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Duplications of *SLC1A3*: Associated with ADHD and autism

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ABSTRACT

We report four patients with a similar gain in 5p13.2 encompassing a single gene: *SLC1A3*. Behavioural problems resembling ADHD and/or autism-like features are observed which is in line with the glial glutamate transporter role of *SLC1A3*.

We consider an association between *SLC1A3* and the behavioural problems which can also be considered a contributing factor to behavioural problems in larger duplications overlapping the 5p13 microduplication syndrome region.

1. Introduction

Neurodevelopmental disorders such as Intellectual Disability (ID) and autism spectrum disorder are frequently caused by genomic copy number variants (CNVs) (Vulto-van Silfhout et al., 2013; Cooper et al., 2011; Hehir-Kwa et al., 2013; de Vries et al., 2005). However, the clinical effect of rare CNVs is often difficult to determine. Most of the CNVs suspected to be pathogenic are large, *de novo* and include multiple genes. The latter makes it difficult to define which of the encompassing gene(s) are dosage-sensitive and causative for the clinical phenotype (Cooper et al., 2011; Coe et al., 2014). One of those pathogenic CNV-related diseases is the 5p13 duplication syndrome (OMIM #613174) caused by a duplication including *NIPBL* and, occasionally, *SLC1A3* (Carrascosa Romero et al., 2012; Oexle et al., 2011; Yan et al., 2009; OMIM, 2011). These 5p13 duplication patients have a variable phenotype that encompasses intellectual disability, frontal bossing with a broad forehead, down slanted and/or short palpebral fissures, low-set ears, micrognathia and obesity in adulthood.

The interpretation of small CNVs might often be more difficult, as these CNVs are not only frequently inherited from an apparently normal parent, but may also lead to a more variable phenotype or incomplete penetrance. The finding of multiple patients with a CNV encompassing a single gene together with an overlapping phenotype can contribute to identify new candidate or causative genes for specific clinical features.

Here we present the detailed phenotype of four patients with behavioural problems and a small gain of ~180 kb in 5p13.2 encompassing a single gene: *SLC1A3*.

1.1. Clinical report

Patient 1 was a 7-year-old girl born after an uncomplicated pregnancy to non-consanguineous parents [Fig. 1]. The girl had no siblings and a son of a maternal aunt had autism. The girl had some delay of the gross motor milestones and a mild developmental delay of about one year which was considered to be caused by learning and concentration problems resulting from severe ADHD. The ADHD was therapy resistant to dexamphetamine and methylphenidate treatment. The girl was restless and was unable to play with other children. She used melatonin to treat her sleeping problems.

Physical examination at the age of 7 years showed a height of 119.2 cm (−1 SD), weight of 21.2 kg (−0.5 SD) and a head circumference of 51 cm (−0.5 SD). Facial dysmorphisms consisted of a wide nasal bridge, a flat philtrum and a mild clinodactyly of the 4th

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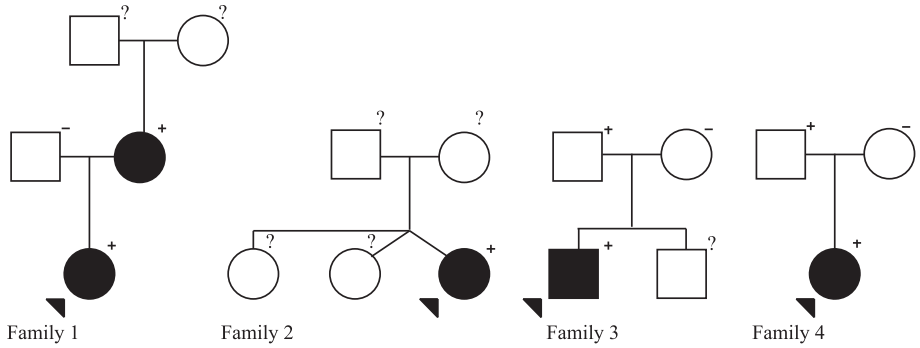

Fig. 1. Pedigrees of the patients.

and 5th fingers which was left more pronounced than right. Further physical examination was unremarkable.

A gain in 5p13.2 of 185 kb (36,534,612–36,719,822) (NCBI Genome Build 37 was revealed by genome-wide array analysis using an Affymetrix CytoScanHD platform) [Fig. 2]. This duplication contained one RefSeq gene, *SLC1A3*, and was inherited from her mother [Fig. 1]. Her mother reported difficulties with concentration in childhood, but detailed clinical examination was not performed. The grandparents were not available for carrier testing.

Patient 2 was a girl of 9.5 months old who was referred because of developmental delay and congenital anomalies. She had non-consanguineous parents, a healthy, older sister and a dizygotic twin sister. After an uneventful twin pregnancy, she was born with a caesarean section at 38 + 1 weeks. There were no additional problems during the pregnancy. The girl had a relative low birth weight of 2650 g (−1 SD) compared to her healthy twin sister of 3350 g (+0.5 SD). She had a cleft lip and jaw and an umbilical hernia.

Developmental delay became apparent at an early stage. She started laughing at age 3 months and showed difficulties in making contact. At 9 months she was not able to sit without support and just recently learned to roll over. She had axial hypotonia and feeding problems. Her growth was on a constant −2 SD. At 3 years of age, she had a severe developmental delay with a complete absence of speech.

At examination at 9.5 months of age, her height was 68 cm (−1.5 SD), weight 6.7 kg (−2.5 SD) and head circumference of 42.7 cm (−1.5 SD). She had facial dysmorphisms consisting of hypertelorism, ptosis, prominent eyes, a flat asymmetric nose associated with the cleft lip, a long philtrum, a small chin and large protruding ears with prominent ear lobes. Furthermore, there were a singular palmar crease at both sides, a short 5th digit at her right hand and a fair rosy skin. Based on her phenotype an underlying syndrome was considered.

A metabolic screen for congenital disorders of glycosylation (CDG) was normal. A CytoScan HD array revealed a 170 kb gain (36,539,781–36,710,378) of 5p13.2 containing the *SLC1A3* gene [Fig. 2]. The parents of this girl declined further parental testing.

Patient 3 was a 12-year-old boy referred because of severe ID and epilepsy. He was born after an uncomplicated pregnancy with a birth weight of 3320 g (0 SD) to non-consanguineous parents and he had a healthy, younger brother. His developmental delay became apparent at 8 months and due to epilepsy his development stagnated further from the 4th year on losing the ability to babble. His epilepsy started as absences and changed into general tonic clonic seizures, which were difficult to control with medication and attacks still occurred on a daily basis. The patient had no speech development, showed no communication and was not able to walk. Although he had a happy disposition he showed compulsive behaviour manifesting in wrenching his hands and gritting his teeth without automutilation. Puberty manifestations were present early with pubic hair and voice changes at 10 years of age.

At physical examination he had a weight of 35 kg and a head circumference of 57 cm (+1.5 SD) without any (facial) dysmorphisms. EEG showed multifocal epileptic encephalopathy without any abnormalities on MRI of the brain. DNA testing for Rett and Angelman syndrome were normal. With a CytoScan HD array a 180 kb gain in 5p13.2 (36,534,612–36 713,438) [Fig. 2] inherited from his father was detected. The father was not clinically examined but was normal functioning. As an additional finding, a 225 kb deletion of unknown relevance inherited from the father was detected in 9q31.1 encompassing the *CYLC2* gene. Subsequently, whole exome sequencing was performed but no potential causal gene mutations were found.

Patient 4 was a girl with a developmental and motor delay speaking 2–3 word sentences at the age of 3 years and 4 months. She was born after an uncomplicated pregnancy and had classical autism. The son of a paternal sister also had autism.

Physical examination at 3 years showed a height of 98 cm (0 SD), weight of 16 kg (+0.5 SD) and a head circumference of 52 cm (+1 SD). She had mild dysmorphisms consisting of a slightly hypotonic face, a small mouth with a tented upper lip and an everted lower lip, and mild clinodactyly of the 5th fingers. Examination at age of 7 showed signs of early puberty.

A 170 kb gain in 5p13.2 (36,542,942–36,710,378) inherited from the father was identified with genome wide CytoScan HD array

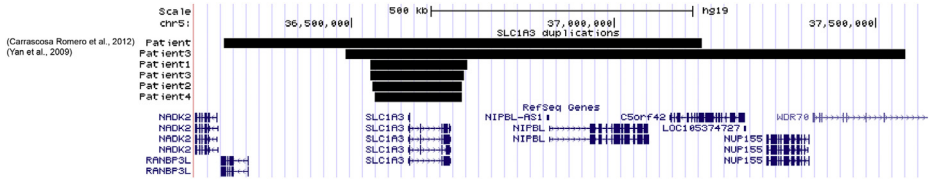

Fig. 2. The duplication of the patients, and of the patients of Carrascosa et al. and Yan et al. were displayed, using UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly (http://genome-euro.ucsc.edu/index.html).