

LETTER

# Duplication of *MAOA*, *MAOB*, and *NDP* in a patient with mental retardation and epilepsy

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Recently, Whibley *et al*<sup>1</sup> reported on a family carrying a microdeletion at Xp11.3 involving only the *MAOA* and *MAOB* genes. The affected brothers in this family suffered from severe mental retardation, epilepsy, stereotypic hand movements, and lip smacking. Here we report on a male patient with mental retardation and intractable epilepsy carrying a duplication of Xp11.3 involving the *MAOA*, *MAOB*, and *NDP* genes.

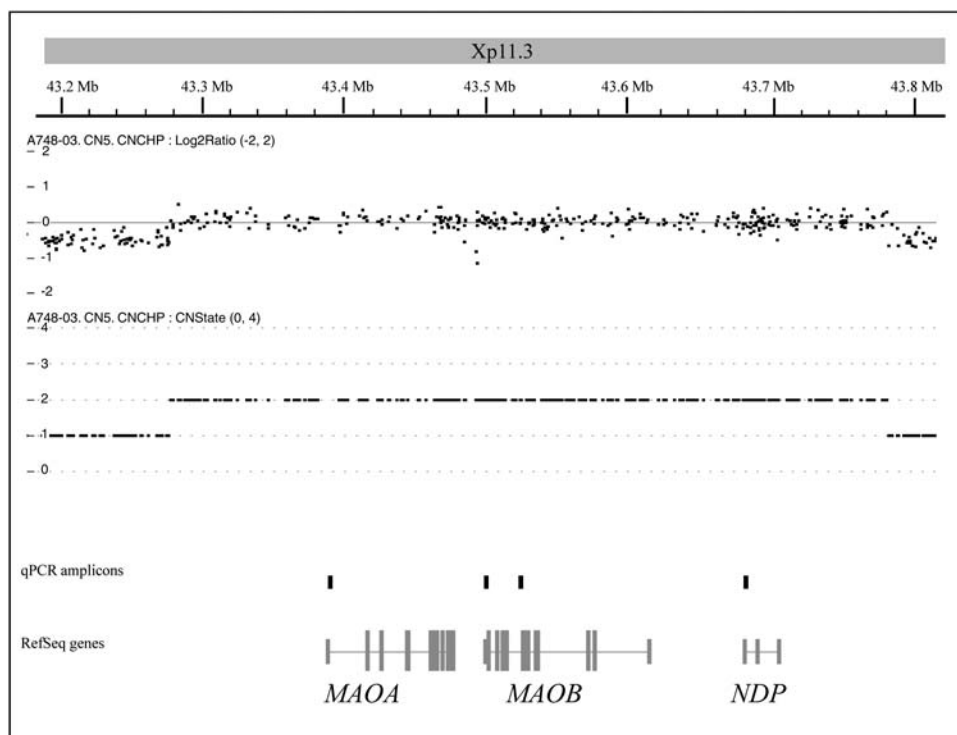
The patient was the first child of unrelated parents. Pregnancy was complicated with oedemas, and benzodiazepine use because of anxiety. The patient was born 2 weeks post term (BL: 57 cm, BW: 4800 g, OFC: 36 cm). The neonatal period was complicated by opisthotonus and by failure to thrive due to Hirschprung disease, for

which he was successfully surgically treated at the age of 16 months. Early developmental milestones were delayed. The patient presented with febrile seizures at the age of 12 months. From 3 years of age, afebrile epileptic seizures in terms of generalised atonic, myoclonic, and tonic–clonic seizures were observed. Despite treatment, the epilepsy was intractable. Clinical examination at 32 years of age revealed moderate-to-severe mental retardation, normal stature (185 cm, 87 kg), osteoporosis, slight scoliosis, friendly mood, and a high-pitched voice. The patient had normal vision, normal hearing, and normal sexual maturation.

Genome-Wide Human SNP Array 6.0 (Affymetrix) performed on DNA from peripheral blood lymphocytes revealed a 0.5-Mb duplication at chromosome Xp11.3 (chrX: 43290667–43794205, Hg18) (Figure 1). The duplication included the *MAOA*, *MAOB*, and *NDP* genes, and was validated using real-time quantitative PCR (qPCR) and the 2<sup>−Delta Delta C(T)</sup> method. One control region outside and four exonic regions inside the duplicated region were amplified using *GAPDH* as an internal standard (Supplementary Figure 1).

In this patient, a total of 16 copy number variants (CNVs) of minimum 100 kb were detected (Table 1). Only four of these did not overlap completely with known CNVs reported in the Database of Genomic Variants, and of these only the Xp11.3 duplication contained RefSeq genes. The three other unknown CNVs did not overlap with reported non-genic regulatory landscapes<sup>2–4</sup> around key developmental genes, making it less likely that they could be pathogenic, for example, involved in long-range position effects.

Reciprocal deletions and duplications of several genes/loci may result in either different or similar clinical features depending on the



**Figure 1** Duplication of Xp11.3 in a male patient with mental retardation and epilepsy. Three genes are located in the duplicated region: *MAOA*, *MAOB*, and *NDP*. The duplication was verified by qPCR with amplicons in all three genes.

**Table 1 Copy number variants (CNVs), larger than 100 kb, detected in a male patient with mental retardation and intractable epilepsy**

Chr.	Cytoband	Size (kb)	Gain/loss	Start position (Hg 18)	End position (Hg 18)	% CNV overlap
1	q23.3–q23.3	142	Gain	159 763 524	159 905 125	100
4	q13.2–q13.2	114	Loss	69 054 586	69 168 562	100
8	p23.1–p23.1	610	Gain	7 237 778	7 847 304	100
8	p11.23–p11.23	133	Loss	39 354 748	39 488 053	100
8	q21.13–q21.13	212	Loss	83 306 931	83 519 284	28
9	p11.2–p11.2	294	Loss	43 445 836	43 740 170	100
14	q11.1–q11.2	632	Loss	18 860 343	19 492 423	100
15	q14–q14	108	Loss	32 510 712	32 618 224	100
16	p11.2–p11.2	497	Loss	32 066 096	32 563 012	100
16	p11.2–p11.2	369	Loss	33 311 629	33 680 554	100
17	q21.31–q21.32	404	Gain	41 703 504	42 107 467	100
19	p12–p12	120	Loss	20 388 034	20 508 217	100
22	q11.21–q11.21	238	Gain	19 937 072	20 175 282	100
<b>X</b>	<b>p11.3–p11.3</b>	<b>504</b>	<b>Gain</b>	<b>43 290 667</b>	<b>43 794 205</b>	<b>0</b>
X	q21.31–q21.31	230	Gain	88 352 639	88 583 010	0
Y	q11.221–q11.221	157	Gain	16 835 918	16 992 884	0

In total, this patient had 16 CNVs, whereof one partially overlaps with a known CNV and three did not overlap any known CNV region. The 0.5-Mb duplication of Xp11.3 is shown in bold.

gene/locus involved.<sup>5</sup> Deletions or point mutations of *NDP* cause Norrie disease (OMIM #310600), an X-linked disorder characterised by early childhood blindness and progressive sensorineural hearing loss. *MAOA* and *MAOB* oxidise biogenic amines in neuronal as well as non-neuronal tissue. Point mutations in *MAOA* have been associated with 'antisocial behaviour following childhood maltreatment' (OMIM #309850). Male patients with contiguous deletions of *NDP*, *MAOA*, and *MAOB* present with atypical Norrie disease with a more severe cognitive outcome than the classical Norrie disease. These findings support the importance of *MAOA* and *MAOB* for cognitive function reported by Whibley *et al.*

Only one of the two previously reported duplications of Xp11.3<sup>6,7</sup> has been molecularly characterised – Tzschach *et al.*<sup>7</sup> described a male patient with mental retardation and epilepsy carrying an inherited 9.3-Mb duplication including *MAOA*, *MAOB*, and *NDP*. Our patient with a much smaller duplication involving only *NDP*, *MAOA*, and *MAOB* also presented with mental retardation and epilepsy. Combined, these findings support that tight dosage regulation of one or more of the three genes is important for normal cognitive function and development of the central nervous system. In contrast to the two patients with Xp11.3 duplication described in the literature, our patient was not obese but only slightly overweight (BMI=25.4). Thus, *MAOA* is not the only gene determining obesity, consistent with a multifactorial aetiology of obesity.<sup>8</sup>

The identification of additional cases with Xp11.3 duplications should further contribute to delineation of the associated clinical spectrum and elucidate the specific candidate gene(s) for mental retardation and epilepsy.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on European Journal of Human Genetics website (<http://www.nature.com/ejhg>)