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Committee Members
EMA

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Contact

Subject
ERDC statement on RPE65-associated disease terminology

Dear EMA Committee Members,

The European Retinal Disease Consortium (ERDC) was initiated in 2008 by a few research groups from Europe as we saw the need to join our efforts in genetics of rare inherited retinal diseases (IRDs). The ERDC has grown gradually over the years and currently consists of 17 research groups from 11 countries, 9 of which are European (see attachment). In the beginning we mostly shared homozygosity mapping data to identify novel IRD-associated genes under the premise that, both in consanguineous and non-consanguineous families, large homozygous regions often contain the causal recessive gene defect. More recently we share whole exome sequencing (WES) data to identify multiple families with mutations in the same gene. In addition, we collaborated to set-up and use a cost-effective NGS-based sequencing procedure to test 108 non-syndromic IRD-associated genes, which enabled us to analyze 4,000 IRD probands in the last 3 years. Collectively, we have ascertained between 15,000 and 20,000 IRD families. In the last 9 years we jointly published at least 125 peer-reviewed papers, among which many in high impact journals.

Many genes underlying IRDs can be associated with various – partially overlapping – phenotypes. This is particularly the case for genes that can be mutated in the phenotypic spectrum between Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). Persons with autosomal recessive *RPE65* variants can be labelled with a range of clinical diagnoses such as LCA, severe early childhood onset retinal dystrophy (SECORD), early onset retinal dystrophy (EORD), early childhood-onset retinitis pigmentosa (ECRP), RP and others.

ERDC inherited retinal disease scientists and clinicians believe that the most optimal diagnosis for these patients should be “inherited retinal disease caused by biallelic

mutations in the *RPE65* gene" or "autosomal recessive RPE65 deficiency" for the following reasons:

1. With the advances in molecular diagnostics and the accompanying growth in pertinent literature have illustrated a spectrum of inherited retinal disease due to mutations in the *RPE65* gene. Mutations in the *RPE65* gene can lead to several phenotypic diagnoses including RP type 20 (RP20), EORD, early onset severe retinal dystrophy (EOSRD), SECORD, and other similar clinical diagnoses, as well as LCA2.
2. There appears to be a large overlap of clinical features among the different clinical diagnoses. It is now known that these diseases can have the same pathophysiology: in the case of LCA2 and RP20, a reduced or absent level of the isomerohydrolase activity, encoded by *RPE65* is the etiology.
3. The clinical diagnoses of LCA and RP account for the vast majority of individuals with *RPE65*-mediated IRD. Alternate terminologies discussed, such as EORD and SECORD due to *RPE65* gene mutations, are typically used instead of (and not in addition to) clinical descriptors of LCA and RP; as such, they are not expected to significantly increase the number of people that would be candidates for AAV2-hRPE65v2 gene therapy.

My team, in particular dr. M.I. Khan, has been analyzing the *RPE65* gene for variants in ~4,000 IRD cases using molecular inversion probes-based sequencing. In addition, through the work of dr. G. Astuti, a *RPE65* variant registry was completed (Astuti et al. *Eur. J. Hum. Genet.* **24**:1071-1079, 2016) which contains all published *RPE65* variants and cases, including their phenotypes. From the results of these studies, and based on my expertise of the last decades, I can say without any doubt that a genetic diagnosis, such as biallelic *RPE65*-mutation associated retinal dystrophy, for patients with biallelic *RPE65* gene mutations, is the most appropriate and accurate diagnostic label.

In addition, the use of a genetic diagnosis (autosomal recessive *RPE65*-deficiency IRD) would not broaden the eligible population beyond the Orphan Designation, defined as a condition that affects no more than 5 in 10,000 people in the European Union, equivalent to fewer than 250,000 people.

On behalf of all members of the European Retinal Disease Consortium,

Yours sincerely,

Prof. dr. Frans P.M. Cremers
Team leader Blindness Genetics &
Director of the Foundation Fighting Blindness PPA Splice Modulation to Treat Inherited Retinal Diseases

cc. Dr. Susanne Roosing, Coordinator ERDC
cc. All ERDC members listed in attachment 1 via e-mail

Attachment 1: ERDC consortium members