UKCGG statement on reporting practice for missense variants in *CHEK2*

Testing of *CHEK2* was introduced in the National Test Directory for the R208 Familial Breast Cancer Panel in April 2022 and more recently on the R430 Familial Prostate Cancer Panel in May 2023[1].

The decision to interpret and report only truncating *CHEK2* variants was made following discussions at National Cancer Genetics Leads meetings based on the following considerations:

1. Laboratory time and resource in interpretation and reporting of missense variants versus clinical utility
2. Published data demonstrates that for most missense variants in *CHEK2,* the magnitude of associated breast cancer risk falls below an odds ratio (OR) of two [2-4], generally considered to be the threshold for clinical reporting and actionability by international guidelines[5].
3. Risk estimates generated by CanRisk[6] are currently based on risks associated with truncating variants in *CHEK2* (with most data pertaining to *CHEK2* c.1100delC), although there are plans to incorporate data related to missense variants in this model in the future

Other countries and commercial laboratories do interpret and report missense variants in *CHEK2*. UKCGG are aware that this discrepancy in reporting practice has resulted in some challenges in clinical practice.

Despite multiple discussions at a national level within UKCGG and CStAG, the situation is difficult to resolve. Published evidence is supportive that missense variants as a combined group are associated with a low-moderate risk breast cancer risk (OR<2) [2-4]. However, it is likely that some individual *CHEK2* variants will be associated with breast cancer risks comparable to truncating variants. Whilst there is case-control data available for groups of missense variants based on common features such as functional domain and/or in silico tools[4,7], there is limited data at the level of each individual variant.

UKCGG recognise that further work is required in this area. We propose that for individual variants classified as likely pathogenic/pathogenic with sufficient case-control data supportive of an equivalent risk to truncating variants, the variant should be reported and cascade testing offered to relatives.

An example of this would be *CHEK2* c.349A>G p.(Arg117Gly), which has across multiple studies demonstrated an OR comparable to *CHEK2* truncating variants [iCOG Study; OR = 2.26, (95% CI: 1.29 - 3.95)[8]; BRIDGES OR =2.69, (95% CI 1.46–4.94)[4] and UK Biobank (unpublished analysis of 21/19,719 female BC patients and 93/219,405 female non-BC controls); OR 2.51 (95% CI: 1.50-4.21). Given the evidence for this variant we would recommend that this variant is analysed and reported on the relevant diagnostic panel and that testing in family member can be offered where clinically appropriate.

UKCGG and CanVIG will continue to curate and review a list of such exception variants available **here**

References

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