Abstract 199

ABCA4-ASSOCIATED RETINOPATHIES PHENOTYPES: GENETIC SPECTRUM AND GEOGRAPHIC DATABASE OF A LARGE LATIN AMERICA COHORT.

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AIMS/PURPOSES: ABCA4-associated retinopathies (ABCA4r) are a group of autosomal recessive retinal dystrophies caused by mutations in the ABCA4 gene. ABCA4r have phenotypic variability due to their high allelic heterogeneity. In this study we describe the clinical and genetic spectrum of a cohort of 220 Mexican probands with ABCA4r and the creation of a mutational map based on the birthplace of affected individuals.

METHODS: Molecular analyses were performed employing either exome sequencing, gene panel sequencing, and/or Sanger sequencing of the complete ABCA4 or ABCA4 sequencing guided by geographic origin. Segregation by sanger sequencing was performed in 109 relatives of index cases.

RESULTS: Molecular analysis was performed in a total of 329 individuals. ABCA4 Biallelic pathogenic variants were demonstrated in 220 non-related probands; An additional group of 109 relative individuals were sequenced demonstrating 30 cases with biallelic mutations. The most frequent clinical diagnosis was Stargardt Disease 88%, followed by cone dystrophy 4%, retinitis pigmentosa 2%, macular dystrophy 2% and cone-rod dystrophy 2%. One hundred and thirty-two different pathogenic variants were identified, 24 of them not previously published. The ABCA4 mutational spectrum in 220 index cases included 458 pathogenic variants with 132 different mutations. The ABCA4 exons most frequently affected by mutations were exons 38 and 35. The most common type of pathogenic variant was single nucleotide substitution (91%) and the most frequent protein effect was missense mutations (83%).

CONCLUSIONS: We demonstrated an extensive mutational ABCA4 spectrum in Mexican ABCA4r patients and identified founder effects for at least two ABCA4 variants (c.5318C>T and c.4854G>C). Indicators of another founder effect need further analysis. This is the largest ABCA4r cohort analyzed in Latin America and our results contribute to characterize the mutational profile of the disease.

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