CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – October 2022

Translational science

The evolutionary dynamics of extrachromosomal DNA in human cancers. Lange *et al.* (2022). *Nat Genet*; 54: 1527-1533. https://doi.org/10.1038/s41588-022-01177-x

- Oncogene amplification on extrachromosomal DNA (ecDNA) is recognised as a common event in human cancer, driving aggressive tumour growth, drug resistance and shorter survival, however the impact of ecDNA on somatic variation and selection is not currently clear. Further, the impact of non-chromosomal oncogene inheritance in cancer (random identity by descent) is not well understood.
- Using theoretical models of random segregation, unbiased image analysis, CRISPR-based ecDNA tagging with live-cell imaging and CRISPR-C, the authors show that random ecDNA inheritance results in extensive intratumoural ecDNA copy number heterogeneity and rapid adaptation to metabolic stress and targeted treatment, and hence contribute to poor outcomes for patients with cancer.
- The authors suggest that their observations may explain why clinical activity from therapies targeting oncogenic amplification events are so limited in tumours such as glioblastoma where ecDNAs are so prevalent. Treating such cancers may require targeting the unique adaptability of ecDNAs in the future.

In the clinic

Clinical applicability of the Polygenic Risk Score for breast cancer risk prediction in familial cases. Lakeman *et al*. 2022. *J Med Genet.* doi:10.1136/jmedgenet-2022-108502.

- Polygenic Risk Score (PRS) have been shown to be useful in stratifying women in the general population into different breast cancer (BC) risk categories, but it is not presently used to guide clinical management of familial BC.
- This study explores the additive impact of a 313-variant-based PRS (PRS_{313}) relative to standard genetic testing in non-*BRCA1/2* Dutch BC families.
    - 3918 BC cases from 3492 Dutch non-*BRCA1/2* BC families and 3474 Dutch population controls
    - 91% of the cases were an invasive tumour, 8% were in situ tumours, and 19% were tumours of unknown invasiveness. Of all cases, 18% developed a second breast tumour.
- Association of standardised PRS_{313} with BC was estimated using a logistic regression model, adjusted for pedigree-based family history.
- Lifetime risks were calculated with and without individual PRS_{313} using the BOADICEA V.5 model.

- The presence of PVs in *ATM, CHEK2*, and *PALB2* was known for 2586 cases.
- Including PRS_{313} in addition to FH-based risk prediction would have changed screening recommendations in up to 27%, 36%, and 34% of cases (non-PV carriers) according to BC screening guidelines from the USA (NCCN), UK (NICE), and the Netherlands (IKNL).
    - For population controls without information on FH, this was up to 39%, 44%, and 58%, respectively.
- For those with PVs in *ATM* or *CHEK2,* inclusion of PRS_{313} changed screening recommendations for 18% and 26%, respectively, for IKNL, and 18% and 23%, respectively, for NICE guidelines.
- In both groups and all age categories, a higher percentage of cases shifted to the moderate-risk and high-risk category compared with the lowest risk category.
- For cases there was a very weak correlation between the PRS_{313} and the $BOADICEA_{FH}$; only 0.3% of the variant in the PRS_{313} is explained by family history.
- The study supports the implementation of the PRS_{313} in risk prediction for genetically uninformative BC families and families with a PV in moderate BC risk genes.

First estimates of diffuse gastric cancer risks for carriers of *CTNNA1* germline pathogenic variants. Coudert *et al*. 2022. *J Med Genet.* doi:10.1136/jmedgenet-2022-108740.

- Pathogenic variants (PVs) in *CTNNA1* are found in families fulfilling criteria for hereditary diffuse gastric cancer (HDGC) but no risk estimates were previously available, making it difficult to provide genetic counselling and to establish recommendations for management, thus limiting the clinical utility of these results.
- *CTNNA1* encodes catenin alpha-1, the intracellular partner of E-cadherin, and plays an important role in cell adhesion.
- IHC showing loss of catenin alpha-1 can predict a *CTNNA1* germline PV.
- This study aims to evaluate and estimate reliable diffuse gastric cancer (DGC) risks for individuals with germline *CTNNA1* PVs (or LPVs).
- Thirteen families with 46 individuals with *CTNNA1* PVs were included.
- The cumulative risks of DGC at 80 years for individuals with *CTNNA1* PVs are 49% and 57%, respectively with the Weilbull genotype restricted likelihood (GRL) and non-parametric (NP) GRL methods.
    - It was not possible to obtain estimates by gender due to small number of families.
    - Low penetrance was observed before 50 years of age, but uncertainty level was high in these estimates and should not be interpreted as an absence of risk – more data is needed to obtain more accurate estimates, especially before the age of 50 years.
- Risk ratios to population incidence reach particularly high values at early ages and decrease with age.

    - Among those with a PV/LPV, the median age of diagnosis of an invasive gastric cancer was 45 years (range: 22-75 years).
- Penetrance estimates in the study are likely to be clinically appropriate in the context of gastric cancer families, but may be higher than the average penetrance in truly unselected carriers, due to other risk factors for DGC that patients with a FH of GC are more likely to be exposed to.
- No association of *CTNNA1* PVs with lobular breast cancer has been shown to date, however the data from this study do suggest a trend towards an excess of breast cancer in women with *CTNN1A* PVs with a predominance towards the lobular type.
- The study supports inclusion of *CTNNA1* in germline testing panels.

Counselling and ethics

Attitudes towards preimplantation genetic testing and quality of life among inividuals with hereditary diffuse gastric syndrome. Shah *et al*. 2022. *Hereditary Cancer in Clinical Practice.* https://doi.org/10.1186/s13053-022-00239-9.

- Little is known about the attitudes of individuals with Hereditary Diffuse Gastric Cancer syndrome (HDGC) towards reproductive options
- 21 participants, recruited from the Early Onset and Familial Gastric Cancer Registry (Memorial Sloan Kettering Cancer Centre), completed questionnaires which provided information about sociodemographics, clinical history, reproductive history, attitudes towards preimplantation genetic testing (PGT) and impact of HDGC on quality of life
- The majority of participants were female, white/caucasian and married/partnered and 71% of participants had a personal cancer history. No participants had used PGT previously
- Most felt it was acceptable for HCPs to talk to patients with HDGC about PGT
- Generally, there were favourable attitudes towards PGT but a wide range of opinions regarding their own likelihood of using PGT. Qualitative analysis showed different factors which shaped participants' attitudes including personal philosophy, attitudes about uncertainty, religion, and personal preferences around family life. The main perceived benefits of PGT were to eliminate mutations and minimise suffering
- 57% of participants reported "sometimes" or "often" worrying about their cancer risk and overall participants felt their genetic result had a moderately severe effect on their overall health and wellbeing. A majority also felt some guilt related to HDGC affecting family members.
- Around 50% of participants felt that having HGDC had caused them to alter important life decisions.
- Data from this study was a "snapshot" perspective of the patients with HDGC. However, the data was collected in 2014 so may not reflect recent advances and

developments. The cohort also did not reflect the larger population of interest, and may not reflect the views of those who do not have a cancer history. The average age of participants was 51 years old, and therefore these findings may not reflect other age groups who may be considering starting a family

- PGT is an acceptable technology for patients with HDGC. Concerns about their genetic diagnosis shapes not only reproductive decisions, but also wider quality of life and behaviours.

Monthly Journal Round-Up brought to you by:

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