P-028 - GENETIC VARIANTS IDENTIFIED BY EXOMIC ANALYSIS IN CONGENITAL DISORDERS OF GLYCOSYLATION

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INTRODUCTION: Congenital Disorders of Glycosylation (CDG) are human genetic diseases due to 130 different defects in the pathway of glycoconjugates. These pathologies encompass defects of nucleotide-sugar biosynthesis or transporters, glycosyltransferases, vesicular transport, as well as in lipid and glycosyl-phosphatidylinositol anchor glycosylation. The clinical features range from a severe multisystem to mild phenotype and often associated with neurological impairments (hypotonia, psychomotor disability, strabismus, etc). Serum transferrin isofocusing (Tf-IEF) is the main standard method for screening of N-glycosylation disorders lacking terminal sialic acids. Nevertheless, biochemical analysis combined with Next-Generation Sequencing (NGS) technology plays a significant role in CDG diagnostic. OBJECTIVE: Report improvements in CDG diagnosis in Argentinean patients using NGS technology

METHODOLOGY: This study included patients referred by pediatricians from Children’s Hospital in Cordoba and other Argentinean medical centers. Ethical permissions and informed consents were obtained from the institutional review boards of CIEIS- Ethics Committee. Transferrin analysis (Tf-IEF) and Tf neuraminidase digestion were performed according to standard METHODS: Genomic DNA from patients with altered Tf-IEF patterns was analyzed. We captured the exome of genes associated with human genetic diseases OMIM database (clinical exome sequencing, CES). RESULTS: A neurological multisystem phenotype was observed in four patients with abnormal transferrin CDG-type I (di- and asialo-Tf increased. We identified an homozygous unreported missense variant in three of them (c.G753T; p.Arg251Leu in exon 2 of ALG-2 gene OMIM #607906). In silico analysis showed a moderately pathogenic variant (DANN score 0.9955; Mutation Taster 0.999; FATHMM-MKL 0.8844; Provean -3.33). Functional tests are underway. The fourth patient had non CDG gene variants, but an abnormal transferrin pattern as a coincidence or part of the syndrome, deserves further study. CONCLUSION: It must to keep in mind a CDG in any unexplained syndrome, in particular when there is neurological involvement. Our results highlight the usefulness of NGS to CDG diagnosis. Together it provides
insights to guide research towards new therapies (precision medicine). CONICET-UCC-UNC