Statutory Approvals Committee - minutes

Centre 0102 (Guys Hospital)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) - application for Epilepsy, familial focal, with variable foci 1 (FFEVF), OMIM #604364 and for Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE)

Date:	26 August 2021
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde Tim Child
Specialist Adviser:	Alan Fryer
Legal Adviser:	Tom Rider - FieldFisher LLP
Members of the Executive:	Moya Berry - Committee Officer Catherine Burwood - Licensing Manager
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
- PGT-M Application Form
- Redacted Peer Review
- Genetic Alliance (UK) Statement
- Supporting Academic Paper - Ververi et al, 2021 (currently unpublished)

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Dr Alan Fryer who noted that the conditions Epilepsy, familial focal, with variable foci 1 (FFEVF), OMIM #604364 and Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), jointly presented within the application, were materially different. The committee noted that Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) is a newly characterised condition, not yet listed on the OMIM website, so has not been assigned a phenotypic OMIM number.

1.2. The committee proceeded to review this application in respect of Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) as it was understood that a patient was awaiting a decision in relation to that condition.

1.3. The committee noted that the description in the PGT-M application for Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), was simply reiterated in the peer review as the peer reviewer did not have access to any publications on the condition as the condition is currently unpublished in the medical and scientific literature. The peer reviewer asked if it would be possible for the applicants to supply the HFEA with a pre-publication copy of the paper describing the condition. The applying centre provided a draft copy of a paper they have submitted for publication.

1.4. The committee noted that the condition being applied for is not on the list of approved PGT-M conditions.

1.5. The committee noted that the Genetic Alliance (UK) statement provided a perspective on the impact of similar conditions 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 PGT-M. The committee was also satisfied that the centre has experience of carrying out PGT-M and that generic patient information about its PGT-M 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, as described, Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) 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.

1.9. The committee noted the penetrance of the condition is 100%.

1.10. The committee noted that those affected by this condition are reported to have refractory epilepsy and severe developmental delay. Diffuse structural brain malformation, including polymicrogyria, are also seen. Seizure onset occurs below one year of age.

1.11. There is no treatment available that alters the natural history of the condition and all individuals affected in the pre-publication report had died in childhood.

1.12. The committee noted that Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) is a new condition, with no OMIM number, and has not yet been published in the peer-reviewed medical and scientific literature.

1.13. The committee were advised by its specialist adviser that the clinical evidence and genetic and scientific data presented to support this application comes solely from the supplied unpublished paper entitled '*Germline homozygous missense DEPDC5 variant causes fatal refractory early-onset epilepsy, macrocephaly and bilateral polymicrogyria'* by Ververi et al. The adviser commented that there were multiple strands of evidence supplied for the pathogenicity of the described homozygous mutation in the paper. However the committee noted that the paper has not yet been peer reviewed and accepted for publication. The peer review system is used to validate academic work, which is of particular importance in the delineation of newly emerging genetic conditions.

1.14. The committee noted the executive's request to consider Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), for inclusion on the list of conditions approved for PGT-M. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee received advice from the specialist adviser who stated that the conditions Epilepsy, familial focal, with variable foci 1 (FFEVF), OMIM #604364 and Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), referred to in the application were materially different.

2.2. The committee noted there was a patient waiting for treatment in relation to Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) and as such decided only to review this condition at this point in time.

2.3. The committee noted from the PGT-M application for Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), that this is a new condition, with no OMIM number.

2.4. In respect of the application for Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE), the committee expressed concern that, as the paper had not yet been peer reviewed or presented for publication, it required the evidence of rigorous scientific peer review to be confident that this particular missense mutation in the DEPDC5

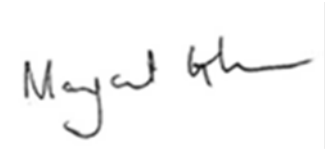
gene is the cause of the described phenotype i.e. Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE). The committee therefore considered that as this condition had not yet been reported in literature, with the one existing paper not yet peer reviewed and accepted for publication, it did not have sufficient evidence to make an informed decision at this current time.

2.5. The committee therefore concluded that consideration of this application be adjourned. Once the paper '*Germline homozygous missense DEPDC5 variant causes fatal refractory early-onset epilepsy, macrocephaly and bilateral polymicrogyria'* has been accepted for publication the committee agreed that both the conditions Epilepsy, familial focal, with variable foci 1 (FFEVF), OMIM #604364 and for Autosomal Recessive DEPDC5-related Developmental and Epileptic Encephalopathy (DEPDC5-DEE) could be considered in the one application, upon provision of the final version of the paper as accepted for publication.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

21 September 2021