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X-Linked Borderline Mental Retardation with Prominent Behavioral Disturbance: Phenotype, Genetic Localization, and Evidence for Disturbed Monoamine Metabolism

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Summary

We have identified a large Dutch kindred with a new form of X-linked nondysmorphic mild mental retardation. All affected males in this family show very characteristic abnormal behavior, in particular aggressive and sometimes violent behavior. Other types of impulsive behavior include arson, attempted rape, and exhibitionism. Attempted suicide has been reported in a single case. The locus for this disorder could be assigned to the Xp11-21 interval between DXS7 and DXS77 by linkage analysis using markers spanning the X chromosome. A maximal multipoint lod score of 3.69 was obtained at the monoamine oxidase type A (MAOA) locus in Xp11.23-11.4. Results of 24-h urine analysis in three affected males indicated a marked disturbance of monoamine metabolism. These data are compatible with a primary defect in the structural gene for MAOA and/or monoamine oxidase type B (MAOB). Normal platelet MAOB activity suggests that the unusual behavior pattern in this family may be caused by isolated MAOA deficiency.

Introduction

Well over 70 different X-linked conditions have been described, in which mental retardation is the primary, or a major, component (Neri et al. 1992). Several X-linked mental retardation (XLMR) syndromes have been regionally mapped, but the defective gene is known for only a few of these disorders. We here describe a large Dutch family with X-linked mild mental retardation and prominent behavioral abnormalities. The results of genetic linkage analyses and of biochemical studies suggest that a mutation affecting the structural gene for monoamine oxidase type A (MAOA) may be responsible for this syndrome.

Material and Methods

Family

The pedigree of the family is shown in figure 1. This family was evaluated after carrier testing had been requested by a sister of one of the affected males. Detailed information about the extended family had been compiled 30 years ago by an unaffected maternal granduncle. A written report of his visits to all family members living at the time states that nine males were affected with mental retardation. Since that time, five additional cases have emerged, bringing the total number of affected males to 14 in this family. We have personally evaluated five affected males and have obtained detailed histories on a further three affected males. Clinical examination included assessment of dysmorphic features, as well as measurement of height, weight, and head circumference.

DNA Studies

Venous blood samples were obtained from 24 individuals. Genomic DNA was isolated from white blood cells by protease K and subsequent salt extraction (Miller et al. 1988). For RFLP studies, 10 μg of DNA was cleaved with the appropriate restriction enzymes and analyzed as described elsewhere (Van Oost et al. 1991). For CA-repeats, primers and amplification conditions were as described elsewhere (Black et al. 1991; Clemens et al. 1991; De Weers et al. 1992). The localization of the polymorphic loci on the X chromosome, the

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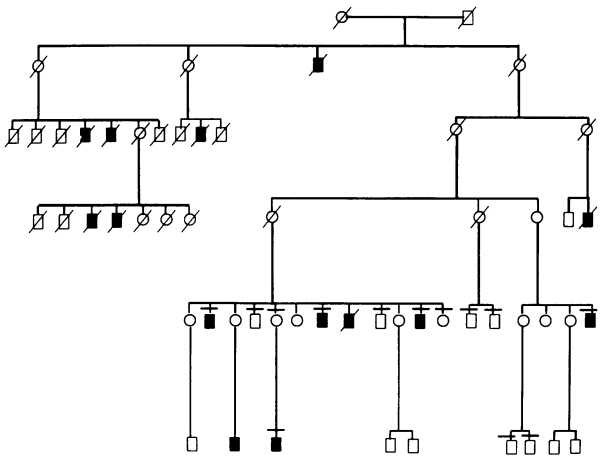

Figure 1 Pedigree of family with borderline mental retardation with prominent behavioral disturbance. Only individuals known to be at genetic risk are shown. Blackened squares denote affected males. Clinically evaluated individuals are indicated by a horizontal line above the symbol.

enzyme used, the fragment sizes, and allele frequencies —on the basis of both data from HGM 11 (Davies et al. 1991; Williamson et al. 1991) and recent data from others (Barker et al. 1991)—are given in table 1.

Linkage Analysis

Two-point linkage analyses were carried out using the MLINK and ILINK programs from the LINKAGE package 5.03 (Lathrop and Lalouel 1984). The gene frequency of the mental retardation syndrome was taken as .0001. In males, penetrance was assumed to be complete, and heterozygous females were assumed to be asymptomatic. Multipoint linkage analyses were carried out with the LINKMAP program by assuming locus order and genetic distances as derived from the literature (Barker et al. 1991; Davies et al. 1991; Williamson et al. 1991).

Biochemical Studies

Studies of monoamine metabolism were performed in seven individuals (three affected males, two unaffected males, and two carrier females).

Determination of Monoamine Oxidase Type B (MAOB) Activity

EDTA-anticoagulated blood samples were collected on the same morning from all participating family members, and platelets were counted within 1 h. Platelet-rich plasma was produced by centrifugating the blood at 150 *g* for 10 min. MAO activity (in $U/10^9$

Table 1

Polymorphic Marker Systems

Locus (probe)	Location	Enzyme	Alleles (kb)	Frequencies	References
DXS9 (RC8)	Xp22.2	*Taq*I	3.2/5.3/3.0	.82/.16/.02	Williamson et al. 1991
DMD	Xp21.3-21.1	CA-repeat	Multiallelic system		Clemens et al. 1991
DXS84 (L754)	Xp21.1	*Pst*I	12.0/9.0	.55/.45	Williamson et al. 1991
DXS77 (pX59)	Xp11.4-11.3	*Eco*RV	7.5/4.2	.92/.08	Williamson et al. 1991
MAOA	Xp11.4-11.3	CA-repeat	Multiallelic system		Black et al. 1991
DXS7 (L1.28)	Xp11.4-11.3	*Taq*I	12.0/9.0	.77/.23	Williamson et al. 1991
DXS146 (pTAK8)	Xp11.22	*Xba*I	3.3/5.0	.64/.36	Williamson et al. 1991
DXS255 (M27β)	Xp11.22	*Pst*I	Multiallelic system		Davies et al. 1991
DXS95 (pXG7)	Xq21.2-21.3	*Taq*I	1.0/2.0	.9/.1	Williamson et al. 1991
DXYS1 (pDP34)	Xq21.31	*Taq*I	10.6/11.8	.66/.34	Williamson et al. 1991
DXS3 (p19.2)	Xq21.3	*Taq*I	2.0/3.0/5.0	.62/.38	Williamson et al. 1991
DXS178	Xq21.33-22	CA-repeat	Multiallelic system		De Weers et al. 1992
DXS17 (S21)	Xq22	*Taq*I	2.2/2.0	.65/.35	Williamson et al. 1991
DXS287 (pYNH3)	Xq22-24	*Rsa*I	3.2/2.8	.38/.62	Williamson et al. 1991
DXS100 (pX45h)	Xq25	*Taq*I	4.5/4.9	.87/.13	Williamson et al. 1991
DXS144E (c11)	Xq26.2	*Taq*I	4.3/4.0	.5/.5	Williamson et al. 1991
DXS102 (cX38.1)	Xq26.1-27.1	*Taq*I	10.0/1.7	.9/.1	Williamson et al. 1991
DXS296 (VK21A)	Xq27.3-28	*Taq*I	10.9/9.9	.87/.13	Williamson et al. 1991
DXS52 (St14-1)	Xq28	*Taq*I	Multiallelic system		Williamson et al. 1991
F8C (p701.1)	Xq28	*Taq*I	9.5/4.0	.72/.28	Williamson et al. 1991

Table 2

Two-Point Linkage Analyses

Locus (probe)	Z at θ (cM) of .001	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
DXS9 (RC8)	−10.252	−6.25	−3.43	−2.21	−1.05	−.45	−.14	−.05	.45
DMD	−5.544	−2.59	−.68	−.30	.35	.33	.14	.37	.25
DXS84 (L754)	−3.528	−1.55	−.27	.19	.45	.41	.23	.46	.24
DXS77 (pX59)	.328	.32	.30	.27	.21	.15	.08	.33	.00
MAOA	2.635	2.60	2.46	2.27	1.82	1.30	.67	2.64	.00
DXS7 (L1.28)	.722	.71	.65	.58	.44	.30	.15	.72	.00
DXS146 (pTAK8)	−3.351	−1.37	−.06	.42	.70	.64	.37	.71	.22
DXS255 (M27β)	−1.995	−.04	1.17	1.51	1.53	1.20	.67	1.58	.15
DXS95 (pXG7)	.345	1.30	1.79	1.83	1.57	1.13	.60	1.84	.08
DXYS1 (pDP34)	1.570	1.56	1.51	1.42	1.19	.87	.45	1.57	.00
DXS3 (p19.2)	1.570	1.56	1.50	1.40	1.16	.84	.43	1.57	.00
DXS178	−5.014	−2.06	−.15	.49	.83	.74	.42	.84	.22
DXS17 (S21)	2.568	2.54	2.38	2.18	1.71	1.18	.60	2.57	.00
DXS287 (pYNH3)	−7.128	−4.14	−2.08	−1.24	−.49	−.15	−.02	.01	.45
DXS100 (pX45h)	−.292	−.29	−.29	−.28	−.24	−.18	−.10	−.05	.45
DXS144E (c11)	−7.130	−4.154	−2.17	−1.41	−.79	−.49	−.23	−.11	.45
DXS102 (cX38.1)	+.328	.32	.30	.27	.21	.15	.08	.32	.00
DXS296 (VK21A)	+.028	.03	.05	.07	.08	.08	.05	.09	.25
DXS52 (St14-1)	−17.06	−10.06	−5.24	−.324	−1.43	−.57	−.14	.04	.45
F8C (p701.1)	−6.654	−3.69	−1.73	−1.01	−.48	−.27	−.12	−.05	.45

platelets) was measured using a fluorometric method, with kynuramin as a substrate (van Kempen et al. 1985; Konings et al. 1992). Kynuramin is converted by MAO into 4-hydroxyquinoline (4HQ), which is measured spectrofluorometrically and quantified by comparison with suitable standards. One unit of MAO activity is defined as 1 μmol 4HQ released in the reaction per hour at 37°C. In this assay, plasma amine oxidases are responsible for less than 2% of total MAO activity in whole blood and for an even smaller proportion of MAO activity in platelet-rich plasma.

Determination of MAO Substrates and MAO Products in Urine

Twenty-four-hour urines were collected on a standardized diet (Abeling et al. 1984), by avoiding intake of catecholamine-rich foodstuffs, and were acidified with concentrated HCl to pH 2–3. Samples were stored at −25°C until analysis. Acidic 3,4-dihydroxyphenyl (catechol)alanine (DOPA) metabolites, 3-methoxy-4-hydroxy-phenyl(vanil)glycol (MHPG), and 5-hydroxy-indole-3-acetic acid (5-HIAA) were analyzed by high-performance liquid chromatography (HPLC) with fluorescence detection, as described elsewhere (Stroomer et al. 1990). Biogenic amines and their O-methylated metabolites were also determined by HPLC as described elsewhere (Abeling et al. 1984). For the acid metabolites vanilacetic acid (VMA), vanilglycolic acid (HVA), and 5-HIAA, substantial conjugation does not occur, and, therefore, only free levels were measured. Since catecholamines, metanephrines, and tyramine (TA) are partially conjugated, we measured free as well as conjugated levels for these substances. For MHPG, only total levels were determined, since this neutral metabolite is excreted predominantly as glucuronide and sulfate conjugates. For 5-hydroxytryptamine (5-HT; serotonin), both free and total levels were measured, but since conjugated forms have very low levels, only the levels of free 5-HT were used for further analysis.

Results

Clinical Examination and Developmental History

All eight affected males for whom detailed information was available were either mildly mentally retarded or in the borderline category. A typically affected male showed a full-scale IQ score of 85. Only one affected

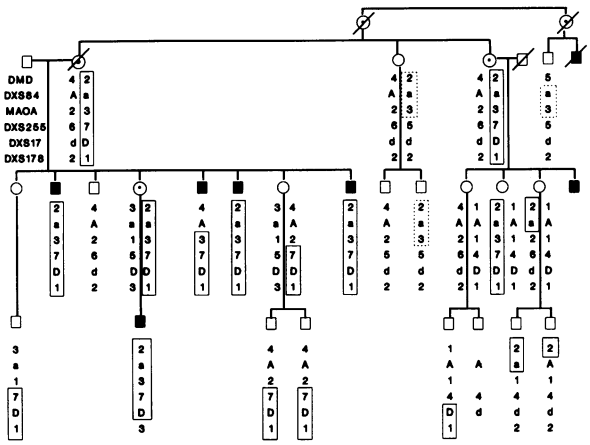

Figure 2 Deduced haplotypes for six polymorphic markers in Xp21-22. The ancestral risk haplotype is boxed. For two partial haplotypes, it was impossible to determine whether they were descended from the ancestral risk haplotype. These are shown in the dashed boxes. For one deceased female, marker haplotypes could be unambiguously derived from her offspring. Circles with dots indicate carrier females.

male has completed regular primary education. This man is the only one who is presently gainfully employed. Unaffected males in this family have attended normal schools, and most have steady jobs. All of the females (including several obligate carriers) also function normally.

Except for one male who was born with a unilateral clubfoot, no congenital abnormalities were noted on physical examination, in five affected individuals. Height, weight, and orofrontal circumference were within the normal range. Specific dysmorphic signs were not present. Inner and outer canthal distances, ear length, and testicular volume were normal when measured. All males displayed a tendency toward stereotyped hand movements such as hand wringing, plucking, or fiddling.

Behavioral problems were reported for all eight affected males. Abnormal behavior was documented for affected males in at least four different sibships living in different parts of the country at different times. Most striking were repeated episodes of aggressive, sometimes violent, behavior, occurring in all eight affected males. Aggressive behavior was usually triggered by anger and was often out of proportion to the provocation. Aggressive behavior tended to cluster in periods of 1–3 d, during which the affected male would sleep very little and would experience frequent night terrors. No obvious relationship existed between the abnormal behavior and either dietary or other external factors. In one instance, an affected male was convicted of the rape of his sister, at age 23 years. He was transferred to an institution for psychopaths, where he was described as quiet and easy to handle. In spite of this, fights occurred with other inmates, and he was repeatedly transferred to a different pavilion. At the age of 35 years, while working in the fields, he stabbed one of the wardens in the chest with a pitchfork, after having been told to get on with his work. Another affected male tried to run over his boss with a car at the sheltered workshop where he was employed, after having been told that his work was not up to par. A third affected male would enter his sisters' bedrooms at night, armed with a knife, and force them to undress. At least two affected males in this family are known arsonists. This latter behavior appears linked to stressful circumstances, such as the death of a relative. Other abnormal behavior that was recorded in individual cases includes exhibitionism and voyeurism. Several affected males were reported to suddenly grasp or hold female relatives. Teenage females in this family would often avoid

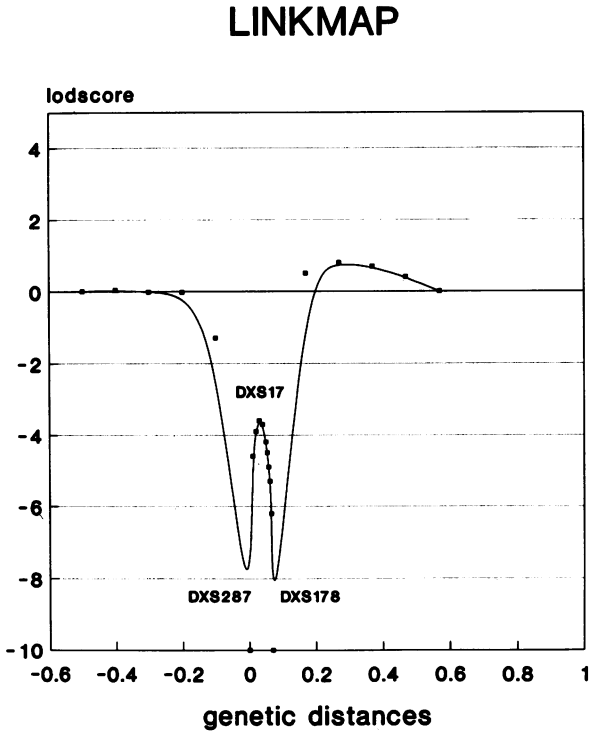

Figure 3 Multipoint analysis for XLMR and three polymorphic marker systems from Xq21-22.

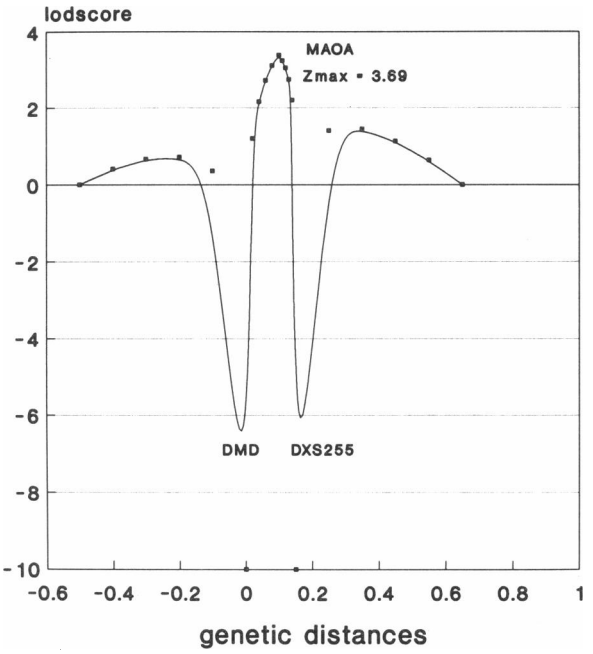

Figure 4 Multipoint analysis for XLMR and three polymorphic marker systems from Xp21-11.

being home alone with their affected brother, and some have left home at an early age because of this problem.

Chromosome Analysis

A normal 46,XY karyotype was demonstrated in one affected male, on good-quality G-banded chromosomes (approximately 850-band level).

DNA Analysis

Of 26 polymorphisms tested, 20 proved informative. Two-point lod scores are given in table 2. A maximum lod score of 2.64 with MAOA and of 2.54 with DXS17 suggested a localization of the defective gene in either proximal Xp or Xq13-22. Haplotype analysis was inconsistent with a localization in proximal Xq, since this would require at least two double-recombinant events between DXS255 and DXS178. In contrast, no inconsistencies were found on haplotype analysis when a localization between DXS255 and DXS84 was assumed (fig. 2). Four-point analysis confirmed the exclusion of Xq21-22 (fig. 3). Another four-point analysis with DMD, MAOA, and DXS255 yielded a maximum lod score of 3.69 at the MAOA locus (fig. 4).

Biochemical Studies

Results of 24-h urine analysis are shown in table 3. Marked elevations were noted for the MAO substrates such as normetanephrine (NMN), 3-methoxytyramine (3-MTA), and TA. Reduced amounts of the MAO products VMA, HVA, MHPG, and 5-HIAA were also found. These results are consistent with a primary deficiency of MAO. Normal (platelet) MAOB activity was found in all three affected subjects (table 4). This rules out clinically relevant MAOB deficiency.

Discussion

We here describe a family with X-linked nondysmorphic borderline mental retardation that is caused by a genetic defect in Xp11-21. A maximum multipoint lod score of 3.69 was obtained with a CA-repeat polymorphism in the structural gene for MAOA. Affected males in this family are borderline retarded, and none has been institutionalized because of mental retardation. The most unusual phenotypic feature is the markedly abnormal behavior. Affected males were described as withdrawn and shy, being often without friends. All have shown aggressive outbursts of some sort, usually with little or no provocation. A number of males exhibit sexually aberrant behavior, including exhibitionism, voyeurism, grasping or holding of female relatives, and (attempted) rape. Arson was noted for two affected males. The combination of borderline mental retardation and prominent behavioral disturbances is easily recognizable throughout this family, although behavioral patterns varied somewhat between individuals.

In view of both the striking behavioral phenotype in this family and its cosegregation with the MAOA structural gene in Xp11.23-11.4, we decided to evaluate our cases for signs of abnormal MAO activity. As can be seen in table 3, a disturbance of monoamine metabolism is very likely, since all three affected males who were evaluated showed increased excretion of substrates for the MAOs, especially of NMN, 3-MTA, 5-HT, and TA (table 3). In two female carriers, a smaller increase in the excretion of these substances was noted. Reduced MAO activity could also explain the reduced excretion of VMA, HVA, MHPG, and 5-HIAA, since these substances are formed from dopamine, norepinephrine, and 5-HT, in reactions that are catalyzed by MAO. In fact, the 24-h urine patterns observed in this family are identical to those found in patients with complex X-chromosomal deletions involving the Norrie disease gene and both the MAOA and MAOB structural genes in Xp11 (Sims et al. 1989; Murphy et al. 1990; Collins et al. 1992). Thus, a mutation involving either or both of the MAOA and MAOB genes could

Table 3

Excretion Values of MAO Substrates and Products

MAO Substrates and Products	Patients			Carriers		Normal Males		Reference Range
	1	2	3	1	2	1	2	
NMN (nmol/mmol creatinine):								
Total	622	666	392	149	217	73	89	34–182
Free	73	78	52	37	41	10	15	1–18
3-MTA (nmol/mmol creatinine):								
Total	234	318	217	164	134	58	79	37–118
Free	14	34	32	25	21	12	12	13–29
5-HT (nmol/mmol creatinine):								
Free	132	233	124	110	98	73	70	11–68
TA (nmol/mmol creatinine):								
Total	1,329	4,554	1,484	745	879	297	502	≤556
Free	428	621	707	644	498	<331[a]	<592[a]	≤556
VMA free (μmol/mmol creatinine)	.3	.4	.2	2.1	2.0	1.6	2.1	.5–7.6
HVA free (μmol/mmol creatinine)	.5	.5	.4	1.7	1.4	1.6	1.7	1.0–5.0
MHPG total (μmol/mmol creatinine)	.1	.2	.1	1.8	.6	1.1	1.0	.1–2.1
5-HIAA free (μmol/mmol creatinine)	nd[b]	1.4	.8	5.2	2.8	3.6	4.4	.3–5.1

[a] Values are given as the upper limit because of a small contribution of unknown hydrolyzable interfering compound.
[b] nd = Not determined.

explain the clinical picture in the family reported here. The normal MAOB activity measured in platelets of three affected males (table 4) rules out MAOB deficiency. This leads us to conclude that the characteristic behavioral phenotype in this family is probably due to isolated MAOA deficiency.

Isolated MAOA deficiency has not yet been reported in the literature. Reports of X-chromosomal deletions in Xp11 have included two cases of Norrie disease who had a disruption of the MAOB gene, apparently without involvement of the MAOA gene (Berger et al. 1992; Chen et al. 1992*a*), although this was not specifically stated in the text. These cases were reported as having normal intelligence and behavior. On the other hand, five patients with deletions involving both the MAOA and MAOB structural genes have shown severe mental retardation (de la Chapelle et al. 1985; Bleeker-Wagemakers et al. 1988) sometimes associated with self-injurious and stereotypical behavior (Donnai et al. 1988; Zhu et al. 1989; Collins et al. 1992). Studies of MAOA activity in fibroblasts (Sims et al. 1989), as well as mutation analysis on genomic DNA (Chen et al. 1992*b*) and on MAOA cDNA (Hotamisligil and Breakefield 1991), are required to resolve whether the disorder in the family reported here is indeed caused by a mutation in the MAOA structural gene. Irrespective of the outcome of such studies, our findings should prompt other investigators to study monoamine metabolism in families with X-linked mental retardation that show linkage to proximal Xp, as well as in families that show prominent behavioral disturbance. In this light, we consider the family reported by Sammans et al. (1991), and, to a

Table 4

MAOB Activity in Platelet-rich Plasma

	Patients			Carriers		Normal Males		Reference Range
	1	2	3	1	2	1	2	
MAOB activity (U/10^9 platelets)	235	225	255	322	238	181	160	114–335

lesser extent, the family originally reported by Wilson et al. (1991) and again reported by Mulley et al. (1992), to be likely candidates. Finally, should a mutation in the MAOA structural gene be identified in our family, this will have implications for the study of the biological mechanisms underlying disturbed aggression regulation in general (Depue and Spoont 1986; van Praag et al. 1990; van Praag 1991). Low 5-HIAA content in lumbar spinal fluid has been reported in adult males with aggressive behavior (Brown et al. 1979), in aggressive children and adolescents (Kruesi et al. 1990), and in impulsive fire setters (Virkkunen et al. 1987). Our results suggest that it may be worthwhile to consider measuring MAOA activity in such cases as well.

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