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

Bigger picture

Seminal papers describing in depth the molecular features which could be identified through next generation sequencing of cancer genomes were published in Cell in 2012 and Nature in 2013. The power of this approach relied on using bioinformatic pattern recognition (non-negative matrix factorization (NMF)) to identify patterns – mutational signatures – within the cancer genome due to specific mutagenic processes. Whole genome sequencing in cancer is being increasingly integrated into routine clinical practice as the implications of this work in diagnostics, prognostics and therapeutics are realised.

An intriguing new study in Science Advances applies the same principles (and NMF) to the germline genome – can we identify specific mutational patterns within germline whole genome sequence data which may influence cancer predisposition and clinical outcome? By comparing germline WGS from 9,712 cancer patients and 16,670 non-cancer individuals, the study identified seven cancer associated germline genomic patterns (CGGPs) and showed enrichment of these germline signatures in patients who developed specific tumour histological subtypes, distinct oncogenic pathways and with clinical outcome. This suggests that certain "sporadic" cancers may have more of an inherited influence than previously considered, and that our germline genomes may influence the likelihood of our cells developing specific somatic changes driving oncogenesis.

Translational science

The role of polygenic risk and susceptibility genes in breast cancer over the course of life. Mars *et al.* (2020). *Nat Commun*; 11, 6383. https://doi.org/10.1038/s41467-020-19966-5

- Polygenic risk scores (PRS) are becoming increasingly popular in assessing individual cancer risk
- Less is known about the interaction between PRS and other risk factors, including personal history of cancer and high-risk cancer susceptibility genes
- This study included n=122,978 women from the FinnGen cohort (~5% of the female population), including n=8,401 breast cancer cases
- Three candidate PRS were compared (one 313 SNP-based PRS, and two genome-wide PRS)
- Two truncating variants which are highly enriched in the Finnish population were assessed:
    - *PALB2* c.1592delT
    - *CHEK2* c.1100delC
- The cancer risk associated with a high PRS (>90th centile) was similar to the risk associated with the *CHEK2* variant - but a high PRS was more common in the population by 7-fold

- PRS significantly modified the individual cancer risks in patients with high-risk single gene variants:
    - For the *PALB2* variant, the risk was 83.9% in patients with PRS >90th centile, compared to 49.1% in patients with PRS <10th centile
    - For the *CHEK2* variant, the risk was 59.2% in patients with PRS >90th centile, compared to 9.3% in patients with PRS <10th centile
- Among patients who developed breast cancer, high PRS was associated with an increased risk of developing a second, contralateral breast cancer (HR 1.6)
- These findings provide further evidence that PRS can be incorporated into individual cancer risk assessment, including in patients with a personal history of cancer or pathogenic variants in high-risk cancer susceptibility genes

Performance of In Silico Prediction Tools for the Detection of Germline Copy Number Variations in Cancer Predisposition Genes in 4208 Female Index Patients with Familial Breast and Ovarian Cancer. Lepkes *et al.* (2021). *Cancers*; 13(1): 118. https://doi.org/10.3390/cancers13010118

- Investigation of the performance of four in silico CNV prediction tools including one commercial (Sophia Genetics DDM) and three non-commercial tools (ExomeDepth, GATK gCNV, panelcn.MOPS) in 17 cancer predisposition genes in a large series of 4208 female index patients with familial breast and/or ovarian cancer.
- Identification of 77 CNVs in 76 out of 4208 patients (1.81%); six CNVs were missed by at least one of the prediction tools.
- CNV predictions were verified via multiplex ligation-dependent probe amplification. 33 CNVs were identified in genes other than *BRCA1/2*, mostly in *ATM, CHEK2*, and *RAD51C* and less frequently in *BARD1, MLH1, MSH2, PALB2, PMS2, RAD51D*, and *TP53*
- The Sophia Genetics DDM software showed the highest sensitivity. The positive predictive values ranged from 5.9% (74/1249) for panelcn.MOPS to 79.1% (72/91) for ExomeDepth.
- The authors concluded that in the framework of genetic counseling for persons at risk for familial BC/OC, CNV detection should be included in routine germline diagnostics for all BC/OC predisposition genes and may not be restricted to *BRCA1/2*, as a relevant proportion of women in their study sample (0.76%) were affected by CNVs in non-*BRCA1/2* genes.

In the clinic

Examining the uptake of predictive BRCA testing in the UK; findings and implications. Martin *et al.* (2020). *Eur J Hum Genet.* https://doi.org/10.1038/s41431-020-00783-9

- Predictive *BRCA* testing can be used to determine an individual's cancer risk, and whether they require additional screening and/or risk-reducing surgery
- This study sought to assess factors affecting uptake and timing of testing in the UK
- The study population included 779 patients who underwent predictive BRCA testing between 2010 and 2017
- 83.4% of the original probands had relatives who subsequently underwent predictive testing
- Median time to predictive testing was 390 days (range, 0-7,090 days)

- Factors assessed as possible determinants of testing uptake included patient gender, BRCA test type, cancer history, deprivation index, and education status
- Factors which significantly affected testing uptake included:
  - Proband unaffected by cancer (lower uptake, OR 0.14)
  - Age (higher uptake in patients >40 years, HR 1.41)
  - *BRCA* gene (higher uptake in *BRCA2* testing compared to *BRCA1*, HR 1.39)
- These findings suggest that uptake of predictive testing does not seem to be strongly determined by social or demographic variables, other than age

Germline *TP53* testing in breast cancers: Why, when and how? Evans *et al.* (2020). *Cancers*; 12, 3762. 10.3390/cancers12123762

- *TP53* variants that are detected in blood are one of the main genetic causes of breast cancers before 31 years of age
- The development of cancer multi-gene panels provides the opportunity for increased and more detailed germline *TP53* testing in breast cancer patients.
- The complex interpretation of *TP53* variants, especially the missense variants, adds up to the complex and variable management of patients, since it sometimes leads to the development of drastic medical consequences.
- This work comments on a lot of important aspects on the *TP53* testing in patients with breast cancer such as: the disease-causing variants, the mosaic variants versus the clonal haematopoiesis and circulating tumour DNA, and the cancer risk associated with germline disease-causing *TP53* variants.
- They also discuss the most recent important features of breast tumours in *TP53* variant carriers, such as the age of tumour-onset and histopathologic features.
- Lastly, the authors elegantly analyse the treatment-related risks in *TP53* variant carriers, the surveillance protocols of carriers and the impact of a germline disease-causing *TP53* variant on genetic counselling and the psychological considerations that need to be taken into account
- The authors concluded that, in breast cancer patients, germline *TP53* testing should be performed before any treatment and shall be offered systematically only to patients with:
  - (i) invasive breast carcinoma or ductal carcinoma in situ (DCIS) before 31; or
  - (ii) bilateral or multifocal or HER2+ invasive breast carcinoma/DCIS or phyllode tumour before 36; or
  - (iii) invasive breast carcinoma before 46 and another *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma); or
  - (iv) invasive breast carcinoma before 46 and one first- or second-degree relative with a *TP53* core tumour before 56.
- They also suggested that women presenting with breast cancer after 46, without suggestive personal or familial history, should not be tested for *TP53*.

Counselling and ethics

Family communication about genomic sequencing: A qualitative study with cancer patients and relatives. Smit et al (2020). *Patient Education and Counselling*
DOI: https://doi.org/10.1016/j.pec.2020.10.022

- Responsibility to inform family members about genomic sequencing and results is often left to the proband and role of healthcare professional varies
- Introduction of unexpected and uncertain roles in genomic sequencing compared to
- Qualitative study of cancer patients and their relatives who have undergone genomic sequencing, but not received results yet
- Sub-study from Australian Psychosocual Issues in Genomics in Oncology (PiGeOn project). One of two types sequencing were undertaken – molecular tumour profiling or germline genome sequencing
- Interviews posing open-ended questions about experiences and views of genomic sequencing, and family communication
- Specific focus on family communication about decision to have sequencing, intention to disclose results, and resources or support needed to facilitate communication.
- 73 participants took part in interviews
- Three broad themes identified: Conversations with family about undertaking genomic sequencing, if perceived as relevant and meaningful; result disclosure intentions guided by ethical obligation to tell and protect; and resource and support needs for communication results
- Several factors influencing discussing undertaking sequencing with family: family member's interest, relevance, existing open communication in family, concern about family member's ability to cope, limited knowledge and feeling there's nothing to discuss until results available
- Themes on family communication: perceived disease severity, availability of management options, family members' ability to cope and implications for insurance
- Participants felt it was hard to anticipate what support would be needed in family communication prior to receiving a genomic result
- Some themes were more prevalent in one sequencing group, compared to the other
- Provides suggestions for family interventions and support based on these themes

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
Phil Ostrowski, Clinical Genetics Registrar, St. George's Hospital, London
Alice Coulson, Genetic Counsellor, Guy's Hospital, London
Ouranio Anastasiou, Genturis Project Manager, ERN GENTURIS Affiliated Partner Cyprus