P-03

RECESSIVE TTN TRUNCATING MUTATION DEFINE A NOVEL ANTENATAL SEVERE FORM OF "CAP-MYOPATHY" IN ABSENCE OF HEART DISEASE

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Background: Arthrogryposis multiplex congenital (AMC) is defined as multiple congenital non-progressive joint contractures involving more than one area of the body. Amyoplasia, is the most common type of arthrogryposis, characterized by a generalized replacement of skeletal muscle by dense fibrous tissue and fat. "CAP myopathy" is a rare congenital myopathy characterized by cap structures consisting of disarranged thin filaments with enlarged Z discs, located at the periphery of the muscle fiber. Four genes have been associated (*ACTA1*, *TPM2*, *TPM3* and *NEB*). To date *TTN* gene has never been associated with "CAP-myopathy".

Methods and results: We report a newborn presenting with AMC, severe axial hypotonia, and muscular biopsy compatible with amyoplasia and "CAP-myopathy". A novel homozygous truncating mutation (c.38661_38669del) in the PEVK segment of *TTN* gene was detected by targeted next generation sequencing assay.

Conclusion: We report for first time an association between *TTN* gene and "CAP-myopathy", showing that mutations in this gene should be considered in all congenital myopathies even if cardiac involvement is absent. We show also the first described *TTN* mutation which leads to totally sarcomere disintegration and placed in an exon only transcribed in fetal period (isoform IC).

Keywords: Arthrogryposis multiplex congenital, amyoplasia, "CAP-myopathy", targeted NGS, TTN-PEVK

P-04

UTILITY OF GENETIC PANELS BASED ON NGS IN THE DIAGNOSIS OF CHILDHOOD EPILEPSIES

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Early-onset epileptic encephalopathies constitute a challenge in daily clinical practice given that, increasingly, genetic and metabolic causes play an important role, incorporating new syndromes that require a diagnosis and a treatment plan. On the other hand, epilepsy prognosis is conditioned mainly by its aetiology. In recent years, CGH-array studies and epilepsy associated gene studies, have been added to high-resolution karyotype. Research has led to the discovery of more than 100 epilepsy genes with important implications for both research and clinical practice. The most important clinical application of these findings is the genetic test, when this information is used to clarify the diagnosis in patients with epilepsy suspicion (diagnostic test) or is used to predict the development of disease risk in individuals with a family history (predictive test). In our paediatric unit it was designed and implemented an epileptic diagnostic panel using next generation sequencing technology, which analyze codifying regions of 110 genes and we have analyzed 52 patients suffering different epilepsy conditions. The average coverage achieved was ~150-200X, being 0.28% the mean percentage of bases with coverage <10X. This panel has been optimized and renewed periodically by adding new genes related to the epileptic phenotype. We have achieved a high diagnostic probability (42.3%) in 22 of 52 patients analyzed. We have considered 8 patients need to be confirmed with further studies (possible diagnosis) either because of being a new gene associated with epilepsy or the inability to make sure about the pathogenicity of the mutation found. We consider the remaining patients (22) as unsolved (42.3%). Twelve of the 30 cases with possible or high diagnostic probability (40%) carried a *de novo* mutation. Two of the diagnosed patients had large deletions / insertions involving one or several genes associated with epilepsy, in which the second CNV is described as pathogenic and confirmed by CGH array.

The use of this panel has allowed us a high rate of diagnosis favouring genetic and family counselling. We also observed that the use of this technology can lead to the discovery of new phenotypes in old genes. But the challenge is to reduce the percentage of non-diagnostic cases through WES trios studies for the discovery of new genes associated with epileptic encephalopathy.

Keywords: epilepsy, paediatrics, next generation sequencing