CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – December 2021

Translational science

Identification of SNPs in hMSH3/MSH6 interaction domain affecting the structure and function of MSH2 protein. Singh *et al.* (2021). *Biotechnology and Applied Biochemistry*; 00: 1-12. https://doi.org/10.1002/bab.2295

- MutS Homolog 2 is a mismatch repair gene that plays a critical role in DNA repair pathways, and its mutations are associated with different cancers.
- Current study aimed to find out the SNPs of MSH2 protein associated with causing structural and functional changes leading to the development of cancer with the help of computational tools.
- Four different tools for predicting deleterious SNPs (SIFT, PROVEAN, PANTHER, and PolyPhen), two tools each for identifying disease association (PhD SNP and SNP&GO) and estimating stability (I-mutant and MUPro) were employed.
- Homology modeling, energy minimization, and root mean square deviation calculation were used to estimate structural variations.
- Twenty-seven SNPs and five SNPs (double amino acid change) were identified based on a consensus approach that might be associated with the structural and functional change in MSH2 protein.
- Molecular docking reveals that six SNPs affect the interaction of MSH2 and MSH6. Twelve SNPs identified were reported to be linked with hereditary nonpolyposis, colorectal cancer, and Lynch syndrome.
- Further, selected SNPs need to be validated in an in vitro system for their precise association with cancer predisposition.

LILRB3 supports acute myeloid leukemia development and regulates T-cell antitumor immune responses through the TRAF2–cFLIP–NF-κB signaling axis. Wu *et al.* (2021). *Nature Cancer*; 2: 1170-1184. https://doi.org/10.1038/s43018-021-00262-0

- Leukocyte immunoglobulin-like receptor B (LILRB), a family of immune checkpoint receptors, contributes to acute myeloid leukemia (AML) development, but the specific mechanisms triggered by activation or inhibition of these immune checkpoints in cancer is largely unknown.
- This work demonstrates that the intracellular domain of LILRB3 is constitutively associated with the adaptor protein TRAF2.
- Activated LILRB3 in AML cells leads to recruitment of cFLIP and subsequent NF-κB upregulation, resulting in enhanced leukemic cell survival and inhibition of T-cell-mediated anti-tumor activity.

- Hyperactivation of NF-κB induces a negative regulatory feedback loop mediated by A20, which disrupts the interaction of LILRB3 and TRAF2; consequently the SHP-1/2-mediated inhibitory activity of LILRB3 becomes dominant.
- Lastly, the authors show that blockade of LILRB3 signaling with antagonizing antibodies hampers AML progression.
- Overall, this study suggests that LILRB3 exerts context-dependent activating and inhibitory functions, and targeting LILRB3 may become a potential therapeutic strategy for AML treatment.

In the clinic

Comprehensive epithelial tubo-ovarian cancer risk prediction model incorporating genetic and epidemiological risk factors. Lee *et al.* (2021). *Journal of Medical Genetics*. doi:10.1136/jmedgenet-2021-107904

- The previous epithelial tubo-ovarian cancer (EOC) risk prediction model considered the effects of PVs in *BRCA1* and *BRCA2* and explicit FH of EOC and breast cancer (BC)
- They have now developed a multifactorial EOC risk model for women of European ancestry incorporating the effects of pathogenic variants (PVs) in *BRCA1, BRCA2, RAD51C, RAD51D,* and *BRIP1*, a Polygenic Risk Score (PRS) of arbitrary size, the effects of risk factors (RFs) and explicit FH using a synthetic model approach.
    - FH includes explicit FH of ovarian, breast, prostate, male breast, and pancreatic cancer. The model considers families of arbitrary size and structure, including affected and unaffected relatives. It considers sex of all family members, and the age at cancer diagnosis or current age/ages at death of family members.
    - Other RFs include height, BMI, parity, endometriosis, use of oral contraception, use of HRT, tubal ligation, breast tumour pathology, country of origin, birth cohort, and Ashkenazi Jewish ethnicity.
    - For individuals carrying more than one PV, the risk is determined by the highest-risk PV and any lower-risk PVs are ignored
    - PRS, PV and RFs were assumed to act multiplicatively
- Partial model validation was carried out in a nested case-control sample of women of self-reported European ancestry participating in UKCTOCS. (Women with a FH of 2 or more relatives with EOC or who were known carriers of BRCA1/2 PVs were not eligible to participate in UKCTOCS.)
- Based on a currently available PRS for EOC that explains 5% of the EOC polygenic variance, the estimated lifetime risks under the multifactorial model in the general population vary from 0.5% to 4.6%. The corresponding range for women with an affected FDR is 1.9-10.3%.
- Based on the combined risk distribution, 33% of *RAD51D* PV carriers are expected to have a lifetime EOC risk of less than 10%
- RFs provided the widest distribution, followed by the PRS.
- The authors conclude that this multifactorial risk model can facilitate stratification, in particular among women with FH of cancer and/or moderate-risk and high-risk PVs. The model is available via the CanRisk tool.

Massive parallel sequencing in individuals with multiple primary tumours reveals the benefit of re-analysis. Karin *et al.* (2021). *Hereditary Cancer in Clinical Practice*; 46. https://doi.org/10.1186/s13053-021-00203-z

- Multiple primary cancers, defined as three or more primary tumours, are rare, and there are few genetic studies concerning them. There is a need for increased knowledge on the heritability of multiple primary cancers and genotype-phenotype correlations.
- The authors here performed whole-genome/exome sequencing (WGS/WES) in ten individuals with three or more primary tumours, with no previous findings on standard clinical genetic investigations.
- In one individual with a clinical diagnosis of MEN1, a likely pathogenic cryptic splice site variant was detected in the *MEN1* gene. The variant (c.654C > A) is synonymous but the authors showed in a cDNA analysis that it affects splicing and leads to a frameshift, with the theoretical new amino acid sequence p.(Gly219Glufs*13).
- In one individual with metachronous colorectal cancers, ovarian cancer, endometrial cancer and chronic lymphocytic leukaemia, they found a likely pathogenic variant in the *MLH1* gene (c.27G > A), and two risk factor variants in the genes *CHEK2* and *HOXB13*. The *MLH1* variant is synonymous but has previously been shown to be associated to constitutional low-grade hypermethylation of the *MLH1* promoter, and segregates with disease in families with colorectal and endometrial cancer.
- No pathogenic single nucleotide or structural variants were detected in the remaining eight individuals in the study. Four of the participants did not fulfil clinical criteria for any specific cancer syndrome, and the authors suggest the cause is likely multifactorial in these patients.
- The authors concluded that in individuals with an unequivocal clinical diagnosis of a specific hereditary cancer syndrome, where standard clinical testing failed to detect a causative variant, re-analysis may lead to a diagnosis.
- The authors also recommend that individuals with three primary tumours, and with their first cancer diagnosed before 60 years of age, are referred to a clinical genetics department for an evaluation.

Counselling and ethics

Using chatbots to screen for heritable cancer syndromes in patients undergoing routine colonoscopy. Heald *et al.* (2021). *Journal of Medical Genetics*; 58(12): 807-814. DOI: https://doi.org/10.1136/jmedgenet-2020-107294

- This was a feasibility study to test the utility of a chatbot in a population of patients undergoing colonoscopy, aiming to identify those at increased risk of hereditary cancer, educate and obtain consent for genetic testing
- Chatbots are artificial-intelligence based computer programmes designed to simulate human behaviours in conversation. This can be used on a smartphone, tablet or computer and users are prompted by the chatbot to select suggested responses
- English-speaking patients presenting for colonoscopies were invited to participate. When logging onto the chatbot, they completed the CCART (colon cancer risk assessment tool), as well as their family history of cancer. If any questions were answered as “unsure”, they were

contacted by a genetics healthcare professional. If the subject answered positively, the chat continued with education, inheritance and management of hereditary cancer syndromes. Participants could choose to be contacted by a genetics healthcare professional at any stage

- All transcripts were reviewed by a GC and checked against medical records
- Participants underwent a 55 gene panel
- 487 people used the chatbot, with 181 proceeding with genetic testing. Genetics healthcare professionals spent a mean time of 14.3 minutes per participant who went ahead with testing, the majority of this time was spent disclosing genetic result. This is less time than spent with patients who go through more traditional testing routes
- The authors recognise that genetic testing should occur alongside genetic counselling and they call the chatbot a "genetic counselling extender"
- There were many subjects who required further history to be clarified or further information was needed. There were also some patients who did not follow through and required reminders, and the chatbot did not screen for all hereditary cancer syndromes
- This study demonstrates the possibility of using chatbots as a genetic counselling extender, and engagement rates are high. However, further research is needed to improve initiation rate

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