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A 380-kb Duplication in 7p22.3 Encompassing the *LFNG* Gene in a Boy with Asperger Syndrome

A.T. Vulto-van Silfhout[a] A.P.M. de Brouwer[a] N. de Leeuw[a] C.C. Obihara[b]
H.G. Brunner[a] B.B.A. de Vries[a]

[a]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, and
[b]Department of Paediatrics, St. Elisabeth Hospital, Tilburg, The Netherlands

Key Words
Autism spectrum disorder · Chromosome 7p22.3 · Duplication · Gain · Lunatic fringe

Abstract
De novo genomic aberrations are considered an important cause of autism spectrum disorders. We describe a de novo 380-kb gain in band p22.3 of chromosome 7 in a patient with Asperger syndrome. This duplicated region contains 9 genes including the *LNFG* gene that is an important regulator of *NOTCH* signaling. We suggest that this copy number variation has been a contributive factor to the occurrence of Asperger syndrome in this patient.

Asperger syndrome (OMIM 608638) is one of the autism spectrum disorders (ASDs). Patients with Asperger syndrome have qualitative impairment in social interactions and show restricted, repetitive and stereotyped patterns of behavior, interests, and activities. It differs from autism because of the higher cognitive abilities and the absence of qualitative impairments in communication [American Psychiatric Association, 2000]. ASDs are highly heritable. Based on twin and family studies the heritability is estimated to be as high as 80% [Freitag, 2007; Ronald and Hoekstra, 2011]. However, as with other complex disorders, in many patients the cause of the ASD remains unknown. One explanation for this missing heritability is the occurrence of de novo aberrations [Manolio et al., 2009; Vissers et al., 2010; O'Roak et al., 2011]. Indeed, rare de novo and inherited copy number variations (CNVs) as well as de novo point mutations are an important cause of autism [Sebat et al., 2007; Pinto et al., 2010; Levy et al., 2011; O'Roak et al., 2011; Sanders et al., 2011]. Here, we present a de novo CNV in 7p22.3 in a patient with Asperger syndrome.

Methods

Single-Nucleotide Polymorphism Array

Genome-wide single-nucleotide polymorphism (SNP) array analysis was performed on DNA isolated from peripheral blood using a 250K SNP array (Affymetrix Inc., Santa Clara, CA, USA) according to the protocol provided by the manufacturer. Data analysis and interpretation was done as previously described [de Leeuw et al., 2011].

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Bert B.A. de Vries
Department of Human Genetics 849
Radboud University Nijmegen Medical Centre
PO Box 9101, NL–6500 HB Nijmegen (The Netherlands)
Tel. +31 24 361 3946, E-Mail b.devries@antrg.umcn.nl

Results

Patient Description

The patient, a 14-year-old boy, had been referred to our department because of Asperger syndrome and chronic fatigue. He was the first child of healthy, non-consanguineous parents, born after an uneventful pregnancy and delivery at 40 weeks of gestation with a weight of 3,220 g (30th centile). He developed normally. He could sit at the age of 5.5 months, walk at the age of 1 year, and said his first words appropriately for age. Before the age of 6 years, behavioral problems became evident. He showed obsessive behavioral patterns, such as repeated on and off switching of light and hiding of keys. Moreover, he often rocked back and forth and had difficulty adjusting to unexpected situations. At the age of 6 years, his parents took him to a child and adolescent psychiatrist, who subsequently diagnosed him with Asperger syndrome. The patient followed normal education, though with some extra coaching. His intelligence quotient (IQ) was estimated to be 102 (WISC-III), although there was a discrepancy between his verbal IQ (109) and performance IQ (94). At the age of 12 years, the patient sought medical help due to chronic fatigue. He also complained of myalgia and pain in his legs. Extensive clinical and laboratory investigations, including metabolic disease screening, were normal. The fatigue symptoms were so severe that the patient was referred for an inpatient rehabilitation program. He was discharged after 9 weeks of rehabilitation and transferred to a special secondary school for children with physical disabilities. At the age of 14 years, the patient had returned to a normal school curriculum, though he was still functioning at a lower academic level than he used to do. His further medical history revealed no abnormalities. He had a normal sleeping pattern, normal hearing and vision, and he used to take part in normal sports activities, without any restrictions.

Physical examination performed at the age of 14 years showed a length of 186 cm (98th centile), a weight of 95 kg (+2.5 SD), and a head circumference of 61 cm (98th centile). There were no facial dysmorphisms, except for a broad nasal base (see fig. 1a). The muscle strength was normal, despite the poor physical condition.

The patient had a younger brother who developed normally. His father was 184 cm (50th centile) with a head circumference of 58 cm (50th centile). His mother was 173 cm (70th centile) with a head circumference of 57 cm (85th centile). A son of a paternal aunt was diagnosed with pervasive developmental disorder not otherwise specified, and a female second cousin on the paternal side (part of a large family) was also diagnosed with Asperger syndrome.

SNP array analysis revealed an interstitial gain in band p22.3 of chromosome 7 with a minimal size of 380 kb (18 SNPs, 2.26–2.64 Mb from the p-telomere, SNP_A-2194214 to SNP_A-2107081) and a maximal size of 450 kb (2.23–2.68 Mb from the p-telomere, SNP_A-1914583 to SNP_A-1785979) (NCBI Genome Build 37/Hg19) (fig. 1b). The duplicated region contains at least 9 known RefSeq genes, namely *MAD1L1*, *FTSJ2*, *NUDT1*, *SNX8*, *EIF3B*, *CHST12*, *LFNG*, *BRAT1*, and *IQCE* (fig. 1c). The absence of the same gain in the SNP array analyses of DNA from the parents revealed that the gain had occurred de novo in their son.

Discussion

We describe a de novo gain in 7p22.3 in a patient with Asperger syndrome. This region has never been associated with ASDs previously [Risch et al., 1999; Szatmari et al., 2007; Yang and Gill, 2007; Glessner et al., 2009; Pinto et al., 2010; Sanders et al., 2011]. In the Decipher (http://decipher.sanger.ac.uk/) and ECARUCA (www.ecaruca.net) databases only much larger overlapping aberrations have been described that are usually part of complex rearrangements in patients with primarily intellectual disability (ID) [Feenstra et al., 2006; Firth et al., 2009].

In healthy control persons 2 overlapping duplications of the 7p22 region have been described in the Study of Addiction: Genetics and Environment (SAGE, http://zork.wustl.edu/gei/) and the study by Park et al. [2010]. Although the controls of the SAGE study have been selected to be not addicted, ASDs were not excluded in these controls. The latter is similar for the study by Park et al. [2010]. In a recent study on autism by Sanders et al. [2011], 2 partially overlapping duplications have been found in healthy parents that were not present in their own autistic children. These duplications contained the genes *MAD1L1*, *FTSJ2*, *NUDT1*, *SNX8*, and *EIF3B*. However, the duplicated region in our patient contained 4 additional known RefSeq genes, namely *CHST12*, *LFNG*, *BRAT1*, and *IQCE*.

The most likely candidate gene for ASDs is *LFNG*, or lunatic fringe. In animal models, *Lfng* is essential for the demarcation of boundaries between groups of cells during development, for example in dorsoventral patterning of the *Drosophila* wing, the hindbrain and the somites [Irvine and Wieschaus, 1994; Johnston et al., 1997; Zeltser et

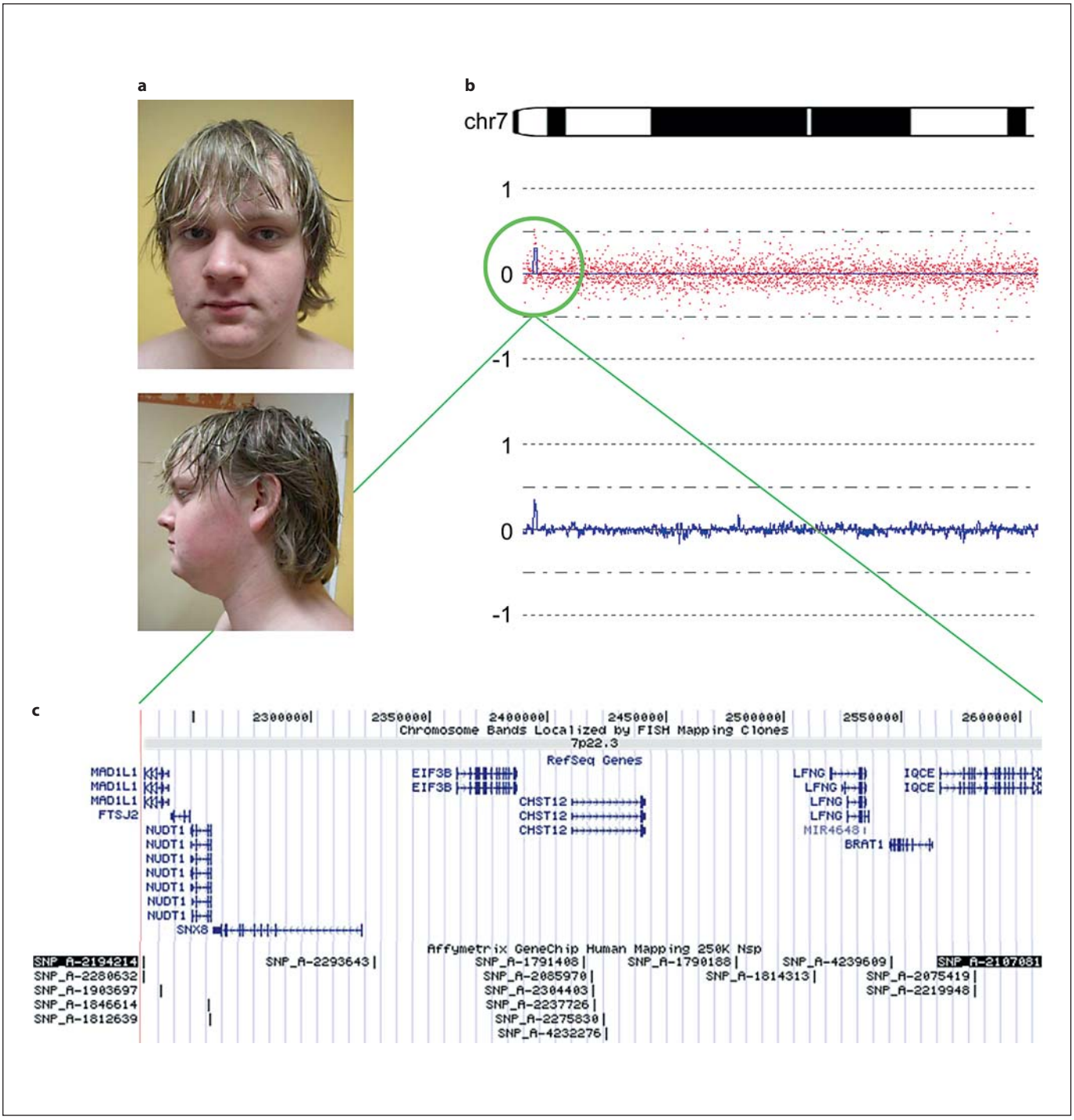

Fig. 1. a Facial features of the patient; **b** idiogram of the distal short arm of chromosome 7p22.3–p15.2 with an interstitial 380-kb gain in 7p22.3 detected by 250K SNP array shown in the lower part of this figure; **c** screen shot of the UCSC Genome Browser (Human Genome, February 2009 (GRCh37/Hg19) Assembly at http://genome.ucsc.edu/) showing the duplicated region in 7p22.3 encompassing a total of 9 coding genes.

al., 2001; Tossell et al., 2011]. In humans an autosomal recessive mutation in *LFNG* has been detected in a family with spondylocostal dysostosis, a vertebral malsegmentation disorder [Sparrow et al., 2006]. In the developing brain, *Lfng* is particularly expressed in the ventricular zone of the neuroepithelium where neurogenesis takes place [Johnston et al., 1997; Ishii et al., 2000]. *LFNG* is a glycosyltransferase that modulates the activity of the *Notch* signaling pathway [Panin et al., 1997; Moloney et al., 2000; Stanley and Okajima, 2010]. During neural development *Notch* plays an essential role in the regulation of cell fate choice through lateral inhibition [Cau and Blader, 2009]. It effectuates the maintenance of neuronal progenitors and the inhibition of neuronal differentiation in the ventricular zone [Yoon and Gaiano, 2005; Louvi and Artavanis-Tsakonas, 2006]. Both loss-of-function of *lfng* in zebrafish and *Notch1* in mice leads to an early increase in the number of differentiating neurons leading to a reduction in the size of brain structures as a result of secondary progenitor pool depletion [Lutolf et al., 2002; Yoon and Gaiano, 2005; Nikolaou et al., 2009], while overexpression results in an increase of neuronal progenitor cells at the expense of differentiating cells [Gaiano et al., 2000; Breunig et al., 2007; Li et al., 2008; Nikolaou et al., 2009; Kato et al., 2010]. The latter may in turn result in an enlargement of brain structures [de Bellard et al., 2007]. Interestingly, ASDs are associated with an enlarged brain volume (and head circumference) [Kanner, 1943; Piven et al., 1995; Woodhouse et al., 1996]. One of the possible mechanisms to explain this increase in brain volume is an increase in neuron number [Vaccarino et al., 2009; Rubenstein, 2011]. Therefore, activation of the *Notch* signaling pathway might be an interesting candidate mechanism for the ASD in our patient. This is supported by the large head circumference that was present in the patient, but not in his parents. Besides, the *Notch* signaling pathway has been previously described to be differentially expressed in patients with ASDs [Seno et al., 2011]. In addition, a causal link with the *Notch* signaling pathway has been hypothesized in other psychiatric diseases, including schizophrenia, and cognition [Costa et al., 2005; Wang et al., 2006]. Therefore, it seems probable that an increased dosage of *LFNG* through this duplication may result in an increased brain volume and an enlarged head circumference. This may have predisposed the patient to an ASD.

Of the other 8 genes that were duplicated in the patient, 3 could also be possible candidates for Asperger syndrome, namely *IQCE*, *FTSJ2*, and *EIF3B*. A related gene of these 3 genes has previously been associated with a neurobehavioral phenotype. *IQCE* contains an IQ domain [Rhoads and Kenguele, 2005], while *IQSEC2*, another IQ domain containing protein, is a known X-linked ID gene [Shoubridge et al., 2010]. The homolog of *FTSJ2, FTSJ1*, is also a known gene for nonsyndromic X-linked ID [Freude et al., 2004; Ramser et al., 2004]. In addition, duplications of Xp11.22–p11.23, including *FTSJ1*, have been described in patients with ID, autistic behavior and seizures. However, autistic features have also been described in patients with smaller duplications that do not overlap *FTSJ1* [El-Hattab et al., 2011]. *EIF3B* encodes for a subunit of one of the family members of the eukaryotic initiation factors that regulate mRNA translation [Maitra et al., 1982; Hinnebusch, 2006]. Deregulation of *EIF4E* expression, another family member of the eukaryotic initiation factors, has been described in patients with severe autism [Neves-Pereira et al., 2009], while *EIF2B* subunit mutations are found in patients with vanishing white matter [Leegwater et al., 2001]. Besides, *EIF3* has recently been shown to interact with collybistin (*ARHGEF9* in humans) and gephyrin, 2 postsynaptic proteins [Sertie et al., 2010]. Defects in synaptic function have already been implicated in the pathogenesis of autism [Sudhof, 2008; van Spronsen and Hoogenraad, 2010].

However, 2 partially overlapping duplications have already been found in healthy parents of an autistic child (and not in the child itself) as mentioned before. One of these duplications encompasses both *FTSJ2* and *EIF3B*, which makes their relation to this phenotype less likely. Being that both *IQSEC2* and *FTSJ1* have been described in ID, while our patient had Asperger syndrome with a normal IQ, this attenuates a possible link between the related genes *IQCE* and *FTSJ2* and the phenotype of our patient. Finally, most of these genes cause these diseases by a loss-of-function mechanism, while a duplication was found in this patient.

Two family members on the father's side of the family of the patient also have an ASD. As the prevalence of ASDs is known to be high (in the range of 6–7 per 1,000) [Fombonne, 2009], this might be due to a coincidence. However, ASDs are known to be complex genetic disorders [Folstein and Rosen-Sheidley, 2001]. It has been hypothesized that for ASDs multiple mutations together reach a certain threshold in order to result in the clinical phenotype. It is therefore possible that an increased background risk for the development of an ASD was already present in the patient's family. The gain in 7p22.3 may then be only a contributing factor to the development of Asperger syndrome. This is in line with the finding of a small CNV including *LFNG* and the neighboring *BRAT1* in an anonymous healthy Asian female by Park et al.

[2010]. Nevertheless, being that the gain in 7p22.3 occurred de novo in the patient, while his parents were healthy, without any signs of ASDs, a causal link with his phenotype could be postulated.

In conclusion, we describe a de novo submicroscopic gain in 7p22.3 in a patient with Asperger syndrome. We suggest that this CNV, which encompasses 9 genes including *LFNG,* has been a possible contributive factor to the occurrence of Asperger syndrome in this patient.

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