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Neuromuscular Junction Defects in Models of Motor Neuron Disease

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Introduction: Motor neuron diseases are neurological disorders characterised primarily by degeneration of motor neurons in the brain and/or spinal cord. Patients present with weakness and wasting of muscles that culminates in often fatal motor dysfunction. Destruction of neuromuscular junctions, the point of contact between motor neurons and muscle, is thought to play a crucial role in the onset of spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS), the two most common motor neuron diseases of infancy and adulthood, respectively. This raises the question of whether there is an overlap between the pathological pathways leading to SMA or ALS.

Results: Making use of the Drosophila model system, we investigated phenotypes resulting from disruption of key genes linked to ALS, including SOD1, TARDBP (TDP-43), FUS and C9orf72. Importantly, we determined whether phenotypes are enhanced in an SMA model. We particularly focused on identifying defects in the neuromuscular junction of fly models in which an ALS-linked gene was combined with an SMA-linked gene. We find genetic interactions for some but not all ALS-linked genes. Interaction is most probably indirect since physical association could not be demonstrated via yeast 2-hybrid analyses.

Conclusion: Our work suggests that perturbation of ALS-linked genes disrupts diverse pathways. Importantly, our results support convergence of pathogenic pathways leading to either ALS or SMA. Overlap between these two major motor neuron degenerative disorders raises the possibility that successful SMA therapeutics may be beneficial to a subset of ALS cases.

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Genetic testing for Granular Corneal Dystrophy type1 in Malta uncovers the causative variant in the transforming growth factor beta induced gene.

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Introduction: Granular corneal dystrophy (GCD) is a condition causing significant visual impairment . It is generally inherited in an autosomal dominant fashion and is phenotypically bilateral, non-inflammatory and progressive. Multiple allelic mutations in the transforming growth factor beta induced (TGFBI) gene produce various phenotypes. The aim of this research project was to determine the molecular genetics and mode of inheritance present in a cohort of Maltese patients who are members of the same family that phenotypically exhibit GCD type1.

Methods: A complete ophthalmological examination of eight consenting Maltese individuals who have been clinically diagnosed with GCD was performed. Genomic DNA from all subjects was extracted from mouthwash samples. Gene sequencing of the TGFBI gene was carried out to identify the mutation(s) present in these Maltese patients.

Results: Eight patients showed patterns of crumb-like corneal anterior stromal lesions. Five out of the eight samples collected were analysed. All the sequenced samples revealed a nucleotide missense mutation in chromosome 5q31, namely a nucleotide change of cytosine being replaced with thymine within exon 12. This caused the amino acid arginine to be replaced with tryptophan at codon 555. By analysing the family tree we could confirm the mode of inheritance. This was further confirmed by the sequencing results.

Conclusion: This study is the first genetic analysis study carried out on Maltese patients that phenotypically exhibit corneal dystrophy. This is the first stepping stone towards understanding the genetic variations present within our population, making it easier for clinicians to identify and provide proper management to subjects at risk.

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Array-CGH analysis in patients with developmental delay, intellectual disability and congenital malformations.

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Introduction: Developmental delay, intellectual disability and congenital malformations have been linked to chromosomal abnormalities in several epidemiological studies. Array-CGH is a specific form of comparative genomic hybridisation which uses DNA microarrays that enable a locus-by-locus measure of CNV (copy number variant) with increased resolution, hence ideal to study the links between chromosomal abnormalities and clinical manifestations.

Methods: From 2007 to 2017, array-CGH was conducted on blood samples of 322 patients, including patients with developmental delay, intellectual disability and congenital malformations, and their parents where possible. The array-CGH report of each patient was reviewed, noting mainly the referral reason for array-CGH and the result of the report.

Results: Out of a total of 322 array-cgh results, 227 result (70.5%) were normal at the resolution used (60 K) while 95 results (29.5%) were abnormal.55 of these abnormal results had a deletion mutation (57.8%), 31 had a duplication mutation (32.6%) and 5 had a translocation mutation (5.3%). 11 of the abnormal results (3.4%) showed the presence of a second abnormality. 10 patients had de novo mutations, six being clinically significant. The highest number of abnormalities occurred in chromosome 2, with 16 abnormal results being recorded on this chromosome,