1 de Dezembro **08h30 | 10h00 – Sala 1**

Retina Médica | Medical Retina

Moderadores | Chairs: Maria Luz Cachulo (CHUC), Diogo Cabral (HGO), Luis Mendonça (HB)

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PHENOTYPIC EXPRESSION OF CFH RARE VARIANTS IN AGE-RELATED MACULAR DEGENERATION PATIENTS IN THE COIMBRA EYE STUDY

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Purpose: To determine the association between rare genetic variants in complement factor H (*CFH*) and phenotypic features in age-related macular degeneration (AMD) patients from the Coimbra Eye Study (CES).

Methods: AMD patients from the Incidence CES (NCT02748824) underwent ophthalmologic examination and color fundus photography (CFP), spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), and near-infrared imaging (NIR). Multimodal phenotypic characterization was carried out in a centralized reading center. The coding and splice-site regions of the *CFH* gene were sequenced through smMIP-based next-generation sequencing in association with the EYE-RISK consortium. Variants with MAF<0.05 resulting in splice-site or protein change were selected. Differences in phenotypic features between carriers and non-carriers were analyzed using generalized estimated equations logistic regression models, considering inter-eye correlations.

Results: We included 39 eyes of 23 patients carrying rare *CFH* variants and 284 eyes of 188 non-carriers. Carrier status was associated with having higher drusen burden in the macula in the inner ETDRS circle (OR,5.44 [95%CI,1.61–18.37]; p=0.006), outer circle (OR,4.37 [95%CI,1.07–17.77]; p=0.04), and full grid (OR,4.82 [95%CI,1.13–20.52]; p=0.033). In SD-OCT, a lower total macular volume and lower inner retinal layers' volume (OR,0.449 [95%CI,0.226-0.894]; p=0.023; OR,0.496 [95%CI,0.252–0.979]; p=0.043), and pigment epithelial detachments (PEDs) (OR,5.24 [95%CI,1.08-25.44]; p=0.04), were associated with carrying a rare *CFH* variant. Carriers with subretinal drusenoid deposits (SDD) had the rare variant P258L in all cases except one.

Conclusions: We identified in our cohort phenotypic differences between carriers and non-carriers of rare variants in the *CFH* gene. Carriers had more severe disease, namely superior drusen burden, PEDs, and thinner retinas. The rare variant P258L may be associated with SDD. Carriers are probably at increased risk of progression.