CGG/ERN GENTURIS Monthly Journal Round-Up – February 2021

Bigger picture

The New England Journal of Medicine is the big read of the month in cancer genetics, with articles by Hu et al and the Breast Cancer Association Consortium from two large case:control studies refining our knowledge on the risks and associations of single monogenic variants with breast cancer risk. The articles are accompanied by an excellent editorial by Steve Narod which distills the major findings and further questions this raises for clinical practice more succinctly than we could here. Suffice to say, there are no major surprises that BRCA1, BRCA2, PALB2, (high risk) CHEK2 and ATM (moderate risk) show the strongest statistical associations with breast cancer risk. Pathogenic variants in *BARD1*, *RAD51C*, and *RAD51D* are associated with oestrogen negative and triple negative BC risk. This work will no doubt feed into evidence-based gene panel testing strategies, which will in turn impact upon the counselling we offer women. It's important that we consider how we form consensus on the approach to counselling for moderate risk genes and gather more evidence on the efficacy of Screening, Prevention and Early Detection (SPED) strategies in individuals who carry pathogenic variants in the moderate risk genes.

Translational science

NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. Weiss *et al.* (2021). *J Clin Oncol.* https://ascopubs.org/doi/full/10.1200/JCO.20.02220

- The authors performed a phase II trial of the MAPK/ERK kinase inhibitor, mirdametinib (PD-0325901), in adult patients with NF1 and inoperable plexiform neurofibromas (PNs).
- They wanted to investigate the response rate based on volumetric magnetic resonance imaging analysis.
- They followed specific criteria for the patients enrolled in the specific study such as: included age ≥ 16 years with NF1, an unresectable PN either with significant progression in the past year (defined as ≥ 20% increase in the volume, ≥ 13% increase in the product of the two longest perpendicular diameters, or ≥ 6% increase in the longest diameter) or with PN-related significant morbidity. The PNs had to be at least 3 mL.
- In general, this study followed a specific approach where patients received mirdametinib orally twice a day (BID) at 2 mg/m2/dose in a 3-week on/1-week off Patients could receive a maximum of 24 four-week courses while they could receive 4, 8, 12, and 18 courses.
- Their results suggested that Mirdametinib was safe and tolerable at the doses used in this clinical trial.
- The authors also show that mirdametinib given at 2 mg/m2/dose (maximum dose, 4 mg) twice daily in a 3-week on/1-week off sequence results in a 42% PR rate.
- They compared this phase II study with the previously performed studies of MEKi selumetinib that have been performed in children with NF1.

- The PK data suggested that the dose chosen seems to be at the minimum effective dose. Dosing above 2 mg/m2/dose might result in more responses, as we found a potential relationship between mirdametinib exposure and tumor response.
- The PK data also imply that although tumor response is associated with drug exposure, drug toxicity resulting in dose reductions is not; thus, a higher dose might be tolerable, perhaps allowing a higher drug exposure.
- In conclusion, this trial demonstrated that mirdametinib is safe and effective in adolescent and adult patients with NF1-associated PNs. A larger trial further examining this agent in both children and adults with NF1 and PNs is currently underway (ClinicalTrials.gov identifier: NCT03962543)
- The authors also suggest that further trials might be considered in order to optimize the dosing of mirdametinib for tumor efficacy.

Mutant TP53 interacts with BCAR1 to contribute to cancer cell invasion. Kunyao Guo *et al.* (2021). *British Journal of Cancer*; 124: 299-312. https://www.nature.com/articles/s41416-020-01124-9

- Mutant TP53 has been shown to interact with other proteins and to produce gain-of-function properties that contribute to cancer metastasis. However, the underlying mechanisms are still not fully understood.
- The authors used immunoprecipitation and proximity ligation assays, they evaluated breast cancer anti-estrogen resistance 1 (BCAR1) as a novel binding partner of TP53R273H, a TP53 mutant frequently found in human cancers. They also examined the biological functions of their binding by the transwell invasion assay.
- This research analyzed the clinical outcome of patients based on TP53 status and BCAR1 expression using public database.
- They discovered a novel interaction between TP53R273H and BCAR1.
- They also found that BCAR1 translocates from the cytoplasm into the nucleus and binds to TP53R273H in a manner dependent on SRC family kinases (SFKs), which are known to enhance metastasis.
- They moved on to show that the expression of full-length TP53R273H, but not the BCAR1 binding-deficient mutant TP53R273HΔ102–207, promoted cancer cell invasion.
- The authors concluded from their results that the patients with mutant TP53, high BCAR1 expression were associated with a poorer prognosis.
- Lastly, the authors suggested a disruption of the TP53R273H–BCAR1 binding as a potential therapeutic approach for TP53R273H-harbouring cancer patients.

In the clinic

Breast Cancer Risk Genes – Association Analysis in More than 113,000 Women. Breast Cancer Association Consortium. (2021). *NEJM*. DOI: 10.1056/NEJMoa1913948

- Sequenced samples from 60,466 women with breast cancer (invasive tumour, in situ tumour, or tumour of unknown invasiveness) and 53,461 controls, using a panel of 34 known or suspected breast cancer susceptibility genes

- Samples came from women participating in 44 BCAC studies – 30 of the studies did not select patients or control on the basis of family history, the remaining 14 studies oversampled patients with a family history of breast cancer
- Protein-truncating variants in *ATM, BRCA1, BRCA2, CHEK2,* and *PALB2* were associated with a risk of breast cancer overall (P <0.0001)
    - Odds ratios: *ATM* = 2.10; *CHEK2* = 2.54; *PALB2* = 5.02; *BRCA2* = 5.85; *BRCA1* = 10.57
- Protein-truncating variants in *BARD1, RAD51C, RAD51D,* and *TP53* were also associated with a risk of breast cancer overall (P <0.05; ORs: 1.80 to 3.06)
- Tumour subtypes:
    - *ATM* and *CHEK2* had a stronger association with ER+ disease than ER- disease
    - *CHEK2* also had an association with ER- non-triple-negative BC, but not with TNBC
    - *BARD1, BRCA1, BRCA2, PALB2, RAD51C*, and *RAD51D* had a stronger association with ER- disease than ER+ disease
    - *BARD1, BRCA1* and *BRCA2* had a stronger association with TNBC than with ER- non-TNBC
    - *BRCA1*, *BRCA2* and *PALB2* had stronger association with invasive tumours than in situ tumours, while for *ATM* and *CHEK2* ORs were similar for invasive and in situ tumours
- Age: ORs decreased significantly with increasing age for *BRCA1, BRCA2, CHEK2, PALB2, PTEN,* and *TP53*
- Absolute risk:
    - *BRCA1, BRCA2,* and *PALB2* = high risk
    - *ATM, BARD1, CHEK2, RAD51C,* and *RAD51D* = moderate risk
- Rare missense variants:
    - Evidence of association with BC overall for rare missense variants in *CHEK2, ATM, TP53, BRCA1, CDH1,* and *RECQL*
        - For *BRCA1* and *ATM,* breast cancer risk differed by the specific domain the variant was in
    - Rare missense variants (in aggregate) in *BRCA1, BRCA2,* and *TP53* that would be classified as pathogenic were associated with a risk of breast cancer similar to that of truncating variants
    - Rare missense variants in *CHEK2* and in specific domains in *ATM* are associated with moderate risk
- Breast cancer risk for several of the genes analysed (such as *FANCM, MSH6, NF1*) remains equivocal

A Population-Based Study of Genes Previously Implicated in Breast Cancer. Hu *et al.* (2021). *NEJM*. DOI: 10.1056/NEJMoa2005936

- Prevalence of pathogenic variants and associated risks of breast cancer have generally been based on high-risk populations of women (FH of breast/ovarian cancer, young age of diagnosis, ER- tumours, and founder mutations), therefore application of risk estimates to the general population is uncertain
- Population-based case-control study using 17 studies from the CARRIERS consortium

    - 12 of the 17 studies were not enriched with patients with FH or early onset disease
- Sequenced samples from 32,247 women with breast cancer and 32,544 unaffected women using a panel of 28 cancer-predisposition genes
    - 12 established breast cancer-predisposition genes and 16 candidate genes
    - LoF variants and variants identified as pathogenic or likely pathogenic in ClinVar were classified as pathogenic variants (PVs)
- Prevalence of PVs in *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D,* and *TP53* was 5.67% among case patients and 1.73% in controls in overall CARRIERS analysis (all 17 studies), and 5.03% in cases and 1.63% in controls in the population-based analysis
- PVs in *BRCA1, BRCA2* and *PALB2* were observed in 8.13% of patients with TNBC
- *BRCA1* carriers had mean age at diagnosis of 50.9 (ER+ disease) and 50.3 (ER- disease)
- *BRCA2* carriers had mean age at diagnosis of 55.4 (ER+ disease) and 58.6 (ER- disease)
- Prevalence of VUS in the 12 established genes: 18.9% in case patients and 18.5% in controls
- PVs in *BRCA1* and *BRCA2* were associated with a **high** risk of breast cancer – Odds ratios (ORs) of 7.62 and 5.23, respectively
- PVs in *PALB2* and *CHEK2* were associated with a **moderate** risk (OR = 3.83 and 2.47) in the population-based analysis
- *PALB2* identified as a **high** risk gene (OR 8.04) among case patients with a FH of breast cancer – highlighting the effect of FH on breast cancer risk
- Absolute risk:
    - PVs in *ATM, BRCA1, BRCA2, CHEK2,* and *PALB2* were associated with lifetime absolute risk of breast cancer of greater than 20% by age 85 years among
    - PVs in *BRCA1* or *BRCA2* yielded a lifetime risk of approximately 50%
    - PVs in *PALB2* yielded a lifetime risk of approximately 32%
- Pathogenic variants in *BARD1, RAD51C,* and *RAD51D* were associated with increased risks of ER- breast cancer and TNBC
- Pathogenic variants in *ATM, CDH1* and *CHEK2* were associate with increased risks of ER+ BC
- Could not assess *PTEN* and *TP53* due to limited numbers of women with PVs in these genes
- None of the 16 candidate genes were significantly associated with increased risk of breast cancer (including the MMR genes)
- Age:
    - Prevalence of PVs in *BRCA1* and *BRCA2* among case patients decreased rapidly after age 40
    - Constant and limited decline in the prevalence of PVs in *ATM, CHEK2* and *PALB2* among case patients 40 to 85 years of age

Counselling and ethics

Influence of lived experience on risk perception among women who received a breast cancer polygenic risk score: "Another piece of the pie". Willis *et al.* (2021). *Journal of Genetic Counselling.* DOI: https://doi.org/10.1002/jgc4.1384

- The impact of polygenic risk information on perceived risk of cancer has not been explored, particularly in unaffected women and those who have not received genetic counselling
- This study aimed to explored women's experiences of receiving a PRS, and how this impacts their breast cancer risk perceptions and health behaviours
- Quantitative phenomenological study with participants recruited from the wider Variants in Practice Psychosocial Study (ViPPS) investigation psychological impact of SNP test for breast cancer
- Women were eligible to participate if they were unaffected by breast cancer, had not attended a genetic counselling appointment, and had received a PRS result
- 20 women took part in semi-structured interviews by telephone, informed by a topic guide. Data explored using thematic analysis
- Participants had broad range of experiences of breast cancer, and most participants described he family experience of breast cancer as being internalised, and part of the family narrative, whether they were personally present or not. This led to a personal awareness of breast cancer risk for most women
- Participants mostly supported a multifactorial model of cancer aetiology both before and after receiving their PRS. There was also an awareness of relevant modifiable risk factors including diet, exercise, weight and alcohol consumption. The role of "bad luck" was frequently raised by participants
- In constructing their perception of breast cancer risk, participants often used non-genetic factors to explain certain parts of the family history, but described a sense of vulnerability to breast cancer strongly linked to the family history
- Most participants reported that their PRS was consistent with their existing perception of breast cancer risk, meaning it was easily accepted and integrated into their understanding
- After receiving their PRS, most women reported no plans to change risk management strategies. However most participants continued to express importance of screening and modifiable risk factors
- Participants gained a sense of reassurance, as they felt they were "doing everything I can do"
- Lived experience of breast cancer in the family was women's primary source of knowledge and played a key role in their beliefs

A systematic review and meta-analysis of telephone vs in-person genetic counseling in BRCA1/BRCA2 genetic testing. Bracke, Roberts and McVeigh. (2020). https://doi.org/10.1002/jgc4.1343

- In light of the on-going COVID19 pandemic, alternatives to face-to-face consultations have had to be considered and adopted, including telemedicine
- Systematic review and meta-analysis to determine whether telephone counselling for *BRCA1* and *BRCA2* genetic testing is non-inferior to in-person genetic counselling for the outcomes of cancer-specific distress and genetic knowledge

- Particular important as high levels of cancer-specific distress and low genetic knowledge have previously been shown to impair the comprehension of genetic risk information, and therefore impair the capacity to give informed consent and negatively impact the decision-making in risk-reducing management options in patients at risk of HBOC

- Review and analysis included randomised controlled trials involving males or females aged over 18 years old, comparing telephone genetic counselling to in-person genetic counselling
  - Four studies were included in the qualitative synthesis and three of those were included in the quantitative synthesis
- Two of the studies measured cancer-specific distress one week after the pre-test counselling session, and both found telephone counselling to be non-inferior to in-person counselling
- All four studies measured cancer-specific distress after the result disclosure, and found telephone-based counselling to be non-inferior to in-person counselling
- The four studies measured genetic knowledge at differing time points after either pre-test genetic counselling or after result disclosure
  - Three of the studies did not show a statistically significant difference between in-person and telephone counselling
  - One study, which evaluated genetic knowledge within one week after result disclosure, found that genetic knowledge was inferior in the telephone group compared to the in-person group.
- Authors suggest the meta-analysis provides a further level of evidence for the use of telephone genetic counselling in circumstances where in-person genetic counselling is not recommended.
- Some limitations, for example the studies reviewed/analysed did not look at the preferences of people who declined to take part in the randomisation of telephone or in-person genetic counselling, demographics of participants were mostly non-Hispanic white women with higher than average income and college education, and different measurement tools for genetic knowledge used in each trial.

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Katie Snape, Consultant Cancer Geneticist, St. George's Hospital, London
Alice Coulson, Genetic Counsellor, Guy's Hospital, London
Ouranio Anastasiou, Genturis Project Manager, ERN GENTURIS Affiliated Partner Cyprus