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

Translational science

***APC* germline pathogenic variants and epithelial ovarian cancer: causal or coincidental findings?**
Vibert et al. 2022. *Journal of Medical Genetics*. doi: 10.1136/jmg-2022-108467

- APC germline pathogenic variants result in predisposition to familial adenomatous polyposis and extraintestinal tumours such as desmoid fibromatosis, medulloblastomas and thyroid cancers. They have also been recently involved in ovarian microcystic stromal tumours.
- This study reports two pathogenic APC variants in two patients in their early 30s with premenopausal epithelial ovarian cancer (EOC) and investigates the role of APC in the development of these tumours.
- No additional pathogenic variants were detected in a gene panel analysis containing 16 predisposition genes for breast or ovarian cancer.
- Patient 1 was diagnosed with stage IIB high-grade serous ovarian carcinoma and a germline monoallelic pathogenic frameshift deletion was identified in *APC* exon 2: NM_000038.6:c.147_150del.
    - Family history - Mother had colorectal cancer in early 40s and died 2 years later from the cancer evolution.
    - Thus this patient had regular colonoscopies which showed no polyps until her most recent where 7 tubular adenomas with low grade dysplasia were resected.
    - The variant found is located in a region previously associated with attenuated familial adenomatous polyposis (AFAP), consistent with her family history and the onset of polyps in her late 30s.
- Patient 2 was diagnosed with stage IC mucinous ovarian carcinoma and a germline monoallelic pathogenic frameshift deletion was identified in *APC* exon 15: NM_000038.6:c.3444_3447del.
    - Family history – Mother had colorectal cancer in a context of polyposis in her late 40s. One brother died of a brain tumour in his early 20s. Two other brothers and a sister had total colectomy for colorectal polyposis.
    - Patient 2 developed numerous duodenal adenomas in her late 30s.
    - The variant found is located in the last exon, where most pathogenic variants are, consistent with her classical FAP phenotype.
- Both APC germline variants were absent from the gnomAD control database and previously reported in ClinVar as pathogenic, thus both classified as pathogenic.
- Further tumour analysis showed the tumours were HR proficient, had no nuclear β-catenin activation (as would be detected in APC inactivation) and no second hit of APC inactivation.
- Other studies suggest APC promoter methylation is higher in epithelial ovarian tumours compared to normal tissue. This could have caused a somatic second hit in these patients' tumours but it was not explored.
- Understanding the role of APC in EOC may explain a part of the missing heritability in ovarian cancer predisposition, particularly for early onset cases.

In the clinic

Differential involvement of germline pathogenic variants in breast cancer genes between DCIS and low-grade invasive cancers. Evans et al. 2022. *Journal of Medical Genetics.* doi: 10.1136/jmg-2022-108790

- Aim to investigate frequency of germline pathogenic variants (PVs) in women with ductal carcinoma in situ (DCIS) and grade 1 invasive breast cancer (G1BC).
- The study undertook *BRCA1/2* analysis in 311 women with DCIS and 392 women with G1BC. 56% and 40%, respectively, of women in each group also had extended panel testing (non-*BRCA1/2* genes such as *TP53, ATM, PALB2* and *CHEK2*).
- Women with DCIS – 9.6% had a *BRCA1/2* PV and 13.6% had a non-*BRCA1/2* PV.
- Women with G1BC – 4.1% had a *BRCA1/2* PV and 4.5% had a non-*BRCA1/2* PV.
- Although the PV rates in DCIS and G1BC decrease with increasing age, detection rates for DCIS are higher than for G1BCs, particularly for non-*BRCA1/2* PVs, most strikingly in women under 40.
    - However, this was substantially contributed to by testing of women under 30 with DCIS, where all six *TP53* PVs were identified. No PVs were found in women under 30 with G1BC.
- Increasing MS (pathology adjusted) was associated with increased likelihood of *BRCA1/2* PV in both DCIS and G1BC, although an MS of 15-19 was not predictive of *BRCA1/2* for G1BC at the 10% threshold.
- The study has shown that DCIS is around twice as likely as G1BC to be associated with both *BRCA1/2* and non-*BRCA1/2* PVs.
- The study findings support G1BC having lower priority for testing unless there is a strong family history, reserving genetic testing for where there is the greatest diagnostic yield and clinical utility.
- The authors concluded that extended panel testing ought to be offered in young-onset DCIS where PV detection rates are highest, particularly in women under 30 where *TP53* should be tested.

UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in cancer predisposition genes: RAD51C, RAD51D, BRIP1 and PALB2. Hanson et al. 2022. *Journal of Medical Genetics.* doi: 10.1136/jmg-2022-108898

- The UK Cancer Genetics Group and CanGene-CanVar project convened a 2-day meeting to reach a national consensus on clinical management of *BRIP1*, *PALB2*, *RAD51D* and *RAD51C* carriers in clinical practice.
- This paper presents a summary of the process used to reach a consensus and key recommendations from the meeting.
- Recommendations for RAD51C and RAD51D carriers
    - Breast surveillance based on individual risk assessment. Lifetime BC risk 17-30% should be offered moderate-risk screening, >30% but <40% offered high-risk screening and >40% risk offered very high-risk screening.
    - RRM can be discussed with carriers with a lifetime BC of ≥30%.
    - Discussion of lifetime risk of OC in carriers based on individual risk assessment.
    - RRSO should be considered at 50 years for carriers with ≥5% lifetime OC risk.
- Recommendations for *BRIP1* carriers
    - *BRIP1* carrier status should not influence breast surveillance.

  - Discussion of lifetime risk of OC in carriers based on individual risk assessment.
  - RRSO should be considered at 50 years for carriers with ≥5% lifetime OC risk.
- Recommendations for *PALB2* carriers
  - Breast surveillance based on individual risk assessment with carriers referred to the NHSBSP VHR screening programme at age 25–30, depending on risk.
  - RRM can be discussed with carriers with a lifetime BC of ≥30%.
  - Discussion of lifetime risk of OC in carriers based on individual risk assessment.
  - RRSO should be considered at 50 years for carriers with ≥5% lifetime OC risk.
- For *BRIP1*, *PALB2*, *RAD51D* and *RAD51C* carriers
  - OC surveillance should not routinely be offered to carriers outside a research study.
  - Discussion of premenopausal RRSO should include a full detailed discussion of risk versus side effects due to an early menopause.
  - Risk-reducing early salpingectomy with delayed oophorectomy should only be offered to carriers within a research study.

Counselling and ethics

Clinical and psychological implications of secondary and incidental findings in cancer susceptibility genes after exome sequencing in patients with rare disorders. Carrasco et al. 2022. *Journal of Medical Genetics.* doi: 10.1136/jmg-2022-108929

- Aimed to investigate the frequency of secondary and incidental findings (SF/IF) in cancer susceptibility genes (CSG), their clinical actionability and the psychological impact of these results.
- Analysis of 533 exomes yielded 2% cancer-related SF/IF in CSG.
- SF/IF led to 20 individuals enrolling in cancer surveillance programmes, which detected a cancer in 4 of them.
- Further clinical implications – identified a candidate for targeted therapy with a PARP inhibitor, three women had prophylactic salpingo-oopherectomy, one had colonic polyps removed.
- Psychological impact was assessed using the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire.
- Psychological impact of identifying pathogenic variants (PV) in CSG as SF/IF was compared to impact of PV identification in individuals with a family history of cancer (control group).
- MICRA scores for uncertainty and distress after the genetic test results were significantly higher in individuals who received SF/IF than in the control.
- These results reinforce the need for genetic counselling to help cope with genetic test results. It is important to emphasis patient choice about receiving SF/IF during the informed consent process.
- This study suggest future research should focus on developing strategies to minimise impact of SF/IF.

The Clinical and Psychosocial Outcomes for Women Who Received Unexpected Clinically Actionable Germline Information Identified through Research: An Exploratory Sequential Mixed-Methods Comparative Study. Forrest *et al.* (2022). *Journal of Personalised Medicine*; DOI: https://doi.org/10.3390/jpm12071112

- People taking part in genomic research studies may be found to carry actionable germline pathogenic variants, and this can be unexpected or unrelated to the reason why they took part in the research study
- The clinical and psychosocial outcomes of these patients are important, as they will inform service models for those who have not had formal pre-test genetic counselling
- This study looked at a cohort of women who had taken part in research studies that returned clinically actionable results for hereditary breast and ovarian cancer risk genes. The authors aimed to compare cancer worry before and after receiving the results, and outcomes such as cancer risk perception, uptake of management options, experiences of adapting to their result, and how the information is communicated in the family
- Patients were recruited in two groups. The first group (n=45) had been identified as having clinically actionable germline pathogenic variants. The second group (n=93) was an age and education-matched control group with no clinically actionable pathogenic variants. Participants completed questionnaires and a subset from group 1 were interviewed via telephone or in person
- 96% of group 1 participants had confirmatory genetic testing and 76% engaged in breast cancer risk management strategies. There were no independent predictors which were associated with update of RRM. Some described waiting for a clinical genetics appointment as distressing and prompted feelings of uncertainty and anxiety
- Attitudes towards risk-reducing breast surgery were more variable than attitudes towards risk-reducing ovarian surgery. The ovarian cancer risk felt more threatening than the breast cancer risk
- A significant difference in cancer worry score was identified between groups, with group 1 having higher worry levels
- 90% of group 1 participants had informed their family members of their genetic result
- Despite being distressing to some, there was little difference in cancer worry scores between those who received their results without pre-testing genetic counselling, and those who entered a more traditional model care
- A model of genetic counselling for those who receive their genetic results before any counselling needs to be established to consider expedited access to services to reduce feelings of anxiety and uncertainty.

Monthly Journal Round-Up brought to you by:

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

Disclaimer: This journal round-up is a voluntary production and represents the personal views of the contributors. None of the contributors have declared any commercial interest or any conflicts of interest.