Results: Total 212 family trios (9 multiplex families, 644 persons) participated. 1) One SNP (rs10877969) was strongly associated with ASD (additive p-value=1.62x10-6; dominant p-value=4.81x10-6). Haplotypes with rs10877969 and rs72945336 revealed statistical significances at the multiallelic mode (additive p-value=2.2x10-5; dominant p-value=1.43x10-5). 2) The rs10877969 was quantitatively associated with Social Responsiveness Scale and all subdomain scores of ADI-R (p<0.01). 3) In the luciferase assay with T98G cell line, the luciferase activity of rs7294536A promoter was higher than that of rs7294536G, while rs10877969 allelic variants didn't influence to promoter activity.
Conclusion: We observed significant association of an SNP of AVPR1A with affection status and social phenotypes of ASD, accompanied with functional activity of the marker.
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P09.028
Copy number variation in 19 Italian multiplex families with autism spectrum disorder: importance of synaptic and neurite elongation genes

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Autism Spectrum Disorder is endowed with impressive heritability estimates and high recurrence rates. Its genetic underpinnings are very heterogeneous and include many common and rare variants located in hundreds of different loci, each characterized by variable levels of penetrance. Multiplex families from single ethnic groups represent a useful means to reduce heterogeneity and enhance genetic load. We screened 19 Italian ASD multiplex families (3 triplets and 16 duplets, total N=41 ASD subjects), using array-CGH (Agilent 180K). Certainly or probably causal CNVs, defined "clinically relevant CNVs", were detected in 17/41 (41%) of ASD probands, corresponding to 9/19 (47%) multiplex families with at least one affected sibling genetically positive. However only in 3/9 (33%) of these families, siblings share the same causal or highly causal CNV. Additional potentially relevant CNVs not shared by affected sib pairs were detected also in these three families. 45 genes are located on the "clinically relevant" CNVs. Through an enrichment analysis, we found that 9/45 (20%) of these genes appear primarily involved in neurite outgrowth and synapse formation/management. Our results highlight the importance of synaptic and neurite elongation genes in the pathogenesis of autism, despite genetic heterogeneity in ASD even within multiplex families belonging to a single ethnic group. Differences in CNV burden may likely contribute to the substantial clinical heterogeneity observed between affected sibs. The genetic and epigenetic mechanisms underlying genomic instability in these families deserve further scrutiny.

P09.029
Increased frequency of the autism broader phenotype in mothers transmitting etiological CNVs to sons affected by Autism Spectrum Disorder (ASD)

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Autism Spectrum Disorder is a frequent neurodevelopmental disorder with a high male to female ratio. An increased prevalence of autism-like personality traits is found in unaffected relatives of ASD children, suggesting a genetic liability of a broader autism phenotype. We therefore hypothesized that the parents of ASD children who transmit etiological CNVs might exhibit ASD traits more frequently than non-transmitting parents. To test this hypothesis, we analysed CNV inheritance and parental behavioral traits in families from the Autism Genome Project, assessed using the Broad Autism Phenotype Questionnaire (BAPQ) (N=341) and the Social Responsiveness Scale (SRS) (N=456). We selected CNVs spanning well-established candidate genes for ASD, and compared transmitting and non-transmitting parental test scores using a t-test corrected for multiple testing by the Group Benjamini-Hochberg Procedure.
Overall, CNV-transmitting parents did not differ significantly in BAPQ and SRS scores from non-transmitting parents. However, independent analyses of relative pairs revealed a significant difference in BAPQ global (t=-2.18; adjusted P=.032), BAPQ aloofness domain (t=-2.61; adjusted P=.032) and SRS scores (t=-2.03; adjusted P=.047) between mothers transmitting and mothers not transmitting etiological CNVs to their affected sons. Our findings indicate that mothers presenting personality traits in the broader autism phenotype are frequently carriers of pathogenic CNVs that they transmit to their ASD sons. The results from the analyses of maternal phenotype and CNV transmission patterns to sons support previous reports of maternal transmission bias to male offspring, and the prevalent hypothesis of a higher genetic risk tolerance in females due to putative protective factors. (FCT PD/BD/52485/2014)

P09.030
AUTS2 syndrome: Further delineation of the phenotype in a 68-years-old female

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Introduction: Genetic evaluation of individuals with neurodevelopmental disorders, with technical improvements in array based technologies and sequencing, has yielded an abundance of new candidate genes for intellectual disability (ID), autism spectrum disorders (ASDs), and developmental delay. We report a 68 year old female with mild-moderate intellectual disability, behavioral findings suggesting ASD, developmental delay and dysmorphic features. The SNP array analysis demonstrated a 257 kb deletion comprising exon 6 of AUTS2 gene.
Case Report: The patient was born at term as the first child of an unrelated couple following an uncomplicated pregnancy and delivery. Mild motor and significant speech delay were evident during childhood. On her physical examination at age 68, she had short stature, microcephaly and abdominal obesity. Mild facial findings and micrognathia were noted. She was followed for scoliosis since early adulthood. Orthopedic findings were present. Her intellectual disability was mild to moderate with behavioral problems. She was noted to be a very friendly, active and girly person. She had limited eye-contact, hyperverbality with limited vocabulary of 40-50 words. She had tics and obsessions, skin pricking, hyperorality and sound-sensitivity. She was not schooled but her family made sure that she was involved in daily activities.
Conclusions: This clinical report provides the natural history in the eldest patients yet to be reported and complements the existing evidence suggesting that disruption of the AUTS2 gene leads to a recently delineated neurodevelopmental phenotype with a wide spectrum, namely "AUTS2 Syndrome".

P09.031
Targeted next-generation sequencing in search of monogenic causes of behavioural disturbance in children

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Introduction: Behavioral disturbance can be the presenting symptom of genetically determined cognitive deficiency caused by de novo dominant, rare recessive and pathogenic copy number variations (CNV). NGS has accelerated diagnosis in genetically heterogeneous disorders with common clinical features.
Patients and methods: 28 children with unclear developmental delay and behavioral disturbance seen at a joint clinical genetic and psychiatric outpatient clinic underwent targeted NGS testing including over 1200 brain related genes (MPIMG-1). Following enrichment 2x300bp paired-end sequencing (Illumina Miseq Kit v3) was carried out on Illumina MiSeq and a modified Medical Resequencing Analysis Pipeline was used for variant calling.
Results: In 3/28 cases pathogenic or likely pathogenic CNVs, in 8/28 a monogenic cause was identified. We found 6 cases with mutations in autosomal dominant neurodevelopmental genes, either reported and matching the patient's phenotype (PTPN11, SETBP1), or likely associated with the phenotype (DYRK1A, GRIN2B, ASXL1, ZEB2) but previously unreported.