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

Translational science

Two novel variants and follow-up findings in four children with Bloom syndrome from two families. Busra *et al.* (2022). *Clinical Dysmorphology*; 31(1): 31-35. doi:10.1097/MCD.0000000000000391

- Bloom syndrome (OMIM 210900) is a rare autosomal recessive severe intrauterine onset growth retardation (IUGR) syndrome characterized by craniofacial dysmorphism with a long-narrow face and prominent ears and nose, sun-sensitive skin lesions of the face and cancer predisposition. Bloom syndrome is caused by biallelic, loss-of-function mutations in the BLM gene. Absent or nonfunctional BLM protein results in chromosome instability, excessive homologous recombination and increased frequency of sister chromatid exchange and is responsible for cancer predisposition. Patients with BS, therefore, have a high risk of developing almost all types of cancers at an earlier age and it is the most common cause of death.
- This paper refers to the follow-up findings and two novel variants in four children with Bloom syndrome.
- The authors here describe two novel variants in the BLM gene. Acanthosis nigricans and some of the skeletal findings in our patients were not previously reported. Recurrent infections, hypothyroidism, hyperinsulinism and hypogenitalism were observed during the followed-up period. Moreover, one patient was diagnosed with non-Hodgkin lymphoma at the age of 18. It is important that Bloom syndrome patients must be screened for cancer and other complications during their follow-up examination.

In the clinic

Pathology of Tumors Associated with Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. Breast Cancer Association Consortium. (2022). *JAMA Oncology.* doi:10.1001/jamaoncol.2021.6744.

- Multi-centre, international case-control analysis using data from the BRIDGES study to assess associations between variants in 9 BC susceptibility genes and pathological features of non-metastasised breast cancers.
    - BRIDGES study included 42,680 patients and 46,387 control participants, comprising women aged 18 to 79 years who were sampled independently of family history from 38 studies.
    - 9 BC susceptibility genes: *ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, RAD51C, RAD51D,* and *TP53*.
        - Included protein-truncating variants (PTVs) in all 9 genes, and rare missense variants in *BRCA1, BRCA2* and *TP53* that were considered likely pathogenic
- *RAD51C*, *RAD51D*, and *BARD1* variants associated mainly with triple-negative (TN) disease. *RAD51D* variants also associated with HR^+ERBB2^- high-grade tumours.
- *CHEK2* variants associated with all subtypes except for TN disease, for which there was no evidence of association.
- *ATM* variants most strongly associated with HR^+ERBB2^- ($HER2^-$) high-grade tumours

- *BRCA1* variants associated with increased risk of all subtypes, but odds ratios (ORs) varied widely and were highest for TN disease.
    - For *BRCA1*, OR was lowest for HR^+ERBB2^- low-grade disease and HR^+ERBB2^+ disease, and was intermediate for HR^+ERBB2^- high-grade and HR^-ERBB2^+ disease. Specifically, ORs were lowest for ER+, PR+ tumours.
    - *BRCA1* pathogenic variant carriers were more likely to be PR negative.
- *BRCA2* and *PALB2* variants associated with HR^+ERBB2^- high-grade disease and TN disease
- *TP53* variants most strongly associated with HR^+ERBB2^+ and HR^-ERBB2^+ subtypes
- All genes except *CHEK2* were more strongly associated with high-grade disease
    - Across genes, 27% to 72% of tumours were grade 3
- Decline in ORs with increasing age was seen for *BRCA1* and BRCA2
    - Trend also similar for all subtypes, as well as for CHEK2.
    - For all genes and subtypes, a decline in ORs was observed with increasing age
    - Together, the 9 genes were associated with 14.4% of all tumours in women 40y or under, but less than 4% in women older than 60y.
    - Combined prevalence of PVs was close to or exceeded 10% for all subtypes in women under 40y and for TN and HR^+ERBB2^- high-grade disease in women aged 40-59 years
- Prevalence of variants overall was higher among women with TN and HR^+ERBB2^- high-grade tumours than with other subtypes.
    - Highest prevalence (27.3%) among women 40yrs or younger with TN tumours
- Other prognostic factors:
    - PTVs in *BRCA2, CHEK2,* and *PALB2* were associated with larger tumour size, lymph node involvement, and higher stage at diagnosis
    - For each gene, most BCs were carcinoma no special type (ductal carcinoma)
    - *BRCA1* tumours were less likely to be lobular than ductal, but more likely to be medullary than non-medullary
    - *TP53* tumours were more likely to be mixed lobular and ductal than ductal carcinoma
- Practice implications: Age and subtype-specific risk estimates may be used to regine BC risk prediction algorithms, such as BOADICEA/CanRisk. These results may also inform guidelines for eligibility for gene panel sequencing and BC surveillance in the general population. Tumour characteristics could also be used to determine whether VUSs are likely to be pathogenic.

Red flags for early recognition of adult patients with PTEN Hamartoma Tumour Syndrome. Drissen *et al*. (2021). *Eur J Med Gen*. https://doi.org/10.1016/j.ejmg.2021.104364

- This retrospective cohort study aims to define phenotypic characteristics that can easily be assessed and manifest by early adulthood and which could serve as red flags for early recognition of adult patients at high risk of PTHS.
- Phenotypic characteristics including macrocephaly, multinodular goitre (MNG), and oral features were examined in 81 paediatric and 86 adult PHTS patients at the Dutch PHTS expert centre between 1997 and 2020.
    - MNG was defined as signs of thyroid nodules and/or goitre
    - Oral features included gingival hypertrophy, high palate (adults only) and oral papillomas

    - Macrocephaly was defined as a head circumference greater than the 97th percentile of the Dutch population at a given age. For adult patients fixed cut-offs were used: >58.5 cm for female and >61.5 cm for male adults. For paediatric patients, cut-offs were dependent on the age of the patient.
- Based on the characteristics' prevalence in different age groups, combinations of phenotypic characteristics were defined and evaluated on their potential to recognise individuals with PHTS
    - Macrocephaly was present in 100% of paediatric and 67% of adult patients
        - Important to note these numbers change depending on what cut-offs are used (i.e. if International cut-offs are used instead of Dutch ones)
    - The prevalence of MNG was ~50% in paediatric and gradually increased to >90% in adult patients
    - The majority of patients had oral features, including gingival hypertrophy (68%), a high palate (89%, adult patients only), and oral papillomas (71% tongue and/or mucosa papillomas; 67% tongue and 31% mucosa papillomas).
    - Prevalence of MNG and oral features was low in paediatric patients and gradually increased with age
- Scoring two out of three of these characteristics including macrocephaly, MNG or ≥1 out of three oral features yielded a sensitivity of 100% (95%CI 94–100%) in adults. This was 91% when the oral component was restricted to ≥2 or all 3 features, and the authors suggest including ≥2 out of three oral features is likely to have higher specificity, and so is preferable
- None of the other PHTS-related clinical signs were present in the majority of adult patients
- The presence of the combination of macrocephaly, MNG, or multiple oral features could serve as a red flag for general practitioners, medical specialists, and dentists to consider further assessment of the diagnosis PHTS in adults.
- The authors suggest that based on their findings, a PHTS diagnosis should still be considered, in both paediatric and adult patients, even when macrocephaly is not present.

Counselling and ethics

Reproductive and Genetic Responsibility: An Interpretive Description of Reproductive Decision-Making for Young People with Li-Fraumeni Syndrome. Shepherd *et al.* (2022). *Qualitative Health Research*. https://doi.org/10.1177/10497323211046240

- Making decisions about reproduction when living with a genetic condition can present challenges to family planning. People may use alternative avenues or assisted reproductive technologies (including pre-implantation genetic testing).
- Reproductive decision-making for individuals with Li-Fraumeni syndrome (LFS) has not been explored in-depth with qualitative data
- People between the ages of 15-39 years old, with a known pathogenic TP53 variant or at 50% risk, were able to take part. The 30 participants were recruited from four genetics services in Australia.

- Semi-structured interviews were conducted by telephone or in-person. An interview guide had been previously developed and piloted. This included topics such as risk perception, identity, relationships, reproductive decision making and support
- Reflexive thematic analysis was used, and a coding framework was developed which identified a series of themes:
    - Balancing the possibility of dying young from cancer and fulfilling parental responsibilities: with limited options to reduce mortality risk from a TP53 variant, there was a tension between this and wanting to become a parent, as there was concern about dying from a cancer.
    - Preventing the passage of a TP53 variant to children: ideals versus the reality of family formation using PGT: participants felt a moral responsibility to ensure the health of their future children. Deciding to use PGT was more complex than had been anticipated and could add tension to relationships.
    - Negotiating genetic responsibility and conventional conception: there were two distinct categories: those who used prenatal diagnosis and those who did not use this and planned to test children in infancy. For some participants, not having a child was better than having a child with LFS. For others, they were comfortable to test children in infancy and were reassured by testing and screening available.
- The authors have developed a checklist for clinicians to use when discussing complexities that arise around TP53 family planning
- The authors note that many participants were not actively engaged in reproductive decision making so would be making hypothetical judgements.
- Reproductive decision making for families with LFS appears to be a moral practice, which can pose challenges including a sense of responsibility, uncertainty around success of options and emotional burden.

Investigating men's motivations to engage in genetic screening for BRCA1 and BRCA2 mutations. Annoni and Longhini. (2022). *PLoS ONE.* 17(3): e0265387. https://doi.org/10.1371/journal.pone.0265387

- Aimed to study the determinants of men's motivations to engage in genetic testing for *BRCA1* and *BRCA2*.
- Questionnaire based approach of 125 men (mean age = 58.53y) using a Health Action Process Approach (HAPA).
    - HAPA is a theoretical model that tries to understand the distal and proximal determinants of behavioural change. It considers the pre-intentional motivational phase, which includes the distal factors which form an individual's intention to act. These factors include risk perception, positive outcome expectancies (the expected social, physical, and emotional consequences of the behavioural change), and the role of self-efficacy (belief in ability to succeed). The intention is considered the middle-level mediator, and volitional factors such as action planning (in this case planning to have testing) are the most proximal predictors of behaviour.
    - See paper for examples of questions asked to assess each of these factors
- Men's motivations were for the self (to take action and understand more about risk) as well as family-focussed if they had children – the presence of children was significantly associated with the more concrete formation of intention.

- Men with a family history of *BRCA1/2* cancers presented higher levels of self-efficacy than those with no family history
- Higher levels of self-efficacy and risk perception lead to higher levels of intention to undergo genetic testing. The authors suggest that the strong association between self-efficacy and intention highlights that confidence in handling potential consequences plays an important role.
- The authors comment on how resources and information about *BRCA1* and *BRCA2* mutations is tailored to women, and how this may lead men to underestimate their risk of having a *BRCA* mutation. They suggest that future research should focus on the best methods of communicating information decision-making for men at risk of having inherited such mutations. They also go as far as suggesting the name 'Hereditary Breast and Ovarian Cancer' should be changed as it is misleading and suggests the mutations are only relevant to women.

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