Statutory Approvals Committee - minutes

Centre 0102 (Guys Hospital)

Preimplantation Genetic Diagnosis (PGD) application for Charcot-Marie Tooth Disease Type 4J, OMIM #611228

Date:	25 March 2021
Venue:	Microsoft Teams Meeting
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde
Specialist Adviser:	Jenny Carmichael
Legal Adviser:	Tom Rider - FieldFisher
Members of the Executive:	Moya Berry - Committee officer Catherine Burwood - Licensing Manager
Observers:	Jason Kasraie - Authority Member (Induction)
Apologies:	No apologies were received for the meeting
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 Licensing and Approvals Pack

The following papers were considered by the committee:

- Executive Summary
- PGD Application form
- Redacted Peer review
- Genetic Alliance UK statement
- Relevant academic papers provided by applicant centre:
  - Nicolson et al 2011
  - Lenk et al 2019
- 2020-12-17, SAC Minutes, PGD for Congenital hypomyelinating neuropathy type 3, OMIM #618186
- 2018-10-25, SAC Minutes, PGD for Charcot Marie Tooth type 2P (CMT2P), OMIM
- #614436
- 2018-05-24, SAC Minutes, PGD for Charcot Marie Tooth type 1B (CMT1B), OMIM
- #118200
- 2012-07-19, LC minutes, PGD for Charcot Marie Tooth Disease Type 1A, OMIM #118220
- 2012-01-26, LC Minutes, PGD for Charcot Marie Tooth Disease Type 2, OMIM #609260

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 description in the PGD application for Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228 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 that Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228, is inherited in an autosomal recessive manner, which means there is a 25% chance of an embryo being affected by the condition in each pregnancy if each parent has a relevant mutation.

1.8. The committee noted that the penetrance of the condition is likely to be very high, although the severity of the symptoms can be variable.

1.9. Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228, is a progressive disorder which often begins in infancy or childhood. Symptoms of the condition can affect the peripheral nervous system causing weakness in the arms and legs, leading to difficulty with everyday

activities including walking. As the condition progresses, patients can have more severe symptoms causing significant disability and may require the use of a wheelchair and be unable to use and feel some or all of their limbs. There is growing evidence that there can be central nervous system involvement and changes in the brain leading to cognitive impairment, limited communication skills and global developmental delay. As the condition progresses, patients may be unable to care for themselves and may struggle to communicate effectively. Other symptoms include scoliosis, hand and foot abnormalities, and difficulties in controlling face, tongue, and eye movements.

1.10. There is no cure for this condition. Treatment is based on treating symptoms and managing the progression of the disease.

1.11. The committee noted the executive's request to consider Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228, 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 recommendation of the peer reviewer to consider a further condition for inclusion on the list for which PGD can be applied and agreed to consider the application on this basis. The condition Hypertrophic Neuropathy of Dejerine-Sottas (HNDS), OMIM #145900, can result from mutations in one of four genes and can be inherited in an autosomal dominant or recessive manner, meaning there may be a 25% or 50% possibility of inheriting the condition, depending on the active gene mutations present in the mother and father.

1.13. Hypertrophic Neuropathy of Dejerine-Sottas (HNDS), OMIM #145900 is a demyelinating peripheral neuropathy, with onset in infancy or early childhood. The symptoms usually begin in the feet and legs and with progression of the disease leads also to upper limb involvement. Affected individuals have delayed motor development due to severe distal motor and sensory impairment, resulting in difficulties in walking or later loss of walking ability. Some patients have generalised hypotonia (decreased muscle tone) from infancy. Other symptoms can include involuntary, uncontrollable eye movements; hand, foot and spinal abnormalities; and peripheral nervous system abnormalities leading to delayed motor development, hypotonia, distal limb muscle weakness and atrophy, 'foot drop', distal sensory impairment (numbness, pins and needles, tingling or pain), sensory ataxia (lack of muscle movement coordination), hyporeflexia and areflexia (below normal or absent reflexes).

1.14. The committee also noted the peer reviewer's second request to revise the PGD condition list to change Charcot Marie Tooth Disease Type 2, OMIM #609260, to Charcot Marie Tooth Disease Type 2A2A (CMT2A2A), OMIM #609260. This will ensure the list of conditions approved for PGD is accurate and reflects the currently used nomenclature in OMIM.

1.15. The committee finally noted the peer reviewer's third recommendation to include Charcot Marie Tooth Disease Type 2A2B, OMIM #617087, on the list of conditions for which PGD can be applied. This condition is caused by variants in the same gene that results in the condition Charcot Marie Tooth Disease Type 2A2A, OMIM #609260, which has already been approved for PGD. Charcot Marie Tooth Disease Type 2A2B, OMIM #617087, is inherited in an autosomal recessive manner, meaning the risk of inheriting the condition is 25% in each pregnancy if each parent carries a relevant mutation. The peer reviewer considers it is justifiable to include Charcot Marie Tooth Disease Type 2A2B, OMIM #617087 on the PGD approved condition list because it is earlier in onset than Charcot Marie Tooth Disease Type 2A2A, OMIM #609260, and more severe in its phenotype.

2. Decision

2.1. The committee considered that, in the worst-case scenario, Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228, is a very severe and rapidly progressive neuropathy that can present from birth or in infancy. Those affected may be unable to sit or walk and have profoundly impaired psychomotor development leading to wheelchair use. Due to brain changes, the condition can result in delayed motor development leaving those affected unable to care for themselves and without the ability to communicate effectively. There is no cure for the condition and the committee considered the potential devastating impact on the quality of life of those affected with the condition.

2.2. The committee also considered that, the condition Hypertrophic Neuropathy of Dejerine-Sottas (HNDS), OMIM #145900, is, in the worst-case scenario, a serious condition presenting from infancy or early child with delayed motor development and severe muscle weakness resulting in difficulties in walking or the loss of the ability to walk.

2.3. The committee also considered the condition Charcot Marie Tooth Disease Type 2A2B, OMIM #617087, which is a severe degenerative condition. In the worst-case scenario it presents in early infancy with progressive muscle weakness leading to wheelchair use. Patients with the condition can also be affected with vision loss.

2.4. With regard to Charcot Marie Tooth Disease Type 2, OMIM #609260, the committee agreed with the peer reviewer, that the name of the condition should be changed to Charcot Marie Tooth Disease Type 2A2A (CMT2A2A), OMIM #609260, to ensure the list of conditions approved for PGD is accurate and reflects the currently used nomenclature in OMIM.

2.5. 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.

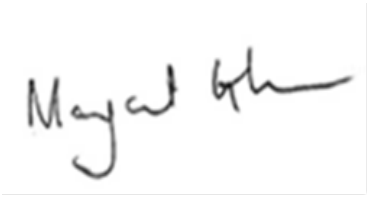
2.6. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act. The committee agreed to authorise testing for:

- Charcot-Marie Tooth Disease, Type 4J (CMT4J), OMIM #611228
- Hypertrophic Neuropathy of Dejerine-Sottas (HNDS), OMIM #145900
- Charcot Marie Tooth Disease Type 2A2B, OMIM #617087

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

16 April 2021