Statutory Approvals Committee – minutes

Centre 0102 (Guys Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010

Thursday, 31 August 2017

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Anne Lampe Tony Rutherford Ruth Wilde Bobbie Farsides	
Members of the Executive	Dee Knoyle	Committee Secretary
External adviser	Dr Jenny Carmichael	
Legal Adviser	Sarah Ellson	Fieldfisher LLP
Observers		

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:

- 8th 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
- Peer reviewer's additional comments by email
- Genetic Alliance opinion
- Minutes of the Statutory Approvals Committee, approving the following as conditions for which PGD can be performed:
  - 17 December 2015 – Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFS6 gene
  - 24 September 2015 - Mitochondrial Complex 1 Deficiency caused by mutations in the ACAD9 gene
  - 29 June 2017 – Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFS4 gene
  - 27 July 2017 - Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFB3 gene

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Jenny Carmichael, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application. The Genetic Alliance opinion was given for Mitochondrial Complex 1 Deficiency in general. However, the Executive consider the opinion to be valid when considering this application, because it states that 'Clinical presentation of complex 1 deficiency is highly variable and it is not generally possible to predict the range or severity of symptoms which will be experienced by an affected individual from their genotype.'

1.3. 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.

1.4. The committee noted that the description in the application for Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010 is consistent with the Peer Review.

HFEA PGD List of Approved Conditions

1.5. The committee noted that Mitochondrial Complex 1 Deficiency caused by mutations in NDUFS6, ACAD9 and NDUFS4 has already been approved for PGD by the HFEA.

1.6. The committee noted that the autosomal recessive causes considered here are usually indistinguishable clinically from each other and the genes already licensed for PGD which include NDUFS4, NDUFS6, ACAD9 and NDUFB3

1.7. The committee noted the causative mutations for Autosomal Recessive Mitochondrial Complex 1 Deficiency, OMIM #252010 in Table 1. This information was derived from the OMIM website.

Table 1: Genetic causes of Mitochondrial complex 1 deficiency, OMIM #252010

Gene/Locus	Gene/Locus OMIM number	Gene location/inheritance pattern
NDUFS2	602985	Autosomal recessive
NDUFB3[A]	603839	Autosomal recessive
NDUFS1	157655	Autosomal recessive
NDUFAF3	612911	Autosomal recessive
TIMMDC1	615534	Autosomal recessive
NDUFS6[A]	603848	Autosomal recessive
NDUFS4[A]	602694	Autosomal recessive
NDUFAF2	609653	Autosomal recessive
NDUFAF4	611776	Autosomal recessive
NDUFB9	601445	Autosomal recessive
NDUFS3	603846	Autosomal recessive
NDUFV1	161015	Autosomal recessive
TMEM126B	615533	Autosomal recessive
FOXRED1	613622	Autosomal recessive
NUBPL	613621	Autosomal recessive
NDUFAF1	606934	Autosomal recessive
NDUFV2	600532	Autosomal recessive
NDUFA11	612638	Autosomal recessive
NDUFAF5	612360	Autosomal recessive
NDUFS7	601825	Autosomal recessive
NDUFS8	602141	Autosomal recessive
NDUFA10	603835	Autosomal recessive
B17.2L	609653	Autosomal recessive
HRPAP20	611776	Autosomal recessive
C20ORF7	612360	Autosomal recessive
ACAD9[A]	611103	Autosomal recessive
MTFMT	611766	Autosomal recessive

[A] Conditions already approved

1.8. The committee noted that the OMIM website for Mitochondrial Complex 1 Deficiency, #252010, also states that 'There are no obvious genotype-phenotype correlations, and inference of the underlying basis from the clinical or biochemical presentation is difficult, if not impossible.' The application similarly states that the Autosomal Recessive types of Mitochondrial Complex 1 Deficiency applied for are 'clinically indistinguishable. Some genes are more likely to cause cardiomyopathy or seizures than others, but the neurological features are severe in all types, as is severely reduced life expectancy.'

1.9. 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'.

1.10. The committee noted that the condition is inherited in an autosomal recessive pattern and there is a 25% chance of an embryo being affected with the condition if each parent has a relevant mutation.

1.11. The committee noted that Autosomal Recessive Complex 1 Deficiency typically presents between the ages of three and twelve months. Around 50% of affected individuals die by three years of age, often from respiratory or cardiac failure. The condition is fully penetrant.

1.12. The committee noted that neurological features include hypotonia (floppiness), spasticity (stiffness with brisk reflexes), movement disorders such as chorea (uncontrolled movements), ataxia (poor coordination and unsteadiness), and peripheral neuropathy (abnormal sensation, pain or numbness in hands and feet). Other organs such as the heart, the kidneys, the liver and the peripheral muscles are also often involved and can present with hypertrophic cardiomyopathy (where the heart muscle becomes thickened and works less efficiently and can cause irregular heartbeat), muscle weakness, kidney impairment, liver impairment and anaemia. Life expectancy is drastically reduced.

1.13. There is currently no curative treatment for Mitochondrial Complex 1 Deficiency.

1.14. The committee noted the inspectorate's request to consider whether Autosomal Recessive Mitochondrial Complex I Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010 should be approved for inclusion on the PGD List. The committee agreed to consider the application on this basis.

1.15. The committee also noted the inspectorate's request to consider the application and how the condition is to be named on the HFEA website if the application is approved. The inspectorate also recommended that, if approved, the committee considers removing previously approved autosomal recessive forms of Mitochondrial Complex 1 Deficiency from the PGD List as these would be included under Autosomal Recessive Complex 1 Deficiency, OMIM #252010. If approved, all centres licensed to conduct PGD will be able to perform PGD for the condition.

2. Decision

2.1. The committee considered that Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010 is serious, given the significant risk of heart, kidneys, liver and brain impairment and breathing difficulties in early infancy.

2.2. The committee had regard to its explanatory note and noted that on the basis of the information presented, given the condition's worst symptoms, it was satisfied that there is both a particular and a significant risk that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition. The committee was therefore satisfied that the condition of Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010 does meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act.

2.3. The committee agreed to authorise the testing for Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome), OMIM #252010 and this is how the condition should be named.

2.4. The committee also agreed to authorise the removal of previously approved autosomal recessive forms of Mitochondrial Complex 1 Deficiency from the PGD List as they would be included under Autosomal Recessive Complex 1 Deficiency, OMIM #252010:

Remove from PGD List:

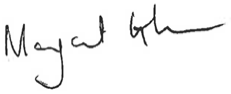
- Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFS6 gene
- Mitochondrial Complex 1 Deficiency caused by mutations in the ACAD9 gene
- Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFS4 gene
- Mitochondrial Complex 1 Deficiency caused by mutations in the NDUFB3 gene

2.5. The committee noted that this application applies to the autosomal recessive genes currently listed under phenotypic description 252010. There are 21 genes listed under this phenotypic description, in addition to those in the application. The committee noted that NDUFB11 (OMIM 300403) and NDUFA1 (300078) are also included and they are X-linked. This application only applies to autosomal recessive disorders and therefore the committee agreed that NDUFB11 (OMIM 300403) and NDUFA1 (300078) should not be included on the PGD List under OMIM #252010.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

2 October 2017