hypotonia and large fontanels. Standard karyotype was normal, 46, XY and molecular analysis for Prader-Willi syndrome was negative. We applied Whole Exome Sequencing (WES) which analyses 214.405 exons dispersed throughout the genome.

Results: A hemizygous pathogenic deletion of 14 nucleotides UBE2A:c.421_434del14 was indentified in exon 6 of the UBE2A gene by WES analysis. The variant has been confirmed by Sanger sequencing. This deletion causes a frameshift predicted to result in a premature stop codon . This variant was novel but due to its truncating nature it is classified as a pathogenic. Parental DNA analysis of the same variant proved the de novo origin.

Conclusion: We identified a novel mutation associated with X-linked syndromic mental retardation, Nascimento-type. The use of NGS technologies help to establish the diagnosis in patients with mental retardation and an atypical phenotype, who until recently remained undiagnosed.

O. Kenteroglou: None. **E. Tsoutsou:** None. **C. Sofocleous:** None. **D. Veltra:** None. **S. Psoni:** None. **S. Amenta:** None. **P. Willems:** None. **H. Fryssira:** None.

E-P08.33

Novel *WAC* frameshift variant in a boy with DeSanto-Shinawi syndrome revealed using whole exome sequencing

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DeSanto-Shinawi syndrome is a rare autosomal dominant neurodevelopmental disorder caused by mutations in the *WAC* gene. It is characterized by global developmental delay, hypotonia, behavioral, sleep and feeding problems, eye abnormalities, constipation and seizures. Facial features can be mildly dysmorphic but are nonspecific. In total, 18 patients have been reported. We describe an 18-year-old boy who has been examined since preschool age because of hypotonia, speech disorder and strabism. His facial phenotype was not remarkable, but with advancing age features such as broad, prominent forehead, bushy eyebrows, deep-set eyes, depressed nasal bridge, bulbous nasal tip, low-set posteriorly rotated ears, wide mouth with thin upper lip and broad chin became more pronounced. He had abnormalities of extremities, abnormal CNS MRI findings and recurrent respiratory infections. He suffered from underweight affecting fat and muscular components, and showed anxiety and autistic traits. Previous specialized investigations failed to explain the etiology of his affection. Exome sequencing revealed a *de novo* heterozygous *WAC* frameshift variant NM_016628.4:c.383del, p.(Pro128Leufs*64) which was absent from all databases. All other patients with *WAC* mutations also carried truncating variants spread across the gene. The long follow-up of our patient allowed delineating of the *WAC*-related phenotype and its developmental trajectory. The facial phenotype was consistent with previous cases, but we show that the main features become more pronounced with age. Nevertheless, the guidance from phenotype is rather limited and it is likely that additional cases of this syndrome will continue to be identified via the genotype-first approach. Supported by 17-29423A and 00064203.

S. Bendova: None. **M. Havlovicova:** None. **M. Hancarova:** None. **D. Prchalova:** None. **V. Stranecky:** None. **Z. Sedlacek:** None.

E-P08.34

Syndromic intellectual disability and developmental delay caused by novel *de novo* truncating variant in AHDC1 gene

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Introduction: Xia-Gibbs syndrome is a rare genetic disorder with autosomal dominant inheritance caused by heterozygous mutations in AHDC1 gene. This condition is characterized by neurological manifestations that include psychomotor delayed, intellectual disability and corpus callosum hypoplasia with distinct facial features.

Case report: We present a 13 years-old female from Colombia, born to non-consanguineous parents. She was diagnosed at age of 2 years for psychomotor and language delay, facial dysmorphic features and sleep apnea with plagiocephaly. She has associated behavioral disorders that include self-harm, poor social interaction with isolation.

Results: Chromosome analysis was normal (Kariotyping and CGH-array). WES (Whole Exome Sequencing) was performed at 12 years and revealed a novel heterozygous *de novo* frameshift variant c.1529delG (p.Gly510Alafs*12) in *AHDC1* gene (NM_001029882.3), variant functional prediction software tools Mutation tester, Polyphen-2, and SIFT classified it as a deleterious variant.

Discussion: The mutation reported here introduces a stop codon at the amino acid 522 of AHDC1 protein (1603 amino acids). This leads to the loss of one DNA-binding motif and PDZ carboxyl-terminal domain, which could

truncate its interaction with other proteins and can be related to the neurobehavioural manifestations in our patient.

Conclusion: The genotype-phenotype correlation in patients with Xia-Gibbs syndrome is not understood. The patient reported by us is the second case in Colombia and differ from previously reported in literature for absence of corpus callosum hypoplasia described in 40% of cases and for her severe neurobehavioral disorder that could be being modulated for the novel frameshift mutation that truncated protein early.

L. Diaz-Ordoñez: None. **D. Ramirez-Montaño:** None. **S. Cruz:** None. **H. Pachajoa:** None.

E-P08.35

Xp11.22 microduplication including IQSEC2 gene in a male with intellectual disability, epilepsy and dysmorphic features

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X-linked intellectual disability (XLID) is a group of genetically highly heterogeneous disorders and one of the most frequent genetic causes of ID occurring in 5-10% of all affected male individuals. Around 100 genes have been considered as determinant of XLID and the role for many of them remains to be elucidated. Here, we described a male with ID, epilepsy, severely impaired speech, abnormal behavior with hyperactivity and some aggressiveness, optic nerve atrophy and craniofacial dysmorphisms as brachycephaly, frontal hair upsweep, prominent nose and ears, everted lower lip, narrow palate, dental crowding, among others; hands and feet minor anomalies were also observed. Array-CGH (Agilent human genome G3 SurePrint 8x60K microarray) disclosed a 416 kb duplication which extends from ChrX (hg19): 53,253,932 to 53,670,215. This variation was confirmed by MLPA technique and Real Time PCR analysis showed the maternal inheritance. The duplicated region encompasses the *IQ motif-and Sec7 domain-containing protein 2 gene* (*IQSEC2*), which has a significant role in the brain maintenance and homeostasis. Although a consistent phenotype of non-syndromic XLID was observed in individuals with *IQSEC2* alterations, the additional features observed in present patient suggest a syndromic form related to Xp11.22 duplications and also support the hypothesis that *IQSEC2* has a role in pathogenesis of syndromic XLID. In addition, the inclusion of *IQSEC2* variations among the causal factors when evaluating ID patients with seizures could be considered.

Clinical details of male patients with Xp11.22 submicroscopic duplications involving the IQSEC2 gene

Patient [Reference]	Intellectual Disability	Epilepsy	Language development	Visual impairment	Behavioural disturbances	Other clinical features	ChrX(hg19) Coordinates and Duplication size
Present Case	Mild-Moderate	Neonatal seizures	Severely impaired speech	Optic nerve atrophy, enophtalmia	Hyperactivity, aggressive behavior	Corpus callosum agenesis and slight ventricular system enlargement, craniofacial dysmorphic features, including enophtalmia	53,253,932-53,670,215 416 kb
A009 [Froyen et al., 2008]	Mild	–	Speech delay	–	Hyperactivity	Normal facial features	53,220,275-53,981,275 761 kb
A057 [Froyen et al., 2008]	Mild	–	Limited speech in later life	–	Hyperactivity	Not present	52,987,689-53,712,958 725 kb
A119 [Froyen et al., 2008]	Mild-Moderate	Febrile seizures	Speech delay	–	Attention deficit hyperactivity disorder	No significant dysmorphic features	52,825,617-53,662,768 837 kb
AU88848 [Froyen et al., 2012]	Mild	–	–	–	–	–	53,169,907-54,101,252 931 kb
FTD[Froyen et al., 2012]	Mild	Cortico-subcortical dysfunction	Speech delay	–	Attention deficit hyperactivity disorder	Functional heart murmur, chronic vomiting and diarrhea, urolithiasis, bilateral inguinal hernia, cryptorchidism, facial dysmorphic features	53,198,95-54,237,527 1,038 kb
F538 [Froyen et al., 2012]	Moderate	–	Limited speech, Stutter	Unequal pupils	–	Large head circumference	53,216,303-54,239,670 1,023 kb
ON1[Froyen et al., 2012]	Mild-Moderate	–	Partial lack of speech	Microphthalmos	Hyperactivity and attention problems, self-destructing behavior	Facial dysmorphic features	52,982,784-53,721,295 730 kb
Patient 1 [Tran Mau-Them et al., 2014]	Severe	Generalised myoclonic seizures	Not aquired	Hypermetropia, strabismus	Stereotypic hand movements	Neonatal hypotonia, postnatal microcephaly, hyperkinesia, normal facial features	53,283,513-53,325,284 42 kb
Patient 3 [Tran Mau-Them et al., 2014]	Severe	Partial epilepsy	Regression	Strabismus	Midline stereotypic hand movements	Neonatal hypotonia, cerebral atrophy, nonspecific hypersignal foci in periventricular white matter, minor facial features	53,276,030-53,298,472 22 kb
P611 [Santos-Rebouças et al., 2015]	Moderate	Not present	Speech delay	Enophtalmia	Hyperactivity and attention problems, aggressive behavior	Abnormal gait, brachycephaly, enophtalmia, dysmorphic facial features	53,316,256-54,074,258 758 kb
P3272 [Santos-Rebouças et al., 2015]	Moderate	Seizures	Speech delay	–	Hyperactivity	Dysmorphic facial features	53,228,169-54,133,735 905 kb
Patient 1 [Moey et al., 2016]	Not determined	–	Speech delay	–	Poor socialization, behavioral problems	Downward corners of the mouth	52,954,520-53,315,542 361 kb
Patient 2 [Moey et al., 2016]	Mild-Moderate	–	–	–	Autism spectrum disorder, challenging behavior, physical aggression, avoided eye contact	–	52,911,287-53,315,010 403 kb
Patient 3 [Moey et al., 2016]	Global delay	–	Speech delay, poor pronunciation	–	Significant behavioral difficulties requiring a special education class	–	52,789,239-53,368,927 579 kb
Patient 4 [Moey et al., 2016]	Severe	Constant generalized sharp slow discharges	No words, little receptive language	–	Smile and shaking hands	Hypotonia, microcephaly, hypogonadism, myoclonus, not walk, dysmorhic facial features	52,341,517-53,782,896 1,441kb