ABSTRACTS COLLECTION

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P01

CANCER GENETICS

P01.001.A Hypoxia-mimetic agent DFO inhibits cancer cell proliferation and induces DNA damage

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Background/Objectives: Hypoxia is common in solid tumour microenvironments and has been associated with radiotherapy resistance and poor clinical outcomes. Replicating hypoxic conditions in vitro requires incubation at 1% O_2, 5% CO_2 and 94% N_2. This nitrogen-induced hypoxia is costly and time-consuming since it needs 24 hours to establish hypoxia. An alternative technique to replicate hypoxic conditions is the use of mimetics like deferoxamine (DFO). This molecule is an iron chelating agent that facilitates the accumulation of hypoxia-inducible factors and has been shown to induce apoptosis in breast tumor cell lines[1].

Methods: MCF7 (breast), VCAP (prostate), CAL33 (head and neck) and OVCAR-8 (ovarian) cancer cell lines were used to test the effect of DFO on proliferation using MTT and annexin-V/propidium iodide assays. DNA damage, specifically double strand break (DSB) formation, was tested by γH2AX foci quantification via immunofluorescence assays.

Results: DFO inhibited cell proliferation and apoptosis in a dose- and time-dependent manner. These effects were more marked than the one achieved through nitrogen-induced hypoxia. Additionally, DFO induces DNA damage through DSB formation.

Conclusion: Although DFO is usually used as a hypoxia-mimetic agent because it is cheaper and less time-consuming than nitrogen-induced hypoxia, our results show that it decreases cell proliferation and induces DNA damage through DSB formation. Therefore, its antitumoral effect should be further explored.

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1. Lynn, J. V. et al. The Role of Deferoxamine in Irradiated Breast Reconstruction: A Study of Oncologic Safety. Plast. Reconstr. Surg. 143, 1666–1676 (2019).

Conflict of Interest: None declared

P01.002.B Mapping of Splicing Regulatory Elements-rich intervals and identification of spliceogenic variants in ATM exon 7

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Background/Objectives: Protein Kinase A (PKA) is a well-known cell signalling complex essential to cellular proliferation, homeostasis and growth. PKA consists of two catalytic subunits under the control of a regulatory subunit dimer encoded by the gene protein kinase cAMP-dependent type II regulatory subunit type II beta (*PRKAR2B*). Here, we report for the first time recessive pathogenic variants in *PRKAR2B* as a cause of a neurodevelopmental disorder.

Methods: Whole-exome sequencing was employed followed by a prioritisation strategy to identify rare variants (absent or MAF <0.001 in gnomAD) predicted to have a deleterious impact (CADD Phred scores >20) within individuals. Suspected variants were validated with Sanger sequencing and functionally investigated utilising in silico and in vitro techniques. We generated HEK293 *PRKAR2B* knockout cells to investigate the impact of PRKAR2B protein loss alongside patient fibroblasts collected.

Results: We present five *PRKAR2B* variants, three loss-of-function variants, one splice variant and one missense variant, in six unrelated families. Patients presented with an overlapping clinical phenotype characterised by dystonia, brain atrophy, spasticity, seizure, delayed speech and language development. Pathogenicity of variants has been supported through the measurement of endogenous PRKAR2B protein from patient cells and through a minigene exon-trapping assay. Results indicate that the loss of PRKAR2B protein reduces the phosphorylation activity of the PKA complex and causes aberrant DRP1 signalling, a checkpoint for mitochondrial fission, suggesting perturbed mitochondrial dynamics as a possible molecular mechanism of PRKAR2B-related disease.

Conclusion: We have identified variants in *PRKAR2B* as a cause of rare monogenic neurodevelopmental disease.

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Conflict of Interest: None declared

P12.029.D A rare muscle disease: 3 cases diagnosed with myotonia congenita

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Background/Objectives: Myotoni Congenita (MC) is a disease characterized primarily by myotonia during childhood, along with muscle hypertrophy and the presence of the warm-up phenomenon. Blood creatinine kinase (CK) increases in these patients. Spontaneous electrical activity can be seen in electromyography. This disease is caused by pathogenic variants in the *CLCN1* gene.

Methods: Genomic DNA from patients were examined for genes associated with Myotonic syndromes using Next-Generation Sequencing method. During the evaluation of variants, we applied the ACMG 2015 criteria.

Results: Patient 1 underwent genotyping following the observation of extensive contractions in the lower extremities, alongside the occurrence of warm-up phenomena and spontaneous electrical activity detected during electromyography. Analysis of the sequencing data revealed a homozygous variant of c.568_569delinsTC in *CLCN1* gene. This missense variant was classified as pathogenic in Clinvar.

Patient 2 and Patient 3, siblings of consanguineous parents, were applied to our clinic with involuntary contractions of arms. Serum CK elevation was detected in both cases. Electromyography was performed in one case and myotonic discharges were detected. In genetic analysis, c.2533G>A homozygous missense variant was detected in the *CLCN1* gene in both patients. Later, the parents were analyzed to be heterozygous carriers of the variant. This variant was reported as a variant of uncertain clinical significance in the Clinvar database.

Conclusion: Variant c.2533G>A is presumed a candidate variant associated with MC because of its predicted functonal effect and affirming segregation analysis. Functional analysis' are expected to better elucidate the clinical outcomes of the observed variant.

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Conflict of Interest: None declared

P12.030.A Neuromuscular junction deficits in PURA syndrome

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Background/Objectives: PURA syndrome is a rare genetic central nervous system disorder caused by heterozygous variants in the *PURA* gene. Several phenotypic features recently suggested a neuromuscular junction (NMJ) source of weakness. We investigated if treatment response to the pyridostigmine, an NMJ agent, is generalizable over centers and questioned if PURA protein is localized at the NMJ on the molecular level.

Methods: Observational study with patients from Poland and Greece. Pyridostigmine was administered at 3 to 7 mg/kg in divided doses 4 to 6 times. Proteomics was performed on one human muscle biopsy and fibroblasts. Murine data were collected from the snRNAseq and the LCMseq (soleus/ extensor digitorum longus).

Results: 7 patients underwent treatment and one is to be included. There was an improvement after pyridostigmine, including neurodevelopmental improvements and muscle strength increase when assessed in a systematic way. Neurophysiological studies performed on 5 patients suggested postsynaptic deficits in 4 patients and pre- and post-synaptic deficits in 1 patient. Proteomics from the muscle biopsy and fibroblasts