Facioscapulohumeral muscular dystrophy: reproductive counseling, pregnancy, and delivery in a complex multigenetic disease

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REVIEW

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Facioscapulohumeral muscular dystrophy—Reproductive counseling, pregnancy, and delivery in a complex multigenetic disease

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Abstract

Reproductive counseling in facioscapulohumeral muscular dystrophy (FSHD) can be challenging due to the complexity of its underlying genetic mechanisms and due to incomplete penetrance of the disease. Full understanding of the genetic causes and potential inheritance patterns of both distinct FSHD types is essential: FSHD1 is an autosomal dominantly inherited repeat disorder, whereas FSHD2 is a digenic disorder. This has become even more relevant now that prenatal diagnosis and preimplantation genetic diagnosis options are available for FSHD1. Pregnancy and delivery outcomes in FSHD are usually favorable, but clinicians should be aware of the risks. We aim to provide clinicians with case-based strategies for reproductive counseling in FSHD, as well as recommendations for pregnancy and delivery.

KEYWORDS
delivery, facioscapulohumeral muscular dystrophy, genetics, pregnancy, preimplantation genetic testing, prenatal diagnosis

1 | INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is a relatively common hereditary muscular dystrophy and has an estimated prevalence of 4 to 12 per 100.000.[1–3] FSHD is characterized by asymmetrical weakness of the muscles of the face and shoulder girdle, often followed by weakness of the trunk and lower limbs.[4] Life-expectancy is normal. Respiratory involvement is rare in ambulatory individuals but occurs in up to one-third of non-ambulatory FSHD patients.[5] Cardiomyopathy is not associated with FSHD, but cardiac arrhythmias have been described, though often asymptomatic.[6,7]

Current treatment options for FSHD are supportive, although therapeutic agents aimed at slowing or halting disease progression are being investigated.[8] Apart from a small subgroup with infantile onset,[9]

FSHD typically manifests between ages 15 and 30: a phase of life in which patients may start to consider pregnancy and visit their neurologist and/or clinical geneticist to ask for advice. Adequate counseling regarding family planning can be challenging in a complex genetic disease like FSHD and there are several important issues that need to be discussed with patients:

1. Both the age at onset and the progression rate of muscle weakness in FSHD vary extensively, resulting in a large variability in disease severity, ranging from patients that experience no discernable symptoms to wheelchair bound patients (20% by age 50).[10] Additionally, penetrance in FSHD is incomplete: a recent cross-sectional study found non-penetrance in 17% of FSHD mutation carriers, but this number decreases with age and with shorter repeat lengths.[11]
2. The two types of FSHD, type 1 (FSHD1) and type 2 (FSHD2) are clinically alike. However, the genetic mechanisms underlying these two types are different: FSHD1 is an autosomal dominant repeat disorder, whereas FSHD2 is a digenic disease. Both are diagnosed using distinct genetic tests.
3. Pregnancy may influence the disease course of an FSHD patient, but the disorder itself may also influence the pregnancy and the delivery. The extent of these influences is not fully known and available literature on the subject is scarce.[12]
4. Recent developments in prenatal diagnosis and preimplantation genetic testing in FSHD have allowed more reproductive options for FSHD patients.

In this review, we provide clinicians with an updated overview of the complex genetic mechanisms of FSHD, as well as case-based strategies for reproductive counseling and recommendations for pregnancy and delivery in FSHD.

2 | GENETIC MECHANISMS IN FSHD

Counseling FSHD patients on inheritance starts with explaining the basic genetic mechanisms causing FSHD, which differ between FSHD1 and FSHD2.

The vast majority of FSHD cases (>95%) is caused by a contraction of the D4Z4 macrosatellite repeat array on chromosome 4 (FSHD1). The size of the D4Z4 repeat array is 8–100 units in the general population, in FSHD1 repeat size is reduced to 1–10 units. The D4Z4 repeat contraction results in relative D4Z4 hypomethylation, resulting in de-repression of the *Double Homeobox 4* (*DUX4)* gene and subsequent variegated production of DUX4 protein in skeletal muscle. DUX4 is a transcription factor which is normally expressed during early embryonic development and is subsequently silenced in somatic cells. DUX4 protein expression induces a cascade of events that ultimately results in muscle cell death.[8]

FSHD2, which causes less than 5% of all FSHD cases, has a digenic pattern of inheritance. FSHD2 is caused by the combination of a (1) pathogenic variant in a chromatin modifier gene and (2) a moderate D4Z4 repeat contraction of 8–20 units. This combination causes D4Z4 hypomethylation and subsequent DUX4 protein expression in skeletal muscle, similar to FSHD1. Three chromatin modifier genes have been identified, the most common being *SMCHD1* (structural maintenance of chromosomes flexible hinge domain containing 1 gene), which accounts for 79% of FSHD2 cases.[13] The other two, *DNMT3B* (de novo methyltransferase 3B) and *LRIF1* (ligand-dependent nuclear receptor-interacting factor 1) are far less common.[14,15] After accounting for pathogenic variants in *SMCHD1*, *DNMT3B* and *LRIF1* a small number of FSHD2 patients with D4Z4 hypomethylation remains, which suggests that additional chromatin modifier genes involved in FSHD2 are yet to be identified.

Several features of FSHD genetics add to the complexity of genetic counseling in this disease:

1. A stabile *DUX4* transcript can only be expressed when the last repeat of the D4Z4 array is followed by a specific 4qA haplotype which contains a polyadenylation signal. The 4qB haplotype does not contain a polyadenylation signal. As a result, only D4Z4 repeat contractions associated with the 4qA haplotype are disease permissive and associated with FSHD.
2. Chromosome 10q also contains a D4Z4-like repeat which is not associated with FSHD. However, pathogenic repeat translocations between 4q and 10q can occur during early embryogenesis, resulting in FSHD1.[16–19]
3. In the general European population, 8–10 unit D4Z4 repeat contracts combined with a 4qA permissive haplotype have been described in 1%–3% of the general population.[20]

To summarize, FSHD1 and FSHD2 have distinct underlying genetic mechanisms which both result in D4Z4 repeat hypomethylation and the production of DUX4 protein. This impacts reproductive counseling. Next, we will discuss the inheritance pattern and reproductive options for both FSHD1 and FSHD2.

3 | FSHD 1

3.1 | Case 1.1

A 34-year-old man with genetically confirmed FSHD1 (7 unit D4Z4 repeat) has a mild FSHD phenotype, whereas his 32-year-old sister is more severely affected. They have two healthy siblings who do not have the genetic predisposition for FSHD. The 34-year-old man experiences very mild FSHD symptoms: minimal facial asymmetry and weakness of shoulder abduction without lower extremity weakness (Ricci Clinical Severity Score 2/10 – the Ricci Clinical Severity Score is ten-point scale which grades overall disease severity with higher scores indicating more severe weakness). He and his partner consider pregnancy, but wish to know more about FSHD inheritance and the reasons for clinical variability between family members.

3.2 | Case 1.2

The 32-year-old sister of the patient in case 1.1 also has genetically confirmed FSHD1 (7 unit D4Z4 repeat). She has a moderately severe phenotype with facial weakness, limitation of shoulder abduction >90° and weakness in both hamstrings (Ricci Clinical Severity Score 6/10). The patient and her partner are also considering pregnancy, but do not want the child to be affected with FSHD. The neurologist refers them to the clinical geneticist for reproductive counseling (Figure 1).

3.2.1 | Inheritance

When counseling FSHD1 patients it is important to explain that FSHD1 has an autosomal dominant inheritance pattern, resulting in a 50% chance of passing on the genetic trait to their children. However, due to incomplete penetrance of the disease, a child with the genetic predisposition for FSHD1 will not necessarily become symptomatic during his or her life. Furthermore, even when a person develops clinical features of FSHD there is considerable variability in disease severity even within families,[11] as illustrated in case 1.1 and case 1.2.

Variability in FSHD1 disease severity is partially explained by disease duration and by the size of the D4Z4 repeat contraction: repeat contractions of 7–10 units result in less severe phenotypes, whereas repeat contractions of 1–3 units often cause severe, early onset FSHD.[21,22] Early onset FSHD can be associated with systemic features such as hearing loss, retinal vasculopathy, and developmental delay.[23,24] No severe early onset phenotype has been described in FSHD2. Systemic features are rare in the classic form of FSHD (D4Z4 repeat size of 4–10 units).

FSHD is not associated with anticipation and repeat size remains stable throughout generations. Still, disease severity can vary considerably within families, which can include symptomatic cases, asymptomatic cases who experience no symptoms of the disease (although minor weakness can be detected on neurological examination), and non-penetrant cases (in whom physical examination by a neurologist is completely normal).[11] In families with larger repeat sizes of 7–10 units, cross-sectional studies have found that up to 23% of individuals with the pathogenic D4Z4 repeat contraction can be

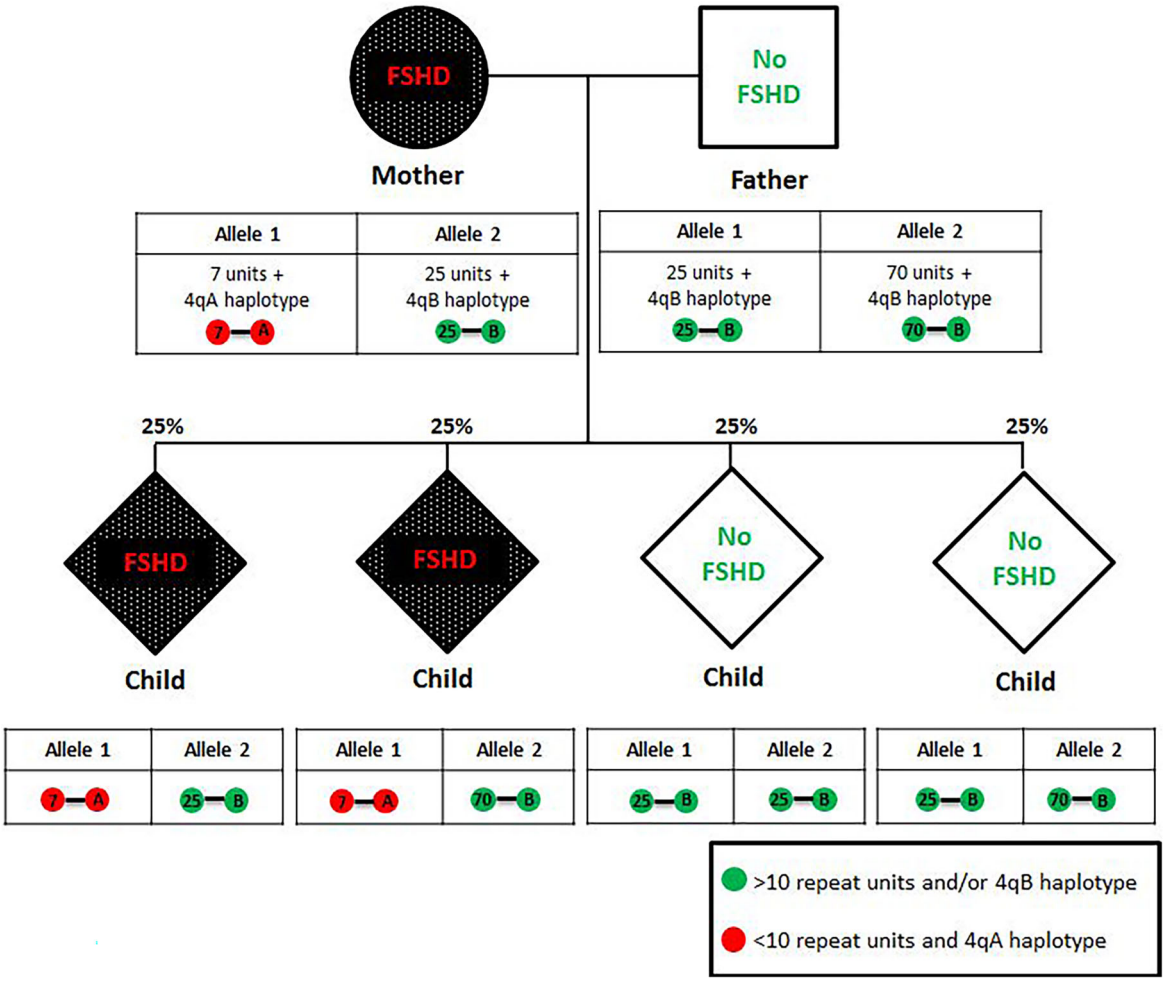


FIGURE 1 Case 1. Inheritance in FSHD1 with a partner with two normal sized alleles. The chance of offspring with a genetic disposition for FSHD is 50% in this scenario

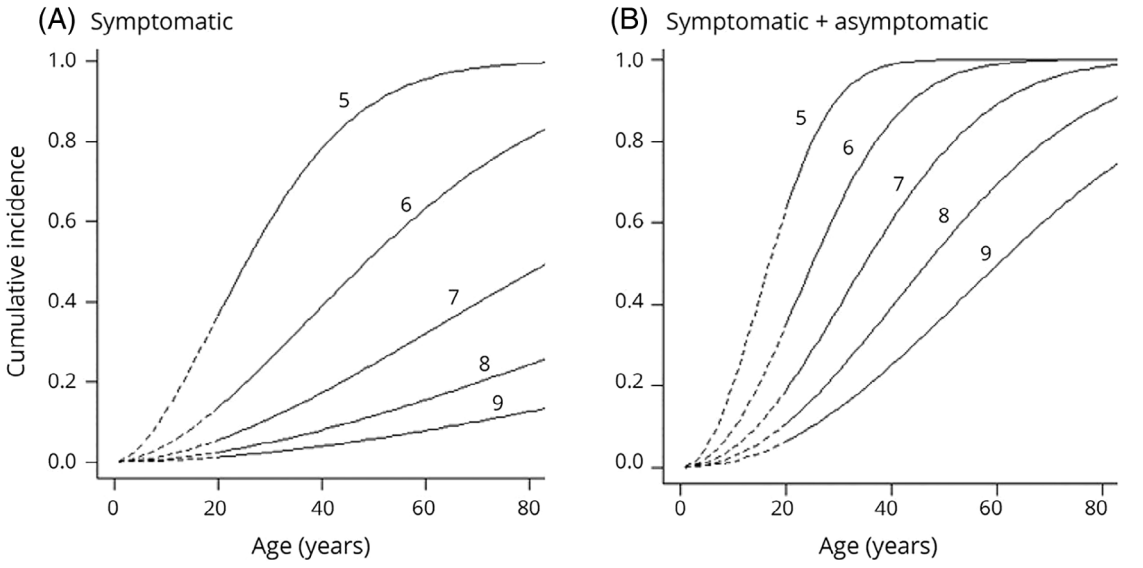
asymptomatic and up to 36% can be non-penetrant (Figure 2).[11] These percentages probably overestimate asymptomatic and non-penetrant cases as some will develop symptoms with aging, however significantly lower numbers are found in families with shorter repeat sizes of <7 units.[11,25] The variability in disease severity in FSHD remains largely unexplained and is thought to be attributable to a complex interplay of known and unknown (epi-)genetic, lifestyle and environmental factors.[22]

3.2.2 | Genetic diagnosis

Genetic testing for FSHD is performed by measuring the length and the derived number of D4Z4 repeat units specifically for chromosome 4 using conventional Southern blot analysis.[26] The Southern blot method is used to detect a specific DNA locus in the genomic DNA derived from a blood or tissue sample. It uses a restriction enzyme (such as *EcoRI*, *BinI*, and *ApoI*) to cut the genomic DNA into specific fragments, after which the fragments are separated by size using gel electrophoresis. Next, these fragments are transferred to a filter membrane, followed by exposure to a DNA probe labeled with a radioactive or DIG (digoxigenin) tag. The probe binds to the complementary DNA fragments on the membrane, and thereby identifies the size of the specifically addressed genomic locus, provided that the probe sequence is present in the sample. Southern blotting requires a large amount of high-quality DNA, is labor intensive and the entire test (Southern blot and accompanying steps) takes several weeks to process.[27] The results of Southern blotting for FSHD diagnosis indicate the length of the repeat through the size of the EcoRI bands in kilobases (kb): a D4Z4 contraction of 40 kb or less (≤10 repeat units) on chromosome 4q is associated with FSHD1.

FSHD genetic diagnosis using Southern Blot can be complicated by several phenomena that clinicians need to be aware of:

1. The 4qA pathogenic haplotype is not investigated during the standard diagnostic process, hence false-positive results can occur when a D4Z4 repeat contraction is present on a non-permissive chromosome. Because the 4qA and 4qB haplotype occur at similar frequencies in the general population (in the entire range of repeat sizes



Repeat units	Median age of onset (years)	Maximum likelihood estimates of penetrance at age				
		30	40	50	60	70
5	25.5	0.602	0.782	0.895	0.955	0.983
6	48.7	0.257	0.389	0.517	0.632	0.730
7	84.0	0.108	0.172	0.244	0.319	0.396
8	-	0.049	0.079	0.115	0.155	0.198
9	-	0.024	0.039	0.057	0.078	0.101

Repeat units	Median age of onset (years)	Maximum likelihood estimates of penetrance at age				
		30	40	50	60	70
5	16.8	0.908	0.988	0.999	1.000	1.000
6	25.0	0.640	0.849	0.953	0.989	0.998
7	34.9	0.394	0.604	0.775	0.890	0.953
8	46.7	0.236	0.392	0.552	0.695	0.808
9	60	0.144	0.251	0.372	0.497	0.615

FIGURE 2 Maximum likelihood curves of the penetrance. Maximum likelihood estimates of the penetrance of symptomatic (A) and symptomatic plus asymptomatic facioscapulohumeral muscular dystrophy (FSHD) (B) for 5, 6, 7, 8, and 9 D4Z4 units (from up to down) for age. This represents the likelihood of reported symptoms by the patient at a certain age (A: symptomatic mutation carriership) and of reported symptoms by the patients or observed signs by the neurologist at a certain age (B: symptomatic and asymptomatic mutation carriership). Both penetrances were modeled as Cox regression models with a Weibull baseline distribution and the logarithm of the number of D4Z4 units as a covariate. (A) Carriers with 8 repeats have a 20% (0.198) chance of being symptomatic at age 70. (B) Carriers of repeat size of 8 units have only a 24% (0.236) chance of being detected by clinical examination at age 30. These likelihood estimates are helpful in counseling; however, the number of patients on which the estimates are based calls for cautiousness. (A) Maximum likelihood estimates of penetrance of symptomatic FSHD (both symptoms + signs). (B) Maximum likelihood estimates of penetrance of symptomatic plus asymptomatic FSHD (only signs and both symptoms and signs). (Reproduced with permission from M. Wohlgemut, Neurology 2018)

up to 200kB), it is important to have a clear clinical diagnosis and high pretest probability of FSHD before requesting FSHD genetic testing.[28]

2. Potentially pathogenic repeat translocations can occur between the 4q and 10q D4Z4 regions. These translocations often require additional testing, however the resulting hybrid bands can be detected and therefore will not lead to false-negative test results.

3. Somatic mosaicism is a rare phenomenon, but it can lead to false-negative test results in FSHD patients. About 30% of the novo cases of FSHD (which comprise 10% of all cases) are associated with somatic mosaicism.[29] If none or only a few of the cells in a blood sample contain the FSHD genetic defect the result of Southern blot analysis is less distinct, which can result in false negative results.[16–19,30,31]

Other methods to detect FSHD have been described in research settings, however these are not yet used in routine genetic testing. First, DNA methylation analysis can detect hypomethylation of the pathogenic D4Z4 array.[32,33] Second, the presence of DUX4 can be detected in cultured FSHD muscle, however this has proven to be very difficult due to low and variable levels of expression.[34]

Finally, it is important to consider that FSHD1 cannot be detected through next generation sequencing (NGS) methods because repeat arrays cannot be specifically aligned to the reference genome and thereby analyzed.

In conclusion, genetic testing for FSHD using the Southern blot method can indicate a genetic predisposition for FSHD. However, the results should be interpreted with caution, bearing in mind the caveats associated with testing as described above. Furthermore, D4Z4 repeat size cannot accurately predict the severity or course of the disease during a lifetime due to phenotypic variability and incomplete penetrance.

3.2.3 | Reproductive counseling

For a long time, FSHD patients considering pregnancy had only two options: accepting the risk of passing on FSHD or refraining from having biological children. After discovery of the underlying genetic defect for FSHD1 it became possible to test the unborn offspring of an FSHD1 patient for a genetic predisposition for FSHD before or during a pregnancy with use of preimplantation genetic testing (PGT) or prenatal diagnostics (PND), respectively (Table 1). These added options, and measures taken after testing, will of course be subject to differences in local laws and regulations apart from personal choices and believes.

TABLE 1 Reproductive options

Reproductive options	FSHD1	FSHD2
Prenatal diagnostic trajectory using chorionic villus testing or amniocentesis (PND)	X	
Preimplantation genetic testing (PGT)	X	
Refrain from having (biological) children	X	X
Adoptive or foster children	X	X
Egg- or sperm donation	X	X
Accepting the risk of having a child affected with FSHD	X	X

3.2.4 | Prenatal diagnosis

In PND a chorionic villus biopsy or amniocentesis is performed to obtain DNA from the fetus, which is then tested for FSHD1 using the Southern blot method. A prerequisite for PND is that the D4Z4 size of the parent with FSHD is known to verify the familial band (and in specific cases the genetic testing results of the other parent as well).

Chorionic villus biopsy is usually performed around the 11th week of pregnancy and involves removing chorionic villi either vaginally or through the abdominal wall. The risk of miscarriage due to performing this test is low, <0.5%, but not negligible.[35] In other hereditary disorders, genetic testing of a chorionic villus biopsy for known familiar DNA pathogenic variants generally takes about 2 weeks. However, prenatal testing for FSHD with use of Southern Blot takes at least 4 weeks. Therefore, results of PND are usually only available in the 16th or 17th week of pregnancy. Repeated testing may be necessary when an insufficient amount of DNA material is collected for chorionic villi cell culture.

In amniocentesis, an amniotic fluid puncture is performed through the abdominal wall during or after the 16th week of pregnancy. The risk of miscarriage due to amniocentesis is also <0.5%.[35] After amniocentesis, Southern Blot analysis also takes 4 weeks, with results available around the 20th week of pregnancy. Because of this timeline, diagnostic labs prefer to perform chorionic villus biopsy to be able to provide timely results. Pregnancy termination can be considered if the prenatal test detects the genetic predisposition for FSHD.

Before initiating the PND process, and preferably even before conception, reproductive counseling in specific subgroups of FSHD patients should consider the following:

(1) Patients with longer repeat sizes (7–10 units): due to incomplete penetrance and variable clinical expression of FSHD it is uncertain if their offspring will ever develop symptoms of FSHD. Parents need to be fully aware of these insecurities and the ethical issues that pregnancy termination in this group may raise (Figure 2).

(2) Patients with somatic mosaicism: their offspring may be more severely affected, because the pathogenic D4Z4 contraction will most likely be present in all of their cells. In this subgroup it also remains unsure if the pathogenic variant is present in all oocytes/spermatozoon, resulting in potentially lower chances of passing on the genetic trait <50%.

3.3 | Case 1.2, continuation

During reproductive counseling the clinical geneticist informs the couple that given the 7-unit D4Z4 repeat size, there is a chance that their offspring will never develop symptoms of FSHD. However, the patient is not

willing to take this risk because she is affected with the disease herself. The couple decides that they want to discuss their other options and are referred to discuss preimplantation genetic testing (PGT).

3.3.1 | Preimplantation genetic testing

Preimplantation genetic testing (PGT) enables testing before an established pregnancy and can be used to test for monogenic disorders such as FSHD1.[36] For PGT it is necessary to perform an IVF cycle in which oocytes are obtained and microinjected with a single spermatozoon (ICSI). This results in in vitro embryos, of which one or multiple cells are tested for the presence of the genetic disorder. Only embryos that test negative for the monogenic disorder will be transferred to the uterus. Pregnancy chances are 25%–30% per embryo transfer (ET).

The principle of PGT for monogenic disorders (PGT-M) is based on haplotyping (i.e. determination of grouped alleles within a genetic segment on a single chromosome which are inherited together). Traditionally, monogenetic disorders in PGT have been tested with multiplex micro-satellite Short-Tandem Repeat marker (STR)-PCR-based methods, to create locus specific haplotypes which only require small amounts of DNA and can be performed in a short time frame. The pathogenic mutation itself does not have to be included in the test, provided that flanking haplotypes derived from affected family members are included.[37]

In the PGT process, STR-PCR based methods have often been used to test a day 3 blastomere biopsy (6-12 pg DNA), with results available within 24–48 h, after which a "fresh" embryo is transferred within the same stimulation cycle. More recently, day 5 trophectoderm biopsies and generic genome wide haplotype-based methods are used in PGT. This next generation sequencing (NGS)-based method requires cryopreservation of embryos until the results of the PGT analysis are available and transfer of an embryo is performed in a later stimulation cycle.

The Southern Blot method (which is normally used to test for FSHD) cannot be used in PGT because the required amount of DNA is too large (>500 ng).[38] Indirect PCR based marker haplotyping in FSHD1 is complicated by the telomeric location of the D4Z4 array on chromosome 4q, which makes it impossible to include micro-satellite markers distal to the D4Z4 array. Hence, the traditional indirect test for FSHD1 only used microsatellite markers proximal to the D4Z4 locus, resulting in a > 5% error rate as recombination could go undetected. Because a false negative result will result in an affected child, mandatory PND is used to detect possible recombination after PGT. In the Netherlands, for a long time it was not recommended to perform PGT for FSHD because of this relatively high error rate.[39]

The generic genome-wide haplotyping-by-sequencing method (OnePGT test) was recently developed, mainly for novel indications for which no traditional locus specific PCR test was available. In this method embryonic DNA (day 5 trophectoderm biopsy) is amplified through whole genome amplification (WGA) by multi displacement amplification (MDA) prior to analysis. The whole genome amplified DNA from the embryo is processed together with the DNA from the parents and a (preferably affected) referent using next-generation sequencing (NGS), after which automated data analysis takes place. In this analysis haplotype blocks inherited at the locus of interest are identified and then evaluated by a quality control system, checking the haploblocks for informativity and localization close to and flanking the locus of interest. If all quality criteria are met an automated call for haplotyping is made, i.e. affected or unaffected. If the quality criteria are not met, a suggestive conclusion is provided, but the sample may need to be manually inspected.[36]

This haplotyping by sequencing using OnePGT works better for FSHD1 because it uses SNPs rather than micro-satellite STR markers. As SNPs are far more abundant across the genome than micro-satellite STR markers some reference points distal to the D4Z4 array are present, in contrast to the original indirect test method. Therefore, nowadays PGT for FSHD1 can be offered for familial FSHD1 cases in the Netherlands, with a lower risk of a misdiagnosis (<5%). However, prenatal confirmation of the PGT diagnosis is still recommended if the future parents want to be sure that the baby is not affected by FSHD. Finally, this OnePGT method (as the original indirect test) is not suited for sporadic FSHD cases and somatic mosaicism.

3.4 | Case 1.2, continuation

The couple decide to try PGT and their second IVF-trajectory results in a successful pregnancy. A chorionic villus biopsy is performed to test the fetus for a genetic predisposition for FSHD and after 4 weeks test results show that the fetus has two normal sized alleles.

4 | FSHD TYPE 2

4.1 | Case 2

A 30-year-old male patient is diagnosed with FSHD2, caused by a heterozygous SMCHD1 pathogenic variant and an unknown D4Z4 repeat contraction (>10 units). He and his partner consider pregnancy, so they are referred to the clinical geneticist for preconception counseling. Based on the information given during counseling, they want to know if it is possible to test the partner and acquire her genetic profile, to be able to calculate the risk of their child having FSHD.

4.1.1 | Inheritance

Because of the digenic nature of FSHD2, multiple scenarios are possible in the inheritance of this disorders. To develop FSHD2, both a semi-shortened (8–20 units) D4Z4 repeat array on chromosome 4 and a pathogenic variant in a chromatin modifier gene on a different chromosome need to be passed on by one or both parents. Therefore, the genetic profiles of both patient and partner need to be considered, which makes preconception counseling in FSHD2 even more

challenging than in FSHD1. When the partner of an FSHD2 patient does not carry a shortened D4Z4 allele on chromosome 4 nor a pathogenic variant in one of the known chromatin modifier genes, there is a 25% chance that their offspring has the genetic predisposition for FSHD. Their offspring does have a 50% chance of carrying one of the two genetic defects, which do not cause disease individually, but which together cause FSHD2 (Figure 3). The chance that their offspring will have a genetic predisposition for FSHD2 increases up to 50% when the partner has one or two semi-shortened alleles of 8–20 units *or* a pathogenic variant in a chromatin modifier gene such as *SMCHD1*. This is significant, because over 20% of the general population has an 8–20 unit D4Z4 array with a permissive 4qA haplotype (Figure 4).[40] Additionally, it is possible that a child inherits a shortened D4Z4 allele from one parent and a pathogenic variant in a chromatin modifier gene from the other parent. This child will have a genetic predisposition for FSHD, while the parents both are healthy. Clinical variability exists in FSHD2 like in FSHD1, thus also needs to be considered.

Ideally, in couples considering pregnancy, both FSHD2 patient and partner are tested to adequately counsel them on their specific situation. Genetic testing of both patient and partner is currently not possible in a diagnostic laboratory due to the complexity of the

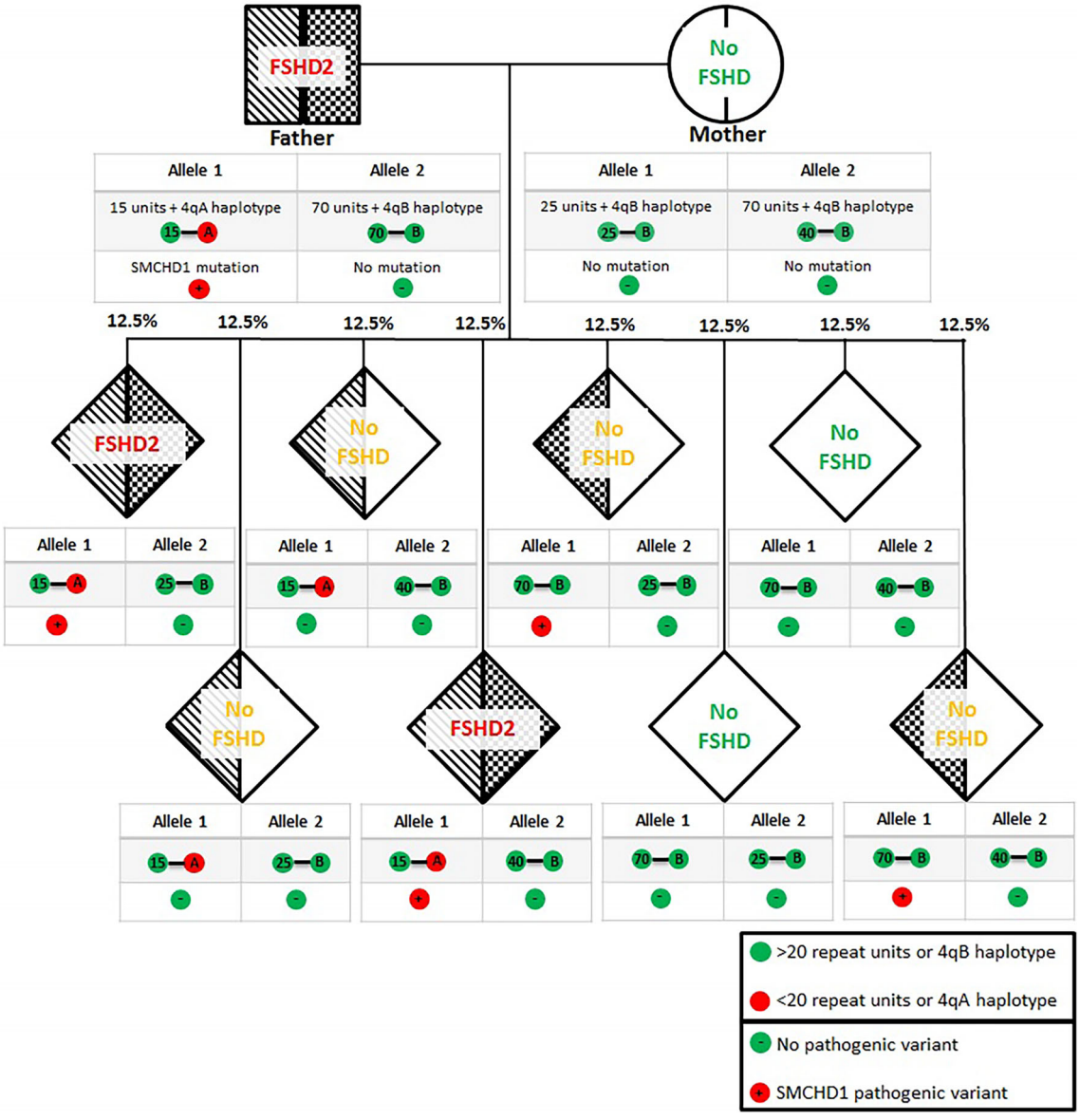


FIGURE 3 Case 2. Inheritance in FSHD2 with a partner without a pathogenic variant in a chromatin modifier gene and without a repeat size <20 units. The chance of offspring with a genetic disposition for FSHD is 25% in this scenario. The chance of offspring with a SMCHD1 mutation or a repeat size <20 units on a permissive haplotype is 50%. The chance of offspring without a SMCHD1 mutation or a repeat size <20 units on a permissive haplotype is 25%

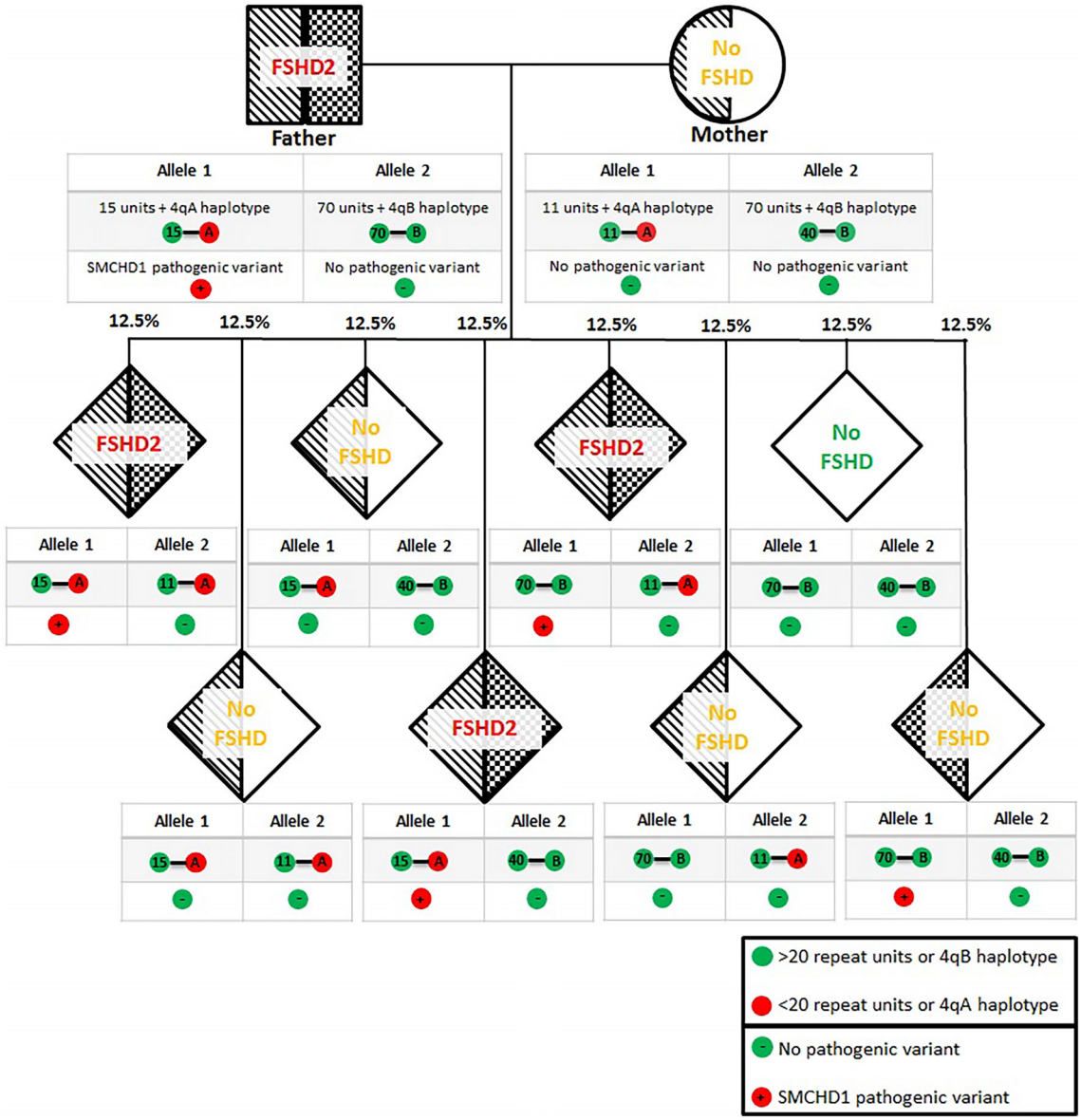


FIGURE 4 Inheritance in FSHD2 with a partner carrying one allele with a repeat size <20 units. The chance of offspring with a genetic predisposition for FSHD is 37.5% in this scenario. The chance of offspring with a SMCHD1 mutation or a repeat size <20 units on a permissive haplotype is 50%. The chance of offspring without a SMCHD1 mutation or a repeat size <20 units on a permissive haplotype is 12.5%.In the rare case the mother has two alleles with repeat sizes <20 on a permissive haplotype the chance of offspring with a genetic predisposition for FSHD increases to 50%

genetical diagnosis of FSHD2, which is usually performed in a research setting. However, improved diagnostic possibilities for FSHD2 patients are being studied and therefore this may change in the near future.

4.1.2 | Genetic diagnosis

FSHD2 is considered in patients with an FSHD phenotype in whom no D4Z4 repeat contraction is found during initial genetic testing using Southern Blot. In the absence of a known pathogenic variant associated with FSHD2 (SMCHD1, DNMT3B, LRIF1) it is recommended to first investigate *SMCHD1*, because pathogenic variants in *SMCHD1* account for 80% of all FSHD2 cases. If available, whole exome sequencing can be performed to investigate SMCHD1, DNMT3B, and LRIF1 all at once. In a patient with an FSHD phenotype and a known familial pathogenic *SMCHD1* variant, it is recommended to investigate both the D4Z4 repeat size and *SMCHD1*. The presence of an *SMCHD1* pathogenic variant is determined using a sequence analysis of the entire coding region (exon 1 to 48) on chromosome 18.

It is important to realize that the exact number of D4Z4 repeat units often remains unknown in FSHD2 patients. Although some

FSHD2 patients have repeat sizes of ≤10 units, which can be identified and quantified using the Southern Blot method, many have larger 11–20 unit D4Z4 repeats. These larger repeat sizes cannot be quantified using routine diagnostic techniques such as the Southern Blot method, which means that we cannot distinguish FSHD2-associated semi-shortened repeat sizes of 11–20 units–from larger repeats (>20). Furthermore, as in FSHD1, the 4q-haplotype is not determined in the standard FSHD2 diagnostic process. Both the actual repeat size and the 4q-haplotypes can be determined in research laboratories, however the tests used are not standardized (yet). Thus, when *SMCHD1* pathogenic variants are detected using next generation sequencing, this finding alone does not confirm the diagnosis of FSHD2 and additional D4Z4 array analysis needs to be performed. Finally, it is possible that FSHD1 (a repeat contraction of the D4Z4 unit) can occur together with a pathogenic variant in a chromatin modifier gene (FSHD2), resulting in a more severe phenotype.[41]

4.1.3 | Reproductive counseling

Neither PND nor PGT are currently available for FSHD2. Although is possible to detect a known pathogenic variant in a chromatin modifier gene, it is not possible to determine 4q haplotype or the size of the D4Z4 array (if over 10 units). This makes it impossible to predict the chance that the fetus has a genetic predisposition for FSHD2 and prohibits accurate counseling of prospective parents. In very few specific cases SSLPs (simple sequence length polymorphisms) can be used to perform a risk analysis for having the permissive haplotype, but only in consultation with diagnostic/research laboratories.[42] Usually, the only available options for patients with FSHD2 are to refrain from having biological children, to accept the risk of having children with a predisposition for FSHD2, to use an egg- or sperm cell donor or to adopt (Table 1).

4.2 | Case 2, continuation

The clinical geneticist explains to the couple that their idea to acquire all the genetic information from both patient and partner and calculate the risks for their offspring is theoretically correct, but their request cannot be performed yet. Research laboratories are working on techniques to test this genetic profile, but these tests are not standardized yet and therefore not available in regular diagnostic laboratories.

5 | PREGNANCY IN FSHD PATIENTS

5.1 | Obstetric complications

Three previous studies have investigated obstetric complications in females affected with FSHD: one in the United States ($n = 38$), and two in Germany ($n = 11$ and 29). These small studies showed that pregnancy in FSHD usually has a favorable outcome.[12,43,44] Based on these limited data, FSHD most likely has no effect on fertility and does not increase the risk of miscarriage, preterm birth or birth defects, nor the risk of preeclampsia, gestational diabetes, infection or other pregnancy complications. Although the USA-based study demonstrated a significantly higher risk of low birth weight, this was not reproduced in a more recent study from Germany.[12,43] However, both studies were performed in small cohorts and complications in pregnancy can be influenced by lifestyle factors and differences in management of pregnancy and delivery across countries. Furthermore, only the USA study described the clinical severity of patients in their cohort: two out of 38 women were wheelchair dependent, but the outcome of these two patients was not specified. More research in larger cohorts is needed to increase our understanding of obstetric complications in FSHD.

5.1.1 | Clinical disease course

Approximately 12% to 24% of FSHD patients, especially those with early onset and/or rapidly progressive disease, report an increasing severity of symptoms during pregnancy, such as a general decrease in muscle strength, increase in frequency of falling or an increase in existing or newly onset pain.[12,22,43]

Severely affected FSHD patients with vertebral column deformities such as lumbar hyperlordosis or severe scoliosis are at risk for a (temporary) reduction in pulmonary function during pregnancy.[45] Therefore, we recommend to perform frequent pulmonary function testing, that is, seated and supine measurement of forced vital capacity, in this specific subgroup of patients: at least once per trimester and in week ~36 of pregnancy, prior to delivery. Patients with compromised pulmonary function (forced vital capacity <60% or a > 15% reduction in supine compared to seated FVC) should be referred to pulmonary or sleep medicine specialists, preferably before pregnancy. It is not required to routinely monitor other vital functions, such as cardiac function, unless specific symptoms appear.[46,47] Despite the risk of worsening of symptoms in some individuals, one study reported that 90% of patients stated they would opt for pregnancy again.[12]

We recommend to refer all female FSHD patients to an outpatient clinic with expertise in neuromuscular disorders for advice before and during pregnancy. Besides counseling patients on the pregnancy and delivery itself, a rehabilitation specialist can also provide specific recommendations on how to take care of the baby postpartum.

6 | DELIVERY IN FSHD PATIENTS

In a very small number of cases reported ($n = 5$), FSHD does not seem to be associated with breech presentation at delivery (0%), in contrast to other neuromuscular dystrophies such as limb girdle muscular dystrophy (26.7%) and myotonic dystrophy type 1 (34.6%).[43]

6.1 | Local and general anesthetics

General anesthesia is associated with several risks in all muscular dystrophies.[48,49] Hence, local anesthesia is preferred in FSHD patients during childbirth whenever possible. General anesthesia may be indicated in emergency caesarian sections or post-partum hemorrhage. Inhalation anesthetics should be avoided because these can cause cardiac complications or rhabdomyolysis in most neuromuscular dystrophies. FSHD is not associated with an increased risk of malignant hyperthermia.[50] Succinylcholine should be used with caution, because it can cause fatal hyperkalemia.[51] Finally, it is important to consider possible respiratory muscle weakness in FSDHD patients prior to delivery and to test respiratory function if anesthetic sedation may be necessary during delivery. Compromised respiratory function should be known to the anesthetist and is defined as spirometry forced vital capacity (FVC) values of lower than 60% predicted.[52] Bearing in mind that spinal deformities can make epidural blockade more difficult, pain relief using epidural anesthesia is possible, as well as spinal anesthesia.[43,53]

6.1.1 | Instrumental delivery

The USA-based study regarding pregnancy in FSHD patients found that instrumental deliveries, that is, birth using vacuum or forceps, are required more often in FSHD patients compared to women without neuromuscular disease (27.0% versus 11.6%).[12] A more recent German study found the same difference in instrumental deliveries between German FSHD patients and the general population (15.4% versus 7%), which did not reach statistical significance.[43] Presumably this difference is due to the abdominal and pelvic muscle weakness, making it difficult to push during the last phase of child birth.[44] Consequently, FSHD patients with axial muscle weakness should be monitored closely during delivery.

6.1.2 | Caesarian section

The USA-based study on pregnancy in FSHD found that secondary caesarian sections (i.e. emergency caesarian sections) are more common in FSHD patients (23.8% versus 16.9%). Primary caesarian delivery rates do not differ from the general population.[12] The German study found a general increase in caesarian sections in all neuromuscular disorder patients when compared to the general population, but not specifically in FHSD (56.2% in all neuromuscular disorders versus 7.7% in FSHD).[43] Because of the possible increased risk of needing a vaginal assisted delivery or caesarian section, FSHD patients are advised to give birth in a hospital, guided by a midwife or gynecologist.

7 | FUTURE PERSPECTIVES

To provide reliable preconception and prenatal counseling in FSHD it is important that neuromuscular specialists and clinical geneticists have thorough knowledge of the genetic mechanisms in FSHD. They need to be able to inform patients considering pregnancy about the possibilities (and risks) of prenatal diagnosis and pre-implantation genetic testing or refer them to a colleague with experience on the matter. Noninvasive prenatal testing will probably be an option in the near future, hereby avoiding the risk of miscarriage after an invasive PND test and probably a timelier result. The most recent developments in PGT using haplotyping by sequencing have already improved PGT for FSHD1, but there remains a considerable risk of a misdiagnosis. Studies investigating PND and PGT for FSHD2 have been initiated, but they face highly complex challenges and require more time. In order to expand knowledge on pregnancy and child birth in FSHD more data are required. Therefore, large prospective studies on FSHD covering the entire disease severity spectrum are needed, using patient reported, physician reported, and laboratory data.

8 | CONCLUSION

Despite the complex genetic mechanisms behind FSHD, prenatal counseling options are expanding and creating new opportunities for FSHD patients who consider pregnancy. However, the available options are still complex for FSHD1 patients and very limited for FSHD2 patients. Pregnancy outcome in FSHD is generally favorable, however there is an increased risk of instrumental or caesarian delivery and some patients may experience increased severity of their FSHD symptoms.

9 | TAKE HOME MESSAGES

- FSHD1 is an autosomal dominant repeat disorder with incomplete penetrance and variable expression
- FSHD2 is a digenic disorder, combining a repeat contraction with a pathogenic variant in a chromatin modifier gene and subsequently complex inheritance
- Preconception counseling regarding the genetic risk, possible options to prevent inheritance of the disease in offspring and possible pregnancy complications in affected women is advised.
- For FSHD1 patients contemplating pregnancy prenatal and preimplantation genetic diagnosis options exist, but they require adequate counseling
- Pregnancy and delivery outcome in FSHD patients is usually favorable, but an increased risk of instrumental or caesarian delivery exists for severely affected women

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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