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Exploring Double Heterozygosities in Hereditary Breast and Ovarian Cancer: Advancing Beyond Single Cases through Comprehensive Analysis

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Background: Risk-adapted surveillance programs and risk-reducing surgery for individuals with hereditary breast and/or ovarian cancer (HBOC) represent a central advancement in clinical management. While risk-adapted measures for carriers of a single HBOC-associated (likely) pathogenic variant (pV) have been established, that for individuals harboring pVs in multiple cancer predisposition genes remain unclear.

Methods: Phenotypic traits of double heterozygous (DH) counselees, including breast cancer (BC) receptor status, onset, and severity, were compared to

those of single heterozygous (SH) carriers in the German Consortium for HBOC (GC-HBOC) registry of more than 27,000 pV carriers.

Result: In total, we identified more than 400 multiple heterozygous counselees. For pV carriers tested for thirteen HBOC core genes, the prevalence of multiple heterozygosity was about 3%. BC in double heterozygous (DH) females displayed a prevalent receptor phenotype, influenced by the distinct variant gene combinations. Triple-negative BC was enriched in most *BRCA1*-involved gene combinations, as in *BRCA1* SH carriers. However, among *BRCA1/CHEK2* DH carriers, BC predominantly exhibited a hormone receptor-positive status. The age at which BC developed in DH females corresponded to the cancer onset of counselees with a single pV in the more penetrant gene. Significantly, *BRCA1/BRCA2* DH females had a higher severity score as compared to *BRCA1* or *BRCA2* SH carriers.

Discussion: Our results emphasize a more frequent presence of multiple heterozygosity, particularly DH, surpassing previous understanding. Moreover, we provide evidence to suggest that the presence of a second pV can influence the disease profile.

Conclusion: Overall, our data underscore the necessity of taking into account multiple heterozygosities when making clinical decisions – both for the index counselees and their family members. Recognizing the potential impact of multiple pVs on the phenotype could thereby enhance the provision of more refined and personalized guidance and support.

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