Chapter 20
The Muscular Dystrophies

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The muscular dystrophies are a heterogeneous group of conditions that cause progressive muscle weakness, characterized on muscle biopsy by degenerating/regenerating muscle fibers, fibrosis, and fatty replacement.

20.1 Dystrophinopathies

The dystrophinopathies include a spectrum of muscle diseases caused by mutations in the dystrophin gene, *DMD*, including Duchenne muscular dystrophy, Becker muscular dystrophy, and isolated dilated cardiomyopathy.

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20.1.1 Clinical Presentation of the Dystrophinopathies

Duchenne muscular dystrophy affects 1 in 3,500 males. Onset is typically at age 3 and results in progressive muscle weakness, cardiomyopathy, respiratory insufficiency, and loss of ambulation at or before age 12, though this can be delayed with corticosteroid treatment [1]. DMD can be associated with specific learning disabilities, autism spectrum disorder, and/or attention-deficit/hyperactivity disorder (ADD/ADHD) [2, 3]. In the last decade, the life expectancy of DMD has increased from the teens to the 30s or 40s [4, 5]. Families should be informed that living into adulthood is now the norm instead of the exception.

Becker muscular dystrophy (BMD) is a less severe form of dystrophinopathy. The age of onset can range from childhood to late adulthood; BMD is defined as loss of ambulation after age 13; however, due to the blurring of boundaries caused by DMD corticosteroid use, a classification of an intermediate form with loss of ambulation between age 13 and 16 is being used. Late-onset BMD may be mutation specific, with some mutations consistently showing a milder clinical presentation, with ambulation being retained much longer [6–10].

Female carriers of DMD can manifest any or all of the symptoms [11], though typically less severely than in males with DMD. For example, only a small percentage of female carriers are at risk to develop cardiomyopathy (10–30 %) or progressive weakness (7–10 %). However, being a manifesting DMD carrier is now recognized as an underdiagnosed form of muscular dystrophy, and can be seen without a family history of an affected male [12, 13].

20.1.2 Diagnosis of Dystrophinopathies

(DMD video clip Part 1)

Dystrophinopathy is generally suspected if a male or female has a highly elevated creatine kinase (CK) (often greater than 10,000 U/L), proximal muscle weakness, and hypertrophic calves. A reduction or absence of dystrophin on muscle biopsy demonstrated either by immunohistochemistry or western blot analysis remains the gold standard in the absence of genetic confirmation. Genetic testing is often the first line of diagnosis due to high sensitivity and specificity of current methodologies.

20.1.3 Genetics of Dystrophinopathies

The *DMD* gene is located on the X chromosome and is the largest known gene in the genome. The large size is thought to play a role in the high *de novo* mutation rate [14]. The dystrophinopathies are hallmark examples of genetic phenomena such as

germ line mosaicism and skewed X-inactivation in manifesting carriers [15–17]. Since the dystrophin protein is involved in maintaining muscle cell membrane integrity, insufficient production or defective dystrophin can cause muscle cell breakdown. When cell breakdown is greater than cell replacement, progressive muscle weakness occurs. Over 5,000 identified dystrophin mutations have been identified, the majority of which (60–70 %) are deletions. The location and type of mutation (reading frame rule) can provide some insight for prognosis [18]. Additionally several genetic modifiers are thought to play a role in disease variability [19, 20].

20.1.4 Genetic Testing for the Dystrophinopathies

(DMD video clip Part 2)

Several methodologies are employed to identify genetic mutations within the dystrophin gene. Since therapeutic approaches may be mutation dependent, genetic confirmation is essential for inclusion in clinical trials [21]. Most laboratories employ a stepwise approach, first searching for the more common mutations—deletions and duplications, and then, if no mutations are identified, sequencing the gene. This process is typically more cost effective. Patient advocacy groups recognize the importance of genetic confirmation, and, when cost is prohibitive, have initiated programs to cover genetic testing. Carrier testing is generally recommended after the identification of a family mutation. However, if an affected individual is unavailable, genetic testing for dystrophin mutations can be performed and is becoming highly sensitive. Due to the high *de novo* mutation rate and germ line mosaicism, genetic counselors can help families understand carrier risk.

20.2 Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) is characterized by progressive proximal muscle weakness, an elevated creatine kinase level, and muscle degeneration/regeneration pattern on muscle biopsy [22].

20.2.1 Clinical Presentation of the LGMD

LGMD refers to a group of inherited muscular dystrophies that are characterized by muscle weakness and wasting of shoulder and pelvic girdle muscles. Depending on the specific subtype, LGMD affects 1/123,000 to 1/14,500 people. LGMD is a progressive condition with onset from childhood to adulthood. Proximal (close to the trunk) skeletal muscles are affected first, but with disease progression, more

distal muscles can become weak. LGMD can also present like a metabolic myopathy; however, in these conditions unlike the metabolic myopathies, CK seldom returns to normal after a rhabdomyolysis event [23].

20.2.2 Diagnosis of LGMD

Generally, the diagnosis of LGMD is made if an individual has predominantly shoulder and hip muscle weakness, elevated creatine kinase (CK) levels, and dystrophic changes on muscle biopsy [24–26]. A muscle biopsy can help reveal the type of LGMD. Special stains can be used to determine the absence or presence of proteins. Finding an absent or reduced protein narrows the causal gene candidates [27]. Because dystrophin is an important part of the dystrophin-sarcoglycan complex, it is important to rule out mutations in dystrophin as the cause of the muscular dystrophy. Finally, muscle imaging is becoming a helpful and noninvasive tool in the diagnosis of LGMD [27].

20.2.3 Genetics of LGMD

The dystrophin-sarcoglycan complex (DSC) is located on the membrane of the muscle cell and helps the muscle withstand everyday wear and tear. Improperly formed DSC can cause a rapid breakdown of muscle, which results in the loss of muscle cells and muscle weakness. Over 20 forms of LGMD are known, and can be divided into two types based on inheritance pattern: autosomal dominant LGMD1 and autosomal recessive LGMD2. LGMD1 and LGMD2 are further divided into subtypes based on the causative mutation. The subgroups are designated by letters (Table 20.1).

20.2.4 Genetic Testing for the LGMD

Because the different forms of LGMD can be clinically indistinguishable, testing with gene panels is the most efficient way to provide genetic confirmation [28]. Families without a genetically confirmed diagnosis may be ideal candidates for whole exome sequencing. As with all muscle diseases, private mutations and variants of unknown significance can complicate results.

Table 20.1 The LGMDs (adapted from [26])

Disease name (synonym)	Populations with founder mutations	Gene symbol	Inheritance
Myotilinopathy (LGMD1A)	None	*MYOT*	AD
LGMD1B	None	*LMNA*	AD
Caveolinopathy (LGMD1C)	None	*CAV3*	AD
LGMD1D	None	*DES*	AD
LGMD1E	None	*DNAJB6*	AD
Alpha-sarcoglycanopathy (LGMD2D)	None	*SGCA*	AR
Beta-sarcoglycanopathy (LGMD2E)	Amish	*SGCB*	AR
Gamma-sarcoglycanopathy (formerly SCARMD) (LGMD2C)	North Africans; Gypsies	*SGCG*	AR
Delta-sarcoglycanopathy (LGMD2F)	Brazilian	*SGCD*	AR
Calpainopathy (LGMD2A)	Amish, La Reunion Island, Basque (Spain), Turkish	*CAPN3*	AR
Dysferlinopathy (LGMD2B)	Libyan Jewish	*DYSF*	AR
LGMD2G	Italian	*TCAP*	AR
LGMD2H	Manitoba Hutterites only	*TRIM32*	AR
LGMD2I	Unknown	*FKRP*	AR
LGMD2J	Finland	*TTN*	AR
LGMD2K	Turkish	*POMT1*	AR
LGMD2L	Northern European	*ANO5*	AR
LGMD2M	Unknown	*FKTN*	AR
LGMD2N	Unknown	*POMT2*	AR
LGMD2O	Unknown	*POMGNT1*	AR
LGMD2Q	Turkish	*PLEC*	AR

20.3 Emery-Dreifuss Muscular Dystrophy (EDMD)

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of MD affecting an estimated 1/100,000 individual [29]. EDMD is characterized by joint contractures that precede muscle weakness and progressive, often severe cardiac involvement with cardiac conduction defects [30].

20.3.1 Clinical Presentation of the EDMD

EDMD is suspected in the presence of contractures prior to weakness. EDMD is considered a slowly progressive muscular dystrophy. It is often associated with cardiac problems including both cardiomyopathy and cardiac conduction defects [31].

20.3.2 Diagnosis of EDMD

Diagnosis is typically made clinically by the presence of contractures, especially at the elbows.

20.3.3 Genetics of EDMD

EDMD is caused by a mutation in any of the three genes that encode proteins associated with the nuclear envelope, *LMNA*, *EMD*, and *FHL1* [29]. Both *EMD* and *FHL1* are X-linked, with *FLH1* being X-linked dominant and female are affected. *LMNA* mutations typically cause an autosomal dominant form of EMD but can be recessive, and is often the result of a *de novo* mutation.

20.3.4 Genetic Testing for EDMD

Genetic testing for EDMD is usually done in a stepwise manner beginning with the most common genes, *LMNA* and *EMD* [29]. Other rare causes, including *FHL1* and other contracture disorder such as the collagen-VI-related disorders, are investigated if the first tier of testing is negative.

20.4 Facioscapulohumeral Muscular Dystrophy (FSHD)

Facioscapulohumeral muscular dystrophy (FSHD) causes slowly progressive muscle weakness and is characterized by scapular winging [32].

20.4.1 Clinical Presentation of the FSHD

FSHD is characterized by muscle weakness in the face, shoulders, upper arms, and lower legs. The weakness may be asymmetric [33]. Typical onset is in the teens or twenties. However, FSHD shows significant inter- and intra-familial variability both in age of onset and presenting symptoms, which can lead to difficulties in diagnosis. Infantile-onset FSHD with hearing loss and retinal changes is considered a rare form of FSHD [33, 34]. Hearing loss and retinal changes (Coats' disease) are also complications sometimes seen in the adult-onset form. The infantile form may be underdiagnosed and symptoms of FSHD may be unrecognized during childhood.

20.4.2 Diagnosis of FSHD

Diagnosis of FSHD is typically made clinically, with genetic testing as the gold standard. Muscle biopsy shows no specific changes [35], but may have an inflammatory infiltrate, which may be misleading, and result in misdiagnosis of myositis.

20.4.3 Genetics of FSHD

FSHD is an autosomal dominant condition primarily caused by a deletion on chromosome 4. The deletion within the D4Z4 repeat region results in changes in methylation [36–38]. A second FSHD gene, *SMCHD1*, has been identified and can be either a genetic cause of FSHD (in the presence of the permissive haplotype) or act as a disease modifier [39].

20.4.4 Genetic Testing of FSHD

A deletion of the D4Z4 repeat region on chromosome 4 is present in 95 % of individuals affected with FSHD. Detection of the deletion is complicated by the large size of the region and a genetically similar region located on chromosome 10. The deletion of D4Z4 repeats on chromosome 10 does not cause FSHD. A translocation between the chromosome 10 region and the D4Z4 region on chromosome 4 occurs frequently, occurring in 20 % of the general population without causing disease [36]. The D4Z4 deletion alone is not sufficient to cause FSHD1; a permissive allele, 4qA161, which allows polyadenylation and stabilization of DUX4 transcripts, is required to manifest FSHD1. Genetic strategies have been developed to detect both copies of D4Z4. In general the normal size of the FSHD region is greater than 40 kbs (or 40,000 base pairs). In individuals with FSHD, the size of the region is less than 35 kbs (or 35,000 base pairs). A grey zone of 35–40 kbs exists where some individuals will be symptomatic and others will not. In the event that genetic testing for the common mutation is negative and clinical suspicion is high, follow-up testing with alternate probes can be helpful. Additionally, testing of *SCHMD1* can be performed for the second less common cause of FSHD, now clinically called FSHD2 [40].

20.5 Oculopharyngeal Muscular Dystrophy (OPMD)

Oculopharyngeal muscular dystrophy (OPMD) is characterized by late-onset ptosis, dysphagia, and lower extremity weakness.

20.5.1 Clinical Presentation of the OPMD

OPMD is a condition that typically affects the muscles necessary for swallowing and eyelid movement. The muscles of the upper arms and legs can also be affected. Typically symptoms start appearing in the 50s and progress slowly; however a great deal of variability exists, even within families. OPMD is more common in the French Canadian population, but may be under-recognized in other populations [41].

20.5.2 Diagnosis of OPMD

OPMD is generally a clinical diagnosis, which is confirmed by genetic testing. EMG or muscle biopsy can be useful in excluding mitochondrial disorders or bulbar onset ALS early in the disease.

20.5.3 Genetics of OPMD

OPMD is an autosomal dominant condition caused by a polyalanine repeat within polyadenylate binding protein nuclear 1 encoded by the *PABPN1* gene located on chromosome 14 [42]. When homozygous, a modifier allele of seven GCG repeats can cause autosomal recessive OPMD, and also increase severity. The size of the polyalanine repeat appears to correlate with the severity of the condition and the age of onset.

20.5.4 Genetic Testing for the OPMD

Genetic test for OPMD involves determining the size of the GCN repeat within the *PABPN1* gene (abbreviated GCN because all four codons, GCA, GCT, GCC, and GCG, encode alanine). The normal size of the GCN repeat is ten repeats. At least one copy of 12 or more GCN repeats confirms the diagnosis of OPMD. When homozygous the GCN repeat size of 11 can cause autosomal recessive OPMD.

20.6 Congenital Muscular Dystrophy (CMD)

Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of disease that presents from infancy through childhood, but will not be discussed in this chapter. Many of the genes associated with CMD can cause an LGMD phenotype [43].

20.7 Genetic Counseling Case History of a Transitional Age Patient

Mr. R, a 23-year-old male patient affected with Duchenne muscular dystrophy, requested a genetic counseling appointment for genetic testing and discussion of research participation. Mr. R was a long-standing patient in the Muscular Dystrophy Association (MDA) clinic. He had genetic testing during childhood, which did not identify a genetic mutation.

Mr. R, accompanied by his mother, arrived for the genetic counseling session. The genetic counselor began by asking Mr. R if he had any specific questions. Mr. R told her how his online research regarding possible treatment strategies had caused him to wonder about his mutation and research participation. The genetic counselor then inquired about his current life. He was enrolled in a part-time master's program in computer science and living independently.

The genetic counselor then reviewed family history and learned that Mr. R was an only child, and that there was no family history of any neuromuscular disorder. She discussed the inheritance of the dystrophinopathies and the fact that one-third of cases are due to a new mutation. She stated that if he wanted to have children, none of his sons would be affected or at risk of passing on the dystrophin mutation; however, all of his daughters would be carriers. Mr. R's mother remained quiet during the session, and denied having any questions or concerns. However, when the genetic counselor discussed the risk to DMD carriers for cardiomyopathy, and that cardiac screening was recommended for DMD carriers, she said that she was not interested in carrier testing and was already undergoing cardiac care for an arrhythmia. The genetic counselor discussed how other women in the family might be at risk, and could be offered carrier testing.

The counselor then explained the changes in technologies that allowed for better analysis of the dystrophin gene, and that most (>90 %) mutations were now identifiable. She discussed different mutation types and the research study for dystrophin nonsense mutations at their clinic. Mr. R elected to have genetic testing, and the genetic counselor and Mr. R made arrangements to discuss the results by phone.

The results revealed a deletion of exons 8–17 within the dystrophin gene. The genetic counselor explained how this meant that he was not eligible for the nonsense mutation clinical trial. The genetic counselor also discussed that the

current exon skipping antisense polymers under development were not directed at this region. Mr. R asked about participation in other clinical studies. The clinical research team was currently enrolling for a natural history study for non-ambulatory DMD patients. The genetic counselor described the study, and facilitated Mr. R's enrollment.

Several years later, the genetic counselor met Mrs. R at an MDA function. Mrs. R remarked about the hope that was generated by her son's genetic counseling, testing, and research participation, and thanked her for arranging them.

Discussion Questions

- In this scenario the genetic counselor was both a genetic counselor and research coordinator. How do genetic counselors balance wearing many hats without creating a conflict of interest?
- How do you tailor a genetic counseling session if the primary information sought is not inheritance and risk to future generations? What is the genetic counselor's responsibility to raise awareness in family members of carrier-associated risks?
- How often should return patients be offered genetic counseling? Is the need for genetic testing or reviewing results the only reason for a follow-up consult?
- Working closely with a patient advocacy group, like the Muscular Dystrophy Association (MDA), often requires attendance at social functions and support groups. What positive and negative impact can this have on the providers' clinical practice?

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