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## Early progressive encephalopathy in boys and *MECP2* mutations

**Abstract**—*MECP2* mutations mainly occur in females with Rett syndrome. Mutations have been described in 11 boys with progressive encephalopathy: seven of nine with affected sisters and two de novo. The authors report four de novo occurrences: three pathogenic and one potentially pathogenic. Common features include failure to thrive, respiratory insufficiency, microcephaly, and abnormal motor control. *MECP2* mutations should be assessed in boys with progressive encephalopathy and one or more of respiratory insufficiency, abnormal movements or tone, and intractable seizures.

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Rett syndrome (RTT) is an X-linked neurodevelopmental disorder that almost exclusively affects females and was previously thought to be lethal in males prior to birth. Typically, RTT is characterized initially by stagnation of development followed by regression lasting up to several months, both occurring between age 6 months and 3 years. The fully developed clinical picture is dominated by cognitive impairment, reduction or loss of communication skills and purposeful hand movements combined with the appearance of hand stereotypies, progressive deceleration in the rate of head growth, and abnormal locomotion.<sup>1</sup> Since the discovery in 1999 of mutations in the *MECP2* gene responsible for RTT,<sup>2</sup> more than 200 different pathogenic mutations have

been reported and identified in 75% or more individuals with classic RTT.<sup>1</sup> On the other hand, the epidemiology of *MECP2* pathology in males remains unknown. The small number of case reports has been grouped into three main categories: 1) classic RTT (most of whom have either Klinefelter syndrome or somatic mosaicism); 2) varying degrees of mental retardation with or without additional symptomatology; and 3) neonatal or infantile encephalopathy.<sup>3</sup> We report four additional infant boys with progressive encephalopathy, all evaluated within the past 2 years. The first two are in the Australian Rett Syndrome Database<sup>4</sup> and the other two have been seen at the Children's Hospital of Alabama. Unlike the majority of previously reported males, these infants represent sporadic occurrences without evidence of RTT in other family members. Three have definitely pathogenic mutations ([mecp2.chw.edu.au/](http://mecp2.chw.edu.au/)); the fourth is potentially pathogenic.

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**Results.** The four young boys with neonatal onset or severe early phenotype are presented in the table along with the only two previously reported sporadic occurrences with *MECP2* mutations<sup>5,6</sup> and the nine previously reported familial male occurrences. Despite some differences, these boys have common features, notably respiratory insufficiency. Thirteen of 14 also had axial hypotonia, 10 of 11 were microcephalic, and a similar proportion had EEG abnormalities. Seven of 10 had limb rigidity and eight of 11 had a movement disorder with marked myoclonic, dyskinetic, and choreiform patterns appearing more florid (see video E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). Hand stereotypies were less common than in girls with RTT. However, three boys (Cases 2, 10, and 13) were described as having repetitive face scratching or nose rubbing. In the 11 instances in which neonatal history was available, all but Case 2, who did have neonatal feeding difficulties, would be classified as having a newborn encephalopathy.

None of the four we present has the same *MECP2* mutation, although the *MECP2* protein defect in the two Australian cases (Cases 1 and 2) is very similar. Case 2 shares the mutation found in a family of three girls and one boy (Case 6), which was key to the discovery of linkage to

**Table** Early postnatal encephalopathy and *MECP2* mutations in boys

Case no.	Ref.	Mutation	Familial	Status	Resp insuff	Mic	Limb rigid	Axial hypo	Mov dis	Progressive head growth deceleration	EEG
1	This report	c.808delC (p.R270fs)	Sporadic; mother had two spontaneous abortions and trisomy 21 fetus	Died at 14 mo	Yes	Yes	No	Yes	No	Yes	Slowing
2	This report	c.806delG (p.G269fs)	Sporadic	Died at 27 mo	Yes	Yes	No	Yes	Yes	Yes	Slowing
3	This report	c.469T>A (p.F157I)	Sporadic; mother had three spontaneous abortions	Alive at 25 mo	Yes	Yes	Yes	Yes	Yes	Yes	Slowing
4	This report	c.1250A>T (p.K417M)	Maternally inherited variant	Died at 14 mo	Yes	Yes	No	No	Yes	Yes	Slowing
5	3	No tissue available	Sister and half-sister	Died at 16 mo	Yes	?	Yes	Yes	No	?	Slowing
6	3	c.806delG (p.G269fs)	Aunt, half-sister; mother a carrier	Died at 12 mo	Yes	Yes	Yes	Yes	Yes	?	Slowing
7	3	c.473C>T (p.T158M)	Sister; mother a carrier	Died at 11 mo	Yes	?	?	Yes	?	?	Normal
8	3	No tissue available	Sister; mother a carrier	Died at 9 mo	Yes	?	?	?	?	?	?
9	10	c.754insG (p.G252fs)	Sister	Ventilator dependent at 6 y	Yes	?	?	Yes	Yes	?	?
10	3	c.754insC (p.252fs)	Sister	Died at 24 mo	Yes	Yes	Yes	Yes	No	Yes	Slowing
11	3	c.1154del32 (p.385fs)	Mother a carrier	Died at 21 mo	Yes	Yes	?	Yes	?	Yes	?
12	3	c.1154del32 (p.385fs)	Mother a carrier	Died at 18 mo	Yes	Yes	?	Yes	?	?	?
13	3	c.488_489delG (p.G163fs)	Sister	Died at 13 mo	Yes	Yes	Yes	Yes	Yes	Yes	Slowing
14	5	c.473C>T (p.T158M)	Sporadic	Died at 14 mo	Yes	No	Yes	Yes	Yes	Yes	Slowing
15	6	c.806delG (p.G269fs)	Sporadic	Died at 36 mo	Yes	Yes	Yes	Yes	Yes	Yes	Slowing

Movement disorders: Case 2, myoclonus; Case 3, myoclonus/choreoathetosis; Case 4, myoclonus; Case 6, tremor; Case 13, dyskinetic; Case 14, choreiform; Case 15, myoclonus; patients of Villard et al. and Geerdink et al. had silvery-grayish and salt-and-pepper hair.

In reference 3, Cases 5 and 6 reported by Schanen et al., Cases 7 and 8 by Villard et al., Case 10 by Ben Zeev et al., Cases 11 and 12 by Hoffbuhr et al., and Case 13 by Geerdink et al.

Resp insuff = respiratory insufficiency; Mic = microcephaly; Limb rigid = limb rigidity; Mov dis = movement disorder.

Xq28.<sup>3</sup> It is also the same mutation present in Case 15,<sup>6</sup> a boy who died at age 36 months (Leuzzi, personal communication, 2005). Neuropathologic findings of the severe early-onset phenotype have been documented in only three instances including one described here. Our observation of frontal lobe neuronal migration disorder in Case 1 represents a pathogenic process that extends beyond the neuropathology of RTT figure.

**Discussion.** Molecular studies of *MECP2* were performed in Cases 3 and 4 because of the prominent movement disorder, respiratory problems, and developmental delay as noted in previous reports. The parents of Case 1 sought genetic counseling in a subsequent pregnancy following his death. *MECP2* was considered as one possibility among the rare metabolic disorders presenting as progressive encephalopathy in boys that might account for his clinical and pathologic findings. Case 2 was referred for testing because of the face-scratching stereotypies

that his clinician had previously seen in a girl with RTT. In all four infants reported here, a high index of suspicion for a mitochondrial disorder existed because of the respiratory involvement and hypotonia.

In Case 4, evidence for pathogenicity of the mutation is unclear, particularly as the variant is also present in maternal DNA. The mother's X-inactivation pattern appeared random in DNA from peripheral blood lymphocytes, but this may not reflect the X-inactivation ratio in brain. Further examination in the maternal family has not been possible, specifically, in the absence of any male relatives. Support for a pathogenic role of this variant is its apparent rarity (no previous reports) and its location within a conserved region toward the carboxy-terminal of MeCP2 that facilitates binding to DNA. Further, there is a high level of evolutionary conservation of the basic charged polar lysine residue at position 417 (methionine is a nonpolar amino acid)

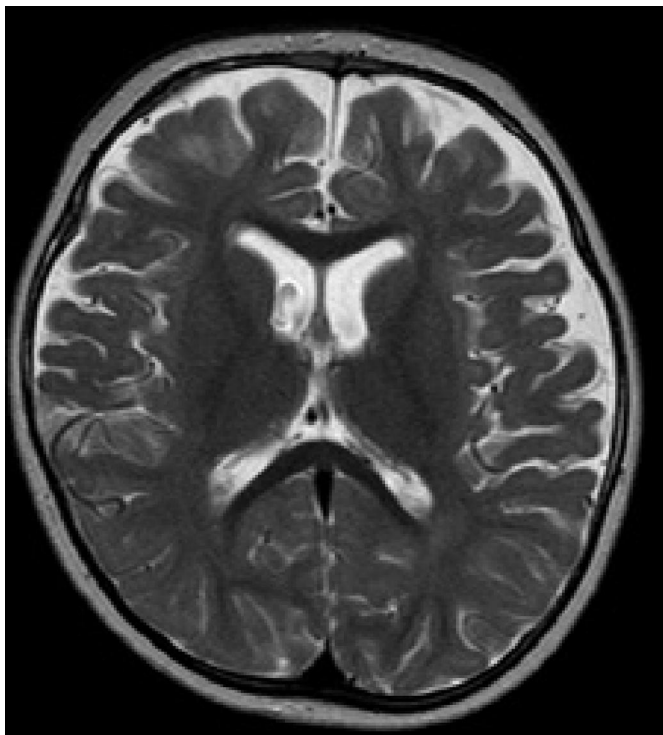


Figure. Cranial MRI at level of lateral ventricles indicating bilateral cortical atrophy in the frontal regions and moderate ventriculomegaly.

that is present in species representing mammals (*Homo sapiens*, *Macaca fascicularis*, *Mus musculus*, *Rattus norvegicus*) and amphibians (*Xenopus laevis*). On balance, the pathogenicity of the variant, particularly in the context of a hemizygous male, cannot be clearly defined.

In addition to the clinical utility of defining the cause and likely prognosis for this disturbing clinical presentation, molecular confirmation is of great assistance for genetic counseling purposes. Specifically, it provides the ability to identify whether the mother carries the mutation and to offer prenatal diagnosis in subsequent pregnancies. We are currently limited to the observations that we have been able to make on these 15 identified cases worldwide. Are these representative of the whole spectrum? Could there be a more severe phenotype associated with stillbirths or neonatal mortality? Could a milder phenotype with less respiratory compromise and longer survival exist? How much of this is influenced by the nature of the mutation and by possible mosaicism not detectable in every tissue? Some evidence of this is presented in a recently reported familial case<sup>7</sup> with a phenotype more reminiscent of RTT than the

boys whom we have described. Another boy with a sporadic 816dup7 truncating mutation<sup>8</sup> had a later presentation and also a much milder and more Rett-like phenotype than the boys shown in the table. Thus, many questions remain to be answered including identifying the contribution of *MECP2* pathology to newborn encephalopathy. A population-based study in Western Australia found the incidence of moderate and severe newborn encephalopathy to be 3.8 per 1,000 births.<sup>9</sup> Of the 166 boys in the cohort of 276 infants, 21 had died by age 3 years, but only seven after the neonatal period, and in five of these, no clear underlying etiology was found (Dixon and Badawi, personal communication, 2005). Cases such as these five would be candidates for *MECP2* pathology. The challenge remains to identify those factors in early life that will be sufficiently predictive to provide a clinically appropriate yield from *MECP2* testing in male infants. To do this could require population-based studies to collect DNA prospectively or to use newborn screening samples retrospectively. At present, we suggest that a high index of suspicion for *MECP2* pathology should be maintained for young boys with two or more of the following: moderate or severe early postnatal, progressive encephalopathy; unexplained central hypoventilation or respiratory insufficiency; abnormal movements; intractable seizures; and abnormal tone, including progressive rigidity.

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