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Abstracts

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stic center and calculated the total costs of these patients' diagnostic trajectory in order to evaluate early WES implementation.
Materials and Methods: We compared 17 patients' trio-WES yield with the retrospective costs of diagnostic procedures by comprehensively examining patient records and collecting resource use information for each patient, beginning with patient admittance and concluding with WES initiation. We calculated cost savings using scenario analyses to evaluate the costs replaced by WES when used as a first diagnostic tool.
Results: WES resulted in diagnostically useful outcomes in 29.4% of patients. The entire traditional diagnostic trajectory average cost was $16,409 per patient, substantially higher than the $3,972 trio-WES cost. WES resulted in average cost savings of $3,547 for genetic and metabolic investigations in diagnosed patients and $1,727 for genetic investigations in undiagnosed patients.
Conclusion: The increased causal variant detection yield by WES and the relatively high costs of the entire traditional diagnostic trajectory suggest that early implementation of WES is a relevant and cost efficient option in patient diagnostics. This information is crucial for centers considering implementation of WES and serves as input for future value-based research into diagnostics.

P08.16
A 1.77 Mb deletion in 3p26.3 encompassing CNTN6 and CNTN4 genes: case report

F. Brito[1], *B. Marques*[1], *S. Pedro*[1], *S. Serafim*[1], *R. Goncalves*[2], *J. Freixo*[2], *H. Correia*[1];
[1]Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisboa, Portugal, [2]Hospital D. Estefânia, Centro Hospitalar de Lisboa Central EPE, Lisboa, Portugal.

Chromosome microarray analysis is a powerful diagnostic tool and is being used as a first-line approach to detect chromosome imbalances associated with intellectual disability, dysmorphic features and congenital abnormalities. This test enables the identification of new copy number variants (CNVs) and their association with new microdeletion/microduplication syndromes in patients previously without diagnosis. We report the case of a 7 year-old female with moderate intellectual disability, severe speech delay and auto and hetero aggressivity with a previous 45,XX,der(13;14)mat karyotype performed at a younger age. Affymetrix CytoScan 750K chromosome microarray analysis was performed detecting a 1.77 Mb deletion at 3p26.3, encompassing 2 OMIM genes, *CNTN6* and *CNTN4*. These genes play an important role in the formation, maintenance, and plasticity of functional neuronal networks. Deletions or mutations in *CNTN4* gene have been implicated in intellectual disability and learning disabilities. Disruptions or deletions in the *CNTN6* gene have been associated with development delay and other neurodevelopmental disorders. The haploinsufficiency of these genes has been suggested to participate to the typical clinical features of 3p deletion syndrome. Nevertheless inheritance from a healthy parent has been reported, suggesting incomplete penetrance and variable phenotype for this CNV. We compare our patient with other similar reported cases, adding additional value to the phenotype-genotype correlation of deletions in this region.

P08.17
Modeling of chromosomal diseases related to intellectual disability using genome editing of induced pluripotent stem cells from a patient with CNTN6 gene microdeletion

T. A. Shnayder[1], *A. G. Menzorov*[1,2], *N. M. Matveeva*[1], *V. S. Fishman*[1], *I. E. Pristyazhnyuk*[1], *T. V. Karamysheva*[1], *A. A. Kashevarova*[3,4], *N. A. Skryabin*[3,4], *E. A. Sazhenova*[3], ***I. N. Lebedev***[3,4,5], *O. L. Serov*[1,2];
[1]Institute of Cytology and Genetics SB RAS, Novosibirsk, Russian Federation, [2]Novosibirsk State University, Novosibirsk, Russian Federation, [3]Insitute of Medical Genetics, Tomsk, Russian Federation, [4]National Research Tomsk State University, Tomsk, Russian Federation, [5]Siberian State Medical University, Tomsk, Russian Federation.

Introduction: Previously we have described three patients with intellectual disability and some dysmorphic features. Patients had microdeletion or microduplication at 3p26.3, affecting a single gene, *CNTN6* (Kashevarova et al., 2014). In *Cntn6* knock-out mice lack of this gene causes abnormal dendritogenesis. We decided to produce patient-specific neurons to study molecular mechanisms of *CNTN6* deletion effect in humans.
Materials and Methods: Induced pluripotent stem cells (iPSCs) were produced from patient skin fibroblasts with 3p26.3 microdeletion and healthy donor using standard protocol with four transcription factors. Array-based comparative genomic hybridization (aCGH), RT-PCR and FISH analyses were used to confirm microdeletion in iPSCs. CRISPR/Cas9 system was used to knock-out *CNTN6* allele. Neuronal differentiation of iPSCs was performed by NGN2 overexpression (Zhang et al., 2013).
Results: Eight iPSC lines had diploid karyotype (46,XY). Pluripotency was assessed by generation of embryoid bodies and teratoma formation in SCID mice. We confirmed microdeletion and lack of *de novo* chromosome aberrations by aCGH. In addition, we produced targeted missense mutation in the remaining intact *CNTN6* allele using CRISPR/Cas9 system to "enhance" effects of *CNTN6* deletion. iPSCs neuronal differentiation was directed by overexpression of transcription factor NGN2. According to preliminary data, nearly all cells were positive for neuron specific markers and had electrophysiological parameters comparable to those of a healthy donor.
Conclusions: Patient-specific iPSC-derived neurons with *CNTN6* deletion and complete knock-out could be used as a unique model for studying effects caused by *CNTN6* copy number changes.
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P08.18
Eight further individuals with intellectual disability and epilepsy carrying biallelic CNTNAP2 aberrations allow delineation of the mutational and phenotypic spectrum

M. Smogavec[1], *A. Smith*[2], *J. Hoyer*[3], *D. Lederer*[4], *M. Nassogne*[5], *E. E. Palmer*[6,7], *M. Deprez*[4], *V. Benoit*[4], *I. Maystadt*[4], *C. Noakes*[2], *A. Leal*[3], *A. Reis*[3], *D. Shears*[8], *K. Brockmann*[9], ***C. Zweier***[3];
[1]Institute of Human Genetics, University Medical Center, Georg August University, Göttingen, Germany, [2]Oxford Medical Genetics Laboratories, Churchill Hospital, Oxford, United Kingdom, [3]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, [4]Centre de Génétique Humaine, Institut de Pathologie et Génétique, Charleroi (Gosselies), Belgium, [5]Pediatric Neurology Unit, Saint-Luc University Hospital, UCL, Brussels, Belgium, [6]GOLD (Genetics of Learning and Disability) Service, Hunter Genetics, Waratah, Australia, [7]University of New South Wales, Sydney, Australia, [8]Department of Clinical Genetics, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [9]Interdisciplinary Pediatric Center for Children with Developmental Disabilities and Severe Chronic Disorders, University Medical Center, Georg August University, Göttingen, Germany.

Introduction: Heterozygous copy number variants (CNVs) or sequence variants in the contactin associated protein 2 gene CNTNAP2 have been discussed as risk factors for a wide spectrum of neurodevelopmental and neuropsychiatric disorders. Biallelic aberrations in this gene are causative for an autosomal-recessive disorder with epilepsy, severe intellectual disability (ID) and cortical dysplasia (CDFES), however, due to the limited number of reported individuals, the full mutational and clinical spectrum has still to be characterized.
Methods and Results: Targeted sequencing, chromosomal microarray analysis or multi gene panel sequencing identified homozygous mutations, compound heterozygous CNVs or compound heterozygous CNVs and mutations in eight individuals from six unrelated families. All aberrations were inherited from healthy, heterozygous parents and are predicted to be deleterious for protein function. Epilepsy occurred in all patients with onset in the first three and a half years of life. Further common aspects were severe ID (7/8), regression of speech development (5/8), and behavioural anomalies (7/8). Interestingly, cognitive impairment in one of two affected brothers was in comparison relatively mild with good speech and simple writing abilities. Cortical dysplasia that was previously reported in CDFES, was not present in MRIs of six individuals and only suspected in one.
Conclusion: By identifying novel homozygous or compound heterozygous, deleterious CNVs and mutations in CNTNAP2 in eight individuals from six independent families with moderate to severe ID, early onset epilepsy and behavioural anomalies, we considerably broaden the mutational and clinical spectrum associated with biallelic aberrations in CNTNAP2.

P08.19
Coffin-Lowry syndrome, a familial "female only" case; natural history and variability of Coffin-Lowry syndrome in females

A. Kattentidt[1], *R. Kersseboom*[1], *T. Rinne*[2], *E. van der Zon*[1];
[1]Zuidwester, Spijkenisse, Netherlands, [2]Department of Clinical Genetics, Radboud University Medical Centre, Nijmegen, Netherlands.

Coffin-Lowry syndrome (CLS) is a rare X linked semi-dominant mental retardation syndrome, in males characterized by severe intellectual disability, growth retardation, distinct facial features and progressive kyphoscoliosis. In females, the phenotype is less explicit and ranges from the full phenotype as seen in males, to completely absent. The diagnosis in females can be challenging. Furthermore, data on the natural history in affected females is still scarce.
We describe a familial case of CLS with two affected adult females and no affected males. The molecular analysis of the *RPS6KA3* gene revealed a heterozygous frameshift mutation in exon 11, once previously reported in the literature. Both sisters presented well-known features of CLS: intellectual