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Leber Congenital Amaurosis Associated with Mutations in *CEP290*, Clinical Phenotype, and Natural History in Preparation for Trials of Novel Therapies

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Purpose: To investigate and describe in detail the demographics, functional and anatomic characteristics, and clinical course of Leber congenital amaurosis (LCA) associated with mutations in the *CEP290* gene (LCA-*CEP290*) in a large cohort of adults and children.

Design: Retrospective case series.

Participants: Patients with mutations in *CEP290* identified at a single UK referral center.

Methods: Review of case notes and results of retinal imaging (color fundus photography, fundus autofluorescence [FAF] imaging, OCT), electrophysiologic assessment, and molecular genetic testing.

Main Outcome Measures: Molecular genetic testing, clinical findings including visual acuity and retinal imaging, and electrophysiologic assessment.

Results: Forty patients with LCA-*CEP290* were identified. The deep intronic mutation c.2991+1655 A>G was the most common disease-causing variant (23/40 patients) identified in the compound heterozygous state in 20 patients (50%) and homozygous in 2 patients (5%). Visual acuity (VA) varied from 6/9 to no perception of light, and only 2 of 12 patients with longitudinal VA data showed deterioration in VA in their better-seeing eye over time. A normal fundus was found at diagnosis in younger patients (mean age, 1.9 years), with older patients showing white flecks (mean age, 5.9 years) or pigmentary retinopathy (mean age, 21.7 years). Eleven of 12 patients (92%) with OCT imaging had preservation of foveal architecture. Ten of 12 patients (83%) with FAF imaging had a perifoveal hyperautofluorescent ring. Having 2 nonsense *CEP290* mutations was associated with worse final VA and the presence of nonocular features.

Conclusions: Detailed analysis of the clinical phenotype of LCA-*CEP290* in a large cohort confirms that there is a window of opportunity in childhood for therapeutic intervention based on relative structural preservation in the central cone-rich retina in a significant proportion of patients, with the majority harboring the deep intronic variant potentially tractable to several planned gene editing approaches. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Leber congenital amaurosis (LCA) was first described by Theodore Leber in 1869 and refers to a heterogeneous group of retinal disorders with early-onset vision loss, nystagmus, and an extinguished electroretinogram (ERG).[1] Leber later described a separate group of milder disease phenotypes, with some preservation of the ERG responses (now referred to as "early-onset severe retinal dystrophy" [EOSRD] or "severe early childhood onset retinal dystrophy").[2,3] There is considerable clinical and genetic overlap between LCA and EOSRD/severe early childhood onset retinal dystrophy. Leber congenital amaurosis and EOSRD account for a significant proportion of blindness in children worldwide,[4–6] with an annual estimated incidence of 1 in 30 000 newborns.[7] In the United Kingdom, 14% of children with newly diagnosed blindness have LCA/EOSRD.[8]

Twenty-five causative genes have been identified to date, accounting for 70% to 80% of all LCA/EOSRD cases. *CEP290* is one of the most common causes, accounting for 15% to 20% of all known cases.[9] The intronic variant c.2991+1655A>G is the most common pathogenic mutation, especially in Europe and the United States,[7] identified in 77% of all patients in 1 cohort with *CEP290*-related disease.[10]

CEP290 encodes a protein that localizes to the transition zone of the connecting cilium, including the cilia of photoreceptors[11]; Leber congenital amaurosis-*CEP290* is one of an increasing number of retinal dystrophies that can be classified as a ciliopathy.[9,12] In addition to isolated LCA/EOSRD, *CEP290* mutations also have been identified in Bardet–Biedl syndrome, Senior–Loken syndrome, Joubert

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Table 1. Molecular Findings in the Study Leber Congenital Amaurosis *CEP290* Cohort

Patient No.	GC No.	Mutation 1	Effect	Grantham Score†	Mutation 2	Effect	Grantham score†
1	17585	c.2991+1655A>G	p.(Cys998*)	n/a	c.2980G>A	p.(Glu994Lys)	56 (probably tolerated, but this missense mutation results in a change of charge from negative to positive that may render the CEP290 protein functionless)
2	18665	c.2991+1655A>G	p.(Cys998*)	n/a	unknown	unknown	n/a
3	17243	c.2991+1655A>G	p.(Cys998*)	n/a	c.1163T>A	p.(Leu388*)	n/a
4	14293	c.2991+1655A>G	p.(Cys998*)	n/a	c.2991+1655A>G	p.(Cys998*)	n/a
5a	1874	c.4393C>T	p.(Arg1465*)	n/a	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
5b	1874	c.4393C>T	p.(Arg1465*)	n/a	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
5c	1874	c.4393C>T	p.(Arg1465*)	n/a	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
5d	1874	c.4393C>T	p.(Arg1465*)	n/a	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
5e	1874	c.4393C>T	p.(Arg1465*)	n/a	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
6	16827	c.2991+1655A>G	p.(Cys998*)	n/a	c.1984C>T	p.(Gln662*)	n/a
7	19073	c.4723A>T	p.(Lys1575*)	n/a	c.712G>T	p.(Glu238*)	n/a
8	19328	c.2991+1655A>G	p.(Cys998*)	n/a	unknown	unknown	n/a
9	17668	c.2991+1655A>G	p.(Cys998*)	n/a	c.6277delG	p.(Val2093fs)	n/a
10	18259	c.4723A>T	p.(Lys1575*)	n/a	c.4966G>T	p.(Glu1656*)	n/a
11	18410	c.2991+1655A>G	p.(Cys998*)	n/a	c.3175dupA	p.(Ile1059Asnfs*11)	149‡ (probably not tolerated)
12	16596	c.2991+1655A>G	p.(Cys998*)	n/a	c.2991+1655A>G	p.(Cys998*)	n/a
13	17341	c.4723A>T	p.(Lys1575*)	n/a	c.6079delG	p.(Glu2027Lysfs*5)	56‡ (probably tolerated)
14	19709	c.2991+1655A>G	p.(Cys998*)	n/a	c.1781T>A	p.(Leu594*)	n/a
15	17947	c.2991+1655A>G	p.(Cys998*)	n/a	c.384_387delTAGA	p.(Asp128Glufs*34)	45‡ (probably tolerated)
16	19085	c.2991+1655A>G	p.(Cys998*)	n/a	unknown	unknown	n/a
17	18805	c.2991+1655A>G	p.(Cys998*)	n/a	c.1066-1G>A	splice	n/a
18	19043	c.2991+1655A>G	p.(Cys998*)	n/a	c.4966G>T	p.(Glu1656*)	n/a
19	18444	c.2991+1655A>G	p.(Cys998*)	n/a	c.4723A>T	p.(Lys1575*)	n/a
20	18269	c.5668G>T	p.(Gly1890*)	n/a	c.5668G>T	p.(Gly1890*)	n/a
21	23097	c.1681C>T	p.(Gln561*)	n/a	c.7027delG	p.(Val2343Phefs*4)	50‡ (probably tolerated)
22a	15931	c.5777G>C	p.(Arg1926Pro)	103 (probably not tolerated)	c.4966_4967delGA	p.(Glu1656Asnfs*3)	42‡ (probably tolerated)
22b	15931	c.5777G>C	p.(Arg1926Pro)	103 (probably not tolerated)	c.4966_4967delGA	p.(Glu1656Asnfs*3)	42‡ (probably tolerated)
23	17147	c.2991+1655A>G	p.(Cys998*)	n/a	c.381_382delAGinsT	p.(Lys127Asnfs36*)	94‡ (possibly not tolerated)
24	16858	c.2991+1655A>G	p.(Cys998*)	n/a	c.1219_1220delAT	p.(Met407Glufs*13)	126‡ (probably not tolerated)
25	23818	c.2991+1655A>G	p.(Cys998*)	n/a	c.7048C>T	p.(Gln2350*)	n/a
26	18721	c.3175dupA	p.(Ile1059Asnfs*11)	149‡ (probably not tolerated)	unknown	unknown	n/a
27	13786	c.2991+1655A>G	p.(Cys998*)	n/a	c.4966G>T	p.(Glu1656*)	n/a
28	18481	c.2991+1655 A>G	p.(Cys998*)	n/a	c.5941G>T	p.(Glu1981*)	n/a
29	19641	c.2991+1655A>G	p.(Cys998*)	n/a	c.4801C>T	p.(Gln1601*)	n/a
30	16829	c.148C>T	p.His50Tyr	83 (possibly not tolerated)	c.148C>T	p.(His50Tyr)	83 (possibly not tolerated)
31a	24072	c.4661_4663delAAG	p.(1554delGlu)	n/a	c.4661_4663delAAG	p.(1554delGlu)	n/a
31b	24072	c.4661_4663delAAG	p.(1554delGlu)	n/a	c.4661_4663delAAG	p.(1554delGlu)	n/a
31c	24072	c.4661_4663delAAG	p.(1554delGlu)	n/a	c.4661_4663delAAG	p.(1554delGlu)	n/a
32	24225	c.2991+1655A>G	p.(Cys998*)	n/a	c.270_274delAGTAA	p.(Lys90Asnfs*6)	94‡ (possibly not tolerated)
33	25255	c.2991+1655A>G	p.(Cys998*)	n/a	c.3175dupA	p.(Ile1059Asnfs*11)	149‡ (probably not tolerated)

c. = coding region; del = deletion; dup = duplication; fs = frameshift; fs*digit = frameshift that results in a translation termination codon occurring downstream at the designated number of amino acids; n/a = not applicable; p. = protein.

*Translation termination codon.

†Grantham scoring, where <60 = probably tolerated; 61–99 = possibly not tolerated; >100 = probably not tolerated.

‡Despite the fact that a missense mutation may be assigned a Grantham score, these mutations result in frameshifts that truncated the CEP290 protein, thus rendering the gene product functionless.