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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Introduction: Array Comparative Genomic Hybridization (aCGH) represents molecular cytogenetic approach for genome-wide detection of copy number variants (CNVs) that allows efficient genetic diagnosis of pathological conditions, such as developmental delay and neurological disabilities. This technique is highly recommended as a first-tier diagnostic test for clinically relevant CNVs due to its cost and time efficiency, as well its high detection rate compared to conventional karyotyping.

Materials and Methods: The aCGH technique was used to determine the genetic background of dysmorphic, developmental and neurological abnormalities in a 5-year-old female Macedonian patient. The blood-derived DNA sample was analyzed using Affymetrix® CytoScanTM 750K Array (Applied Biosystems) that includes 550 k non-polymorphic and 200 k SNP markers. The data were interpreted using Chromosome Analysis Suite (ChAS) Software (v4.0).

Results: The patient showed the following clinical conditions: developmental delay, epileptic seizures, frequent convulsions, as well several dysmorhological features (macrocephaly, dolichocephaly, antimongoloid slanted eyes and micrognathia).The karyotyping demonstrated 47,XXX result, which did not correspond to the phenotype. The aCGH analysis revealed additional CNV represented as pathological microduplication occurring at the 7q31.1 cytoregion (513 kb, including *IMMP2L* and *LRRN3* genes). According to OMIM and ClinVar database for pathological gene expression, microduplication of the *IMMP2L* gene could be responsible for the severe neurodevelopmental disorders of the patient.

Conclusion: The aCGH technique is a high-resolution laboratory setting that allows detection of pathological CNVs. Further studies are needed for complete understanding of the mechanism related to gene duplication in the onset and progression of the presented developmental and neurological disorders.

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P11.016.B Further delineation of the clinical spectrum of variants in the *ASCL1* gene

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Introduction: The ASCL1-HOX2A-PHOX2B developmental cascade has been proposed as a candidate pathway for Congenital central hypoventilation syndrome (CCHS) and Haddad syndrome (CCHS associated to Hirschprung disease). *ASCL1* has been described in association with both CCHS and Haddad syndrome. However, only 3 patients have been described in the literature to date (OMIM# 100790).

Patients and methods: A French and a UK patient were referred to their genetic centres for investigation of syndromic Hirschsprung disease. Trio whole exome or genome sequencing was performed and details of the *ASCL1* variants submitted to the GeneMatcher data sharing platform in both cases.

Results: The patients were two boys aged 9 and 6 years old respectively. Their common phenotype includes Hirschprung disease, strabismus, cardiac dysautonomy and learning disability with speech delay. Neither patient has CCHS. The older patient is under investigation for sleep apnea and has stable T2 hyperintensity in the dentate nuclei on brain MRI. The younger patient has a normal sleep study and brain MRI scan. Both patients have the same *de novo* heterozygous missense *ASCL1* variant (NM_004316.3:c.379G> A p.(Glu127Lys)). This variant is absent from the population database GnomAD and affects a conserved amino acid located in the functional domain HLH. Multiple *in silico* tools predict pathogenicity.

Conclusion: We report two patients with the same *de novo* heterozygous *ASCL1* variant and a strikingly similar clinical phenotype. This observation suggests that the phenotypic spectrum associated with *ASCL1* gene variants is broader than previously reported. Additional patients, as well as functional studies will be required.

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P11.017.C Baraitser-Winter cerebrofrontofacial syndrome the first proved case in Bulgaria

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Introduction: Baraitser-Winter cerebrofrontofacial syndrome (BWCFFS) is a rare multisystem developmental disorder characterized by distinctive craniofacial features, intellectual disability, ocular colobomata, hearing loss, short stature, brain malformation, epilepsy, structural anomalies of palate, heart and kidneys. BWCFFS is caused by mutations in two different genes - ACTB and ACTG1, that encode β- and γ-actins. Individuals with ACTB mutations seem to have more severe phenotype but ACTG1

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