

Functional analysis of genetic variants in PALB2 and CHEK2: linking functional impact with cancer risk

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Stellingen behorend bij het proefschrift getiteld

Functional analysis of genetic variants in *PALB2* and *CHEK2*: linking functional impact with cancer risk

- cDNA-based complementation assays in mouse embryonic stem cells allow for functional characterization of human PALB2 and CHEK2 variants. (this thesis)
- 2. The Coiled-Coil and WD40 domains of *PALB2* represent hotspots for missense variants that impair PALB2 protein function in homologous recombination. (this thesis)
- 3. Missense variants across the entire *CHEK2* coding sequence can impact CHK2 protein function. (this thesis)
- 4. Impaired PALB2 and CHK2 protein function inversely correlates with an increased risk of breast cancer. (this thesis)
- 5. The effectiveness of ACMG-based variant classification improves considerably with the inclusion of functional data.
- 6. The lack of sufficient proven benign or pathogenic variants as controls in functional assays complicates the use of functional data in clinical variant interpretation. (Brnich et al., 2020. Gen. Med.)
- 7. The identification of variants that impair homologous recombination in tumors is critical to select cancer patients for treatment with PARP inhibitors.
- 8. Genetic testing will eventually identify all possible single nucleotide DNA variants in disease-associated genes. (Adapted quote from Douglas M. Fowler at the Mutational Scanning Symposium, 2022).
- 9. Although high-throughput assays for the functional analysis of genetic variants are inherently noisy, they are indispensable for variant classification.
- People have a way of blinking and missing the moment, a moment of enlightenment, or the moment that could have changed everything. (Adapted quote from the fictive character Hank Moody in Californication)