CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – September 2023

Translational science

Exome sequencing identifies breast cancer susceptibility genes and defines the contribution of coding variants to breast cancer risk. Wilcox *et al.* (2023). *Nature Genetics*; 55: 1435-1439. https://doi.org/10.1038/s41588-023-01466-z.

- Meta-analysis across 3 large whole-exome sequencing datasets; 26,368 female cases, 217,673 female controls
- Association between breast cancer and protein truncating variants (PTVs) and rare missense variants were analysed for 15,616 genes and 18,601 genes, respectively.
- Conducted burden tests, which use the aggregate burden of variants in each gene. If the variants effects are in the same direction then these tests are more powerful than single-variant association tests.
- **PTVs**
    - 30 genes associated with BC at P <0.001
        - 28 associated with an increased risk.
    - PTVs in 6 genes showed exome-wide significant association (P <2.5x10^{-6}) with breast cancer: *BRCA1, BRCA2, ATM, CHEK2, PALB2* and *MAP3K1*.
    - Associations at P <1x10^{-4} were also identified for PTVs in *LZTR1, ATRIP* and *BARD1*.
    - Significant associations were not observed for other known susceptibility genes, but PTV frequencies were very low.
    - Enrichment of gene associations in cases under 50 years of age was observed. *MGAT5*, in addition to the 6 already mentioned, met exome-wide significance.
    - Expected subtype specific associations were observed for known genes.
- **Rare missense variants**
    - 28 genes associated with BC at P <0.001
        - 18 associated with an increased risk.
    - Analysis identified exome-wide significant association only for *CHEK2*.
        - P <1x10^{-4} also for *SAMHD1, HCN2, CLIC6* and *ACTL8*.
- **Missense variants predicted deleterious combined with PTVs**
    - For those predicted deleterious by CADD score:
        - 33 genes (22 linked to increase BC risk)
        - Exome wide significance in *BRCA1, BRCA2, PALB2, CHECK2, ATM* and *CDKN2A*.
        - Associations at P <1x10^{-4} observed for *SAMHD1, MRPL27, EXOC4* and *PP1R3B*.
    - For those predicted deleterious by Helix:
        - 29 genes (25 corresponding to increased BC risk)
        - Exome-wide significance was met for the 5 known BC genes.
        - Associations at P <1x10^{-4} observed for *LZTR1, MAP3K1, DCLK1, MDM4, STX3* and *ATRIP*.

- *MAP3K1*
  - Inactivating variants of this gene are one of the commonest somatic driver events in breast tumours.
  - The study evaluated whether the *MAP3K1* PTV burden was driven by GWAS associations, or vice versa, but found that they reflect distinct effects of inactivating coding alterations and regulatory variants that target *MAP3K1* expression.
  - Although the estimated risk associated with *MAP3K1* PTVs is clinically relevant, it may be over-estimated due to the 'winner's curse' – the genetic effect in an association study will be biased upward, conditional on that study being the first to reach statistical significance and be published.
- The study evaluated the overall contribution of PTVs to familial relative risk of BC. It was found that 10.61% of the FRR would be explained by PTVs.
  - 9.64% due to the 5 known BC susceptibility genes
  - 0.14% contributed by *MAP3K1*
- Results suggest that the majority of the remaining risk genes are tumour suppressor genes.

In the clinic

Breast cancer polygenic risk scores derived in White European populations are not calibrated for women of Ashkenazi Jewish descent. Roberts *et al.* (2023). *Genetics in Medicine*; doi: https://doi.org/10.1016/j.gim.2023.100846.

In last month's round-up we included a paper by Levi et al. which concluded that European-based breast cancer PRS has clinically relevant predictive capacity for Israeli AJ women. The below case-control study from Roberts et al. argues that PRSs calibrated to effect allele frequencies from the White European population should not be used to give breast cancer relative risk predictions to AJ women, as this overestimates relative breast cancer risk. The authors argue that ethnicity-specific calibration is essential.

- Case-control study of White European (WE) and Ashkenazi Jewish (AJ) women from the Predicting Trisk of Cancer at Screening Study. The Breast Cancer in Northern Israel Study provided a separate AJ population–based case-control validation series.
- All women underwent SNP analysis and two PRSs were assessed; SNV142 and SNV78
- Effect allele frequencies (EAFs), which are the proportion of a particular risk allele within a population, were obtained from the Genome Aggregation Database
- Forty-seven of the 142-SNV (33%) PRSs and 23 of the 78-SNV (29%) PRSs had EAFs that differed by ≥25% in AJ vs WE populations.
- In the UK study, the mean SNV142 PRS showed good calibration and discrimination in the WE population
  - Mean PRS in cases = 1.33
  - Mean PRS in controls = 1.01
- In AJ women from Manchester, the mean PRS of 1.54 in cases and 1.20 in controls demonstrated good discrimination but overestimation of BC relative risk.

- After adjusting for EAFs for the AJ population, mean risk was corrected (mean SNV142 PRS cases = 1.30 and controls = 1.02). This was also demonstrated in the larger Israeli data set with good discrimination.
- There was a higher degree of overestimation in the Manchester AJ population compared with Israelis, and the authors speculate that this may be because the Israeli population has a much broader genetic pool.
- The authors conclude that AJ women should not be given BC relative risk predictions based on PRSs calibrated to EAFs from the WE population. PRSs need to be recalibrated using AJ-derived EAFs. A simple recalibration using the mean PRS adjustment ratio likely performs well.
- However, as more interracial mixing occurs between individuals of all races, it will become increasingly difficult to determine the best ethnically relevant PRS to use.

Clinical practice guidelines for the diagnosis and surveillance of BAP1 tumour predisposition syndrome. Lalloo *et al.* (2023). *Eur J Hum Genet*; https://doi.org/10.1038/s41431-023-01448-z.

- BAP1 is a tumour suppressor gene, with pathogenic variants in the gene predisposing to multiple tumour types (BAP1-associated tumour predisposition syndrome).
- Lifetime risk of at least one BAP1-associated tumour developing in a PV carrier is up to 85%.
- Management recommendations are needed as BAP1 carriers are increasingly identified through large gene panels and tumour sequencing.
- This paper details clinical practice guidelines for management of BAP1 carriers as developed by Clinical Guideline Working Group of the CanGene-CanVar project and European collaborators, with the aim of standardising surveillance programmes within Europe.
- As with almost all rare cancer predisposition syndromes, finding the balance between too much and too little surveillance is challenging, and limited evidence for appropriate surveillance leads to conflicting recommendations.
- Consensus reached on the phenotype of BAP1-TPDS, prevalence of BAP1 PVs, recommendations for germline BAP1 testing and surveillance recommendations for BAP1 carriers.

Counselling and ethics

Barriers and facilitators to genetic testing for breast and ovarian cancer amongst Black African women in Luton (UK). Kabeya *et al.* (2023). *Journal of Genetic Counselling*; 00: 1-20. https://doi.org/10.1002/jgc4.1742

- There are multiple disparities in health-seeking behaviours by women from Black ethnic groups towards cancer screening services and black women are more likely to be diagnosed at stage 3 or 4 of the disease. They are less likely to be diagnosed through screening
- Women of African descent have a higher proportion of triple negative breast cancer diagnoses and earlier age of diagnosis
- Focused group discussions were carried out, and 24 participants took part. This included 12 women affected by breast cancer, and 12 unaffected

- 9 themes were identified through thematic analysis:
    - Cost and affordability: the overall cost of the test, and possibility of having to self-fund would be a perceived barrier. Financial status would also be a barrier – e.g not being able to take a day off work
    - Lack of knowledge, awareness and family health history knowledge: A lack of promotional materials was seen to be a barrier. As most tests require understanding of a person's family history, this was seen to be a barrier as there may be lack of communication with family or inability to share information due to different views and mindsets – e.g the family history is explained by a curse
    - Language barrier, immigration and distrust in western healthcare services: Language barriers for both attending appointments and with employers was seen as a barrier. Immigration status can also prevent people attending services as they may not have settled status. Distrust of healthcare services due to historical mistreatment of black people and racism was also seen as a barrier
    - Fear: Different fears were acknowledged, including fear of fatality and fear of the unknown. Genetic testing was seen to cause worry and make people reluctant to go ahead with testing
    - Cultural, religious and intergenerational views: Participants felt that certain cultural mindsets and thought patterns influenced health-seeking behaviours. The mindset that God would heal was seen as a heavy influence to some participants
    - Eligibility for genetic testing for the BRCA1/2 pathogenic variants and a lack of referral to specialist genetic clinics: Few participants mentioned eligibility as a barrier to testing
    - Availability of tests cost-free under the NHS: participants felt more encouraged by the possibility of cost-free testing on the NHS
    - Family members' health: A facilitator to accessing testing was the health of their family members. Participants felt that sharing genetic information would be important
    - Awareness and knowledge of genetic testing: awareness and education is needed and participants felt this would be a facilitator
- The authors note that this study had a small sample, and that participants were English speaking. There may be other views and experiences not accounted for
- These findings may allow genetic counsellors to provide more tailored support for these patient groups

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Principal Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Nancy Whish, STP Trainee Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Alice Coulson, Principal Genetic Counsellor, GOSH, London