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

Translational science

Somatic tumor mutations in moderate risk cancer genes: Targets for germline confirmatory testing. Llorin *et al.* (2022). *Cancer Genetics*; 268: 22-27. https://doi.org/10.1016/j.cancergen.2022.09.001

- Recent changes in NCCN oncology practice guidelines indicate that pathogenic variants in cancer susceptibility genes identified on tumour genomic profiling (TGP) should prompt confirmatory genetic testing.
- This study aims to determine the proportion of patients with TGP-identified pathogenic variants in moderate risk breast and ovarian cancer genes (*ATM, BRIP1, CHEK2, PALB2, RAD51C,* and *RAD51D*) who previously would not have been considered for germline testing.
- 45.3% (73/160) of patients would not have been eligible for germline testing if a pathogenic variant had not been identified through TGP.
- Of those undergoing germline testing, 51.5% (33/64) had results which confirmed germline origin of the TGP finding. High rates of germline confirmation were found in *PALB2* (100%), *ATM* (40%), *CHEK2* (61.5%), and *BRIP1* (57.1%)
- The authors conclude that this shows TGP-identified pathogenic variants increase eligibility for germline testing, and that this expanded eligibility captures individuals with hereditary cancer syndromes that would not have otherwise been identified.

Extensive germline-somatic interplay contributes to prostate cancer progression through HNF1B co-option of TMPRSS2-ERG. Giannareas *et al.* (2022). *Nature Communications*; 13: 7320. https://doi.org/10.1038/s41467-022-34994-z

- GWAS have identified 270 loci conferring risk for prostate cancer (PCa), however underlying biology and clinical impact are yet to be investigated
- Growing evidence indicate that GWAS loci are often involved in expression quantitative trait locus (eQTL) conferring cancer risk via altering the DNA-binding affinity of critical transcription factors (TFs) to causal SNP-containing regulatory elements such as enhancers, representing a major driving force of cancerous gene expression program
- In this study, they show an enrichment of TF genes including HNF1B within PCa risk-associated regions. They find a strong eQTL for HNF1B and multiple potential causal variants involved in the regulation of HNF1B expression in PCa
- They also reveal PCa-specific somatic TMPRSS2-ERG fusion as a transcriptional mediator of this locus and the HNF1B eQTL signal is ERG fusion status dependent.
- The authors find HNF1B is involved in several pathways related to cell cycle progression and PCa severity, and that HNF1B interacts with TMPRSS2-ERG to co-occupy large proportion of genomic regions with a remarkable enrichment of additional PCa risk alleles.
- Finally, they show that HNF1B co-opts ERG fusion to mediate mechanistic and biological effects of the PCa risk-associated locus 17p13.3/VPS53/FAM57A/GEMIN4.

- Together, the authors report an extensive germline-somatic interaction between TMPRSS2-ERG fusion and genetic variations underpinning PCa risk association and progression.

Investigating the shared genetic architecture of uterine leiomyoma and breast cancer: A genome-wide cross-trait analysis. Wu *et al.* 2022. *American Journal of Human Genetics.* doi: 10.1016/j.ajhg.2022.05.015

- Little is known about the shared genetic architecture or causality underlying phenotypic association observed for uterine leiomyoma (UL), also known as fibroids, and breast cancer (BC).
- Using statistics from the largest genome-wide association study (GWAS) for each trait, the authors investigated the genetic overlap and causal associations of UL with BC.
- Analysis demonstrates a shared genetic basis;
    - Positive genetic correlation between UL and BC overall, which was consistent in ER+ subtype but not ER- subtype.
- pleiotropic loci;
    - Local genetic correlation was identified at 22q13.1 for UL with BC overall and with ER+ subtype.
    - 50 shared loci between UL and BC were identified, 41 of which were previously reported as significantly associated with UL and/or BC.
- as well as a putative causal relationship between UL and BC;
    - Genetically predicted UL was significantly associated with an increased risk of BC overall, restricting to the ER+ subtype.
    - Reverse analysis showed no significant association.
- highlighting an intrinsic link underlying these two complex female diseases.
- However, larger analysis is needed to definitively establish (or rule out) a potential causal link between UL and BC and experimental research to understand the biological mechanism of the observed genetic relationship.
- Findings from future larger analyses might provide important directions for future therapeutic strategy as well as risk prediction.

In the clinic

Cancer Prevention with Resistant Starch in Lynch Syndrome Patients in the CAPP2-Randomized Placebo Controlled Trial: Planned 10-Year Follow-up. Mathers *et al.* 2022. *Cancer Prevention Research*. doi.org/10.1158/1940-6207.CAPR-22-0044

- The CAPP2 trial investigated the long-term effects of aspirin and resistant starch on cancer incidence in patients with Lynch syndrome (LS).
- Participants with LS were randomized double-blind to 30 g resistant starch (RS) daily or placebo for up to 4 years.
- This paper reports findings after up to 20 years follow-up.
- There was no effect of RS on colorectal cancer incidence, or endometrial cancer, the most common extracolonic site.

- RS offered a protective effect against non–colorectal LS cancers, particularly for cancers of the upper gastrointestinal tract (stomach, duodenal, bile duct and pancreatic cancers).
    - This reduction was detectable in the first 10 years and continued in the next decade.
    - This has substantial potential benefits for LS patients as these cancers have much lower survival rates than for other LS cancers.
- There was no evidence of an effect of RS on non-LS cancer incidence.
- There was no interaction between aspirin and RS treatments which suggests RS treatment is beneficial for patients regardless of whether they are taking aspirin.

Counselling and ethics

BRCAShare – Assessment of an animated digital message for intrafamilial communication of pathogenic variant positive test results: A feasibility study. Aeilts *et al.* (2022). *Journal of Genetic Counseling*; 00: 1-11. https://doi.org/10.1002/jgc4.1656

- In this study a two-minute animated digital message (ADM) intervention was tested guided by the Health Belief Model (HBM) to determine hypothetical individual perceptions of susceptibility and severity and behavioural intention to act on the information provided in the ADM.
- 'Genetic testing naïve' adults from the United States with no personal history of cancer were recruited to the study (n=373) and presented with a hypothetical scenario describing a relative's recent HBOC diagnosis. They viewed the ATM and then answered a questionnaire which assessed their perception of the HBM constructs in relation to the hypothetical scenario and participants' intentions to pursue cascade genetic testing, talk to a healthcare professional, or talk to family members after ADM viewing.
- Participants largely perceived HBOC as serious and believed they could benefit from information provided by genetic testing;
    - 76% hypothetically intended to pursue genetic testing at a cost of $100 or less;
    - 90% intended to either pursue testing or talk to a healthcare provider or family members
- The authors conclude that the participants demonstrated behavioural intention toward cascade testing at a higher rate than literature indicates is typical in high-risk families, and so suggest a simple to use intervention such as an ADM may be useful in clinical practice.

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Nancy Whish, STP Trainee in Genomic Counselling, Addenbrooke's Hospital, Cambridge