Statutory Approvals Committee – minutes

Centre 0044 (The Centre for Reproductive and Genetic Health)

Pre-implantation Genetic Diagnosis (PGD) application for Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930

Thursday, 26 March 2020

HFEA Teleconference Meeting

Committee members	Margaret Gilmore (Chair) Emma Cave Anne Lampe Tony Rutherford Ruth Wilde	
Members of the Executive	Moya Berry Catherine Burwood	Committee Officer Licensing Manager
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Gerard Hanratty	Brown Jacobson- LLP

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:

- 9th edition of the HFEA Code of Practice.
- Standard licensing and approvals pack for committee members.

The following papers were considered by the committee:

- Executive Summary
- PGD Application Form
- Redacted Peer Review
- Genetic Alliance Statement
- 2014-01-30 Statutory Approvals Committee Minutes – PGD application for Congenital Myasthenic Syndrome - type 5

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 Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930, 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 Genetic Alliance UK statement provided a perspective on the impact of the condition on patients, their families and carers.

1.5. 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.

1.6. 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'.

1.7. The committee noted Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930, is inherited in an autosomal recessive manner which means there is 25% chance of having an affected child in each pregnancy if each parent has a relevant mutation. Occasionally dominant inheritance is observed in a family, in which case there is a 50% chance of inheritance if either parent has a relevant mutation.

1.8. The committee noted the penetrance of the condition is close to 100%.

1.9. Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930 is characterised by respiratory insufficiency with sudden apnoea and cyanosis, problems with sucking, chewing, and swallowing leading to feeding difficulties and choking spells, disabling fatigable weakness involving ocular, facial, bulbar, respiratory and limb muscles. The onset of symptoms can occur from birth or early childhood. Those patients who do survive into adulthood, may require ongoing ventilatory support, tube feeding and ambulatory aids.

1.10. There is no cure for the condition and in some patients, response to drug treatment can be partial and become less effective with time, with some drugs also causing severe side effects.

1.11. The committee noted the executive's request to consider Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930, for inclusion on the list of conditions approved for PGD. The committee agreed to consider the application on this basis.

1.12. The committee noted the request of the executive to consider a number of additional conditions for inclusion on the list of conditions approved for PGD. The peer reviewer considers there is reasonable evidence that the following conditions have a phenotype similar in severity to that of CMS1B.The conditions are:

- Myasthenic syndrome, congenital, 1A, Slow-channel, OMIM #601462
- Myasthenic syndrome, congenital, 2A, Slow-channel, OMIM #616313
- Myasthenic syndrome, congenital, 3B, Fast-channel, OMIM #616322
- Myasthenic syndrome, congenital, 4A, Slow-channel, OMIM #605809
- Myasthenic syndrome, congenital, 4B, Fast-channel, OMIM #616324
- Myasthenic syndrome, congenital, 4C, OMIM #608931
- Myasthenic syndrome, congenital, 6, OMIM #254210
- Myasthenic syndrome, congenital, 7, OMIM #616040
- Myasthenic syndrome, congenital, 8, OMIM #615120
- Myasthenic syndrome, congenital, 9, OMIM #616325
- Myasthenic syndrome, congenital, 10, OMIM #254300
- Myasthenic syndrome, congenital, 11, OMIM #616326
- Myasthenia syndrome, congenital, 12, OMIM #610542
- Myasthenic syndrome, congenital, 13, OMIM #614750
- Myasthenic syndrome, congenital, 14, OMIM #616228
- Myasthenic syndrome, congenital, 16, OMIM #614198
- Myasthenic syndrome, congenital, 19, OMIM #616720
- Myasthenic syndrome, congenital, 20, OMIM #617143
- Myasthenic syndrome, congenital, 21, OMIM #617239

- Myasthenic syndrome, congenital, 22, OMIM #616224
- Myasthenic syndrome, congenital, 24, OMIM #618198
- Myasthenic syndrome, congenital, 25, OMM #618323

1.13. Most of the conditions listed above are inherited in an autosomal recessive manner which means there is 25% chance of having an affected child in each pregnancy if each parent has a relevant mutation. CMS1A, slow-channel, OMIM #601462; CMS2A, slow-channel, OMIM #616313; and CMS7, OMIM #616040, follow autosomal dominant inheritance and the risk of inheritance is 50% in each pregnancy if either parent carries a relevant mutation. CMS4A Slow-channel, OMIM #605809 can exhibit either autosomal recessive or dominant inheritance, thus the risk may be either of those described above. The penetrance of these condition types is generally close to 100%.

1.14. Symptoms of all these condition types include respiratory insufficiency, stridor, problems with sucking, chewing and swallowing leading to feeding difficulties and choking spells, and progressive disabling weakness. The age of onset of symptoms for all the condition types listed, is from birth to later childhood.

1.15. The committee noted the executive's recommendation, based on the evidence of the peer reviewer, not to include the following conditions on the list for which PGD can be applied, as gene assignments are this far based on a very small number of families affected with the conditions. These conditions are Myasthenic Syndrome, Congenital 2C, OMIM #616314, Myasthenic Syndrome, Congenital 3A slow-channel, OMIM #616321, Myasthenic Syndrome, Congenital 3C, OMIM #616323, Myasthenic Syndrome, Congenital 15, OMIM#616227, Myasthenic Syndrome, Congenital 17, OMIM #616304, Myasthenic Syndrome, Congenital 18, OMIM #616330, Myasthenic Syndrome, Congenital 23, OMIM #618197.

2. Decision

2.1. The committee considered that, in the worst-case scenario Myasthenic Syndrome, Congenital, 1B, Fast-channel (CMS1B), OMIM #608930, is a rare, serious and progressive condition resulting in severe muscle weakness which can be life-limiting. Symptoms may present at, or soon after birth, resulting in failure to thrive and possible early death. There is no cure for the condition. Those who do survive into adulthood may be severely debilitated, requiring a lifetime of medical care. The committee noted the serious implications and possible impact on the quality of life for those affected with the condition.

2.2. The committee considered in the worst-case scenario the following conditions present similarly to CMS1B or with physical and sometimes intellectual disability, and have similar treatment options and possible poor prognosis:

- Myasthenic syndrome, congenital, 1A, Slow-channel, OMIM #601462
- Myasthenic syndrome, congenital, 2A, Slow-channel, OMIM #616313
- Myasthenic syndrome, congenital, 3B, Fast-channel, OMIM #616322
- Myasthenic syndrome, congenital, 4A, Slow-channel, OMIM #605809
- Myasthenic syndrome, congenital, 4B, Fast-channel, OMIM #616324
- Myasthenic syndrome, congenital, 4C, OMIM #608931
- Myasthenic syndrome, congenital, 6, OMIM #254210
- Myasthenic syndrome, congenital, 7, OMIM #616040
- Myasthenic syndrome, congenital, 8, OMIM #615120
- Myasthenic syndrome, congenital, 9, OMIM #616325
- Myasthenic syndrome, congenital, 10, OMIM #254300
- Myasthenic syndrome, congenital, 11, OMIM #616326
- Myasthenia syndrome, congenital, 12, OMIM #610542
- Myasthenic syndrome, congenital, 13, OMIM #614750
- Myasthenic syndrome, congenital, 14, OMIM #616228
- Myasthenic syndrome, congenital, 16, OMIM #614198

- Myasthenic syndrome, congenital, 19, OMIM #616720
- Myasthenic syndrome, congenital, 20, OMIM #617143
- Myasthenic syndrome, congenital, 21, OMIM #617239
- Myasthenic syndrome, congenital, 22, OMIM #616224
- Myasthenic syndrome, congenital, 24, OMIM #618198
- Myasthenic syndrome, congenital, 25, OMM #618323

2.3. With regards to condition types Myasthenic Syndrome, Congenital 2C, OMIM #616314, Myasthenic Syndrome, Congenital 3A slow-channel, OMIM #616321, Myasthenic Syndrome, Congenital 3C, OMIM #616323, Myasthenic Syndrome, Congenital 15, OMIM#616227, Myasthenic Syndrome, Congenital 17, OMIM #616304, Myasthenic Syndrome, Congenital 18, OMIM #616330, Myasthenic Syndrome, Congenital 23, OMIM #618197, the committee decided it did not have sufficient information to consider these as part of this specific application but did not rule out considering them for PGD, should they be raised in future applications.

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

2.5. 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:

- Myasthenic syndrome, congenital, 1A, Slow-channel, OMIM #601462
- Myasthenic syndrome, congenital, 1B, Fast- channel, OMIM #608930
- Myasthenic syndrome, congenital, 2A, Slow-channel, OMIM #616313
- Myasthenic syndrome, congenital, 3B, Fast-channel, OMIM #616322
- Myasthenic syndrome, congenital, 4A, Slow-channel, OMIM #605809
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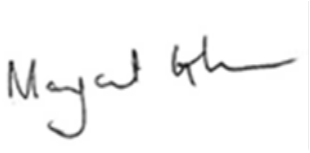
- Myasthenic syndrome, congenital, 25, OMM #618323

3. Chairs signature

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

Signature



Name
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Date
23 April 2020