Statutory Approvals Committee - minutes

Centre 0102 (Guys Hospital)

Preimplantation Genetic Diagnosis (PGD) application for Myofibrillar Myopathy-9 with early respiratory failure (MFM9), OMIM #603689

Date:	25 February 2021
Venue:	Microsoft Teams Meeting
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde
Specialist Adviser:	Alan Fryer
Legal Adviser:	Sarah Ellson - FieldFisher LLP
Members of the Executive:	Moya Berry - Committee officer Catherine Burwood - Licensing Manager
Observers:	Sarah Steadman - Inspector (Induction) Karen Campbell - Inspector (Induction)
Apologies:	No apologies were received for the item
Declarations of Interest:	Members of the committee declared that they had no conflicts of interest in relation to this item.

The Committee had before it:

- HFEA Code of Practice 9th edition
- Standard Licencing and Approvals Pack

The following papers were considered by the committee:

- Executive Summary
- PGD Application form
- Redacted Peer review
- Genetic Alliance (UK) Statement
- Academic Paper provided by the applicant (Tasca and Udd, 2018)

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Dr Alan Fryer, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the PGD application for Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689 is consistent with the peer review.

1.3. The committee noted that the condition being applied for is not on the list of approved PGD conditions.

1.4. The committee noted that the condition, Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689 is also known as Myofibrillar Myopathy-9 with early respiratory failure, OMIM #603689. However, as the OMIM website entry lists Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689 as the primary name of the condition, the condition, for the purposes of this application, will be termed Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689.

1.5. The committee noted that the Genetic Alliance (UK) statement provided a perspective on the impact of the condition on patients, their families and carers.

1.6. The committee had regard to its decision tree. The committee noted that the Centre is licensed to carry out PGD. The committee was also satisfied that the Centre has experience of carrying out PGD and that generic patient information about its PGD programme and associated consent forms had previously been received by the HFEA.

1.7. The committee noted that the proposed purpose of testing the embryos was as set out in paragraph 1ZA(1)(b) of Schedule 2 of the Act, i.e., 'where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality'.

1.8. The committee noted that Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689, is inherited in an autosomal dominant manner, which means there is a 50% chance of an embryo being affected by the condition in each pregnancy if either parent has a relevant mutation.

1.9. The committee noted that the penetrance of the condition is very high but its severity is very variable within and between families. Some patients have mild symptoms and are largely unaffected into their 70s, whilst others are severely disabled by the condition while in their 40s and are presumed to have a reduced life expectancy due to pulmonary complications. Heart muscle involvement can occur but less often than in some other forms of myofibrillar myopathy.

1.10. Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689 can cause progressive weakness in the muscles involved in movement and in breathing. Symptoms are first expressed in early to mid-adulthood and worsen over time so that in severe cases patients can be severely disabled in their 40s, requiting a wheelchair and/or a machine to help them to breathe (ventilator). Breathing problems predispose to respiratory infections and pulmonary complications, which can reduce life expectancy and may impact on physical and mental well-being.

1.11. There is no cure for the condition. Treatment is supportive and focuses on reducing the impact of symptoms.

1.12. The committee noted the executive's request to consider Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689, for inclusion on the list of conditions approved for PGD. The committee agreed to consider the application on this basis.

1.13. The committee also noted the recommendation of the peer reviewer to consider eleven other sub types for inclusion on the list for which PGD can be applied and agreed to consider the application on this basis. Some of these conditions are inherited in an autosomal recessive manner (types 7,8,10 and Myopathy, Myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related) and type 1 may be inherited in either an autosomal dominant or autosomal recessive manner. Some of these other conditions have or can have a childhood-onset.

1.14. The condition types are mostly characterised by adult onset progressive muscle weakness resulting in reduced mobility. Impairment of the respiratory muscles resulting in respiratory failure may occur in some cases but is a less prominent feature than in Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9). Cardiac muscle involvement and potential premature death are more common in many of these conditions. The conditions are:

- Myopathy, Myofibrillar 1, OMIM #601419
- Myopathy, Myofibrillar 2, OMIM #608810
- Myopathy, Myofibrillar 3, OMIM #609200
- Myopathy. Myofibrillar 4, OMIM #609452
- Myopathy, Myofibrillar 5, OMIM #609524
- Myopathy, Myofibrillar 6, OMIM #612954
- Myopathy, Myofibrillar 7, OMIM #617114
- Myopathy, Myofibrillar 8, OMIM #617258
- Myopathy, Myofibrillar 10, OMIM #619040
- Myopathy, Myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related, OMIM #613869
- Myopathy, spheroid body, OMIM #182920 (due to mutations in the same gene as myopathy, myofibrillar 3 and with similar phenotype).

2. Decision

2.1. The committee considered that, in the worst-case scenario, Myopathy, Myofibrillar, 9, with early respiratory failure (MFM9), OMIM #603689, is an incurable, progressive and potentially life-threatening neuromuscular condition that can present during early adult life and cause severe disability. There is no cure for the condition and affected individuals usually require walking aids within a few years of onset and may progress to wheelchair dependence. Some may require ventilatory support. The committee considered the possible serious physical and psychological impact on those living with the condition.

2.2. The committee considered the following conditions, some of which present from infancy and in the worst-case scenario are progressive and potentially fatal with diffuse muscle weakness associated with cardiomyopathy and respiratory insufficiency. The conditions are:

- Myopathy, Myofibrillar 1, OMIM #601419
- Myopathy, Myofibrillar 2, OMIM #608810
- Myopathy, Myofibrillar 3, OMIM # 609200
- Myopathy. Myofibrillar 4, OMIM #609452
- Myopathy, Myofibrillar 5, OMIM #609524
- Myopathy, Myofibrillar 6, OMIM #612954
- Myopathy, Myofibrillar 7, OMIM #617114

- Myopathy, Myofibrillar 8, OMIM #617258
- Myopathy, Myofibrillar 10, OMIM #619040
- Myopathy, Myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related, OMIM #613869
- Myopathy, spheroid body, OMIM #182920 (due to mutations in the same gene as myopathy, myofibrillar 3 and with similar phenotype).

2.3. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that for each of these conditions, there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk that a person with such an abnormality will, given each of the conditions' worst symptoms, have or develop a serious physical disability, a serious illness, or any other serious medical condition.

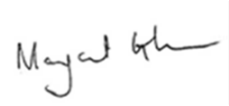
2.4. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act. The committee agreed to authorise testing for:

- Myopathy, Myofibrillar 1, OMIM #601419
- Myopathy, Myofibrillar 2, OMIM #608810
- Myopathy, Myofibrillar 3, OMIM #609200
- Myopathy. Myofibrillar 4, OMIM #609452
- Myopathy, Myofibrillar 5, OMIM #609524
- Myopathy, Myofibrillar 6, OMIM #612954
- Myopathy, Myofibrillar 7, OMIM #617114
- Myopathy, Myofibrillar 8, OMIM #617258
- Myopathy, Myofibrillar 9 with early respiratory failure, OMIM #603689
- Myopathy, Myofibrillar 10, OMIM #619040
- Myopathy, Myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related, OMIM #613869
- Myopathy, spheroid body, OMIM #182920 (due to mutations in the same gene as myopathy, myofibrillar 3 and with similar phenotype).

3. Chair's signature

3.1. I confirm this is a true and accurate record of the meeting,

Signature



Name

Margaret Gilmore

Date

17 March 2021