CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – July & August 2023

Translational science

Dissecting the genetic heterogeneity of gastric cancer. Hess *et al.* 2023. *Ebiomedicine*. doi: 10.1016/j.ebiom.2023.104616

- Meta-analysis of ten European GWAS of gastric cancer and its subtypes, aiming to assess the heterogeneity of gastric cancer (GC) with information on patient tumour location and histopathology; 5816 patients and 10,999 controls.
- Subtypes: Anatomically subdivided into cardia (in the proximal stomach at the gastro-oesophageal junction) and non-cardia type (in the distal stomach), histopathologically subdivided into Lauren's diffuse- and intestinal-type.
- Analysis identified four significant GWAS loci.
    - 2 have been reported previously (but not with subtype specificity)
    - 1q22
        - SNP rs760077, near *MUC1*, showed strongest association with non-cardia and diffuse GC, while the association was nearly absent in cardia GC.
        - SNP rs67579710 showed genome-wide significant association to entire and non-cardia GC.
    - 8q24
        - SNP rs2920293, near *PSCA*, had the strongest GC association. Particularly in non-cardia and diffuse GC subtypes.
        - No association with cardia GC.
    - 2 which have not been identified before:
    - 2p23
        - SNP rs11677924 in intron 4 of *ALK*.
        - Suggestive association in the entire GC sample.
        - Genome-wide significant association in intestinal GC.
        - Moderate association to diffuse GC.
    - 17q12
        - SNP rs17138478 within intron 4 of *HNF1B*.
        - Suggestive association in the entire GC sample.
        - Genome-wide significant association to intestinal GC.
        - No association to diffuse GC.
- When focusing on 10 GC risk loci reported previously, researchers were able to replicate disease-associations at 3 loci.
    - 4q28 - strong association for rs10029005 near *ANKRD50* in non-cardia GC.
    - 5q13 – strong association for rs6897169 near *PTGER4* in non-cardia GC.
    - 9q24 – rs532436 within intron 1 of *ABO* (encoding ABO blood group) associated to non-cardia GC and even more strongly to diffuse GC.

        - By inferring blood group from nearby SNPs which determine the ABO system, researchers could determine that blood-group 0 protects against non-cardia and diffuse GC and blood-group A increases risk for both GC subtypes.

        - Future studies could show how *ABO* contributes to GC at a cellular level.
    - Of the other GWAS loci that were not functionally characterised, variants are located in close proximity to promising GC candidate genes *ALK* and *HNF1B.*
- Known risk loci - 1q22 (*MUC1*), 4q28 (*ANKRD50*), 5p13 (*PTGER4*), 8q24 (*PSCA*), and 9q34 (*ABO*) - contribute almost exclusively to non-cardia GC.
    - With upregulated expression of *MUC1, ANKRD50, PTGER4,* and *PSCA* revealed in the TWAS/eQTL analysis to be the most plausible GC-pathomechanism at these loci.
- 1q22 (*MUC1*), 8q24 (*PSCA*), and 9q34 (*ABO*) confer substantially higher risk to diffuse than to intestinal GC.
- 2p23 (*ALK*) and 17q12 (*HNF1B*) contribute almost exclusively to intestinal GC.
- Also examined whether oesophago-gastric adenocarcinomas at the gastric-oesophageal junction share genetic aetiology.
    - Researchers could imply from a highly significant association between cardia GC and PRS derived from oesophageal adenocarcinoma and its precursor lesion Barrett's oesophagus that these cancer types share polygenic risk architecture.
    - Newly identified risk SNPs for oesophago-gastric adenocarcinoma are in close vicinity to promising candidate genes *HNF4G* and *NR2F2*, both involved in intestinal-like cell transformations in gastric cell lineages.

Evaluation of European-based polygenic risk score for breast cancer in Ashkenazi Jewish women in Israel. Levi *et al.* (2023). *J Med Genet* Epub ahead of print; 0: 1-12. http://dx.doi.org/10.1136/jmg-2023-109185

- It is well known that most breast cancer (BC) GWAS to date have been performed in individuals of European (EUR) ancestry. The generalisation of EUR-based PRS to other populations poses a major challenge since PRS peformance declines substantially as the genetic distance increases between the *discovery population* and the *target population*.
- Studies in women of EUR ancestry have shown that women in the top 1% of an optimised PRS model have a >4-fold elevated risk of developing breast cancer compared to those in the middle quintile (40-60%).
- This study looks at the performance of EUR-based BC PRS models in Ashkenazi Jewish (AJ) women in Israel. Given the relatively low genetic distance between the EUR and AJ populations, the authors hypothesised that EUR BC PRS could be used to develop clinically relevant PRS models for AJ women in Israel.
- The PRS performance was tested on a cohort of 2161 AJ women from Israel (1437 cases and 724 controls) from the BCAC cohort. They also tested the EUR-based BC PRS and an established 313-SNP EUR BC PRS in an independent cohort of 181 AJ women from Hadassah Medical Center (HMC) in Israel.
- Results:
    - OR for AJ women in the top 10% compared to the middle quintile was >2.0.
    - Women in the top 10% were estimated to have fourfold higher OR for BC compared with AJ women in the bottom 10%, and these OR estimates were comparable to those reported using EUR BC PRS on women of EUR ancestry.

  - BCAC-Israeli cohort is too small to calculate reliable risk estimates for women in the top 5% and 1%, follow-up studies needed with larger samples of AJ women.
  - Lassosum PRS program had the best predictive performance for the Israeli cohort.

- Results indicated that EUR-based BC PRS has clinically relevant predictive capacity for Israeli AJ women. The authors conclude that their study suggests the possibility of personalised BC screening programmes in Israel that could potentially improve early detection of BC while reducing overdiagnosis.

In the clinic

Clinical case study meets population cohort: identification of a *BRCA1* pathogenic founder variant in Orcadians. Kerr *et al.* 2023. *European Journal of Human Genetics.* doi.org/10.1038/s41431-023-01297-w

- This study reports on the identification of a *BRCA1* pathogenic founder variant in Orkney in the Northern Isle of Scotland.
- *BRCA1* pathogenic missense variant c.5207T > C; p.Val1736Ala (V1736A)
- The variant was ascertained in 9 diagnostic tests of breast and ovarian cancer cases.
- Predictive testing of relatives identified 14 carriers of the variant and 6 female obligate carriers were picked up.
  - Oral history and birth, marriage and death registrations indicated genealogical linkage of the clinical cases to ancestors from the Isle of Westray, Orkney, traced back to the 1800s.
- Exome sequence data from the ORCADES research cohort (over 2000 volunteer participants with three or more Orcadian grandparents) was also interrogated for the Orcadian population prevalence of the variant.
  - Found in 20 individuals (~1%)
  - ~480-fold higher than prevalence found in UK Biobank participants.
- Authors propose that women with two or more Orcadian grandparents should be offered targeted testing for the founder BRCA1 variant.
  - NHS Grampian genetics service are offering targeted testing to Orcadians with breast and ovarian cancer family history.
  - Currently trying to pilot population-based screening for the variant on Westray for those with known Westray ancestry.
  - CLAN Cancer Support offering monthly drop-in sessions to provide emotional and practical support for Orcadians as they come to understand their genetic risk.
- Authors also propose that all women of Orcadian ancestry with a diagnosis of breast cancer should have a targeted test for this variant if a BRCA1/2 test is not offered as part of their clinical care.
- This study shows the value of diverse population cohorts in understanding the burden of rare clinical variants in different groups.

Counselling and ethics

UK recommendations for the management of transgender and gender-diverse patients with inherited cancer risks. Giblin *et al.* (2023). *Nature: BJC Reports*; 1; https://doi.org/10.1038/s44276-023-00002-0

- UK CGG and Central & South GMSA facilitated a 2-day virtual meeting in October 2022 to develop national consensus to support the management of transgender or gender diverse (TGD) patients with inherited cancer risks.
- Background documents (available at https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/) were produced and circulated to all registrants prior to the meeting.
- The meeting was divided into seven sessions, with each session starting with a talk from an expert speaker, followed by group discussion, and then voting on each proposed statement for best practice.
- Most statements were presented with five options for voting using a Likert scale of "strongly agree", "agree", "neither agree nor disagree", "disagree" and "strongly disagree".
    - Proposed statements were considered to reach consensus if 80% of respondents voted "strongly agree" or "agree", when a minimum of 80% of attendees (at the time of voting) had cast their vote.
- Consensus reached on: Family History Questionnaires; Pedigree Charting; Clinical Information; Breast Tissue Management; Gynaecological and Prostate Management, Patient Pathways; and Education. See table 2 in the paper for a summary of the statements on which consensus was reached.
- Further work required to reach consensus on breast screening recommendations for TGD patients assigned female at birth who have had masculinising chest surgery.
- A major limitation of the guidance is the dearth of data on which discussions and recommendations are based. Further research is needed, particularly on the impact of gender-affirming treatment on cancer risks, and on the experiences of TGD patients accessing cancer genetics services.

Monthly Journal Round-Up brought to you by:

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