Association of the CASP10 V410I variant with reduced familial breast cancer risk and interaction with the CASP8 D302H variant.

Dysregulation of apoptosis plays a crucial role in carcinogenesis. As part of death receptor- and mitochondrion-mediated apoptosis, the homologues caspases 10 and 8 may act as low-penetrance breast cancer (BC) susceptibility genes. In death receptor-mediated apoptosis, engagement of death receptors by their ligands involves the assembly of the death-inducing signalling complex (DISC). In mitochondrion-mediated apoptosis, the release of cytochrome c into the cytosol results in apoptosome formation. Recruitment of both caspases 10 and 8 (CASP10 and CASP8, respectively) to DISC and apoptosome leads to their activation by dimerization. We investigated the influence of the coding CASP10 variant V410I (G1228A) by performing a case-control study - using 511 familial BC cases and 547 control subjects - on BC risk and revealed a significant association of V410I with a reduced risk (OR = 0.62, 95% CI = 0.43-0.88, P = 0.0076) related to the number of variant alleles (P(trend) = 0.0039). As CASP10 and CASP8 functionally co-operate during apoptosis, we analysed the mutual effect of both CASP10 V410I and CASP8 D302H, resulting in a significant association between the number of the variant alleles I410 and H302 and a highly decreased familial BC risk (OR = 0.35, P(trend) = 0.007), pointing to the interaction between the
CASP10 and CASP8 polymorphisms in breast carcinogenesis.

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