dup	g.2762125_2762130dup		D	P-ORF	exon 36	10	-39	-4												PMID: 25256356 (Lemmers, HMG 2015)
F84	GMC	1		c.4614_4615insTATAATA	g.2763682_2763683insTATAATA		D	D-ORF	exon 37	11	NA	NA												PMID: 27634379 (Gaillard, 2016)
F85	Rf1121	1	M	c.4738del	g.2769710delA		D	D-ORF	exon 38	9	-39	-5												PMID: 24075187 (Sacconi, 2013)
F86	LOVD31	1	M	c.5787_5790del	g.2796014_2796017del		D	D-ORF	exon 46	15	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F87	IW14	1	F	2,5 Mb deletion SMCHD1	2,5 Mb deletion SMCHD1		D	D-ORF		14	NA	NA												
F88	Rf898	2	F	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		16	-29	3												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F89	Rf929	1	M	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		14	-25	4												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F90	Rf922	1	M	c.412C>T	g.2667018C>T		N	D-ORF	exon 3	7	-31	-2												PMID: 25256356 (Lemmers, HMG 2015)
F91	IW15	1	M	c.907G>T	g.2694558G>T		N	D-ORF	exon 8	5	NA	NA												
F92	Rf391	3	M	c.1030C>T	g.2694681C>T		N	D-ORF	exon 8	14	-34	0	rs886041918											PMID: 25256356 (Lemmers, HMG 2015)
F93	IW29	1	M	c.1186C>T	g.2697883C>T		N	D-ORF	exon 10	7	NA	NA												

				SMCHD1	SMCHD1	SMCHD1								EXAC (Minor Allele Frequency)				Ensemble	Alamut				Total (1+2+3)	
ID	Family	Nr	M/F	cDNA (NM_015295.2)	gene (hg19 (GRCh37.p5)	protein (NP_056110.2)	type	ORF	position	FseI	delta1	delta2	dbSNP	AFR	EUR	EAS	SAS	PolyPhen (1)	SIFT(2)	AGVGD (3)	GV	GD	Prediction	Publication
F94	IW33	1	M	c.1186C>T	g.2697883C>T		N	D-ORF	exon 10	14	NA	NA												
F95	IW34	1	M	c.1186C>T	g.2697883C>T		N	D-ORF	exon 10	13	NA	NA												
F96	LOVD24	1		c.1594G>T	g.2700863G>T		N	D-ORF	exon 12	NA	NA	NA	rs780874216											ASHG conference 2015 (Smith, 2015)
F97	Rf1640	1	F	c.1654C>T	g.2703696C>T		N	D-ORF	exon 13	15	-31	2	rs1224850132											
F98	Rf1575	1	M	c.1738A>T	g.2703780A>T		N	D-ORF	exon 13	15	NA	NA												
F99	LOVD28	1	M	c.1819A>T	g.2703861A>T		N	D-ORF	exon 13	13	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F100	Rf562	1	F	c.2191C>T	g.2707849C>T		N	D-ORF	exon 17	16	-26	5												PMID: 25256356 (Lemmers, HMG 2015)
F101	Rf2255	1	F	c.2377C>T	g.2718351C>T		N	D-ORF	exon 19	4	-23	-1												
F102	Rf947	1	M	c.2656C>T	g.2724949C>T		N	D-ORF	exon 21	9	-28	0	rs201632358											PMID: 27153398 (Boogaard, 2016)
F103	IW28	1	M	c.2656C>T	g.2724949C>T		N	D-ORF	exon 21	6	NA	NA	rs201632358											
F104	Rf1416	1	M	c.2785C>T	g.2728466C>T		N	D-ORF	exon 23	10	NA	NA												
F105	Rf1473	1	M	c.3010A>T	g.2729369A>T		N	D-ORF	exon 24	13	NA	NA												
F106	Rf1468	1	F	c.3469G>T	g.2739473G>T		N	D-ORF	exon 27	9	NA	NA												
F107	Rf1727	2	F	c.3631C>T	g.2740817C>T		N	D-ORF	exon 28	10	-34	-2												
F108	Rf1552	203	M	c.4267C>T	g.2751377C>T		N	D-ORF	exon 33	20	-24	8												
F109	LOVD29	1	M	c.4267C>T	g.2751377C>T		N	D-ORF	exon 33	8	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F110	LOVD6	1	F	c.4988T>G	g.2771552T>G		N	D-ORF	exon 40	16	NA	NA												PMID25370034 (Larsen, 2014)
F111	Rf2369	4	F	c.5005C>T	g.2771569C>T		N	D-ORF	exon 40	4	-38	-7	rs1241705515											
F112	Rf1837	1		c.5065G>T	g.2772260G>T		N	D-ORF	exon 41	21	NA	NA	rs1174155307											
F113	Rf400	3	M	c.5383C>T	g.2777820C>T		N	D-ORF	exon 43	22	-25	8	rs867694014											PMID: 25256356 (Lemmers, HMG 2015)
F114	Rf1256	1	M	c.5383C>T	g.2777820C>T		N	D-ORF	exon 43	14	-33	0	rs867694014											
F115	Rf629	6	F	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	12	-27	2	rs1229050345											PMID: 25256356 (Lemmers, HMG 2015)
F116	Rf1754	1	F	c.5866G>T	g.2796093G>T		N	D-ORF	exon 46	9	-36	-4												
F117	Rf1657	1	M	c.5866G>T	g.2796093G>T		N	D-ORF	exon 46	11	NA	NA												
F118	LOVD32	1	M	c.187-6G>A	g.2666150G>A		S3	D-ORF	intron 1	21	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F119	Rf1818	1		c.263A>G	g.2666869A>G	D88G	S3+M	P-ORF	exon 3	17	NA	NA	rs200521548	0	2,04E-04	0	1,02E-03	benign(0)	Tolerated(0.06)	C0	247	0	0	
F120	Rf702	1	M	c.754-2A>G	g.2688624A>G		S3	P-ORF	intron 6	8	-43	-7												PMID: 25256356 (Lemmers, HMG 2015)
F121	Rf744	1	M	c.1843-15A>G	g.2705677A>G		S3	P-ORF	intron 13	19	-27	6												
F122	Rf644	1	F	c.1843-1G>T	g.2705691G>T		S3	P-ORF	intron 13	5	-32	-4												PMID: 25256356 (Lemmers, HMG 2015)
F123	IW2	1	F	c.1843-1G>A	g.2705691G>A		S3	P-ORF	intron 13	6	NA	NA	rs886043146											
F124	Rf549	3	M	c.2147-1G>C	g.2707804G>C		S3	P-ORF	intron 16	9	-44	-7												PMID: 25256356 (Lemmers, HMG 2015)
F125	LOVD13	1		c.2147-1G>C	g.2707804G>C		S3	P-ORF	intron 16	NA	NA	NA												ASHG conference 2015 (Smith, 2015)
F126	IW4	1	F	c.2147-1G>C	g.2707804G>C		S3	P-ORF	intron 16	<25	NA	NA												
F127	Rf1749	1	M	c.2914-5A>G	g.2729268A>G		S3	D-ORF	intron 23	8	-33	-3	rs1215623273											
F128	Rf394	213	M	c.3426-2A>G	g.2739428A>G		S3	D-ORF	intron 26	3	-36	-7												
F129	Rf1352	1	M	c.3634-19A>G	g.2743740A>G		S3	D-ORF	intron 28	20	-24	8												PMID: 25256356 (Lemmers, HMG 2015)
F130	Rf1831	1		c.3928-3T>G	g.2750038T>G		S3	D-ORF	intron 31	7	NA	NA												
F131	Rf1034	1	M	c.4347-236A>G	g.2760414A>G		S3	D-ORF	intron 34	10	-29	0												
F132	Rf1507	1	F	c.4720-2del	g.2769690del		S3	P-ORF	intron 37	18	-28	4												
F133	LOVD34	1	M	c.5367-1G>C	g.2777803G>C		S3	D-ORF	intron 42	23	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F134	Rf1043	1	M	c.5720-2A>C	g.2795945A>C		S3	D-ORF	intron 45	14	-26	3												PMID: 25256356 (Lemmers, HMG 2015)
F135	Rf1614	1	M	c.5720-1G>C	g.2795946G>C		S3	D-ORF	intron 45	27	NA	NA												
F136	Rf691	3	M	c.186+1G>A	g.2656261G>A		S5	P-ORF	intron 1	10	-35	-3												
F137	Rf833	1	F	c.424+1G>A	g.2667031G>A		S5	P-ORF	intron 3	5	-38	-7												PMID: 25256356 (Lemmers, HMG 2015)
F138	LOVD35	1	M	c.638+5G>C	g.2674149G>C		S5	D-ORF	intron 5	19	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F139	Rf394	204	F	c.873+1G>A	g.2688746G>A		S5	P-ORF	intron 7	4	-33	-5												PMID: 25256356 (Lemmers, HMG 2015)
F140	LOVD25	1	M	c.1040+1G>A	g.2694692G>A		S5	D-ORF	intron 8	11	NA	NA	rs1245372794											PMID: 24755953 (Winston, 2014)
F141	Rf1426	1	M	c.1040+5G>A	g.2694696G>A		S5	D-ORF	intron 8	13	NA	NA												
F142	Rf1470	1	F	c.1131+2_1131+5del	g.2697122_2697125del		S5	D-ORF	intron 9	10	NA	NA												
F143	LOVD10	1	M	c.1463+5G>A	g.2700662G>A		S5	D-ORF	intron 11	NA	NA	NA												PMID25370034 (Larsen, 2014)
F144	Rf696	1	M	c.1647+3A>G	g.2700919A>G		S5	D-ORF	intron12	12	-40	-4												PMID: 23143600 (Lemmers, 2010)
F145	Rf849	1	M	c.2146G>A	g.2707643G>A	G716S	S5+M	D-ORF	intron 16	15	-23	5						probably_damaging(0.96)	Deleterious(0)	C55	0	55	3	PMID: 25256356 (Lemmers, HMG 2015)
F146	Rf2747	1		c.2260+1G>T	g.2707919G>T		S5	P-ORF	intron 17	5	NA	NA												
F147	Rf1353	1	M	c.2260+5G>A	g.2707923G>A		S5	P-ORF	intron 17	4	-43	-10												PMID: 25256356 (Lemmers, HMG 2015)
F148	Rf1124	1	F	c.2338+1G>T	g.2718234G>T		S5	P-ORF	intron 18	22	NA	NA												
F149	Rf1451	1	M	c.2338G>A	g.2718233G>A	E780K	S5+M	P-ORF	intron 18	19	NA	NA	rs886044357					probably_damaging(0.978)	Deleterious(0.04)	C0	98	46	2	
F150	Rf1002	1	M	c.2338G>T	g.2718233G>T		S5+N	D-ORF	intron 18	15	-25	4												PMID: 25256356 (Lemmers, HMG 2015)
F151	Rf1262	1	M	c.2458+2T>A	g.2718434T>A		S5	P-ORF	intron 19	6	NA	NA												
F152	LOVD16	1		c.2458+5G>A	g.2718437G>A		S5	P-ORF	intron 19	NA	NA	NA												ASHG conference 2015 (Smith, 2015)
F153	Rf268	3	M	c.2603G>A	g.2722661G>A	S868N	S5+M	D-ORF	intron 20	9	-24	2						benign(0.346)	Deleterious(0.01)	C0	58	39	1	PMID: 23143600 (Lemmers, 2010)
F154	Rf947	1	M	c.2700+1G>T	g.2724994G>T		S5	D-ORF	intron 21	9	-28	0												PMID: 27153398 (Boogaard, 2016)
F155	IW28	1	M	c.2700+1G>T	g.2724994G>T		S5	D-ORF	intron 21	6	NA	NA												
F156	Rf1825	1		c.2913+1G>A	g.2728595G>A		S5	D-ORF	intron 23	10	NA	NA												
F157	Rf1504	1	M	c.2913+1G>A	g.2728595G>A		S5	D-ORF	intron 23	12	NA	NA												
F158	Rf725	1	F	c.3048+1G>T	g.2729408G>T		S5	P-ORF	intron 24	8	-35	-4												PMID: 25256356 (Lemmers, HMG 2015)
F159	Rf1110	1	M	c.3048+2T>C	g.2729409T>C		S5	P-ORF	intron 24	8	-36	-4												PMID: 24075187 (Sacconi, 2013)
F160	Rf1828	1		c.3273_3276+1delTAAAG	g.2732486delTAAAG		S5	P-ORF	intron 25	4	NA	NA												
F161	LOVD3	1	F	c.3274_3276+1del	g.2732488_2732492del		S5+N	P-ORF	intron 25	12	NA	NA												PMID25370034 (Larsen, 2014)
F162	LOVD9	1	F	c.3274_3276+1del	g.2732488_2732492del		S5+N	P-ORF	intron 25	NA	NA	NA												PMID25370034 (Larsen, 2014)
F163	LOVD33	1	M	c.3274_3276+1del	g.2732488_2732491del		S5	P-ORF	intron 25	4	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F164	Rf844	1	M	c.3274_3276+1del	g.2732488_2732491del		S5	P-ORF	intron 25	7	-36	-5												PMID: 23143600 (Lemmers, 2010)
F165	Rf874	2	F	c.3274_3276+1del	g.2732488_2732491del		S5	P-ORF	intron 25	15	-42	-3												PMID: 23143600 (Lemmers, 2010)
F166	LOVD18	1		c.3274_3276+1del	g.2732488_2732491del		S5	P-ORF	intron 25	NA	NA	NA												ASHG conference 2015 (Smith, 2015)
F167	LOVD2	1	F	c.3276_3276+4del	g.2732487_2732492del		S5+N	P-ORF	intron 25	6	NA	NA												PMID25370034 (Larsen, 2014)
F168	Rf580	1	M	c.3276_3276+4del	g.2732490_2732494del		S5+N	P-ORF	intron 25	11	-30	0												PMID: 25256356 (Lemmers, HMG 2015)
F169	Rf936	1	F	c.3276_3276+4del	g.2732490_2732494del		S5+N	P-ORF	intron 25	6	-35	-5												PMID: 25256356 (Lemmers, HMG 2015)
F170	Rf1418	1	M	c.3276_3276+4del	g.2732490_2732494del		S5+N	P-ORF	intron 25	8	NA	NA												
F171	Rf1414	1	M	c.3276_3276+4del	g.2732490_2732494del		S5	P-ORF	intron 25	6	-37	-6												PMID: 27153398 (Boogaard, 2016)
F172	Rf1865	1	M	c.3276+1G>A	g.2732491G>A		S5	P-ORF	intron 25	8	-30	-2												
F173	Rf878	2	F	c.3276+4_3276+7del	g.2732494_2732497del		S5	P-ORF	intron 25	16	-35	1												PMID: 25256356 (Lemmers, HMG 2015)
F174	Rf1309	1	M	c.3276+4_3276+7del	g.2732494_2732497del		S5	P-ORF	intron 25	11	-31	-1												PMID: 25256356 (Lemmers, HMG 2015)
F175	LOVD19	1		c.3276+4_3276+7delAGTA	g.2732494_2732497delAGTA		S5	P-ORF	intron 25	NA	NA	NA												ASHG conference 2015 (Smith, 2015)
F176	Rf1786	1	M	c.3276+5G>A	g.2732495G>A		S5	P-ORF	intron 25	10	NA	NA												
F177	Rf1155	1	M	c.3425G>C	g.2738543G>C	R1142T	S5+M	P-ORF	intron 26	12	NA	NA						benign(0.307)	Tolerated(0.14)	C0	106	25	0	
F178	Rf649	1	M	c.3801+1G>A	g.2743927G>A		S5	P-ORF	intron 29	16	-27	4	rs886042417											PMID: 23143600 (Lemmers, 2010)
F179	Rf1203	1	F	c.3801+1G>A	g.2743927G>A		S5	P-ORF	intron 29	16	-25	5	rs886042417											PMID: 25256356 (Lemmers, HMG 2015)
F180	Rf879	1	M	c.3801+2T>C	g.2743928T>C		S5	P-ORF	intron 29	10	-33	-2	rs778079305	0	1,85E-05	0	0							PMID: 25256356 (Lemmers, HMG 2015)
F181	IW24	1	F	c.4007+1G>A	g.2750121G>A		S5	D-ORF	intron 32	16	NA	NA												
F182	IW9	1	F	c.4008-4_4008-2delTTAinsCT	g.2750344_2750346delTTAinsCT		S5	D-ORF	intron 32	15	NA	NA												
F183	LOVD4	1	F	c.4346G>A	g.2752550G>A	R1449K	S5+M	P-ORF	intron 34	15	NA	NA						probably_damaging(0.967)	Deleterious(0)	C25	0	26	3	PMID25370034 (Larsen, 2014)
F184	Rf1254	1	M	c.4346+1G>C	g.2752551G>C		S5	D-ORF	intron 34	9	-29	-1												PMID: 25256356 (Lemmers, HMG 2015)
F185	Rf392	201	M	c.4566G>A	g.2762234G>A		S5	P-ORF	intron 36	23	-27	8												PMID: 23143600 (Lemmers, 2010)
F186	Rf1014	1	M	c.4566G>A	g.2762234G>A		S5	P-ORF	intron 36	17	NA	NA												PMID: 23143600 (Lemmers, 2010)
F187	Rf2408	1	F	c.5547+5G>A	g.2778242G>A		S5	D-ORF	intron 44	5	-29	-3												

				SMCHD1	SMCHD1	SMCHD1								EXAC (Minor Allele Frequency)				Ensemble	Alamut				Total (1+2+3)	
ID	Family	Nr	M/F	cDNA (NM_015295.2)	gene (hg19 (GRCh37.p5)	protein (NP_056110.2)	type	ORF	position	FseI	delta1	delta2	dbSNP	AFR	EUR	EAS	SAS	PolyPhen (1)	SIFT(2)	AGVGD (3)	GV	GD	Prediction	Publication
F3	Rf6	265	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	13	-38	-2	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F3	Rf6	52	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	11	-34	-2	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F3	Rf6	262	M	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	7	-36	-5	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F3	Rf6	37	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	6	-35	-5	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F3	Rf6	53	M	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	7	-39	-6	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F3	Rf6	51	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	3	-42	-10	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 29980640 (Mul, 2018)
F12	IW1	1	F	c.724G>A	g.2688477G>A	A242T	M	P-ORF	exon 6	19	NA	NA						probably_damaging(0.999)	Deleterious(0)	C55	0	58	3	PMID: 29980640 (Mul, 2018)
F18	Rf742	4	M	c.1058A>G	g.2697047A>G	Y353C	M	P-ORF	exon 9	9	-42	-6						probably_damaging(0.997)	Deleterious(0)	C65	0	194	3	PMID: 23143600 (Lemmers, 2010)
F28	Rf1021	3	M	c.1580C>T	g.2700849C>T	T527M	M	P-ORF	exon 12	11	-27	1	rs397518422					probably_damaging(0.992)	Deleterious(0)	C0	78	52	2	PMID: 24075187 (Sacconi, 2013)
F28	Rf1021	2	F	c.1580C>T	g.2700849C>T	T527M	M	P-ORF	exon 12	24	-25	10	rs397518422					probably_damaging(0.992)	Deleterious(0)	C0	78	52	2	PMID: 24075187 (Sacconi, 2013)
F34	Rf399	2	F	c.2068C>T	g.2707565C>T	P690S	M	P-ORF	exon 16	10	-30	-1	rs397514623					probably_damaging(0.996)	Deleterious(0)	C65	0	73	3	PMID: 23143600 (Lemmers, 2010)
F40	Rf385	203	M	c.2941T>G and c.5596C>G	g.2729300T>G and g.2784496C>G	Y981D	M	P-ORF	exon 24	5	-38	-7						benign(0.158)	Deleterious(0)	C35	56	140	2	PMID: 27153398 (Boogaard, 2016)
F40	Rf385	206	F	c.2941T>G and c.5596C>G	g.2729300T>G and g.2784496C>G	Y981D	M	P-ORF	exon 24	1	-37	-9						benign(0.158)	Deleterious(0)	C35	56	140	2	PMID: 27153398 (Boogaard, 2016)
F47	Rf1126	205	M	c.4404G>A	g.2760707G>A	M1468I	M	P-ORF	exon 35	12	-35	-1						benign(0)	Tolerated(0.64)	C0	163	0	0	PMID: 25256356 (Lemmers, HMG 2015)
F47	Rf1126	208	F	c.4404G>A	g.2760707G>A	M1468I	M	P-ORF	exon 35	22	-34	5						benign(0)	Tolerated(0.64)	C0	163	0	0	PMID: 25256356 (Lemmers, HMG 2015)
F55	Rf975	101	M	c.24del	g.2656098del		D	D-ORF	exon 1	27	-26	11												PMID: 25256356 (Lemmers, HMG 2015)
F55	Rf975	301	F	c.24del	g.2656098del		D	D-ORF	exon 1	13	-38	-3												PMID: 25256356 (Lemmers, HMG 2015)
F55	Rf975	302	F	c.24del	g.2656098del		D	D-ORF	exon 1	13	-36	-1												PMID: 25256356 (Lemmers, HMG 2015)
F57	Rf743	2	F	c.182_183dup	g.2656256_2656257dup		D	D-ORF	exon 1	12	-34	-1												
F57	Rf743	5	F	c.182_183dup	g.2656256_2656257dup		D	D-ORF	exon 1	9	-31	-1												
F57	Rf743	4	M	c.182_183dup	g.2656256_2656257dup		D	D-ORF	exon 1	17	-26	5												
F60	Rf1101	1	M	c.582dupT	g.2674088dup		N	D-ORF	exon 5	11	-28	1												PMID: 25256356 (Lemmers, HMG 2015)
F67	Rf1033	2	F	c.1302_1306delTGATA	g.2697999_2698003del		D	D-ORF	exon 10	10	-22	3	rs387907319											
F69	Rf393	101	M	c.1608del	g.2700875del		D	D-ORF	exon 12	12	-38	-3												PMID: 23143600 (Lemmers, 2010)
F69	Rf393	302	F	c.1608del	g.2700875del		D	D-ORF	exon 12	19	-35	2												PMID: 23143600 (Lemmers, 2010)
F69	Rf393	303	M	c.1608del	g.2700875del		D	D-ORF	exon 12	19	-26	6												PMID: 23143600 (Lemmers, 2010)
F69	Rf393	305	M	c.1608del	g.2700875del		D	D-ORF	exon 12	21	-33	4												PMID: 23143600 (Lemmers, 2010)
F69	Rf393	206	F	c.1608del	g.2700875del		D	D-ORF	exon 12	11	-36	-3												PMID: 23143600 (Lemmers, 2010)
F71	Rf1637	4	F	c.2088_2138del	g.2707585_2707635del		D	D-ORF	exon 16	8	-30	-2												
F71	Rf1637	5	F	c.2088_2138del	g.2707585_2707635del		D	D-ORF	exon 16	10	-31	-1												
F77	Rf909	202	F	c.2665dupA	g.2724958dup		D	D-ORF	exon 21	7	-22	1												PMID: 25256356 (Lemmers, HMG 2015)
F77	Rf909	102	F	c.2665dupA	g.2724958dup		D	D-ORF	exon 21	5	-28	-3												PMID: 25256356 (Lemmers, HMG 2015)
F88	Rf898	3	M	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		12	-26	2												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F88	Rf898	4	F	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		12	-31	0												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F88	Rf898	1	M	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		13	-28	2												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F88	Rf898	5	M	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		16	-25	5												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F89	Rf929	3	F	1,2 Mb deletion SMCHD1	1,2 Mb deletion SMCHD1		D	D-ORF		20	-25	7												PMID: 25820463 (Lemmers, Hum Mut. 2015)
F90	Rf922	2	F	c.412C>T	g.2667018C>T		N	D-ORF	exon 3	12	-42	-5												PMID: 25256356 (Lemmers, HMG 2015)
F99	LOVD28	2	F	c.1819A>T	g.2703861A>T		N	D-ORF	exon 13	10	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F102	Rf947	3	M	c.2656C>T	g.2724949C>T		N	D-ORF	exon 21	8	-33	-3	rs201632358											
F102	Rf947	2	F	c.2656C>T	g.2724949C>T		N	D-ORF	exon 21	13	-26	3	rs201632358											
F107	Rf1727	1	F	c.3631C>T	g.2740817C>T		N	D-ORF	exon 28	13	-31	1												
F108	Rf1552	201	M	c.4267C>T	g.2751377C>T		N	D-ORF	exon 33	17	-27	5												
F108	Rf1552	102	F	c.4267C>T	g.2751377C>T		N	D-ORF	exon 33	17	-25	6												
F113	Rf400	4	M	c.5383C>T	g.2777820C>T		N	D-ORF	exon 43	18	-33	3	rs867694014											
F115	Rf629	2	F	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	8	-24	1	rs1229050345											PMID: 25256356 (Lemmers, HMG 2015)
F115	Rf629	3	M	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	3	-26	-3	rs1229050345											PMID: 25256356 (Lemmers, HMG 2015)
F115	Rf629	4	M	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	8	-21	2	rs1229050345											PMID: 25256356 (Lemmers, HMG 2015)
F115	Rf629	5	M	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	8	NA	NA	rs1229050345											
F115	Rf629	10	F	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	14	-26	3	rs1229050345											
F115	Rf629	11	F	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	12	-28	1	rs1229050345											
F115	Rf629	12	F	c.5602C>T	g.2784502C>T		N	D-ORF	exon 45	6	-29	-2	rs1229050345											PMID: 25256356 (Lemmers, HMG 2015)
F118	LOVD32	2	M	c.187-6G>A	g.2666150G>A		S3	D-ORF	intron 1	10	NA	NA												PMID: 27061275 (Hamanaka, 2016)
F121	Rf744	4	F	c.1843-15A>G	g.2705677A>G		S3	P-ORF	intron 13	10	-34	-3												
F124	Rf549	1	M	c.2147-1G>C	g.2707804G>C		S3	P-ORF	intron 16	7	NA	NA												
F129	Rf1352	2	M	c.3634-19A>G	g.2743740A>G		S3	D-ORF	intron 28	4	-28	-3												PMID: 25256356 (Lemmers, HMG 2015)
F131	Rf1034	4	F	c.4347-236A>G	g.2760414A>G		S3	D-ORF	intron 34	9	-30	-1												
F131	Rf1034	5	F	c.4347-236A>G	g.2760414A>G		S3	D-ORF	intron 34	9	-30	-1												
F131	Rf1034	3	F	c.4347-236A>G	g.2760414A>G		S3	D-ORF	intron 34	29	-26	12												
F136	Rf691	1	M	c.186+1G>A	g.2656261G>A		S5	P-ORF	intron 1	14	-31	1												
F136	Rf691	5	M	c.186+1G>A	g.2656261G>A		S5	P-ORF	intron 1	9	-34	-3												
F139	Rf394	301	F	c.873+1G>A	g.2688746G>A		S5	P-ORF	intron 7	10	-37	-4												
F154	Rf947	3	M	c.2700+1G>T	g.2724994G>T		S5	D-ORF	intron 21	8	-33	-3												
F154	Rf947	2	F	c.2700+1G>T	g.2724994G>T		S5	D-ORF	intron 21	13	-26	3												
F159	Rf1110	3	F	c.3048+2T>C	g.2729409T>C		S5	P-ORF	intron 24	10	-41	-6												PMID: 24075187 (Sacconi, 2013)
F165	Rf874	3	F	c.3274_3276+1del	g.2732488_2732491del		S5	P-ORF	intron 25	12	-35	-2												PMID: 23143600 (Lemmers, 2010)
F171	Rf1414	4	F	c.3276_3276+4del	g.2732490_2732494del		S5	P-ORF	intron 25	6	-36	-5												
F178	Rf649	3	F	c.3801+1G>A	g.2743927G>A		S5	P-ORF	intron 29	9	-30	-1	rs886042417											PMID: 23143600 (Lemmers, 2010)
F178	Rf649	5	M	c.3801+1G>A	g.2743927G>A		S5	P-ORF	intron 29	13	-31	1	rs886042417											PMID: 23143600 (Lemmers, 2010)
F181	IW24	2	F	c.4007+1G>A	g.2750121G>A		S5	D-ORF	intron 32	13	NA	NA												
F182	IW9	2	F	c.4008-4_4008-2delTTAinsCT	g.2750344_2750346delTTAinsCT		S5	D-ORF	intron 32	17	NA	NA												
F184	Rf1254	3	F	c.4346+1G>C	g.2752551G>C		S5	D-ORF	intron 34	9	NA	NA												
F184	Rf1254	2	F	c.4346+1G>C	g.2752551G>C		S5	D-ORF	intron 34	12	NA	NA												
F185	Rf392	202	F	c.4566G>A	g.2762234G>A	T1522T	S5	P-ORF	exon 36	11	-39	-4												PMID: 23143600 (Lemmers, 2010)
F185	Rf392	102	F	c.4566G>A	g.2762234G>A	T1522T	S5	P-ORF	exon 36	17	-30	3												PMID: 23143600 (Lemmers, 2010)
F186	Rf1014	3	M	c.4566G>A	g.2762234G>A	T1522T	S5	P-ORF	exon 36	16	NA	NA												PMID: 23143600 (Lemmers, 2010)
F186	Rf1014	4	F	c.4566G>A	g.2762234G>A	T1522T	S5	P-ORF	exon 36	24	-32	6												PMID: 23143600 (Lemmers, 2010)
B1	NG15	1	F	c.320T>C	g.2666926T>C	L107P	M	P-ORF	exon 3	NA	NA	NA	rs1135402737					probably_damaging(0.998)	Deleterious(0)	C65	0	98	3	PMID: 28067909 (Shaw, 2017)
B2	Rf2324	1	M	c.386T>A	g.2666992T>A	M129K	M	P-ORF	exon 3	8	-40	-6	rs1135402738					benign(0.295)	Deleterious(0.01)	C0	81	46	1	PMID: 28067909 (Shaw, 2017)
B3	IW27	1	F	c.386T>G	g.2666992T>G	M129R	M	P-ORF	exon 3	4	-40	-8						benign(0.369)	Deleterious(0.01)	C0	81	36	1	
B4	NG11	1	F	c.400G>T	g.2667006G>T	A134S	M	P-ORF	exon 3	NA	NA	NA						probably_damaging(0.991)	Deleterious(0)	C0	208	18	2	PMID: 2806791 (Gordon, 2017)
B5	NG12	1	F	c.400G>T	g.2667006G>T	A134S	M	P-ORF	exon 3	NA	NA	NA						probably_damaging(0.991)	Deleterious(0)	C0	208	18	2	PMID: 2806791 (Gordon, 2017)
B6	NG2	1	F	c.403A>T	g.2667009A>T	S135C	M	P-ORF	exon 3	NA	NA	NA	rs1057519645					probably_damaging(0.996)	Deleterious(0)	C65	0	112	3	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B7	NG4	1	F	c.403A>T	g.2667009A>T	S135C	M	P-ORF	exon 3	15	NA	NA	rs1057519645					probably_damaging(0.996)	Deleterious(0)	C65	0	112	3	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B8	IW18	1	M	c.404G>A	g.2667010G>A	S135N	M	P-ORF	exon 3	6	-40	-7	rs1057519646					probably_damaging(0.986)	Deleterious(0)	C45	0	46	3	PMID: 28067909 (Shaw, 2017)
B9	NG16	1	F	c.404G>A	g.2667010G>A	S135N	M	P-ORF	exon 3	NA	NA	NA	rs1057519646					probably_damaging(0.986)	Deleterious(0)	C45	0	46	3	PMID: 28067909 (Shaw, 2017)
B10	NG3	1	M	c.404G>A	g.2667010G>A	S135N	M	P-ORF	exon 3	NA	NA	NA	rs1057519646					probably_damaging(0.986)	Deleterious(0)	C45	0	46	3	PMID: 2806791 (Gordon, 2017)
B11	NG17	1	M	c.404G>T	g.2667010G>T	S135I	M	P-ORF	exon 3	NA	NA	NA	rs1057519646					probably_damaging(0.994)	Deleterious(0)	C65	0	142	3	PMID: 28067909 (Shaw, 2017)
B12	NG1	1	M	c.407A>G	g.2667013A>G	E136G	M	P-ORF	exon 3	NA	NA	NA						probably_damaging(0.994)	Deleterious(0)	C65	0	98	3	PMID: 2806791 (Gordon, 2017)
B13	NG18	1	M	c.408A>C	g.2667014A>C	E136D	M	P-ORF	exon 3	18	-25	6	rs1057519643					probably_damaging(0.978)	Deleterious(0)	C35	0	45	3	PMID: 28067909 (Shaw, 2017)
B14	Rf2320	1	F	c.410G>A	g.2667016G>A	G137E	M	P-ORF	exon 3	24	-23	10	rs1057519644					probably_damaging(0.989)	Deleterious(0.01)	C0	79	30	2	PMID: 28067909 (Shaw, 2017)
B15	Rf2316	1	F	c.415A>C	g.2667021A>C	N139H	M	P-ORF	exon 3	16	-29	3	rs1135402739					probably_damaging(0.992)	Deleterious(0.02)	C0	94	15	2	PMID: 28067909 (Shaw, 2017)
B16	Rf2328	1	F	c.415A>C	g.2667021A>C	N139H	M	P-ORF	exon 3	9	-34	-3	rs1135402739					probably_damaging(0.992)	Deleterious(0.02)	C0	94	15	2	PMID: 28067909 (Shaw, 2017)
B17	Rf2323	1	M	c.423G>C	g.2667029G>C	L141F	M	P-ORF	exon 3	3	-39	-8	rs1057519641					probably_damaging(0.999)	Deleterious(0)	C15	0	22	2	PMID: 28067909 (Shaw, 2017)

				SMCHD1	SMCHD1	SMCHD1								EXAC (Minor Allele Frequency)				Ensemble	Alamut				Total (1+2+3)	
ID	Family	Nr	M/F	cDNA (NM_015295.2)	gene (hg19 (GRCh37.p5)	protein (NP_056110.2)	type	ORF	position	FseI	delta1	delta2	dbSNP	AFR	EUR	EAS	SAS	PolyPhen (1)	SIFT(2)	AGVGD (3)	GV	GD	Prediction	Publication
B18	NG19	1	F	c.423G>C	g.2667029G>C	L141F	M	P-ORF	exon 3	NA	NA	NA	rs1057519641					probably_damaging(0.999)	Deleterious(0)	C15	0	22	2	PMID: 28067909 (Shaw, 2017)
B19	Rf2325	1	M	c.423G>C	g.2667029G>C	L141F	M	P-ORF	exon 3	3	-38	-8	rs1057519641					probably_damaging(0.999)	Deleterious(0)	C15	0	22	2	PMID: 28067909 (Shaw, 2017)
B20	NG20	1	M	c.423G>C	g.2667029G>C	L141F	M	P-ORF	exon 3	NA	NA	NA	rs1057519641					probably_damaging(0.999)	Deleterious(0)	C15	0	22	2	PMID: 28067909 (Shaw, 2017)
B21	NG21	1	M	c.511T>G	g.2674017T>G	F171V	M	P-ORF	exon 5	NA	NA	NA	rs1135402740					possibly_damaging(0.795)	Deleterious(0)	C45	0	49	3	PMID: 28067909 (Shaw, 2017)
B22	Rf2317	1	M	c.725C>G	g.2688478C>G	A242G	M	P-ORF	exon 6	NA	NA	NA	rs1135402741					probably_damaging(0.998)	Deleterious(0)	C55	0	60	3	PMID: 28067909 (Shaw, 2017)
B23	NG10	1	F	c.1025G>C	g.2694676G>C	W342S	M	P-ORF	exon 8	NA	NA	NA						probably_damaging(0.996)	Deleterious(0)	C65	0	177	3	PMID: 2806791 (Gordon, 2017)
B24	NG21	1	F	c.1034A>G	g.2694685A>G	Q345R	M	P-ORF	exon 8	NA	NA	NA	rs1057519639					possibly_damaging(0.787)	Deleterious(0.01)	C0	29	43	2	PMID: 28067909 (Shaw, 2017)
B25	Rf2326	1	M	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017)
B26	NG13	1	F	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B27	NG5	1	M	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B28	NG22	1	F	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017)
B29	NG23	1	M	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017)
B30	Rf2318	1	M	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	9	-28	0	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017)
B31	Rf2319	1	M	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	17	-29	4	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 28067909 (Shaw, 2017)
B32	NG14	1	F	c.1043A>G	g.2697032A>G	H348R	M	P-ORF	exon 9	NA	NA	NA	rs1057519640					probably_damaging(0.955)	Deleterious(0)	C25	0	29	3	PMID: 2806791 (Gordon, 2017)
B33	Rf2321	1	F	c.1199A>T	g.2697896A>T	Q400L	M	P-ORF	exon 10	8	-44	-8	rs1057519642					possibly_damaging(0.702)	Deleterious(0)	C65	0	112	3	PMID: 28067909 (Shaw, 2017)
B34	NG6	1	M	c.1259A>T	g.2697956A>T	D420V	M	P-ORF	exon 10	NA	NA	NA	rs1135402742					benign(0.296)	Deleterious(0)	C35	45	121	2	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B35	NG9	1	M	c.1259A>T	g.2697956A>T	D420V	M	P-ORF	exon 10	NA	NA	NA	rs1135402742					benign(0.296)	Deleterious(0)	C35	45	121	2	PMID: 2806791 (Gordon, 2017)
B36	Rf2327	1	M	c.1417G>C	g.2700611G>C	E473Q	M	P-ORF	exon 11	NA	NA	NA	rs1135402743					probably_damaging(0.981)	Deleterious(0.01)	C0	45	29	2	PMID: 28067909 (Shaw, 2017)
B37	NG8	1	F	c.1552A>G	g.2700821A>G	K518E	M	P-ORF	exon 12	NA	NA	NA						possibly_damaging(0.696)	Deleterious(0.01)	C15	26	44	2	PMID: 2806791 (Gordon, 2017)
B38	NG24	1	M	c.1568C>A	g.2700837C>A	T523K	M	P-ORF	exon 12	NA	NA	NA	rs1135402744					probably_damaging(0.994)	Deleterious(0)	C65	0	78	3	PMID: 28067909 (Shaw, 2017)
B39	NG25	1	F	c.1568C>A	g.2700837C>A	T523K	M	P-ORF	exon 12	NA	NA	NA	rs1135402744					probably_damaging(0.994)	Deleterious(0)	C65	0	78	3	PMID: 28067909 (Shaw, 2017)
B40	Rf2322	1	M	c.1571A>G	g.2700840A>G	N524S	M	P-ORF	exon 12	NA	NA	NA	rs1135402745					probably_damaging(0.985)	Deleterious(0)	C45	0	46	3	PMID: 28067909 (Shaw, 2017)
B41	NG7	1	M	c.1655G>A	g.2703697G>A	R552Q	M	P-ORF	exon 13	NA	NA	NA	rs886042392					probably_damaging(0.992)	Deleterious(0)	C35	0	43	3	PMID: 28067909 (Shaw, 2017); PMID: 2806791 (Gordon, 2017)
B24	NG21	2	F	c.1034A>G	g.2694685A>G	Q345R	M	P-ORF	exon 8	NA	NA	NA	rs1057519639					possibly_damaging(0.787)	Deleterious(0.01)	C0	29	43	2	PMID: 28067909 (Shaw, 2017)
B33	Rf2321	3	M	c.1199A>T	g.2697896A>T	Q400L	M	P-ORF	exon 10	NA	NA	NA	rs1057519642					possibly_damaging(0.702)	Deleterious(0)	C65	0	112	3	PMID: 28067909 (Shaw, 2017)
B33	Rf2321	5	F	c.1199A>T	g.2697896A>T	Q400L	M	P-ORF	exon 10	NA	NA	NA	rs1057519642					possibly_damaging(0.702)	Deleterious(0)	C65	0	112	3	PMID: 28067909 (Shaw, 2017)
C1	Rf2071	1		c.116A>C	g.2656190A>C	E39A	M	P-ORF	exon 1	53	NA	NA	rs990903424					benign(0)	Deleterious(0.02)	C0	227	39	1	
C2	Rf1820	1		c.1186C>A	g.2697883C>A	Q396K	M	P-ORF	exon 10	41	NA	NA	rs377471712	0	3,00E-05	0	0	benign(0)	Tolerated(0.7)	C0	139	0	0	
C3	13	1		c.2122G>A	g.2707619G>A	V708I	M	P-ORF	exon 16	Normal	Normal	NA	rs2276092	0,719	0,702	0,610	0,638	benign(0)	Tolerated(1)	C0	89	0	0	
C4	16	1		c.2637A>T	g.2724930A>T	K879N	M	P-ORF	exon 21	Normal	Normal	NA	rs633422	0,110	0,506	0,25	0,239	benign(0)	Tolerated(0.1)	C0	143	0	0	
C5	Rf2541	1	M	c.2837C>T	g.2728518C>T	A946V	M	P-ORF	exon 23	54	5	40						possibly_damaging(0.629)	Deleterious(0.04)	C0	99	63	2	
C6	Rf1827	1		c.3007A>G	g.2729366A>G	I1003V	M	P-ORF	exon 24	43	NA	NA	rs777768323	0	8,23E-05	0	0	benign(0.158)	Tolerated(0.06)	C0	89	0	0	
C7	Rf2372	2		c.3247A>G	g.2732461A>G	I1083V	M	P-ORF	exon 25	Normal	NA	NA	rs199901577	0	8,04E-05	0	0	benign(0.049)	Deleterious(0.04)	C15	5	29	1	
C8	Rf1414	2	F	c.3538G>A	g.2740724G>A	G1180R	M	P-ORF	exon 28	62	18	50	rs768096462	0	1,50E-05	0	0	probably_damaging(0.999)	Deleterious(0.01)	C0	94	71	2	
C9	Rf2520	1		c.3769C>T	g.2743894C>T	L1257F	M	P-ORF	exon 29	47	NA	NA	rs766226383	0	1,64E-05	0	0	benign(0.228)	Deleterious(0.01)	C0	31	21	1	
C10	Rf1795	1		c.3838C>G	g.2747556C>G	P1280A	M	P-ORF	exon 30	50	NA	NA	rs1322896954					probably_damaging(0.994)	Deleterious(0)	C25	0	27	3	
C11	Rf1229	4	F	c.3872A>G	g.2747590A>G	N1291S	M	P-ORF	exon 30	43	-2	31	rs201497685	0	4,54E-04	0	0	benign(0.357)	Deleterious(0.04)	C0	158	25	1	
C12	Rf2278	1	M	c.4226G>T	g.2751336G>T	R1409H	M	P-ORF	exon 33	37	NA	NA	rs746741499	0	7,54E-05	0	0	benign(0.32)	Deleterious(0.02)	C15	99	98	1	
C13	Rf1832	1		c.4328A>G	g.2752532A>G	D1443G	M	P-ORF	exon 33	32	NA	NA	rs756531175	0	1,61E-05	0	0	benign(0.043)	Deleterious(0.02)	C0	260	0	1	
C14	Rf1833	1		c.4544G>A	g.2762212G>A	R1515K	M	P-ORF	exon 36	58	NA	NA	rs372451234	0	4,50E-05	0	0	benign(0)	Tolerated(1)	C0	65	0	0	
C15	Rf1846	1	M	c.4599G>T	g.2763667G>T	L1533F	M	P-ORF	exon 37	Normal	Normal	NA	rs770018521	0	5,14E-05	0	0	possibly_damaging(0.462)	Deleterious(0.01)	C0	14	21	2	
C16	Rf1836	1		c.4786C>T	g.2769758C>T	R1596W	M	P-ORF	exon 38	47	NA	NA	rs746646525	0	3,14E-05	0	1,85E-04	benign(0.109)	Tolerated(0.05)	C0	188	47	0	
C17	Rf2279	1		c.4849G>A	g.2769989G>A	V1617I	M	P-ORF	exon 39	38	NA	NA	rs774306466	0	1,54E-05	0	0	benign(0.026)	Tolerated(0.1)	C0	49	0	0	
C18	Rf2430	1	F	c.5317G>C	g.2775873G>C	V1773L	M	P-ORF	exon 42	48	NA	NA						probably_damaging(0.994)	Deleterious(0)	C25	0	31	3	
C19	Rf1567	1		c.5914C>T	g.2796440C>T	R1972C	M	P-ORF	exon 47	64	NA	NA	rs778853203	0	0	0	1,04E-04	benign(0)	Tolerated(0.08)	C0	265	0	0	
C20	Rf1405	1	M	c.874-6T>C	g.2694519T>C		S3	P-ORF	intron 7	25	-9	17												
C21	Rf2430	1	F	c.1132-14C>T	g.2697815C>T		S3	D-ORF	intron 9	Normal	NA	NA	rs184510956	2,14E-04	6,13E-04	0	0							
C22	Rf1858	1	F	c.1648-31A>G+c.1419A>G	g.2703659A>G; g.2700613A>G		S3	D-ORF	intron12	35	-2	26	rs76103139	4,25E-04	3,95E-03	0	2,33E-03							
C23	11	1		c.1843-17T>A	g.2705675T>A		S3	P-ORF	intron 13	Normal	Normal	NA	rs8090988											
C24	Rf1449a	2	M	c.1843-16A>T	g.2705676A>T		S3	P-ORF	intron 13	59	16	47	rs569911568	1,24E-04	5,09E-04	0	2,14E-04							
C25	Rf1220	4	F	c.1957-3C>T	g.2706359C>T		S3	P-ORF	intron 14	44	1	32	rs201069970	3,48E-04	1,07E-03	8,70E-04	3,99E-03							
C26	15	1		c.2338+32A>G	g.2718265A>G		S3	P-ORF	intron 17	Normal	Normal	NA	rs62084229	0,216	0,119	0,0719	0,273							
C27	21	1		c.3277-42_3277-39dupAGAC	g.2738352T>TAGAC		S3	P-ORF	intron 25	Normal	Normal	NA	rs71365196	0,273	0,297	0,510	0,448							
C28	Rf1785	1	M	c.4967-15G>T	g.2771516G>T		S3	P-ORF	intron 39	46	NA	NA	rs300291	0,941	1,000	1	1,000							
C29	Rf1821	1		c.1956+7C>T	g.2705812C>T		S5	P-ORF	intron 14	40	NA	NA	rs145755468	5,24E-04	3,93E-03	0	7,41E-04							
C30	Rf1711	1	F	c.2063+20G>T	g.2706488G>T		S5	P-ORF	intron 15	28	-6	20	rs368528253											
C31	Rf2520	1		c.3425+37C>T	g.2738580C>T		S5	P-ORF	intron 26	47	NA	NA	rs8094260	0,276	0,285	0,504	0,466							
C32	Rf1795	1		c.4966+31delA	g.2770137delA		S5	P-ORF	intron 39	Normal	NA	NA	rs547466679	8,15E-04	5,85E-03	0	1,13E-03							
C33	34	1		c.5476+10A>G	g.2777923A>G		S5	P-ORF	intron 43	Normal	Normal	NA	rs3213926	0,259	0,302	0,566	0,419							
C34	Rf1838	1		c.5878+8T>G	g.2796113T>G		S5	P-ORF	intron 46	52	NA	NA	rs144115061	3,83E-04	1,60E-03	0	0							
C35	Rf2704	3	M	c.639-9T>G	g.2688383T>G		S3	D-ORF	intron 5	Normal	Normal	NA												
C36	Rf799	1		c.2147-7C>T	g.2707798C>T		S3	P-ORF	intron 16	Normal	Normal	NA	rs113524119	9,10E-04	6,96E-03	0	5,93E-04							
C37	Rf701	4	F	c.3802-16T>G	g.2747504T>C		S3	P-ORF	intron 29	Normal	Normal	NA	rs79829175	6,48E-02	1,78E-04	0	6,37E-05							
C38	Rf2384	1	M	c.262+25G>C	g.2666256G>C		S5	P-ORF	intron 2	Normal	Normal	NA	rs634246	0,549	0,071	5,79E-04	0,0395							
C39	Rf2384	1	M	c.262+48T>C	g.2666279T>C		S5	P-ORF	intron 2	Normal	Normal	NA	rs531379	0,516	0,059	0,001	0,0362							
C40	Rf2384	1	M	c.424+33T>C	g.2667063T>C		S5	P-ORF	intron 3	Normal	Normal	NA	rs648105	0,532	0,059	0	0,0423							
C41	Rf976	1	F	c.873+33delT	g.2688776delT		S5	P-ORF	intron 7	Normal	Normal	NA												
C42	Rf2384	1	M	c.2603+25T>G	g.2722686T>G		S5	P-ORF	intron 20	Normal	Normal	NA	rs73365837	0,162	7,22E-04	1,16E-04	1,87E-04							
C43	Rf2384	1	M	c.3634-35C>T	g.2743724C>T		S5	P-ORF	intron 28	Normal	Normal	NA	rs59023685	0,172	8,01E-04	1,36E-04	1,89E-04							
C44	Rf2384	1	M	c.5052+33dupT	g.2771643A>AT		S5	P-ORF	intron 40	Normal	Normal	NA	rs33935864	0,252	0,280	0,516	0,440							
C45	Rf1565	1	M	c.159C>T; c.2147-7C>T	g.2656233C>T; g.2707798C>T	Y53Y	SYN	P-ORF	exon 1	70	NA	NA	rs1206890396											
C46	4	1		c.174G>C	g.2656248G>C	A58A	SYN	P-ORF	exon 1	Normal	Normal	NA	rs2430853	0,852	0,551	0,343	0,637							
C47	Rf1858	1	F	c.1419A>G + c.1648-31A>G	g.2700613A>G; g.2703659A>G	E473E	SYN	P-ORF	exon 11	Normal	Normal	NA	rs117771893	4,60E-04	4,44E-03	0	2,43E-03							
C48	Rf2520	1		c.1608A>G	g.2700877A>G	K536K	SYN	P-ORF	exon 12	47	NA	NA	rs72862973	0	2,11E-04	0	0							
C49	Rf1785	1	M	c.1689G>A	g.2703731G>A	L563L	SYN	P-ORF	exon 13	46	NA	NA	rs78073508	2,02E-02	3,00E-05	0	6,06E-05							
C50	12	1		c.1851A>G	g.2705700A>G	T617T	SYN	P-ORF	exon 14	Normal	Normal	NA	rs635132	0,335	0,723	0,674	0,649							
C51	Rf955	3	M	c.2433T>G	g.2718407T>G	S811S	SYN	P-ORF	exon 19	58	11	44	rs760899591	0	3,00E-05	0	0							
C52	Rf1824	1		c.2529C>A	g.2722587C>A	I843I	SYN	P-ORF	exon 20	51	NA	NA	rs761184318	0	0	0	1,21E-04							
C53	Rf1658	1	M	c.2925T>A	g.2729284T>A	A975A	SYN	P-ORF	exon 24	Normal	NA	NA	rs763236583	0	8,47E-05	0	0							
C54	24	1		c.3528A>G	g.2740714A>G	T1176T	SYN	P-ORF	exon 28	Normal	Normal	NA	rs12327477	0,270	0,280	0,504	0,450							
C55	Rf1830	1		c.3537C>T	g.2740723C>T	Y1179Y	SYN	P-ORF	exon 28	46	NA	NA	rs372029124	1,02E-04	3,00E-05	0	9,09E-04							
C56	27	1		c.4137A>G	g.2750477A>G	A1379A	SYN	P-ORF	exon 32	Normal	Normal	NA	rs2304859	0,297	0,325	0,533	0,471							
C57	Rf1158	1	M	c.4281T>C	g.2751391T>C	N1427N	SYN	P-ORF	exon 33	57	NA	NA	rs757680634	0	4,62E-05	0	0							
C58	29	1		c.4629C>T	g.2763697C>T	G1543G	SYN	P-ORF	exon 37	Normal	Normal	NA	rs483547	0,301	0,450	0,174	0,198							
X1	Rf653	1	F	c.1939G>A	g.2705788G>A	E647K	M	P-ORF	exon 14	28	-16	16						possibly_damaging(0.715)	Deleterious(0.01)	C15	5	29	1	
X2	Rf668	1	M	c.4G>C	g.2656078G>C	A2P	M	P-ORF	exon 1	18	-12	12						probably_damaging(0.981)	Tolerated(0.11)	C0	238	2	1	
X2	Rf668	3	F	c.4G>C	g.2656078G>C	A2P	M	P-ORF	exon 1	24	-15	14						probably_damaging(0.981)	Tolerated(0.11)	C0	238	2	1	

Supplementary table 2

Table summarizing the variant analysis in 187 unrelated FSHD2 families (F1-F187), 41 BAMS (B1-B41) families, 58 non-pathogenic variants (C1-C58) and 2 for which the pathogenicity is unclear (X1-X2), with proband in white and family members carrying the variant in grey (column 1). For each individual the family, personal number (nr) and gender (if known) is shown (columns 2, 3 and 4). For each variant, we provide cDNA (based on accession number NM_015295.2), genomic (based on hg19, GRCh37.p5) and protein (NP_056110.2) information (columns 5, 6 and 7). Column 8 describes the variant type (M=missense, D=insertion/deletion, N=nonsense, S3/S5 splice site variant at the 3' or 5' and SYN=synonymous). The variants are sorted by type and by position. ORF-disrupting (D-ORF) and ORF-preserving (P-ORF) consequence of the variant and the SMCHD1 exon number is shown in columns 9 and 10. The D4Z4 methylations values; FseI, delta 1 and delta2 for the individual are shown in columns 11,12 and 13. Values that were not determined or could not be calculated were indicated with NA. And for control individuals, variants that were analyzed in multiple individuals showing normal methylation values were marked normal. The dbSNP number and the frequency of the variant in the EXAC database (AFR=African, EUR=European; EAS=East Asian and SAS=South Asian populations) in columns 14-18). For missense variants we evaluated the pathogenic effect by the following prediction algorithms: PolyPhen (from Variant Effect Predictor in Ensemble; column 19), SIFT (from Alamut, column 20) and Align GVGD Class (columns 21, 22 and 23). Each program has a different pathogenicity score. A pathogenic prediction within one of the programs received a score of 1 (marked grey) and a benign prediction a score of 0 (marked white). The total prediction score for all 3 algorithms is shown in column 24, where we highlighted the variants in grey that obtained a false negative prediction (D4Z4 hypomethylation, but total prediction score <2), or a false positive prediction (normal D4Z4 methylation, but total prediction score >1). The last column shows the publication, in which the variant was first described.

	Mutation spectrum 2015[3]		other published variants		new variants current study		total variants	
	n	%	n	%	n	%	n	%
Indel	8	15,7%	11	20,8%	16	19,3%	35	18,7%
Missense	13	25,5%	20	37,7%	21	25,3%	54	28,9%
Nonsense	5	9,8%	5	9,4%	18	21,7%	28	15,0%
Splice site	25	49,0%	17	32,1%	28	33,7%	70	37,4%
Total	51		53		83		187	

Supplementary table 3

SMCHD1 variant type for all variants published in our previous study (n=51)[3], in 12 other publications (n=53, Supplementary table 1)[5-15], and new variants (n=83) in the current study.

Distribution	ATPase domain	%	Remaining protein	%	P value	Total
Exons	3-12		1-2 / 13-48			
Amino acids	445	22,2%	1560	77,8%	NA	2005
Indels[1]	10	28,6%	25	71,4%	0,49	35
Missense	27	50,0%	27	50,0%	3,61E-06	54
Nonsense	7	25,0%	21	75,0%	0,90	28
Splicing (S3)	1	5,9%	17	94,4%	0.16[2]	182
Splicing (S5)	8	15,4%	44	84,6%	0,32	52
						351

[1] Complete gene deletions were not included

[2] Chi-squared approximation may be incorrect

Supplementary table 4

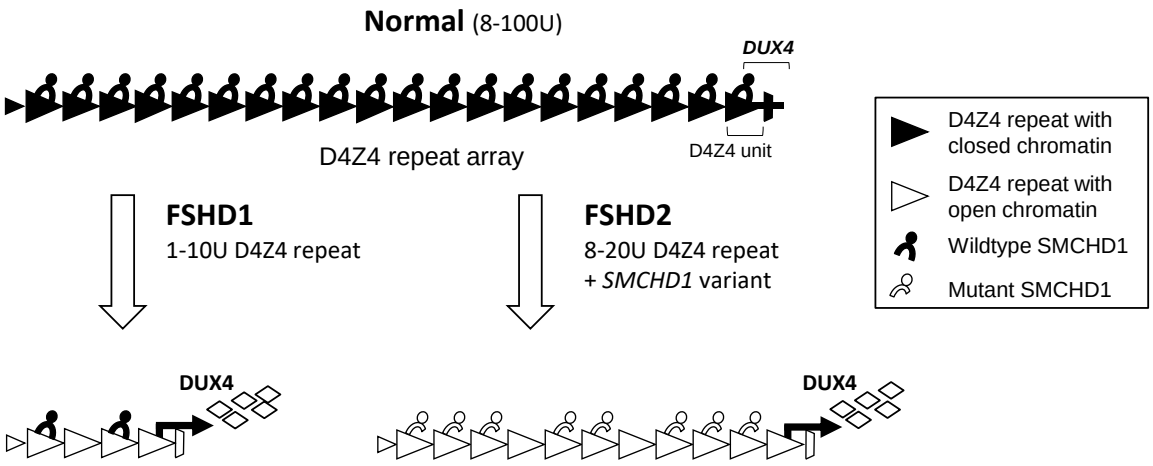
Distribution of the 187 FSHD2-related SMCHD1 variants in the C-terminal extended ATPase domain and in the rest of the protein. C-terminal extended ATPase domain is based on Gordon et al. 2017.[16] In contrast to the other variant types, we observe a significant enrichment (P value 1.59E-05) of missense variants in the extended ATPase domain compared with the size (445/2005 amino acids) of this region.

Proband ID	Sex	cDNA	Protein	Exon	Inheritance	PMID publication
K1	F	c.320T>C	L107P	3	NA	28067909[17]
D1	M	c.386T>A	M129K	3	NA	28067909[17]
New	F	c.386T>G	M129R	3	NA	new
11	F	c.400G>T	A134S	3	de novo	28067911[16]
12	F	c.400G>T	A134S	3	de novo	28067911[16]
M1 and 2*	F	c.403A>T	S135C	3	de novo	28067909[17]/28067911[16]
AF1 and 4*	F	c.403A>T	S135C	3	de novo	28067909[17]/28067911[16]
I1	M	c.404 G>A	S135N	3	de novo	28067909[17]
R1	F	c.404G>A	S135N	3	Probably familial	28067909[17]
3	M	c.404G>A	S135N	3	de novo	28067911[16]
AK1	M	c.404G>T	S135I	3	de novo	28067909[17]
1	M	c.407A>G	E136G	3	de novo	28067911[16]
T1	M	c.408A>C	E136D	3	Paternal	28067909[17]
AG1	F	c.410 G>A	G137E	3	NA	28067909[17]
A1	F	c.415A>C	N139H	3	de novo	28067909[17]
Y1	F	c.415A>C	N139H	3	NA	28067909[17]
C1	M	c.423G>C	L141F	3	NA	28067909[17]
E1	M	c.423G>C	L141F	3	NA	28067909[17]
S1	F	c.423G>C	L141F	3	NA	28067909[17]
V1	M	c.423G>T	L141F	3	de novo	28067909[17]
AB1	M	c.511T>G	F171V	5	Probably familial	28067909[17]
AA1	M	c.725C>G	A242G	6	de novo	28067909[17]
10	F	c.1025G>C	W342S	8	de novo	28067911[16]
O1	F	c.1034A>G	Q345R	8	Maternal	28067909[17]
F1	M	c.1043A>G	H348R	9	NA	28067909[17]
L1 and 13*	F	c.1043A>G	H348R	9	NA	28067909[17]/28067911[16]
N1 and 5*	M	c.1043A>G	H348R	9	de novo	28067909[17]/28067911[16]
X1	F	c.1043A>G	H348R	9	de novo	28067909[17]
Z1	M	c.1043A>G	H348R	9	NA	28067909[17]
AC1	M	c.1043A>G	H348R	9	de novo	28067909[17]
AE1	M	c.1043A>G	H348R	9	de novo	28067909[17]
14	F	c.1043A>G	H348R	9	NA	28067911[16]
AH1	F	c.1199A>T	Q400L	10	Paternal	28067909[17]
P1 and 6*	M	c.1259A>T	D420V	10	de novo	28067909[17]/28067911[16]
9	M	c.1259A>T	D420V	10	de novo	28067911[16]
W1	M	c.1417G>C	E473Q	11	NA	28067909[17]
8	F	c.1552A>G	K518E	12	NA	28067911[16]
J1	M	c.1568C>A	T523K	12	NA	28067909[17]
U1	F	c.1568C>A	T523K	12	NA	28067909[17]
B1	M	c.1571A>G	N524S	12	NA	28067909[17]
AJ1 and 7*	M	c.1655G>A	R552Q	13	de novo	28067909[17]/28067911[16]

Supplementary table 5

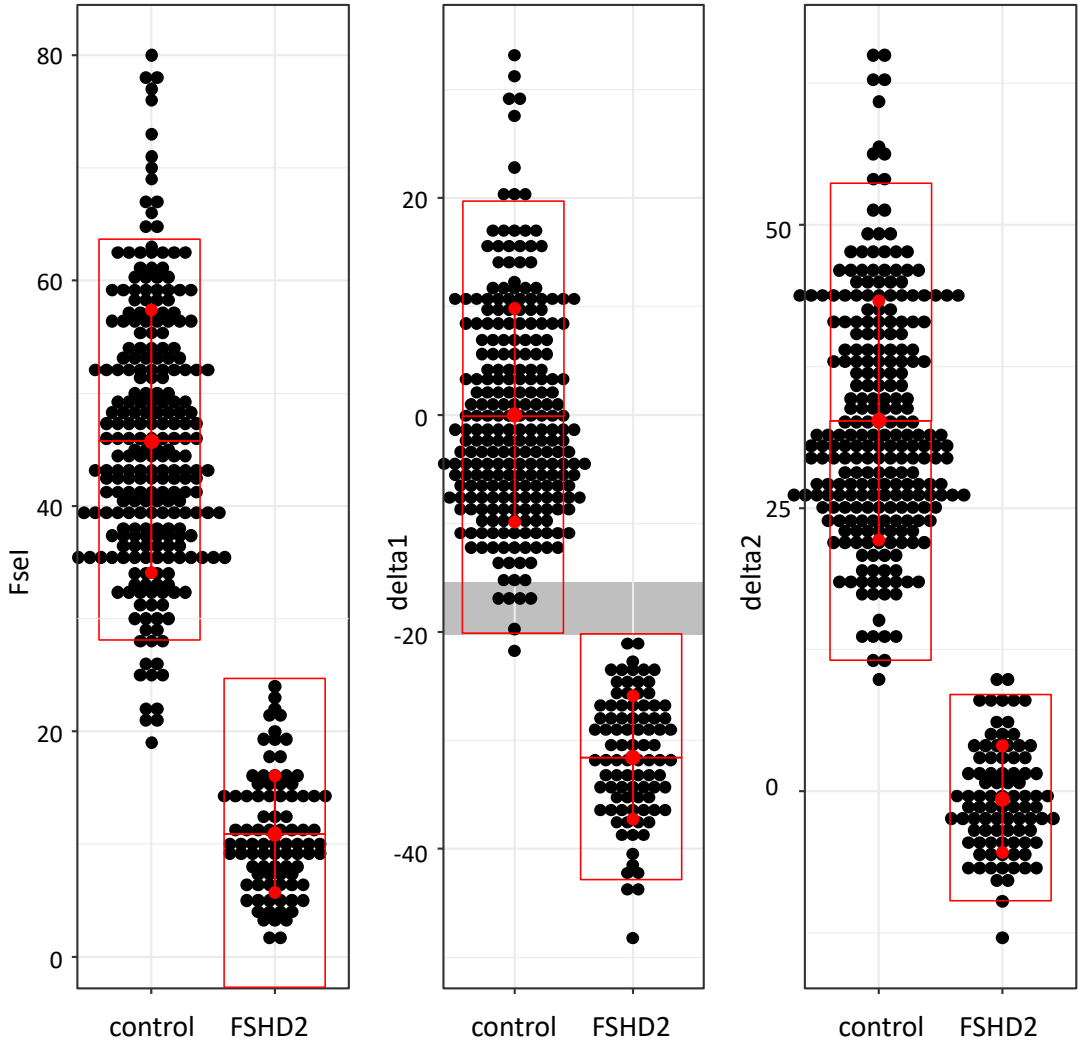
Overview of SMCHD1 variants identified in 41 BAMS families from previous publications.[16, 17] The 1st and 2nd columns show the reference ID and gender of the proband. The 3rd, 4th and 5th columns shows the position of the variant in the cDNA, the protein and the exon and whether the variants occurred de novo, or not. The PMID of the publication describing the family is shown in the last column.

Supplementary Figures



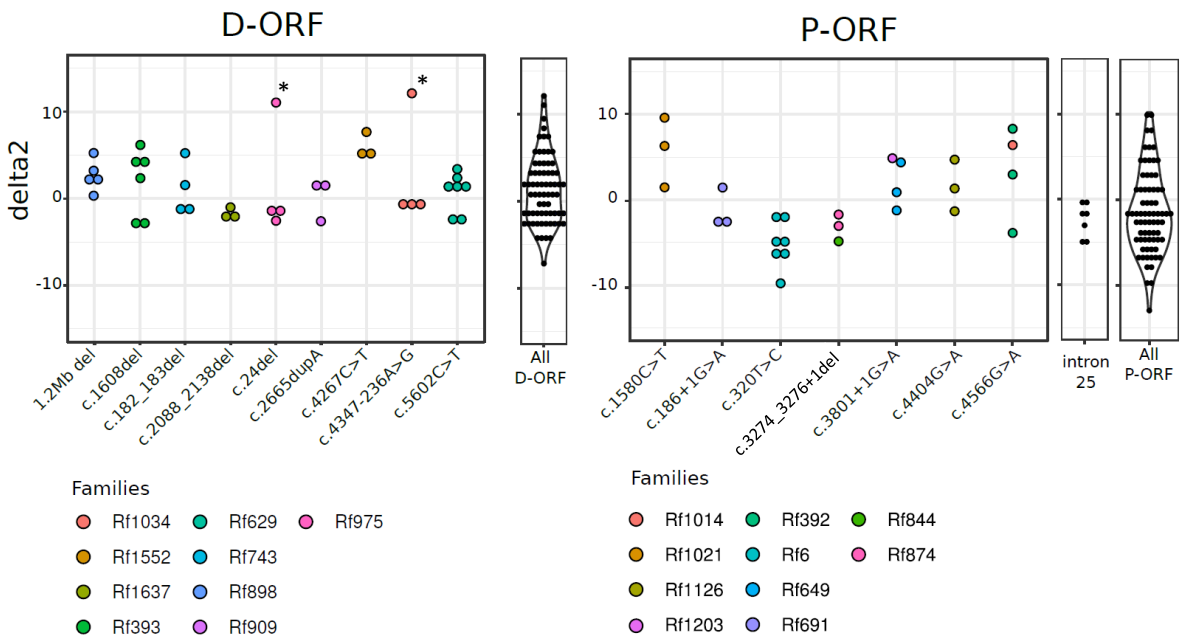
Supplementary figure 1

FSHD is caused by mis-expression of the transcription factor DUX4 in skeletal muscle, where it is normally repressed. A complete copy of the DUX4 retrogene is embedded in the most distal unit of the D4Z4 macrosatellite repeat on chromosome 4 and the region immediately distal to the repeat. In control individuals the repeat varies between 8-100 units, In most FSHD cases, the disease is caused by a D4Z4 repeat contraction to a size of 1-10 units (FSHD1). The less common form FSHD2 is caused by heterozygous variants in the chromatin modifier SMCHD1 in combination with a D4Z4 repeat of 8-20 units, also resulting in DUX4 expression in skeletal muscle. Individual D4Z4 units are depicted as open and filled (representing open and closed chromatin structure) triangles, DUX4 protein expression is indicated with diamonds. Wildtype and mutant SMCHD1 protein are indicated with a closed and open symbol, respectively.



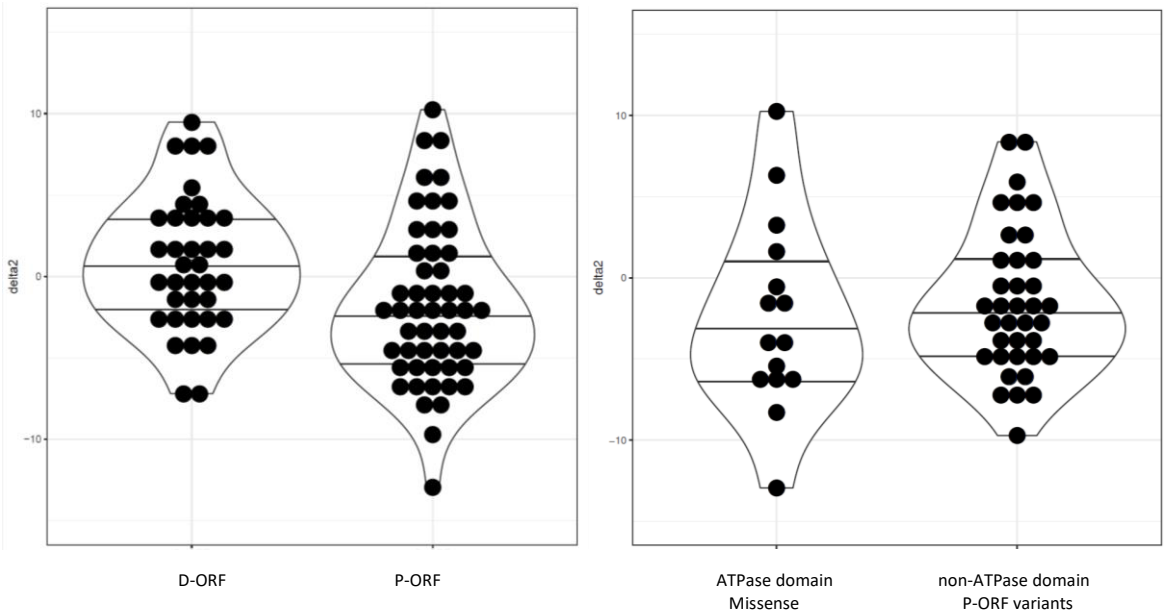
Supplementary figure 2

Threshold methylation values for control individuals (n=249) and for unrelated FSHD2 patients in this study (n=89). The red vertical line with dots indicates the average methylation and 1 SD, while the red box indicates the control and FSHD2 threshold for the different methylation values (1.5 or 2 SD). The FseI methylation value shows the highest variability due to the contribution of the D4Z4 repeat size. The average methylation in controls is 46.8% with a SD of 14.1% and the threshold for FSHD2 is defined at 25% (1.5 SD below the average). The delta1 value has an average value in controls of 0% with an SD of 10.0% and the threshold for FSHD2 is defined at -20.0% (2 SD below the average). We also define a delta1 grey zone between -15.0% to -20.0% where the milder methylation defect might occur due to variants in unknown epigenetic modifiers. The delta2 value is only valid for SMCHD1 mutation carriers. The average is -0.7% and the standard deviation is 4.7%.



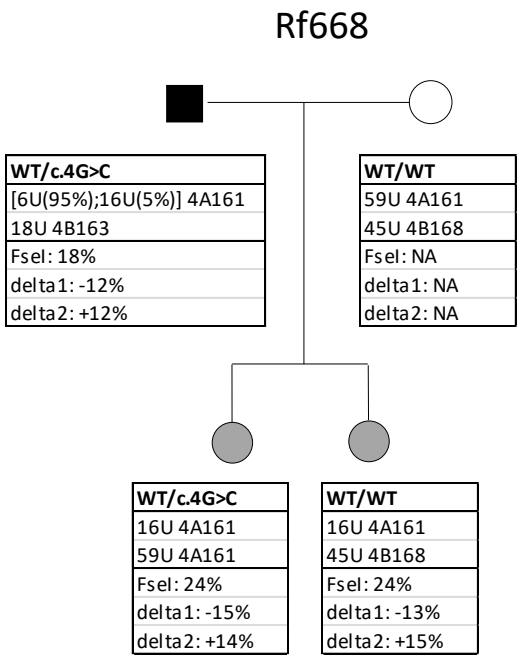
Supplementary figure 3

Delta2 methylation values for carriers of the same SMCHD1 variant in comparison to the distribution of all carriers of a disrupting ORF (D-ORF, left) or preserving ORF (P-ORF, right) variant. For most variants the methylation level of different carriers is comparable. Also different intron 25 variants which probably all result in the skip of exon 25 have a comparable delta2 methylation value (P-ORF, right). Individuals with exceptionally high D4Z4 methylation levels discussed in the text are marked with an asterisk.



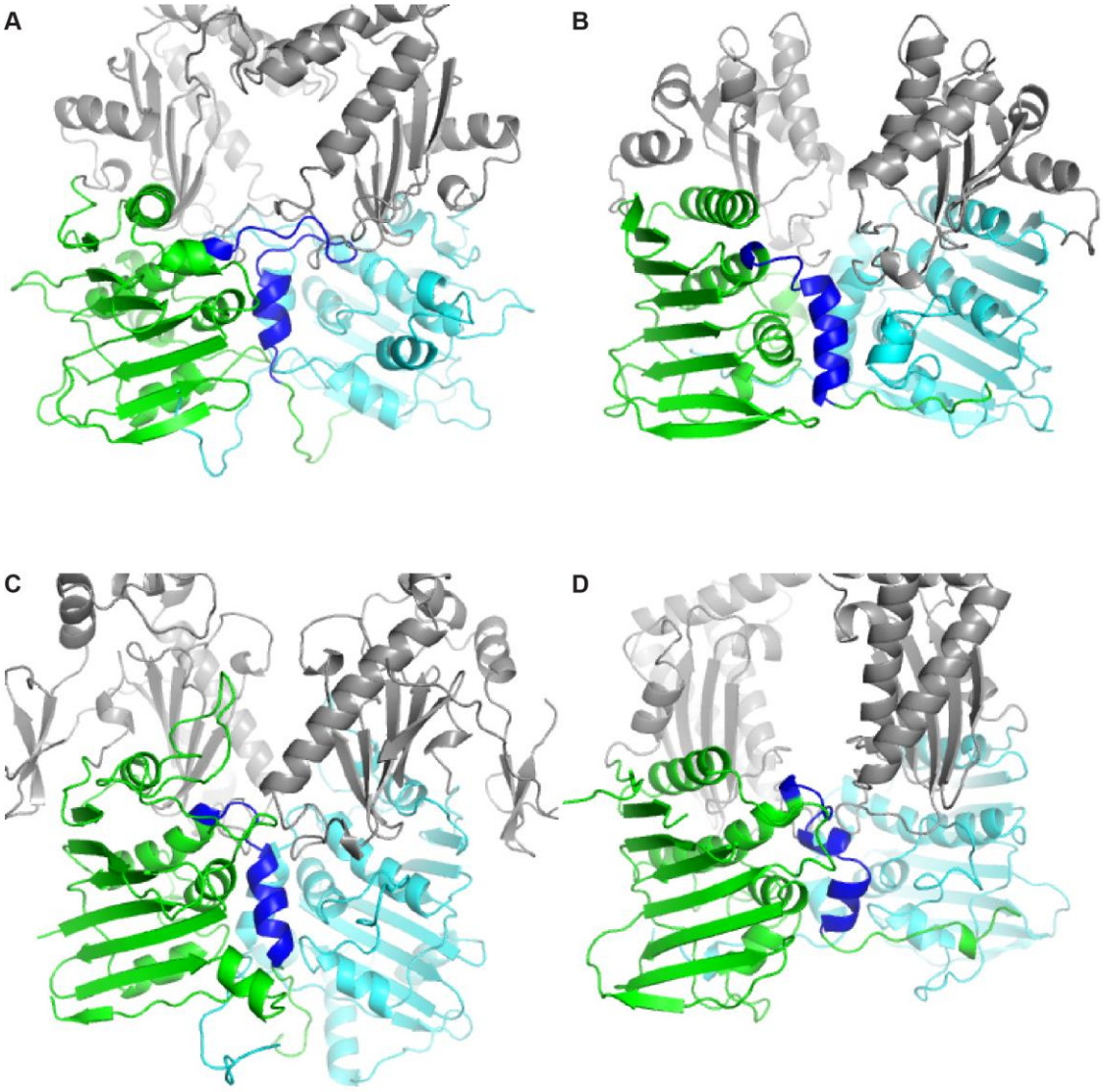
Supplementary figure 4

Violin plot with delta2 methylation values for unrelated carriers of an D-ORF or P-ORF SMCHD1 variant (left) and for ATPase domain P-ORF missense variants and the other P-ORF variants (right). The lines indicate the average, the 25th and 75th percentiles.



Supplementary figure 5

Pedigree of family Rf668. Father and both daughters have an FseI methylation below the FSHD2 threshold and low, but normal, delta1 scores. The father and oldest daughter are heterozygous for the SMCHD1 variant A2P, while the youngest daughter does not carry the variant. The first column shows information on the SMCHD1 variant, the 2nd and 3rd columns show repeat size and haplotype of both D4Z4 alleles at chromosome 4. The other columns show information on the FseI, delta1 and delta2 methylation values.



Supplementary figure 6

Comparison of four GHKL ATPase dimers and their downstream ,or C-terminal extended, domains. (A) Computational model of SMCHD1, (B) E. coli MutL, (C) MORC2 and (D) Mycobacterium tuberculosis GyrB. In each panel, the two ATPase domains are colored in green and cyan, with a helix and loop at the dimer interface marked in dark blue. In SMCHD1, several BAMS mutations localize to this loop. Downstream domains (M-domain, transducer domain) are colored in grey. The ATPase domains show strong structural conservation, while the downstream domains show a much greater structural diversity.

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