Introduction: Alpha-mannosidosis is a rare inherited disorder caused by mutations in the MAN2B1 gene that encodes the lysosomal alpha-mannosidase. Our aim was to describe the phenotypes of a middle-aged siblings with alpha-mannosidosis type 2 and two causative mutations.

Patients and Methods: A 45-year old man (Patient A) and his 51-year old sister (Patient B) were investigated. Neurological, psychiatric, electrophysiological, biochemical and genetic tests were performed. MAN2B1 gene was analysed by Sanger sequencing. Segregation analysis was completed in the mother.

Results: Patient A had macrocephaly, coarse face, hypacusis and hepatomegaly in early childhood. Gait and limb ataxia, mild cognitive impairment occured in adulthood. Patient B has prominent forehead, hypacusis, generalized muscular atrophy and lower limb paresis in early childhood. Delusions with a diagnosis of schizophrenia and multiple joint deformities appeared at young adulthood. Brain MRI detected cerebellar atrophy, X-ray showed multiple sclerotic-edged cysts in humerus. Significant loss of axon of motoneurons was found in lower limbs according to the ENG.The alpha-mannosidase activities were decreased, under 2% of the health control. The serum and urine oligosaccharide analysis showed abnormal patterns. The siblings are compound heterozygous for c.283G>C(Ala95Pro) and c.523G>A(Gly175Arg), which are likely pathogenic variants according to the scientific databases. The mother is heterozygous for c.283G>C(Ala95Pro).

Conclusions: Based on family and clinical history, type 2 alpha mannosidosis was confirmed in the siblings with novel compound heterozygous mutations classified as pathogenic. The result of the segregation analysis strengthened the mutations in trans.This study was supported by KTIA_13_NAP-A-III/6; KTIA_NAP and with FIKP program.

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P11.011.A Preclinical studies on Alport Syndrome mice treated with chemical chaperons

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Introduction: Alport Syndrome (AS) is a severe inherited glomerulopathy caused by mutations in the genes encoding the α-chains of type IV collagen, the most abundant component of the glomerular basement membrane (GBM). Alport patients lack effective therapies beyond blockade of the renin-angiotensin system.

Materials and Methods: This work describes the repurposing of two FDA-approved chemical chaperones (4-PBA and TUDCA) to the rescue of two AS mouse models: one that carries the Col4a3-p.Gly1332Glu in homozygosity and one that carries the Col4a3-p.Gly1332Glu substitution in compound heterozygosity with a Col4a3 knocked-out allele. Mice from each group were treated with chaperones or vehicle for 2, 6 or 12 months.

Results: Electron microscopy studies showed that the GBM of the 4-PBA treated AS mice after the 6-12-month treatment has a considerable improvement in the morphology, compared with placebo-treated or TUDCA-treated mice AS mice. Importantly, EM measurements displayed a 43% reduction of lesions and a significant decline of the lesions-severity in the GBM of 4-PBA treated mice. No adverse effects were noted in the GBM of the chaperone-treated wild type mice. Additionally, albuminuria and serum urea after a 12-month treatment of mice with 4-PBA have not reached the high values demonstrated by the non-treated AS mice (p-value <0.01).

Conclusions: The 6-12-month treatment with 4-PBA could effectively restore to a sufficient degree the morphology of GBM in both AS mouse models. Grants: Funded by the Alport Syndrome Foundation, Inc. (ASF), Pedersen Family and the Kidney Foundation of Canada (KFOC) and by the Cyprus Research and Innovation Foundation.

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P11.013.C Detection of giant chromosomal material on 7p+ with conventional karyotyping and aCGH

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Introduction: Array CGH is widely used in cytogenetics centers for postnatal constitutional genome analysis with higher resolution than conventional karyotyping in patients with intellectual disabilities and multiple malformations. The technique represents an unsurpassed tool for detecting copy number variations (CNVs) and reveal origin of derivative chromosomes.

Materials and Methods: aCGH analysis was performed on a DNA sample from a 5-year-old child using the Affymetrix® CytoScan™ 750K Array (Applied Biosystems). Each array was consisted of 200k SNP and 550k non-polymorphic markers. The data was analyzed and interpreted using Chromosome Analysis Suite (ChAS) Software (v4.0).

Results: The clinical manifestation of the patient included major developmental delay, hypotonia, inability to sit and walk independently, absence of speech and facial dysmorphia. Karyotype showed mosaic presentation of 46,XY,der(7)(p+) in 10% of the cells. Since the mother had normal karyotype and father was unavailable for eventual translocation, array CGH was performed with the presence of major duplication of 7p21.3p11.2 encompassing 46,925 kbp, with 334 genes, estimated as 90% of the cells. Duplication of 7p is rarely described in the literature, with variable phenotypic spectrum depending on mosaicism and duplicated region.

Conclusion: Microarray-based comparative Genomic Hybridization (aCGH) is essential for evaluating derivative chromosomes of unknown origin. The reason for different level of mosaicism of partial trisomy 7p in our case with both techniques remains unexplained. One of the explanations is that cells with derivative chromosomes divide rarely in cell cultures, leading to conclusion that aCGH is more accurate technique for detecting mosaic chromosomal imbalances.

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P11.014.D Clinical and genomic characterization of 7q31.1 microduplication in a patient with developmental and neurological disabilities

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CERTIFICATE OF ATTENDANCE

This is to certify that

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ESHG

has participated in the

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