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De novo microdeletion of Xp11.3 exclusively encompassing the monoamine oxidase A and B genes in a male infant with episodic hypotonia: A genomics approach to personalized medicine

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Abstract

Monoamine oxidase A and B (MAOA and MAOB) play key roles in deaminating neurotransmitters and various other biogenic amines. Patients deficient in one or both enzymes have distinct metabolic and neurologic profiles. *MAOB* deficient patients exhibit normal clinical characteristics and behavior, while *MAOA* deficient patients have borderline intellectual deficiency and impaired impulse control. Patients who lack both *MAOA* and *MAOB* have the most extreme laboratory values (urine, blood, and CSF serotonin 4–6 times normal, with elevated O-methylated amine metabolites and reduced deaminated metabolites) in addition to severe intellectual deficiency and behavioral problems. Mice lacking *maoa* and *moab* exhibit decreased proliferation of neural stem cells beginning in late gestation and persisting into adulthood. These mice show significantly increased monoamine levels, particularly serotonin, as well as anxiety-like behaviors as adults, suggesting that brain maturation in late embryonic development is adversely affected by elevated serotonin levels. We report the case of a male infant with a de novo Xp11.3 microdeletion exclusively encompassing the *MAOA* and *MAOB* genes. This newly recognized X-linked disorder is characterized by severe intellectual disability and unusual episodes of hypotonia, which resemble atonic seizures, but have no EEG correlate. A customized low dietary amine diet was implemented in an attempt to prevent the cardiovascular complications that can result from the excessive intake of these compounds. This is the second report of this deletion and the first attempt to maintain the patient's cardiovascular health through dietary manipulation. Even though a diet low in tyramine, phenylethylamine, and dopa/dopamine is necessary for long-term management, it will not rescue the abnormal monoamine profile seen in combined *MAOA* and *MAOB* deficiency. Our patient displays markedly elevated levels of serotonin in blood, serum, urine, and CSF while on this diet. Serotonin biosynthesis inhibitors like para-chlorophenylalanine and p-ethynylphenylalanine may be needed to lower serotonin levels in patients with absent monoamine oxidase enzymes.

Keywords

Monoamine oxidase; Copy Number Variant; Xp11.3 deletion; Catecholamines; Serotonin; Tyramine; X-linked intellectual deficiency

1. Introduction

MAOA and MAOB metabolize serotonin/5-hydroxytryptamine (5-HT), catecholamines (dopamine (DA), norepinephrine (NE), epinephrine (E)) and various other biogenic and dietary amines. Patients missing these enzymes have distinct metabolic and neurologic deficiencies. *MAOB* deficient patients have normal plasma concentrations of catecholamines and catecholamine metabolites, but *MAOA* deficient patients have abnormal concentrations of these molecules and patients who are deficient in both *MAOA* and *MAOB* tend to have the most extreme values [1–4]. MAOA and MAOB play major roles in regulating the concentration of neurotransmitters in the brain [1–3], and thus, play an important role in development of the normal brain [2, 3]. Some patients with Norrie disease have genomic deletions that include *MAOB* and *MAOA* in addition to the *NDP* gene, which is the causative gene of Norrie disease [4, 5]. These patients manifest congenital blindness, excretion of catecholamines, o-methylated metabolites, and trace amines, decreased urinary excretion of deaminated metabolites, low levels of MAOB activity in platelets, and increased concentrations of 5-HT in platelets [4].

We report a male infant with a de novo microdeletion of Xp11.3 exclusively encompassing the *MAOA* and *MAOB* genes. Our case and the other cases with deletions involving only *MAOA* and *MAOB*, reported by Whibley et al. (2010), showed episodic hypotonia and developmental delay [9]. Our patient also shares the clinical features of epicanthal folds and an unusual posterior parietal hair whorl with at least one of the patients reported by Whibley et al. [9]. Stereotypic repetitive hand movements were reported in the patients described by Whibley et al. and in patients exclusively deficient in *MAOA* described by Brunner et al. (1993) [9,11]. Both authors describe these abnormal movements as repetitive hand wringing. Our patient was also noted to have repetitive hand movements, he continuously presses his palms together in the midline. The previously reported cases by Wibley et al. also showed microcephaly [9], but our patient at the age of 12 months has a normal head circumference.

Rodriguez-Revenge et al. reported the case of a patient with a contiguous deletion of *NDP*, *MAOA*, *MAOB*, and *EFHC2* in 2007. This patient with Norrie disease was found to have “bilateral retinal detachment, microcephaly, severe psychomotor retardation without verbal language skills acquire, and epilepsy [12].” They reported that the patient had a normal MRI and no epileptiform activity by EEG, but responded well to valproic acid and had no more seizure episodes [12]. Out of the two living *MAOA* and *MAOB* deficient patients reported by Whibley et al., only one was found to have an abnormal EEG, but his hypotonic episodes were not resolved with phenobarbital or sodium valproate [9]. In our patient, identical episodes have been captured multiple times on five separate video EEGs and have never correlated with any epileptiform changes on EEG. Rodriguez-Revenge et al. attributed their patient’s myoclonic epilepsy to the deletion of *EFHC2*, but our case and those reported by Whibley et al. raise the possibility that these episodes are actually the result of *MAOA* and *MAOB* deletions.

Animal models of this condition are available [6]. Mice deficient in *maoa* have elevated levels of 5-HT, NE, and DA concentrations in the brain and show aggressive behavior [7,13]. while *maob* null mice do not show aggressiveness and only display increased beta-phenylethylamine (PEA) levels in the brain [14]. These modes demonstrate that *maoa* and

maob play distinct roles in neurotransmitter metabolism and behavior in mice, *maoa* and *maob* double KO mice show significantly higher levels of all four substrates (5-HT, NE, DA and PEA), suggesting that, in the absence of *maoa*, *maob* oxidizes *maoa* substrates and vice versa [6,7]. Mice lacking both *maoa* and *maob* exhibit decreased proliferation of neural stem cells beginning in late gestation and persisting into adulthood. These mice show significantly increased monoamine levels, particularly serotonin, as well as anxiety-like behaviors as adults, suggesting that brain maturation in late embryonic development might be adversely affected by elevated serotonin levels [6,7]. These models could be employed to screen reagents that might improve the condition of patients with deletions of both *MAOA* and *MAOB* and define foods/beverages that these patients should avoid.

MAOA and *MAOB* also play key roles in inactivating the biogenic and dietary amines: phenylethylamine, m-tyramine, and p-tyramine [4, 15]. Tyramine and phenylethylamine can cause hypertensive crises by acting as indirect sympathomimetics at sympathetic nerve terminals and in the adrenal glands [15,16]. High levels of these compounds can cause dramatic elevations in systolic blood pressure, which can lead to cardiac arrhythmias, intracerebral hemorrhage, and cardiac failure [15,16]. Therefore, excessive intake of foods and/or beverages containing these compounds could potentially cause lethal events in patients lacking normal *MAOA* and *MAOB* function. A study by Lenders et al. (1996) showed that *MAOA* deficient patients experience significantly greater increases in systolic blood pressure following the intravenous administration of tyramine, compared to normal controls [4]. Collins et al. showed that patients who are deficient in both *MAOA* and *MAOB* are up to four times more sensitive to intravenous tyramine than those who are exclusively deficient in *MAOA* [5].

Personal communication with Dr. Dian Donnai, a coauthor of the publication by Whibley et al., revealed that one adolescent male with a selective *MAOA* and *MAOB* deletion had a sudden collapse requiring intensive care following a large ingestion of chocolate. Chocolate contains high amounts of phenylethylamine. This boy's obligatory carrier grandmother had a cerebrovascular accident following the ingestion of blue cheese and wine, both of which contain large quantities of tyramine. Thus, it will be crucial to regulate the dietary intake of these compounds in order to prevent both acute and chronic cardiovascular disease in patients with deficiencies in both MAO isoforms.

We have used knowledge about MAO inhibitors, which are commonly used to treat psychiatric disorders, to develop our diet recommendations. However, it should be noted that patients with combined *MAOA* and *MAOB* deficiencies may be at a significantly higher risk of developing adverse cardiovascular events than those patients who are simply on MAO inhibitors. It is clear that our a typical feature of Norrie disease, as well as severe intellectual disability [4,5]. With deletion of *MAOA* and *MAOB*, urine serotonin and dopamine levels were increased, with marked elevations in O-methylated amine metabolites and marked reductions in deaminated metabolites, but no measurements of blood or CSF serotonin in humans have been reported previously. Knockout mice deficient in *maoa* or both *maoa* and *maob* have markedly elevated brain 5-HT and NE levels [6,7].

Array genomic comparative hybridization (array-CGH) is a powerful method to detect microdeletion of disease-causing genes, which would not be detectable by standard karyotyping [8]. In 2010, Whibley et al. reported a family with deletion of Xp11.3, targeting only *MAOA* and *MAOB*, which was detected by array-CGH [9]. The two affected brothers showed unique clinical features, which were not described in cases of Norrie disease with deletion of *MAOA* and *MAOB* [4, 5, 9]. These consisted of episodic hypotonia and stereotypic repetitive movements [9]. We report a male infant with episodic hypotonia in

whom array-CGH found a de novo microdeletion of Xp11.3 encompassing only the *MAOA* and *MAOB* genes.

2. Material and methods

The oligonucleotide-SNP chromosomal microarray, performed by Quest Diagnostics, utilized 1.8 million probes at 0.7 kb level of resolution. Serum and urine serotonin levels were determined by liquid chromatography-tandem mass spectrometry at the Mayo Clinic Medical Laboratories in Rochester Minnesota, and urine catecholamines were determined by high-pressure liquid chromatography at the same laboratory. A total volume of 513 mL of urine was collected over a 24 h period while the patient was on a tyramine-restricted diet, and urine creatinine was measured (12 mg/dL.) to calculate molar values that could be compared with those reported by Lenders et al. [4]. CSF neurochemistry and whole blood 5-HT measurements were performed by Dr. Keith Hyland at Medical Neurogenetics Laboratory in Atlanta Georgia using high-pressure liquid chromatography electrochemistry.

3. Clinical report

Our patient is a Caucasian male infant, who was born without complication at a gestational age of 40 weeks. Birth length was 46 cm (5th percentile), and birth weight was 4000 g (75th percentile). His mother was 32 years-old and his father was 39 years-old at the time of his birth. After leaving the hospital, he was found to have mild feeding difficulties and episodes of hypotonia (Fig. 1 Supplementary material online), which lasted 1–30 s and occurred at a frequency of 0–50 times per day.

Supplementary video related to this article can be found at doi: 10.1016/j.ejmg.2012.01.007.

His parents described him as being very sensitive to touch with some self-stimulatory behaviors and head-banging when frustrated. His parents also noted that he had temperature sensitivity and perspired heavily, especially when tired. He was found to have normal hearing acuity after birth, and his parents note that he is especially sensitive to sound. Our patient had no righting reactions at the head or trunk at 6 months of age.

Examination at the age of 8 months revealed delayed speech and gross motor skills, as well as generalized hypotonia. He had failed to thrive after birth, height and weight were both less than the 5th percentile. However, his head circumference had remained normal (50th percentile). He had epicanthal folds, a laterally displaced posterior parietal hair whorl on the right, macrostomia, and a single bridged transverse palmar crease on the left hand (Fig. 1). Neurologic evaluation revealed normal deep tendon reflexes with generalized hypotonia in all four extremities, slip-through at the axilla, and a persistent frog-leg position with intermittent involuntary left leg movements. At age 9.5 months, his gross motor skills were at 4–5 months, and language was at 6–7 months. He displayed unusual repetitive hand movements, continuously pressing his palms together in the midline. A 72-hr. EEG was normal for his age, and there was no EEG correlate with multiple clinical events of episodic hypotonia. Brain CT and MRI showed normal brain structure. Routine tests for metabolic disorders were normal, except for urine amino acid chromatography, which revealed an unknown peak around the retention time of homocystine.

The patient's parents and a 3-year-old sister are in good health. His family history was not suggestive of any genetic/ metabolic disorders including X-linked intellectual disability syndromes.

4. Results

A SNP chromosomal microarray was performed on the patient's peripheral blood and revealed a deletion of Xp11.3, exclusively encompassing both *MAOA* and *MAOB* (Fig. 2). This deletion involved genomic coordinates on the short arm of the X chromosome: 43,580,896 – 43,736,206 nt. (GRCh37/hg19). The patient's mother was also tested through array-CGH and was found to have no deletion with intact *MAOA* and *MAOB* genes (data not shown).

Liquid chromatography studies revealed that CSF, blood, serum, and urine levels of 5-HT were extremely elevated, especially in urine, while urine NE, E, and DA were within normal limits. Urine metanephrine was within normal limits, while urine normetanephrine was elevated, and these changes were less extreme than the levels reported by Lenders et al. [4]. Urine 3-methoxytyramine was also elevated and consistent with levels in similarly deleted patients reported by Lenders et al. [4]. The levels of 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) in CSF and urine were extremely low, as would be expected with absent *MAOA* and *MAOB* activity. These results are detailed in Table 1 and are compared to normal controls and other patients deficient in *MAOA* and *MAOB* as reported by Lenders et al. [4], and age-matched controls for CSF.

5. Discussion

MAOA and *MAOB* play an important role in the normal development and function of the brain [2, 3]. These two genes are occasionally deleted along with the *NDP* gene in Norrie disease, resulting in severe cognitive impairment in addition to blindness, which is typical for Norrie disease [4, 5]. Brunner syndrome results from an *MAOA* deficiency and has been reported in a family with a mutation in exon 8 of the *MAOA* gene. This family was found to have X-linked cognitive impairment and impulsive aggressive behavior [10]. Recently, familial cases involving the deletion of only *MAOA* and *MAOB* were reported as an X-linked recessive genomic disorder [9].

Distinct neurochemical and clinical phenotypes are associated with each type of monoamine oxidase deficiency [4]. Deletion of both *MAOA* and *MAOB* genes is strongly associated with abnormal behavior and cognitive impairment, but these disturbances are not seen in patients with microdeletions of only *NDP* and/or *MAOB*. *MAOB* deficient patients display no abnormal clinical features; normal plasma concentrations of catecholamines, o-methylated amine metabolites, and deaminated metabolites; slightly elevated urinary excretion of phenylethylamine; and significantly decreased *MAOB* activity in platelets [4]. *MAOA* deficient patients are intellectually impaired with poor impulse control; have increased plasma concentrations of o-methylated amine metabolites and decreased plasma concentrations of deaminated metabolites; elevated urinary excretion of o-methylated metabolites and 5-HT, decreased urinary excretion of deaminated metabolites; normal levels of *MAOB* activity in platelets and increased concentrations of 5-HT in platelets [4].

In our patient at age 12 months on a dietary amine restricted diet, serum, whole blood, urine, and CSF 5-HT were all elevated up to 6 times higher than normal levels, and levels of urine and CSF 5-HIAA were undetectable, consistent with absent monoamine oxidase activity. Previous patients who were exclusively deficient in *MAOA* and *MAOB* had developmental delay, episodic hypotonia, and stereotypical hand movements. Specific metabolic values for such patients have not been published until now, but patients with deletions involving *MAOA*, *MAOB*, and *NDP* were found to have high plasma concentrations o-methylated metabolites, low plasma concentrations of deaminated metabolites; elevated urinary patient should avoid aged meats and cheeses and alcoholic beverages, along with other foods and beverages that contain high levels of tyramine (Table 2 Supplementary Material). In addition

to tyramine and phenylethylamine, dopa should also be restricted because it is easily converted to dopamine, which has pressor effects as well. Foods containing dopa and/or dopamine include banana peels and broad bean pods (fava beans) [17].

A significant amount of tyramine is produced from tyrosine in the gastrointestinal tract by bacteria that express tyrosine decarboxylase. It might be possible to further decrease levels of tyramine by introducing commensal bacteria without tyrosine decarboxylase into the GI tracts of patients with combined *MAOA* and *MAOB* deficiencies. This approach has been used in patients with familial dysautonomia, with strains of lactobacilli, *Leuconostoc spp.*, *Weissella spp.*, and pediococci, which do not produce tyramine [18]. Taking probiotics exclusively containing these non-amine producing species may alter the gut flora enough to further lower tyramine levels even in patients who have eliminated tyramine from their diet.

In addition to preventing adverse cardiovascular events in patients with combined *MAOA* and *MAOB* deficiencies, it will also be important to control the levels of serotonin in an attempt to preserve cognitive function. Para-chlorophenylalanine (pCPA) is a selective irreversible inhibitor of tryptophan hydroxylase, which catalyzes the rate-limiting step in the biosynthesis of serotonin. pCPA has successfully lowered brain concentrations of serotonin in multiple animal models. This drug has not been studied extensively in humans, but it was found to reduce urinary excretion of 5-HIAA and the emetic response in chemotherapy patients [19]. Other methods to decrease levels of 5-HT, like using 6-fluorotryptophan, 5,7-dihydroxytryptamine, or creating lesions in the raphe nucleus have had limited success in animal models [20]. P-ethynylphenyl-alanine is a newer irreversible inhibitor of tryptophan hydroxylase, which was found to be more potent and more specific to tryptophan hydroxylase than pCPA. However, this drug has not been studied in humans [20,21].

By presenting these distinguishing clinical features in an infant and reviewing those observed in older patients with selective deficiencies in both *MAOA* and *MAOB*, we hope that other healthcare providers will have the ability to better diagnose this newly recognized X-linked disorder. Our case provides strong support for the use of new genomic approaches in medicine because, in addition to providing us with valuable diagnostic information, the use of oligonucleotide and SNP chromosomal microarrays has shown major implications for patient management. The clinical utility of microarray-based comparative genome hybridization has already proven useful in cases of cancer predisposition syndromes. Early detection of *TP53*, *APC*, *PTEN*, *WT1*, and *RB1* deletions can significantly improve patient outcomes by optimizing medical management [22,23]. Although we have yet to find a safe and reliable way to normalize our patient's total monoamine profile, our microarray data and subsequent literature review have allowed us make recommendations that will prolong the life of our patient by preventing cardiovascular disease. We will continue to learn from our patient and adapt our management plan appropriately. We also hope to encourage further study of pharmacologic treatment, which could potentially benefit patients with combined *MAOA* and *MAOB* deficiencies, Brunner syndrome, and Norrie disease with deletions of *MAOA* and *MAOB*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejmg.2012.01.00.

Fig. 1.

At the age of 8 months, our patient had epicanthal folds, a laterally displaced posterior parietal hair whorl on the right, macrostomia, and a single bridged transverse palmar crease on the left hand.

Fig. 2. Array-CGH revealed deletion on Xp11.3, involving both *MAOA* and *MAOB*. The patient's mother was also tested and was found to have intact *MAOA* and *MAOB* genes (data not shown).

Table 1

Urine, CSF, whole blood, and serum biogenic amine and metabolite levels.

	Patient values	Previous <i>MAOA/B</i> deletion patients	Lenders Ref range (AMC)	Lenders Ref range (NIH)
Urine serotonin	3752	256	11–68	10–78
Urine 5-HIAA	Undetectable	Not measured		10–40
Urine norepinephrine	34	106–461	27–146	180 ± 127
Urine normetanephrine	2718	1524–2908	34–182	240 ± 74
Urine epinephrine	<3.01	189	<3.01	
Urine metanephrine	84	162–247	10–90	63 ± 34
Urine dopamine	640	905–2666	147–951	516 ± 162
Urine 3-methoxytyramine	2061	947–2910	37–188	40 ± 10
MNG Ref Range (12 months)				
CSF serotonin	17	Not measured	<2.5	
CSF 5-HIAA	<5	Not measured	129–520	
CSF 3-O-methyldopa	27	Not measured	<300	
CSF homovanillic acid	<5	Not measured	294–1115	
Whole blood serotonin	5620	Not measured	1238–1772	
Serum serotonin	5497	Not measured	<1307	520 ± 94

Biogenic amine and metabolite levels in urine (expressed in nmol/nmol creatinine) and CSF, serum, and whole blood (expressed in nmol/L) in our patient, previously reported patients (ref), and normal controls.