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López-Garrido MP, Medina-Trillo C, **Morales L, Garcia-Feijoo J, Martínez-de-la-Casa JM, García-Antón M**, Escribano J.

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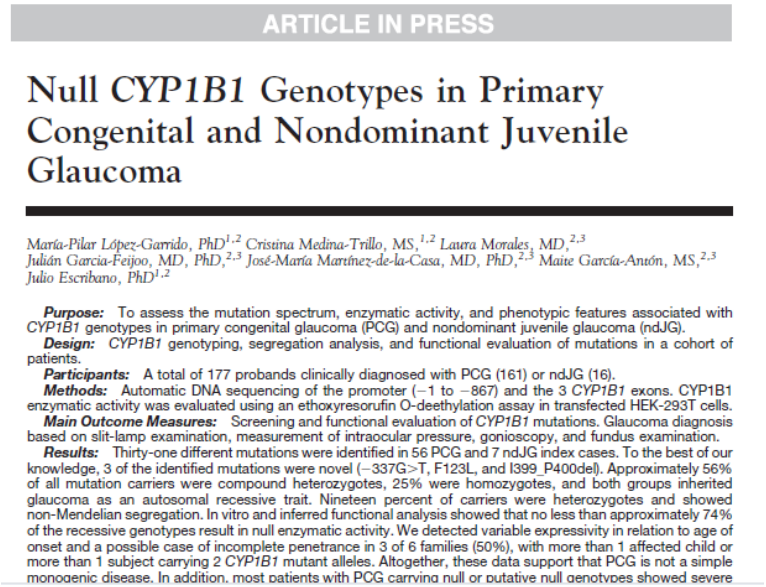

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Null *CYP1B1* Genotypes in Primary Congenital and Nondominant Juvenile Glaucoma

María-Pilar López-Garrido, PhD[1,2] Cristina Medina-Trillo, MS,[1,2] Laura Morales, MD,[2,3] Julián Garcia-Feijoo, MD, PhD,[2,3] José-María Martínez-de-la-Casa, MD, PhD,[2,3] Maite García-Antón, MS,[2,3] Julio Escribano, PhD[1,2]

Purpose: To assess the mutation spectrum, enzymatic activity, and phenotypic features associated with *CYP1B1* genotypes in primary congenital glaucoma (PCG) and nondominant juvenile glaucoma (ndJG).
Design: *CYP1B1* genotyping, segregation analysis, and functional evaluation of mutations in a cohort of patients.
Participants: A total of 177 probands clinically diagnosed with PCG (161) or ndJG (16).
Methods: Automatic DNA sequencing of the promoter (−1 to −867) and the 3 *CYP1B1* exons. CYP1B1 enzymatic activity was evaluated using an ethoxyresorufin O-deethylation assay in transfected HEK-293T cells.
Main Outcome Measures: Screening and functional evaluation of *CYP1B1* mutations. Glaucoma diagnosis based on slit-lamp examination, measurement of intraocular pressure, gonioscopy, and fundus examination.
Results: Thirty-one different mutations were identified in 56 PCG and 7 ndJG index cases. To the best of our knowledge, 3 of the identified mutations were novel (−337G>T, F123L, and I399_P400del). Approximately 56% of all mutation carriers were compound heterozygotes, 25% were homozygotes, and both groups inherited glaucoma as an autosomal recessive trait. Nineteen percent of carriers were heterozygotes and showed non-Mendelian segregation. In vitro and inferred functional analysis showed that no less than approximately 74% of the recessive genotypes result in null enzymatic activity. We detected variable expressivity in relation to age of onset and a possible case of incomplete penetrance in 3 of 6 families (50%), with more than 1 affected child or more than 1 subject carrying 2 *CYP1B1* mutant alleles. Altogether, these data support that PCG is not a simple monogenic disease. In addition, most patients with PCG carrying null or putative null genotypes showed severe

Miembros del grupo de Glaucoma, retina y vías visuales del Instituto de Investigación Sanitaria del Hospital Clínico San Carlos han participado en un estudio genético centrado en el gen CYP1B1 en pacientes con glaucoma congénito primario y glaucoma juvenil no dominante, que acaba de ser publicado en la prestigiosa revista *Ophthalmology,* y en el que se evidencia que la ausencia de actividad de dicho gen conlleva, con frecuencia, fenotipos de glaucoma muy graves.

Se trata del estudio más grande publicado en Europa sobre el glaucoma congénito primario en el que han participado 161 pacientes. El estudio también demuestra que esta patología asociada a defectos en el gen CYP1B1 no puede considerarse una enfermedad monogénica y que los niveles de actividad del citado gen pueden influir en el fenotipo del glaucoma.

El estudio ha sido llevado a cabo junto con al Área de Genética de la Facultad de Medicina e Instituto de Investigación en Discapacidades Neurológicas de la Universidad de Castilla-La Mancha, en Albacete.