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

Translational science

Neurofibromatosis Type 1 Gene Alterations Define Specific Features of a Subset of Glioblastomas.
Scheer *et al.* (2022). *Int J Mol Sci*; 23(1): 352. https://doi.org/10.3390/ijms23010352

- Neurofibromatosis type 1 (*NF1*) gene mutations or alterations occur within neurofibromatosis type 1 as well as in many different malignant tumours on the somatic level. In glioblastoma, *NF1* loss of function plays a major role in inducing the mesenchymal (MES) subtype and, therefore defining the most aggressive glioblastoma (GBM). This is associated with an immune signature and mediated via the NF1–MAPK–FOSL1 axis. Specifically, increased invasion seems to be regulated via mutations in the leucine-rich domain (LRD) of the *NF1* gene product neurofibromin.
- Novel targets for therapy may arise from neurofibromin deficiency-associated cellular mechanisms that are summarized in this review.
- In this review, the authors discuss the molecular characteristics of MES GBM, *NF1* gene mutation, and dysregulation in NF1-associated and non-NF1 associated cancers, particularly GBM.
- The most important key points discussed are the following:
    - MES GBM gene expression is influenced by dysregulated neurofibromin signalling and the tumour microenvironment. In NF1-null or silenced MES GBM, the microenvironment is heterogeneous with a hypoxic core and perivascular niche, each secreting different cytokines and chemokines that drive tumour malignancy. Given the complexity of the bi-directional interaction, the design of therapeutics must take into consideration the dynamic crosstalk among the various players such as glioma cells, immune cells (immunosuppressive versus pro-inflammatory), and endothelial cells, among others.
    - Studies conducted by Pyonteck *et al.* using a brain-penetrant inhibitor of colony-stimulating factor 1 receptor (CSF-1R) showed a significant decrease in pro-tumourigenic tumour-associated macrophages, suggesting that blocking CSF-1R signaling may re-educate the immunosuppressive macrophage to pro-inflammatory cells. This may allow to re-educate macrophages and microglia cells in the NF1-null microenvironment to achieve the anti-tumour function
    - CSF-1R tyrosine kinase inhibitor, PLX3397, prevented the differentiation of monocytes into immunosuppressive macrophages. Unfortunately, PLX3397 was ineffective in a phase II trial in treating recurrent GBM. This suggests that the understanding the intricate relationship between these cells and their associated gene expression changes may help develop more effective immunotherapeutics
    - Previous publications have shown that CEBP-β, STAT3, NF-kB, and FOSL2 are some of the transcription factors (TFs) that play a role in NF1-loss-associated MES transition. Gabrusiewicz et al. showed that GBM-derived exosomes triggered the release of STAT3 in monocytes and led to the upregulation of programmed death-ligand 1 (PD-L1) and a shift to the immunosuppressive phenotype. Several STAT3 inhibitors are

currently in clinical trials. These inhibitors were designed to be used concurrently with conventional radiation (NCT03514069) and chemotherapy (NCT02315534).

- Other inhibitors that target the molecules in the STAT3 pathway, such as JAK1/JAK2, are also being evaluated in phase I trial for patients with newly diagnosed GBM (NCT03514069). While we await the results from these trials, identifying other NF1-loss associated master regulators and their inhibitors may improve the treatment options for patients with MES GBM.

Multiple primary cancers in patients undergoing tumor-normal sequencing define novel associations. Liu *et al.* (2022). *Cancer Epidemiol Biomarkers Prev.* doi: 10.1158/1055-9965.EPI-21-0820.

- Cancer survivors are developing more subsequent tumours. The authors sought to characterise patients with multiple (>=2) primary cancers (MPC) to assess associations and genetic mechanisms.
- Patients underwent tumour-normal sequencings and tumour pairs were created to assess relationships between cancers
- Age-adjusted, sex-specific, standardized incidence ratios (SIR) for 1st-2nd cancer event combinations were calculated using SEER rates.
- Of 24,241 patients, 4,340 had MPC (18%); 20% were synchronous. Most (80%) had 2 primaries; however, 4% had >=4 cancers.
- SIR analysis found lymphoma-lung, lymphoma-uterine, breast-brain, and melanoma-lung pairs in women and prostate-mesothelioma, prostate-sarcoma, melanoma-stomach, and prostate-brain pairs in men in excess of expected after accounting for synchronous tumours, known inherited cancer syndromes, and environmental exposures.
- Of 1580 (36%) patients who received germline results; 324 (21%) had 361 pathogenic/likely pathogenic variants (PV), 159 (44%) in high penetrance genes.
- Of tumour samples analysed, 55% exhibited loss of heterozygosity at the germline variant.
- In those with negative germline findings, melanoma, prostate, and breast cancers were common.
- This study identified tumour pairs without known predisposing mutations that merit confirmation and will require novel strategies to elucidate genetic mechanisms of shared susceptibilities.

Disorders and roles of tsRNA, snoRNA, snRNA and piRNA in cancer. Xiao *et al.* (2022). *Journal of Medical Genetics.* doi: 10.1136/jmedgenet-2021-108327.

- Most small non-coding RNAs (sncRNAs) with regulatory functions are encoded by majority sequences in the human genome, and the emergence of high-throughput sequencing technology has greatly expanded our understanding of sncRNAs. They play a crucial role ranging from gene expression regulation, genome defence to epigenetic inheritance.
- sncRNAs are composed of a variety of RNAs, including tRNA-derived small RNA (tsRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA), PIWI-interacting RNA (piRNA), etc.

- The implication of some sncRNAs in several pathologies is now well established; miRNA and siRNA have been widely studied during the last few decades and are known to contribute to the development of various physiological and pathological conditions
- The potential involvement of tsRNA, snoRNA, snRNA and piRNA in human diseases is only beginning to emerge. In recent years they have been shown to be active in the regulation of transcription, translation, splicing, and RNA chemical modification, and have been shown to have an involvement in chronic human disease, including cancer
- Abnormal expression of tsRNA, snoRNA, snRNA and piRNA participates in the occurrence and development of tumours through different mechanisms, such as transcriptional inhibition and post-transcriptional regulation.
- This review describes the research progress in the classification, biogenesis and biological function of tsRNA, snoRNA, snRNA and piRNA. The review also emphasises their dysregulation and mechanism of action in cancer and discusses their potential as diagnostic and prognostic biomarkers or therapeutic targets.

In the clinic

Cost-effectiveness model of renal cell carcinoma (RCC) surveillance in hereditary leiomyomatosis and renal cell carcinoma (HLRCC). Thompson *et al.* (2022). *Journal of Medical Genetics*. doi: 10.1136/jmedgenet-2021-108215

- HLRCC is associated with a 21% risk to age 70 years of RCC. More than 60% of symptomatic presentations are of stage 3/4 disease. Presentations with advanced RCC are associated with poor outcomes, whereas renal imaging surveillance (RIS) detects early-stage RCC. This study aimed to determine the cost-effectiveness of annual RIS in HLRCC.
- The authors developed a decision-analytic model to compare, at different age starting points (11 years, 18 years, 40 years, 60 years), the costs and benefits of lifetime contrast-enhanced renal MRI surveillance (CERMRIS) vs no surveillance in HLRCC.
- Benefits were measured in life-years gained (LYG), quality-adjusted life years (QALYs) and costs in British Pounds Sterling (GBP).
- Surveillance was cost-effective in the base-case 11-year age cohort
- Incremental net monetary benefit (NMB) was £3522 per patient, incremental LYG were 1.25, incremental QALYs were 0.29
- Surveillance was also cost-effective in other age cohorts and the most cost-effective strategy was in the 40-year old subgroup:
- Incremental NMD was £12,655, incremental LYG were 1.52, incremental QALYs were 0.58
- The authors concluded that annual CERMRI in HLRCC is cost-effective across the age groups modelled.

Counselling and ethics

Neurofibromatosis type 1 families with first-degree relatives harbouring distinct NF1 pathogenic variants. Genetic counselling and familial diagnosis: what should be offered? Garcia et al. (2022). Journal of Medical Genetics. DOI: http://dx.doi.org/10.1136/jmedgenet-2021-108301.

- NF1 is an autosomal dominant disorder caused by PVs in *NF1*. Recently, *NF1* testing has been included as a clinical criterion for NF1 diagnosis. Additionally, preconception genetic counselling in patients with NF1 focuses on a 50% risk of transmitting the familial variant as the risk of having a sporadic NF1 is considered the same as the general population.
- *NF1* is one of the genes with the highest mutation rate reported in humans. The germline mutation rate for *NF1* is defined as 3-6 x 10^{-5}, 10-fold to 100-fold higher than the average mutation rate for hereditary conditions.
    - Hence, for approx. 50% of patients with NF1 the disorder has arisen from a de novo LOF variant in *NF1*.
    - Paternal age effect has been well-described as a risk factor for NF1
- In this study, 829 individuals (583 NF1 sporadic cases and 246 patients with NF1 with documented FH) underwent genetic testing for NF1.
- Mutational analysis of NF1 in 154 families with two or more affected cases studied showed the co-occurrence of two different *NF1* germline pathogenic variants in four families.
    - The estimated mutation rate in those families was 20 times higher than the *NF1* mutation rate – important to consider that data could be biased due to small cohorts studies, needs to be confirmed in larger cohorts.
    - The co-occurrence of two different *NF1* germline PVs in these families was 1:39, 60 times the frequency of sporadic NF1
    - In all cases, the de novo *NF1* PV was present in a descendant of an affected male
    - In two cases, variants were detected in the inherited paternal wild-type allele
- Results from this study and previous cases reported suggest that the offspring of male patients with NF1 could have an increased risk of experiencing de novo *NF1* PVs. This could have relevant implications for NF1 genetic counselling, family planning and *NF1* genetic testing.

Monthly Journal Round-Up brought to you by:

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