CTNNA1 germline variants associate with a disease spectrum extending beyond Hereditary Diffuse Gastric Cancer

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ABSTRACT:

CDH1-associated Hereditary Diffuse Gastric Cancer (HDGC) predisposes to diffuse gastric cancer (DGC) and/or lobular breast cancer (LBC). *CTNNA1*/αE-catenin germline truncating pathogenic variants cause HDGC and missense pathogenic variants cause Macular Dystrophy Patterned-2. The full *CTNNA1*-disease spectrum and variant-type associated causality is unknown. Large cohorts and *in vivo* models are essential to disclose genotype-phenotype associations.

Collaboration with ERN-GENTURIS partners, external Institutions and literature search, allowed collecting clinical data on 67 probands and 142 relatives *CTNNA1* germline variant carriers/relatives. We molecularly/clinically classified variants, categorized families according to HDGC-criteria and analyzed genotype-phenotype correlations. We developed a *Drosophila melanogaster* αE-catenin-knockdown model to study *CTNNA1* impairment in different tissues.

Sixty-seven families carried rare *CTNNA1* germline variants, being 32% Pathogenic (PV) and 32% Likely Pathogenic (LPV), all truncating. Early-onset DGC and Breast Cancer of unknown-histotype (BC) were the predominant phenotypes. In PV-carriers, DGC predominated (42%), followed by LBC (5%) and other HDGC non-classical cancer phenotypes, such as Colorectal, Prostate and Thyroid cancer (6%, 5% and 4%, respectively). LPV-carriers developed mainly BC and Melanoma (59% and 7%, respectively). Phenotypes differed significantly between PV- and LPV-families ($p<0.00001$). Most PV- and LPV-related cancers were early-onset. Drosophila α-catenin knockdown in wing and eye primordial tissues induced fly lethality, and surviving flies presented aggressive phenotypes and comorbidities. Human wild-type αE-catenin expression in the eye rescued fly survival and organ development, while a human αE-catenin bearing a HDGC PV, failed to rescue both abovementioned parameters.

Early-onset DGC/LBC are frequent cancers in *CTNNA1* PV-carriers, however, disease spectrum extends beyond HDGC-classical phenotypes. *CTNNA1* LPV-carriers disease spectrum diverges from classical-HDGC. Current data claims for phenotype-driven *CTNNA1*-specific variant classification rules, which can be supported by robust *in vivo* testing models, as the one we developed. The humanized *Drosophila* model enables functional analysis of *CTNNA1* germline variants in a tissue specific manner.

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