CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – January 2023

Translational science

Germline mutations in WNK2 could be associated with serrated polyposis syndrome. Soares de Lima *et al.* 2022. *Journal of Medical Genetics.* doi: 10.1136/jmg-2022-108684

- Familial clustering and a high colorectal cancer risk for first-degree relatives of serrated polyposis syndrome (SPS) patients have been described, but the inherited genetic basis of SPS is mostly unknown.
- This study aimed to identify new germline predisposition factors for SPS by functionally evaluating a candidate gene.
- The WNK2 gene stood out for being a negative regulator of the MAPK pathway, a central signalling pathway that regulates cell proliferation, differentiation, stress responses and apoptosis. Mutations in these pathways lead to their constitutive activation and uncontrolled cell proliferation.
    - Previous studies have detected WNK2 downregulation in serrated polyps.
    - MAPK pathway is of particular interest in SPS because activating mutations in one of the components is found in 75% of sessile serrated polyps.
- The *WNK2* gene is located at chromosomal region 9q22.31, a region previously linked to familial CRC.
- In the discovery cohort (39 patients with SPS), two *WNK2* variants were detected including c.4820C>T (p.Ala1607Val) and c.6157G>A (p.Val2053Ile).
- In a validation cohort of 211 unrelated SPS patients, gene panel sequencing revealed four additional rare, missense variants in *WNK2.*
- Cellular models for each of 3 missense variants (c.2105C>T (p.Pro702Leu), c.4820C>T (p.Ala1607Val) and c.6157G>A (p.Val2053Ile)) were developed using CRISPR-Cas9 technology, in order to functionally characterise the variants, focusing on whether they altered the MAPK signalling cascade.
- Functional studies suggested germline *WNK2* variants affect protein function in the MAPK pathway.
    - WNK2 variant expression caused increased phosphorylation of downstream proteins in the MAPK pathway, implying WKN2 depletion promoted pathway activation.
    - WNK2 variant expression showed moderately increased Cyclin D1 (CCND1) expression, though not statistically significantly.
    - WNK2 variant expression caused increased metalloproteinase and greater cellular adhesion, suggesting a possible impact of *WNK2* impairment in extracellular matrix remodelling.
    - The most prominent effects were observed for the variant c.2105C>T (p.Pro702Leu).
- These findings indicate germline WNK2 variants in SPS patients may be implicated in inherited predisposition to SPS and suggest that disruption to WKN2 as a MAPK regulation could be the underlying mechanism.
- More research is needed in order to clarify a causative role for germline *WNK2* variants in SPS.

In the clinic

Germline mismatch repair (MMR) gene analyses from English NHS regional molecular genomics laboratories 1996–2020: development of a national resource of patient-level genomics laboratory records. Loong *et al.* 2022. *Journal of Medical Genetics.* doi: 10.1136/jmg-2022-108800

- This study aimed to describe national patterns of NHS analysis of MMR genes in England.
- Individual-level data from patients undergoing NHS MMR germline genetic testing were submitted from all 13 English laboratories performing MMR analyses, was submitted to the National Disease Registration Service (NDRS).
- The NDRS dataset is estimated to comprise >60% of NHS germline MMR analyses performed to date, including all of the MMR full-gene analyses since 2016. Data from a total of 16,722 patients.
- Encrypted pseudo-IDs were created for each patient record from NHS laboratories and the National Cancer Registry and then linked.
    - Data linkage demonstrated 70% of patients who had full-gene MMR analysis had one or more pre-test diagnosis of cancer, the most frequent type of which was colorectal cancer.
    - About 15% of patients who had targeted analysis had a registered cancer.
- The study estimates the number of mutation carriers detected from April 1996–March 2020 to be 2129 (from full gene testing) and 5593 (from cascade testing). Thus it is likely that fewer than 5% of MMR mutation carriers in England have been identified.
- Additional analyses of the NDRS germline MMR dataset are underway to further evaluate the extracted variants, their nomenclature and pathogenicity according to current classification systems.
- The NDRS MMR dataset is a unique national pan-laboratory amalgamation of individual-level clinical and genomic patient data with pseudonymised identifiers enabling linkage to other national datasets.
- This growing resource will enable longitudinal research and can form the basis of a live national genomic disease registry.

A Translational Approach to Spinal Neurofibromatosis: Clinical and Molecular Insights from a Wide Italian Cohort. Paterra *et al.* (2022). *Cancers*; 15(1):59. https://doi.org/10.3390/cancers15010059.

- The manuscript delineates the spinal neurofibromatosis (SNF) phenotype from a clinical perspective, outlining that SNF patients are at high risk of problematic neurofibromas, presenting not only bilateral neurofibromas involving all spinal roots but also a higher incidence of internal neurofibromas and nerve-root swelling. From a histopathological view not only neurofibromas but also neurogangliomas are present in SNF.
- The analysis of 19 families included in the cohort with at least one member affected by SNF showed a high phenotypic variability within the cohort of SNF families. Two unrelated familial SNF cases harbour in trans double NF1 variants that seem to have a subclinical effect worsening the clinical phenotype. Besides the two here described cases, only another patient has been reported, by Fauth, with double in trans NF1 variants (Fauth et al. 2009).
- Few papers reported on the prevalence of NF1 missense mutations in SNF compared with classical NF1, without sufficient predictive data that allow to identify a molecular signature

associated with SNF phenotype. In our cohort the proportion of missense mutations was higher in SNF cases than in the classical NF1 group (21.40% vs 7.5% p=0.007 conferring an odds ratio (OR) of 3.34 (C.I = 1.33 -10.78). By including in the study our SNF cohort and the SNF cases reported in literature, we showed a statistically significant increase of missense mutations (25.3% vs 7.5%, p value =0.001 (OR 4.14; CI= 1.76 -9.75) in the SNF cohort compared to our classical patient cohort, the p value remains statistically significant after correcting with Benjamini-Hochberg correction method for multiple testing with a false discovery rate at 0.025 and 0.01.

Counselling and ethics

Assessing patient attitudes toward genetic testing for hereditary hematologic malignancy. Johnson *et al.* 2022. European Journal of Haematology. doi: 10.1111/ejh.13880

- Surveyed 1093 leukaemia patients' attitudes towards genetic testing and leukaemia-related distress. Of note this is an American study and some barriers to testing are likely to be specific to the American healthcare system.
- The aim was to understand patients' attitudes to genetic testing, the distress of their diagnosis and the relationship between the two in order to optimise genetic testing in hereditary hematologic malignancy (HHM).
- The Impact of Event Scale-Revised (IES-R) was used to assess distress.
- 78% would choose to undergo genetic testing at the time of the survey.
- Barriers to genetic testing were reportedly
    - Worry about the cost (58%),
    - Impact of genetic testing on health, life, or disability insurance (35%),
    - Confidentiality of test results (25%),
    - Discrimination based on test results (23%) and
    - Concern about the burden of leukaemia risk on relatives (22%).
- Barriers to genetic testing such as cost and insurance coverage are addressed during genetic counselling, often taking away this concern for patients.
- Attitudes towards genetic testing were significantly associated with demographic factors, for example, a significant association was presented between ethnicity and themes of discrimination and confidentiality.
    - Those with Hispanic ethnicity reporting significantly greater agreement with statements such as 'I worry that my genetic test results might not be kept confidential' and 'I worry about discrimination based on genetic test results' than other groups.
    - Being an ethnic minority in the United States may lead to increased experience of discrimination and underlie their concern about genetic testing.
- Respondents with acute leukaemia were more likely to agree with statements concerning psychological and familial impacts of testing than those with chronic leukaemia.
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- Most respondents reported low distress in relation to their leukaemia diagnosis (median cumulative IES-R score of 7, range: 0-86), despite less than half (45%) being in remission.
- This study is limited by lack of diversity in respondent demographics. Participants were largely highly educated, wealthy and highly insured relative to the general population.

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