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

1. 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.

10. 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)