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

Bigger picture

Shuai Li and colleagues have recently published a study which provides more precise age-related risk estimates of cancers, other than female breast and ovarian cancers, which are associated with pathogenic variants in *BRCA1* and *BRCA2*. They used data from 3,184 *BRCA1* and 2,157 *BRCA2* families in the Consortium of Investigators of Modifiers of *BRCA1/2* to estimate age-specific relative and absolute risks.

Their analysis showed that *BRCA1* pathogenic variants were associated with a 4.30 relative risk of male breast cancer, 2.36 relative risk of pancreatic cancer, and 2.17 relative risk of stomach cancer. The data also suggested associations with colorectal and gallbladder cancers, but no associations were found for prostate cancer. The absolute risks to age 80 years ranged from 0.4% for male breast cancer, to approximately 2.5% for pancreatic cancer.

BRCA2 pathogenic variants were associated with a 44.0 relative risk of male breast cancer, 3.69 relative risk of stomach cancer, 3.34 relative risk of pancreatic cancer, and 2.22 relative risk of prostate cancer. They also showed that the stomach cancer RR was higher for females than males. Absolute risks to age 80 years ranged from approximately 2.5% for pancreatic cancer, to 27% for prostate cancer.

The authors also include a helpful table which shows age-specific absolute risks for breast cancer, pancreatic cancer, stomach cancer, and prostate cancer (*BRCA2* only) at age 50, 60, 70 and 80 years.

Translational science

Proteogenomics of non-small cell lung cancer reveals molecular subtypes associated with specific therapeutic targets and immune-evasion mechanisms. Lehtiö *et al.* (2021). *Nature Cancer*; 2: 1224-1242. DOI: https://doi.org/10.1038/s43018-021-00259-9

- Despite major advancements in lung cancer treatment, long-term survival is still rare and a deeper understanding of molecular phenotypes would allow the identification of specific cancer dependencies and immune-evasion mechanisms.
- The authors in this paper performed in-depth mass-spectrometry-based proteogenomic analysis of 141 tumors representing all major histologies of non-small cell lung cancer (NSCLC).

- They identified six distinct proteome subtypes with striking differences in immune cell composition and subtype-specific expression of immune checkpoints.
- They also identified that high neoantigen burden was linked to global hypomethylation and complex neoantigens mapped to genomic regions, such as endogenous retroviral elements and introns, in immune-cold subtypes.
- Then they linked immune evasion with LAG-3 via STK11 mutation-dependent HNF1A activation and FGL1 expression and finally, they develop a data-independent acquisition mass-spectrometry-based NSCLC subtype classification method, validated it in an independent cohort of 208 NSCLC cases and demonstrated its clinical utility by analyzing an additional cohort of 84 late-stage NSCLC biopsy samples.

Radiation therapy enhances immunotherapy response in microsatellite stable colorectal and pancreatic adenocarcinoma in a phase II trial. Parikh *et al.* (2021). *Nature Cancer*; 2: 1124-1135. DOI https://doi.org/10.1038/s43018-021-00269-7

- Overcoming intrinsic resistance to immune checkpoint blockade for microsatellite stable (MSS) colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC) remains challenging.
- The authors here conducted a single-arm, non-randomized, phase II trial (NCT03104439) combining radiation, ipilimumab and nivolumab to treat patients with metastatic MSS CRC (n = 40) and PDAC (n = 25) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- The first endpoint was disease control rate (DCR) by intention to treat. DCRs were 25% for CRC (ten of 40; 95% confidence interval (CI), 13–41%) and 20% for PDAC (five of 25; 95% CI, 7–41%).
- In the per-protocol analysis, defined as receipt of radiation, DCR was 37% (ten of 27; 95% CI, 19–58%) in CRC and 29% (five of 17; 95% CI, 10–56%) in PDAC.
- Analysis of pre-treatment biopsies revealed low tumor mutational burden for all samples but higher numbers of natural killer (NK) cells and expression of the HERVK repeat RNA in patients with disease control.
- Overall, this study provides proof of concept of combining radiation with immune checkpoint blockade in immunotherapy-resistant cancers.

Quantifying evidence toward pathogenicity for rare phenotypes: The case of succinate dehydrogenase genes, *SDHB* and *SDHD*. Garrett *et al.* (2021). *Genetics in Medicine*. Doi: https://doi.org/10.1016/j.gim.2021.08.004

- Inherited predisposition to pheochromocytomas and paragangliomas (PCC/PGL) is associated with constitutional pathogenic variants (PVs) in >15 genes, including *SDHA, SDHAF2, SDHB, SDHC, SDHD, VHL, FH, MAX, TMEM127, RET, MEN1*, and *NF1*. Among the Mendelian PCC/PGL cases, the most sizable contribution is from PVs in *SDHB* followed by *SDHD*.
- Loss-of-function, protein-truncating variants in *SDHB/SDHD* are typically pathogenic. However, interpretation and classification of missense variants is more challenging.
- The weight of the evidence to attach to observation of a novel rare missense variant in *SDHB* or *SDHD* in individuals with PCC/PGL is uncertain.
- The authors compared the frequency of *SDHB* and *SDHD* very rare missense variants (VRMVs) in 6328 and 5847 cases of PCC/PGL, respectively, with that of population controls. They used this comparison to generate a pan-gene VRMV likelihood ratio (LR).
- As previously demonstrated by Tavtigian et al. (*Genet Med.* 2018) the ACMG/AMP categorical evidence strengths can be converted to LRs (supportive LR = 2.08, moderate LR = 4.33, strong LR = 18.8, and very strong LR = 350).
- The authors of the current study used windowing analysis to measure regional enrichments of VRMVs to calculate a domain-specific (DS-) VRMV-LR. They also calculated sub-phenotypic LRs for variant pathogenicity for various clinical, histologic, and molecular features.
- The pan-gene VRMV-LR was estimated to be 76.2 for *SDHB* and 14.8 for *SDHD*.
    - After removal of recurrent-pathogenic-VRMVs, the PG-VRMV-LR was reduced to 34.6 for *SDHB* and 14.8 for *SDHD*.
- Clustering analysis revealed an *SDHB* enriched region (aa 177-260; 30% of coding region) for which the DS-VRMV-LR was 127.2 and an *SDHD* enriched region (aa 70-114; 28% of coding region) for which the DS-VRMV-LR was 33.9.
    - Excluding the recurrent-pathogenic-VRMVs reduced the DS-VRMV-LR to 59.7 for *SDHB*; for *SDHD*, the DS-VRMV-LRs were unchanged.
- Sub-phenotypic LRs exceeded 6 for invasive disease (*SDHB*), head-and-neck disease (*SDHD*), multiple tumours (*SDHD*), family history of PCC/PGL, loss of *SDHB* staining on IHC, and succinate-to-fumarate ratio >97 (*SDHB, SDHD*).
- The authors conclude that the LRs relating to rarity and phenotypic specificity for a single observation in PCC/PGL of a *SDHB/SDHD* VRMV can afford substantial evidence toward pathogenicity.
- They also suggest the principles, requisite data sets, and methodologies used are universally applicable to any other gene/phenotype/variant-class scenario.

In the clinic

Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives. Salikhanov *et al.* (2021). *J Med Genet*. doi:10.1136/jmedgenet-2021-108062

- Lynch syndrome has an estimated population frequency of 1:279, but it remains largely undetected. Only a fraction of LS cases is referred for genetic evaluation and less than 10% receive genetic testing.
- The authors estimated the cost-effectiveness of universal DNA screening for Lynch syndrome (LS) among newly diagnosed patients with colorectal cancer (CRC) followed by cascade screening of relatives from the Swiss healthcare system perspective.
- They calculated incremental cost per quality-adjusted life-year saved by screening all patients with CRC (alternative strategy) for LS compared with CRC tumour-based testing (IHC, BRAF V600E testing) followed by DNA sequencing (current strategy).
- They found that the alternative strategy has an incremental cost-effectiveness ratio (ICER) of CHF65 058 per QALY gained compared with the current strategy, which is cost-effective according to Swiss standards.
- Based on annual incidence of CRC in Switzerland, universal DNA screening correctly identifies all 123 patients with CRC with LS, prevents 17 LS deaths and avoids 19 CRC cases, while the current strategy leads to 32 false negative results and 253 LS cases lost to follow-up.
- They showed that universal DNA testing is cost-effective in around 80% of scenarios, and that the cost of DNA testing and the number of invited relatives per LS case determine the cost-effectiveness ratio.
- The authors conclude that results can inform policymakers, healthcare providers and insurance companies about the costs and benefits associated with universal screening for LS and cascade genetic testing of relatives.

Counselling and ethics

Family planning in carriers of BRCA1 and BRCA2 pathogenic variants. Haddad *et al.* (2021). *Journal of Genetic Counseling*; XX: XXX. DOI: https://doi.org/10.1002/jgc4.1423

- People with hereditary breast and ovarian cancer syndromes face complex decisions about cancer risk reduction, and risk management. However, there is a lack of data about partnering and family planning decisions, particularly in male carriers of *BRCA1* and *BRCA2* pathogenic variants
- This study examined the factors associated with family planning and reproduction for those carrying *BRCA1* and *BRCA2* pathogenic variants, determine partner contributions, and whether there are differences in attitudes between male and female carriers

- This was a cross-sectional survey of 139 participants, aged 18 years old or older with either a *BRCA1* or *BRCA2* pathogenic variant (5 participants had both). 16.7% of participants were male.
- Participants reported having more biological children prior to genetic testing, compared to after. They tended to feel more guilt about passing on the pathogenic variant to their daughters, compared to sons.
- Only 24 female participants and 1 male participant reported discussing the option of preimplantation genetic diagnosis with their healthcare provider.
- Female participants under the age of 35 at the time of genetic testing were significantly more likely to feel a greater urgency to be in a committed relationship after their genetic test result. Younger females reported that their HBOC syndrome had a great impact on their reproductive plans and romantic relationships
- Male participants were more likely to report no urgency to have a family, compared to female participants. Other sex-based comparisons did not reach statistical significance but some differences were noted
- Those with a stronger family history of breast cancer were more likely to report that their risk-reducing mastectomies factored into family planning decisions
- Participants over 45 were less likely to report that their genetic status had an impact on reproductive plans and less likely to report that their genetic status had an impact on romantic relationships
- Overall, there is a sense of urgency regarding childbearing that younger carriers feel and both men and women feel guilt around passing on a pathogenic variant to offspring. Both male and female carriers should be provided with evidence-based information about family planning options.
- The authors report that a larger, more diverse study sample is needed to confirm the study's findings

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Alice Coulson, Genetic Counsellor, Guy's Hospital, London
Ouranio Anastasiou, Genturis Project Manager, ERN GENTURIS Affiliated Partner Cyprus