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# 7TH INTERNATIONAL MEETING ON CNVS AND GENES IN INTELLECTUAL DISABILITY AND AUTISM

## PROGRAM AND ABSTRACT BOOK

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**Array CGH identifies a 823 kb Microduplication at 22q11.22 encompassing the Rab36 gene in a Child with Autism Spectrum Disorder and Mild Dysmorphism**

The proband, a 3.5-year-old male and second child of non-consanguineous parents, was born at term after an uneventful pregnancy by caesarean section due to complicated breech presentation. At birth the newborn child's parameters were: weight 3.050 g ($26^{th}$C), head circumference 34 cm ($35^{th}$C), length 50 cm ($51^{th}$C); Apgar scores were 8 at 1 min and 9 at 5 min. His family history was characterized by congenital deafness in mother and in a maternal uncle without further evidence of cognitive and/or other neurologic impairments. His psychomotor development was retarded: he acquired control of trunk at 14 months and walked without support at 20 months. From the age of 12 months on, he received special training to improve motor skills. At the age of 18 months he started to say a few words but a subsequent arrest of language development was observed. According to DSM-IV revised criteria he was diagnosed with Autistic Spectrum Disorder and referred to the Genetics Department because of mild dysmorphism. At the age of 3.5 years he weighed 17 kg ($75^{th}$C), his height was 105 cm ($95^{th}$C), OFC was 50.5 cm ($50^{th}$C). On physical examination he had: high forehead, downslanted palpebral fissures, bulbous nose, long philtrum, wide mouth, full lips and large and protruding ears with average antitragus and extra concha folds. Furthermore, hyperextensible finger joints and generalized hypotonia were noted. Our patient's evaluation included chromosome analysis of peripheral blood and molecular analysis for fragile X syndrome, which were normal. Additional performed testing were thyroid function tests, hearing tests, echocardiogram, abdominal ultrasound, bone age studies, sleep deprived EEG and brain MRI. Even if the EEG detected anomalies in the left F7 derivation, the brain MRI showed normal myelinisation and CSF volume without structural alterations; all other studies were normal. A 823 kb microduplication at 22q11.22q11.23 was finally identified by CGH array and subsequently categorized as a de novo event by FISH analysis. Chromosome 22, particularly the q11.2 sub-band, has long been recognized as responsible for multiple congenital anomaly disorders. While recent data suggest that the frequency of 22q11.2 microduplications could be approximately half of all deletions, only 50 unrelated cases have been reported thus far. It is reasonable to suppose that microduplications of 22q11.2 may be largely undetected as a result of a less-distinct, unpredictable, and/or milder phenotype. However, the presence of cognitive deficits ranging from learning disabilities or isolated speech delay to intellectual disability are uniformly reported. According to previous data, several patients with seizures or an abnormal EEG had been described and reports on the neurological and psychiatric aspects of 22q11.2 duplication have shown attention deficit, hyperactivity disorder and aggressive behaviour. One patient had a diagnosis of Asperger syndrome, three others were diagnosed with autistic disorder but none of these, except ours, was studied with CGH Microarray. Actually, about 30% of autism cases were traceable to an underlying genetic cause, and it is hypothesized that this number may significantly increase with further research. Moreover, neurological and psychiatric disorders are present in a large percentage of 22q11.2 population patients supporting the hypothesis that complex human traits are influenced by numerous genes that interact with one another and with the environment to produce a specific phenotype. The 823 kb microduplication at 22q11.22q11.23 we report on, harbors only few known genes, most of which are involved in the synthesis of the immunoglobulin chain. Since there is no gross functional imbalance, we can speculate that the neurological impairments are probably caused by an increased dosage effect of one or more genes located within the duplicated region. In this view, it could be relevant to clarify the not yet known role of the *RAB36* gene and its ras-associated protein Rab36 may be involved, like some other Rab family proteins, in vesicular transport. In

conclusion, our case illustrates once again the clinical heterogeneity of 22q11.2 microduplication as well as the complexity of the Autistic Spectrum Disorder, emphasizing that this rare association could be one of the many yet unrecognized underlying aspects.