

REVIEW

MECP2 mutations in males

Laurent Villard

J Med Genet 2007;44:417–423. doi: 10.1136/jmg.2007.049452

Rett syndrome (RS; MIM 312750) is a severe neurological disorder affecting exclusively females. Its prevalence is about 1 in 10 000 female births, and it is a prominent cause of profound mental handicap in women. RS is caused by mutations in the X-linked methyl CpG-binding protein 2 (*MECP2*) gene. These mutations were initially thought to be lethal in males. However, *MECP2* mutations are now frequently identified in mentally retarded male patients. The frequency of disease-causing *MECP2* mutations in this population is between 1.3% and 1.7%. Surprisingly, *MECP2* mutations in males are responsible for a wide spectrum of neurological disorders, ranging from mild mental retardation to severe neonatal encephalopathy. The aim of this review is to describe the nature of the *MECP2* mutations identified in male patients to date and their associated phenotypes.

X-linked dominant disorders (see Franco, Ballabio⁹ for a recent review). The fact that an excess of male miscarriages was not observed in the known familial cases of RS could be attributed to their exceptionally small number, and to the small number of children in these rare families. The discovery by Wan *et al*⁷ instantly revealed that the presence of a mutation in the *MECP2* gene on the single X chromosome of a male embryo was compatible with development and life. This important and unexpected discovery prompted most laboratories involved in mutation screening for RS to include male cases in their screens. Today, it is clear that *MECP2* mutations in male patients are not rare. Surprisingly, they are responsible for a wide spectrum of neurological disorders, ranging from mild mental retardation (MR) to severe neonatal encephalopathy. The aim of this review is to describe the nature of the *MECP2* mutations identified in male patients (table 1) and their associated phenotypes (table 2). Cases reported between December 1999 and December 2006 are included. Non-pathogenic variants are not considered.

Rett syndrome (RS; MIM 312750) is a severe neurological disorder affecting exclusively females.¹ Its prevalence is about 1 in 10 000 female births.² It is a prominent cause of profound mental handicap in women.³ The clinical course of the disease is typical, and consists of a normal neonatal period, followed by an arrest of development between 6 and 18 months of age. The patients show a number of clinical signs indicating a neurodevelopmental defect: arrest of brain development, regression of acquired skills and behavioural problems (stereotypic hand movement, autism).⁴ The vast majority of cases are sporadic, although a few families have been reported.⁵ Mutations in the methyl CpG-binding protein 2 (*MECP2*) gene were identified in 1999 in females affected by RS,⁶ ending a relentless hunt that lasted for >15 years since the condition was brought to the attention of the medical community by Hagberg *et al*.¹ Soon after this major breakthrough, the first mutation in the *MECP2* gene in a male patient was described.⁷ This mutation was identified in several individuals from a familial case of RS that had contributed to map the disease in Xq28.^{5, 8} In this unique family, two sisters were carriers of the G269fs mutation in *MECP2*. One of these women had two affected children: a girl affected by the classical form of RS, and a boy who died in early infancy from a severe neonatal encephalopathy of unknown origin. They were both carriers of the G269fs mutation. Until that date, due to the exclusive female occurrence of RS, it was believed that any mutation causing the disease led to early termination of putative male pregnancies. This is a classical situation for several

FREQUENCY OF MECP2 MUTATIONS IN MALES

MECP2 mutation screening was reported for 2697 male individuals affected by a neurological disorder. In this heterogeneous population of patients, 46 potentially disease-causing mutations were identified in different families and sporadic cases. They can be divided into two groups: 34 mutations that are certainly pathogenic (nonsense, frameshift and other mutations found in several girls with RS) and 12 unclassified variants consisting mainly of missense mutations found in a single family. The frequency of potentially disease-causing *MECP2* mutations in the population of mentally retarded male patients is thus between 1.3% and 1.7%. This is an important figure, considering that the incidence of fragile X syndrome, the most frequent familial cause of MR in males, is 2.8% in the same population.⁴⁴

Five out of seven mutations identified by Del Gaudio *et al*^{29, 33} are not taken into account in the numbers given above, as they were identified in a population of 1380 individuals whose phenotype and gender are not specified (these mutations are nonetheless listed in tables 1 and 2).

Many non-pathogenic nucleotide changes were also identified in the *MECP2* gene. This gene has a very high rate of de novo mutations, and several

Abbreviations: MR, mental retardation; PWS, Prader–Willi syndrome; RS, Rett syndrome; XCI, X-chromosome inactivation

Correspondence to:
L Villard, INSERM, U491,
Faculté de Médecine de La
Timone, 27 boulevard Jean
Moulin, 13385 Marseille
cedex 5, France; laurent.
villard@medecine.
univ-mrs.fr

Received 25 January 2007
Revised 28 February 2007
Accepted 28 February 2007
Published Online First
9 March 2007

Table 1 Summary of the different mutations found in the *MECP2* gene in male patients

Mutation	Pos	RS	De novo	Affected XY relatives	Affected XX relatives	Mother XCI	Comments	Ref
Missense mutations								
R133C	MBD	92	No	None	RTT/MR	85:15	Mother has mild MR	Masuyama <i>et al</i> ¹⁰
S134C	MBD	12	No	None	Atypical RTT	98:2		Budden <i>et al</i> ¹¹
E137G	MBD	0	No	MR	None	Random	Unclassified variant	Couvert <i>et al</i> ¹²
A140V	MBD	0	No	Severe MR	Mild MR	Random	Unclassified variant	Orrico <i>et al</i> ¹³
	MBD	0	No	Severe MR	None	Random	Unclassified variant	Couvert <i>et al</i> ¹²
	MBD	0	No	PPM-X	Mild MR	Random	Unclassified variant	Klauck <i>et al</i> ¹⁴
F157I	MBD	0	Yes				Unclassified variant	Kankirawatana <i>et al</i> ¹⁵
T158M	MBD	191	No	SNE	RTT	99:1		Villard <i>et al</i> ⁶
	MBD	191	Yes					Lynch <i>et al</i> ¹⁷
R167W		0	No	Moderate MR	None	Random	Unclassified variant	Couvert <i>et al</i> ¹²
P225L	TRD	0	Yes				Unclassified variant	Moog <i>et al</i> ¹⁸
P322S		0	No	None	MR	Random	Mother has mild MR	Ventura <i>et al</i> ¹⁹
							Unclassified variant	
R344W		0	NA	NA	NA	NA	Unclassified variant	Laccone <i>et al</i> ²⁰
P405L		0	No	None	MR	NA	Mother has mild MR	Moog <i>et al</i> ²¹
							Unclassified variant	
K417M		0	No	None	None	Random	Unclassified variant	Kankirawatana <i>et al</i> ¹⁵
R453Q		0	NA	NA	NA	NA	Unclassified variant	Couvert <i>et al</i> ¹²
In-Frame deletions								
P387del80		0	No	Mild MR	None	100:0		Yntema <i>et al</i> ²²
Frameshifts and nonsense mutations								
G163fs		1	No		RTT	NA		Geerdink <i>et al</i> ²³
G252fs	TRD	3	No	None	RTT		Germline mosaicism	Zeev <i>et al</i> ²⁴
G269fs	TRD	9	No	None	RTT	Skewed	Mother has mild MR	Wan <i>et al</i> ²⁵
	TRD	9	Yes					Leuzzi <i>et al</i> ²⁵
	TRD	9	Yes					Kankirawatana <i>et al</i> ¹⁵
R270fs	TRD	3	Yes					Kankirawatana <i>et al</i> ¹⁵
G273fs	TRD	0	Yes					Ravn <i>et al</i> ²⁶
L386fs		7	No	None	None	95:5		Daye <i>et al</i> ²⁷
Q406X		0	No	Severe MR	None	Random	Mild MR in a carrier female	Meloni <i>et al</i> ²⁸
E472fs		0	Yes					Kleefstra <i>et al</i> ²⁹
Large duplications								
430 kb		0	No	None	None	90:10	Duplication of AVPR2 to FLNA	Meins <i>et al</i> ³⁰
0.4–0.8 Mb		0	No	Severe MR	None	>85:15	4 duplications	Van Esch <i>et al</i> ³¹
0.4–0.8 Mb		0	No	Severe MR	None	>90:10	6 duplications	Friez <i>et al</i> ³²
0.2–2.2 Mb		0	U	None	None	Skewed	6 duplications and 1 triplication	Del Gaudio <i>et al</i> ³³
Abnormal karyotypes								
Y141X/XXY	MBD	6	Yes					Schwartzman <i>et al</i> ³⁴
T158M/XXY	MBD	191	Yes				76% of XXY cells	Leonard <i>et al</i> ³⁵
E455X/XX		1	Yes				Heterozygous male	Maiwald <i>et al</i> ³⁶
Somatic mosaicism								
P56fs		0	Yes					Clayton-Smith <i>et al</i> ³⁷
R133H	MBD	3	Yes					Armstrong <i>et al</i> ³⁸
T158M	MBD	191	Yes				25% mutant cells	Kleefstra <i>et al</i> ²⁹
R270X	TRD	146	Yes				40% mutant cells	Topcu <i>et al</i> ⁴⁰

MBD, methyl binding domain; MR, relative presenting mental retardation; NA, not available; Pos, position with respect to known functional domains in the *MECP2* protein; PPM-X, psychosis, pyramidal signs and macro-orchidism; RS, number of times this mutation was identified in a girl with Rett syndrome (according to the IRSA *MECP2* variation database, <http://mecp2.chw.edu.au/>), RTT, relative affected by RS; SNE, severe neonatal encephalopathy; TRD, transcription repression domain; XCI, X-chromosome inactivation.

Non-pathogenic variants are not listed.

polymorphisms were found in affected and healthy individuals in the same family.⁴⁵ These polymorphisms are not taken into account in the figures given here.

Frequencies can be calculated only if the number of screened patients is large enough. The first report of a large male population screened for mutations in *MECP2* involved 185 mentally retarded patients negative for fragile X syndrome testing.¹² In total, four (2.1%) mutations were reported as disease causing in this cohort. This surprisingly high figure prompted other laboratories to screen more similarly selected patients. However, the results showed a much lower incidence of mutations. In the subsequent reports involving a total of 829 patients,^{46–47} a single disease-causing mutation was identified (0.1%). Hence, testing negative for the expansion of the FMR1 CGG repeat does not seem to be a very useful criterion to select a population for *MECP2* mutation screening.

After these misleading initial findings, subsequent screens were extended to include males affected by non-specific MR. In the 658 patients reported to date,^{21–22, 48–52} 2 (0.3%) disease-causing

mutations were identified. The first mutation was present in a two-generation family with three affected males,²² and the second in a male patient with unexplained MR.²¹

Targeted screens were also performed following the description of four patients with non-specific MR and the A140V mutation,^{12–13} and five affected males in a single family with the psychosis, pyramidal signs and macro-orchidism (PPM-X) syndrome and the same A140V mutation.¹⁴ In total, 433 males with various forms of MR were screened for the presence of the A140V mutation,^{52–53} but no mutation was found, questioning the real frequency of this amino acid change in the mentally retarded male population.

Because of the partial phenotypic overlap between RS and patients having a defect of the 15q11q13 region causing Angelman or Prader–Willi syndrome (PWS),^{34–35} several studies tried to determine whether mutations could be found in *MECP2* in patients negative for defects in this imprinted region. In a screen of 92 male patients negative for methylation defects at the UBE3A locus,^{39–52, 56–57} mosaic mutation was found in just 1

(1.2%) patient.³⁹ The patient in the report by Hitchins *et al*⁵⁷ with the P56fs mutation had already been described twice.^{37 54} A G428S mutation described as pathogenic in such a patient⁵⁶ was shown to be a rare non-pathogenic variant.²⁰ Because the patient reported by Kleefstra *et al*²⁹ had a phenotype evocative of PWS, 71 male patients negative for PWS were also screened for *MECP2* mutation but no mutation was identified.^{39 52} A cohort of 154 male autistic patients were screened, but no disease-causing mutation, was found.⁵⁸ More recently, large duplications involving the *MECP2* locus were identified in 18 male patients with a severe neurological phenotype.^{30–33} These duplications represent 18 out of 34 (53%) of the currently known pathogenic mutations in this gene (18/34).

SCREENING METHODS

Different screening methods were used to search for mutations in the *MECP2* gene. Direct sequencing was used most often because *MECP2* is a small gene (1.5 kb of coding sequence). Denaturing gradient gel electrophoresis,¹² denaturing high-performance liquid chromatography⁴⁷ or single-strand conformation polymorphism screening⁵² were also used to screen large series of patients. These different techniques yield different mutation detection rates (between 0 and 3%). However, it is not possible to compare the yield because both the technique and the population that was screened are different (see above).

Since 2004, a new *MECP2* exon has been known.⁵⁹ It is a small 5' exon coding for 21 amino acids. Studies performed before this discovery did not include this small exon 1 in their screens. However, a large screen of 410 mentally retarded males originating from familial cases (with at least two affected individuals) for mutations in this exon of *MECP2* found no mutation.⁶⁰ This indicates that mutations in exon 1 will not be a frequent cause of neurological disorders in male patients. It is also the case for RS, in which mutations in exon 1 account for only 1–3% of the known mutations.^{61 62}

Multiplex ligation-dependent probe amplification,^{32 63 64} microarray-based comparative genomic hybridisation,^{31 33} quantitative PCR³⁰ and dosage-sensitive Southern blots³³ were used to detect large rearrangements involving the *MECP2* locus in mentally retarded males. These techniques allowed the detection of a large number of new mutations (17 duplications and one triplication).

POINT MUTATIONS FOUND IN MALES AND IN FEMALES WITH RS

The first group of mutations was identified in male patients, because they had a sister with RS. The first mutation in *MECP2* was identified in a boy who died before the age of 1 year. He was a carrier of the G269fs mutation.⁷ He had a sister with the same mutation and a classical RS phenotype. Their mother was also a carrier of the same mutation, but was protected by a favourably skewed X-chromosome inactivation (XCI) pattern. The next cases were two brothers having severe neonatal encephalopathy who died before the age of 12 months and were carriers of the T158M mutation.¹⁶ Their mother was asymptomatic, although she was a carrier of the same mutation. She also had a totally skewed XCI. Since then, these two mutations (T158M and G269fs) have been found in boys with severe neonatal encephalopathy who did not have a sister affected by RS.^{17 25} In these latter cases, the mothers were not carriers of the mutation.

Other mutations reported in boys were G252fs,²⁴ G163fs,²³ R133C¹⁰ and S134C.¹¹ All these boys had a sister having the classic form of RS, and they were all affected by a very severe neurological phenotype since birth. Two additional mutations were described in males affected by a severe phenotype: R270fs

and G269fs.¹⁵ These two patients died before the age of 3 years. They all had respiratory insufficiency, microcephaly, limb rigidity and movement disorder. More recently, the L386fs mutation was identified in a boy and his unaffected mother.²⁷ The mother had a completely skewed XCI.

POINT MUTATIONS FOUND IN MALES BUT NOT IN FEMALES WITH RS

The A140V mutation has never been described in a girl with a classical RS phenotype. However, it was described several times in mentally retarded males. It was found in four severely retarded males from the same family.¹³ A female individual in this family is also a carrier of the mutation and has mild MR. The four affected males, aged 27–40 years, have a normal head size but severe MR. They have no history of regression after an initial normal development. The only constant features in affected individuals were spastic paraparesis and distal atrophy of the legs.⁶⁵ This A140V mutation was subsequently found in two males with non-specific MR¹² and in affected males from the MRX79 family mapped to Xq28.⁶⁶ In the MRX79 family, there is a large phenotypic heterogeneity, even among affected individuals. All carrier females have random XCI, which has prompted questions about the pathogenicity of this A140V mutation.²⁰ The A140V mutation was also described in a 12-year-old boy with developmental receptive language disorder and childhood-onset schizophrenia.⁶⁷ The mutation was present in the patient's unaffected mother, whose XCI pattern was not reported.

The study by Couvert *et al*¹² also described mutations in *MECP2* in three families with non-specific MR mapping to Xq28. The first family had an in-frame deletion of 80 amino acids (P387del80). Affected patients have severe to mild non-progressive MR, with better motor skills than verbal ability.⁴³ The second family carries the R167W mutation. The patients have essential tremor with mild and non-progressive MR, poor motor coordination and difficulties with written language. The third family carries the E137G mutation. The patients have mild to moderate MR, poor speech articulation and, in some patients, verbal stereotypies with suspicion of regression of language skills in three. The R167W and E137G mutations are currently listed as unclassified variants, since there is no strong argument to favour pathogenicity.

Sporadic cases with mutations in *MECP2* were also reported by Couvert *et al*.¹² The P399L and R453Q mutations were found in two patients with moderate to severe MR. Unfortunately, parental DNA was not available for these two cases. Since its description, the P399L mutation has been shown to be a polymorphism.²⁰ This same paper demonstrates that the G428S mutation reported in a patient with moderate MR⁵⁶ is also a non-pathogenic variant. These two examples called for caution with the interpretation of de novo missense mutations in *MECP2*. For this reason, most missense mutations in table 1 are listed as unclassified variants, unless they were found in several unrelated cases of RS in female patients.

The R344W mutation was reported in a male patient with an RS-like phenotype with no clinical details.²⁰ It is maternally inherited, but the XCI pattern of the mother was not specified. It is thus another unclassified variant. Ventura *et al*¹⁹ described a 6-year-old boy with the P322S mutation, which was also present in his mother. This patient has moderate MR with autistic features and epilepsy. A de novo P225L mutation²¹ was found in a patient with severe MR, spastic tetraplegia, dystonia, complete apraxia, neurogenic scoliosis and breathing irregularities.¹⁸ The same study reported the P405L mutation in a male individual with MR, epilepsy and autism. This mutation was also found in the mother and the sister of this patient who had borderline IQ. Unfortunately, XCI ratios were not described for

Table 2 Summary of the clinical signs presented by male patients having a mutation in the *MECP2* gene

Mutation	Mic	Res	Reg	Ste	Sco	Age	MR	Other clinical details	Ref
Misense mutations									
R133C	Yes	Yes	Yes	Yes	Yes	11 years	S	Rigidity of four limbs, dystonic posture, early convulsions	Geerdink <i>et al</i> ¹⁰
S134C	Yes	Yes	Yes	Yes	Yes	10 years	S	Axial and peripheral hypotonia, rigidity of four limbs, seizures	Budden <i>et al</i> ¹¹
E137G	U	No	No	U	U	21–56 years	Mi to S	No neonatal hypotonia, speech handicap (U)	Gendrot <i>et al</i> ¹¹
A140V	No	No	No	No	No	27–40 years	S	Resting tremor, slow movements	Orrico <i>et al</i> ¹³
A140V	No	No	No	U	U	11–41 years	Mi to S	No details given	Couvert <i>et al</i> ¹²
A140V	Yes	Yes	No	U	U	25 months	Mo to S	Psychosis, pyramidal signs, macro-orchidism, short stature (U)	Lindsay S <i>et al</i> ¹²
F157I	Yes	Yes	No	U	U	25 months	SNE	Limb rigidity, axial hypotonia, movement disorder, head growth deceleration	Kankirawatana <i>et al</i> ⁵
T158M	Yes	Yes	Yes	Yes	Yes	9–11 months	SNE	Pepper and salt hair	Villard <i>et al</i> ⁶
T158M	Yes	Yes	Yes	Yes	Yes	14 months	SNE	Limb spasticity, choreiform movements	Lynch <i>et al</i> ¹⁷
R167W	Yes	No	No	Yes	Yes	17–55 years	Mi	Four cases, obesity, poor motor coordination, resting tremor	Couvert <i>et al</i> ¹²
P225L	No	Yes	Yes	Yes	Yes	21 years	S	Abnormal temperature control, spastic tetraplegia, dystonia, epilepsy until 7 years	Moog <i>et al</i> ¹⁸
P322S	No	No	No	Yes	Yes	6 years	Mo	Adiposity, uncontrolled seizures, hypotonia, lower limb weakness, intention tremor, ataxia	Ventura <i>et al</i> ⁹
R344W	No	No	No	Yes	No	29 years	S	Ret-like phenotype (no details given)	Laccone <i>et al</i> ²⁰
P405L	Yes	Yes	Yes	Yes	Yes	14 months	S	No spasticity, can walk, generalised epilepsy	Moog <i>et al</i> ²¹
K417M	Yes	Yes	Yes	Yes	Yes	14 months	S	Head growth deceleration, movement disorder	Kankirawatana <i>et al</i> ⁵
R453Q	Yes	Yes	Yes	Yes	Yes	14 months	S	No details given	Couvert <i>et al</i> ¹²
In-frame deletions									
P387del80	Yes	Yes	No	U	U	24–55 years	Mi to S	No tremor	Gomot <i>et al</i> ¹³
Frameshifts and nonsense mutations									
G163fs	Yes	Yes	Yes	Yes	Yes	13 months	SNE	Pepper and salt hair, limb rigidity, seizures	Geerdink <i>et al</i> ²³
G252fs	Yes	Yes	Yes	Yes	Yes	17 months	SNE	Severe hypotonia, recurrent infections	Zeev <i>et al</i> ²⁴
G269fs	Yes	Yes	Yes	Yes	Yes	9 months	SNE	Axial hypotonia, severe gastro-oesophageal reflux, intermittent tremor	Schonen <i>et al</i> ⁸
G269fs	Yes	Yes	Yes	Yes	Yes	28 months	SNE	Uncontrolled seizures, axial hypotonia, limb rigidity	Leuzzi <i>et al</i> ²⁵
G269fs	Yes	Yes	Yes	Yes	Yes	27 months	SNE	No limb rigidity, axial hypotonia, movement disorder	Kankirawatana <i>et al</i> ⁵
R270fs	Yes	Yes	Yes	Yes	Yes	14 months	SNE	Axial hypotonia, no limb rigidity	Kankirawatana <i>et al</i> ⁵
G273fs	Yes	Yes	Yes	Yes	Yes	11 years	S	Ataxia, spasticity, uncontrolled seizures	Lugtenberg <i>et al</i> ²⁶
L386fs	Yes	Yes	Yes	Yes	No	4 years	S	Intention tremor, axial hypotonia, seizures	Dayer <i>et al</i> ²⁷
Q406X	No	Yes	Yes	Yes	No	34 years	S	Ataxia, spasticity, convulsions, macrocephaly, death at 39 from pneumonia, recurrent infections	Meloni <i>et al</i> ²⁸
E472fs	Yes	Yes	Yes	Yes	Yes	10 years	Mo	Obesity, gynecomastia, hypotonia	Kleefstra <i>et al</i> ²⁹
Large duplications									
430 kb	No	No	Yes	Yes	No	8 years	S	Uncontrolled generalised epilepsy, no spasticity	Meins <i>et al</i> ³⁰
0.4–0.8 Mb	U	Yes	Yes	Yes	Yes	3–35 years	S	Recurrent infections, early death (U), progressive spasticity, axial hypotonia (U), seizures (U)	Van Esch <i>et al</i> ³¹
0.4–0.8 Mb	U	Yes	Yes	U	Yes	3–25 years	S	Recurrent infections, early death (U), neonatal hypotonia, childhood spasticity, seizures (U)	Friez <i>et al</i> ³²
0.2–2.2 Mb	U	No	U	U	No	3 months–16 years	S	Recurrent infections (U), axial hypotonia, childhood spasticity, genital abnormalities (U)	Del Gaudio <i>et al</i> ³³
Abnormal karyotypes									
Y14X/XXY	No	Yes	Yes	Yes	Yes	5.5 years	S	Hypotonia	Schwartzman <i>et al</i> ³⁴
T158M/XXY	No	Yes	Yes	Yes	Yes	9 years	S	A brother with del22q11	Leonard <i>et al</i> ³⁵
E455X/XX	Yes	Yes	Yes	Yes	Yes	2 years	S	SRY translocated on one X chromosome	Maiwald <i>et al</i> ³⁶
Somatic mosaicism									
P56fs	No	Yes	Yes	No	Yes	6 years	S	Seizures, truncal hypotonia, ataxic gait	Clayton-Smith <i>et al</i> ³⁷
R133H	Yes	Yes	Yes	Yes	Yes	11 years	S	Typical RTT phenotype (no details given)	Armstrong <i>et al</i> ³⁸
T158M	Yes	Yes	Yes	Yes	Yes	11 years	S	Convulsions and diffuse EEG abnormalities	Kleefstra <i>et al</i> ³⁹
R270X	Yes	No	Yes	Yes	Yes	12 years	S	Poor lower limb musculature, hypertension	Topcu <i>et al</i> ⁴⁰

Age, age at last evaluation; Mi, mild; Mic, microcephaly; Mo, moderate; MR, degree of mental retardation; Reg, regression; Res, respiratory dysfunction; S, severe; Sco, scoliosis; SNE, severe neonatal encephalopathy; Ste, stereotypies; U, not present in all patients of a series.

these women. The F157I and K417M mutations were described in two patients with a severe neurological phenotype.¹⁵ The mother of the patient with the F157I mutation had several spontaneous abortions before having this affected child, raising the suspicion of a potential germinal mosaicism. The K417M mutation is inherited from a clinically normal mother who has a random XCI pattern in her blood cells. Its pathogenicity is thus questionable.

Pathogenicity is more obvious for frameshift or nonsense mutations. A Q406X mutation was identified in an Xq28-linked MR family.²⁸ Two severely retarded males and two mildly affected females are carriers. The females have a random XCI profile. A 1415del2 de novo mutation was described in a 10-year-old boy with moderate MR, obesity and gynaecomastia.²⁹ An 816dup7 mutation was found in a male patient said to have a classical RS phenotype.²⁶ However, signs of encephalopathy were visible from birth. He never crawled, never spoke and shows no stereotypic hand movements similar to the ones seen in female patients.

LARGE DUPLICATIONS

An unexpected number of Xq28 duplications involving the *MECP2* gene have been described in male patients with severe MR. The first study reporting such a case described a 430 kb duplication in a boy with severe MR and features of RS.³⁰ Soon after, four duplications with sizes ranging from 400 to 800 kb were characterised in patients with a similar phenotype consisting of infantile hypotonia, recurrent respiratory infections and severe MR.³¹ Friez *et al*³² used MLPA amplification of the *MECP2* gene to identify six additional families in which a large duplication of the *MECP2* gene was present. Two *MECP2* duplications were described recently,⁶⁸ but they have already been reported in a previous paper.³¹ Del Gaudio *et al*³³ described six patients with a duplication of *MECP2* and one patient with a triplication of this locus. The triplicated patient has the most severe phenotype. However, in the report by Del Gaudio *et al*,³³ the criteria to select patients for screening are not described. The duplications in Xq28 usually involve several genes, and very often involve *L1CAM*. When they are transmitted, carrier mothers have a totally skewed XCI pattern favouring the expression of the normal X chromosome.

MALES WITH ABNORMAL KARYOTYPES

In a very small number of cases, a classical RS phenotype was described in male patients. The first two cases were two boys with Klinefelter syndrome (47,XXY) and the Y141X³⁴ or T158M mutation.³⁵ In this latter case, the patient had somatic mosaicism, since only 76% of his cells were XXY (see below). This case should remain exceptional, since the risk of being affected by Klinefelter syndrome (1/1000 male births) and to carry a disease-causing mutation in *MECP2* (1/10 000) is 1/10 000 000.

Another male patient had a female 46,XX karyotype, but he was found to carry a copy of the SRY sex-determining gene attached to one of his X chromosomes. In addition to this rare event, he was also a carrier of the E455X mutation in *MECP2*.³⁶ His motor development was delayed, he could not speak at 24 months, and had truncal muscular hypotonia, microcephaly and spasticity. He lost purposeful hand skills at 6 months of age, and a deceleration of head growth at about 7 months of age.

SOMATIC MOSAICISM

The first case of somatic mosaicism was reported in a patient with a P56fs mutation.³⁷ He was presenting with a classical RS phenotype. Soon after, another boy with a 47,XXY population of cells in his muscle lineage was shown to carry the R270X

mutation.⁶⁹ His blood and skin cells had a normal karyotype. He was also affected by a classical form of RS. The same R270X mosaic mutation was reported in an unrelated male patient with typical RS.⁴⁰ Two other male patients were shown to carry the mosaic R133H and T158M mutations.^{38–39} Both of them have the classical RS phenotype.

CONCLUSION

The phenotype of girls with RS has been perfectly described, and consensus inclusion and exclusion criteria were adopted and revised on several occasions.^{70–73} They include the description of variant cases. The situation is not so clear concerning males with mutations in the *MECP2* gene. However, 7 years after the description of the first mutation in a boy with a severe phenotype, it is now possible to make a number of genotype/phenotype correlations and to distinguish the three groups of patients. The first group is composed of patients who have a mutation which is also found in typical cases of RS. These boys have severe neonatal encephalopathy, and they usually die in their first year of life. These mutations can lead to a milder phenotype (and to clinical RS) when they are diluted among normally expressing cells. This is the case of XXY boys, or when somatic mosaicism is present. The second group of patients has mutations that are not found in females with RS. These mutations are usually compatible with life into adulthood. The neurological presentation ranges from severe to mild non-specific MR. The third group is composed of males having a duplication of the whole *MECP2* gene (and sometimes genes in its vicinity). The primary clinical features associated with this microduplication are non-specific, but they comprise a severe phenotype. Affected individuals experience infantile hypotonia, recurrent respiratory infection, severe MR, absence of speech development, seizures and spasticity. The recurrence of respiratory infections may be a criterion to distinguish these cases from other syndromes, as they occur in a context of normal growth.

In conclusion, MR caused by mutations in *MECP2* is not rare in male patients. With an estimated frequency of 1.3–1.7% in males with moderate or severe MR, it must be considered when neurological, metabolic, genetic, biochemical, electrophysiological and imaging investigations are not informative.

ACKNOWLEDGEMENTS

This review is dedicated to the families of children affected by RS and other diseases caused by mutations in *MECP2*. This work was supported by INSERM, Association Française du Syndrome de Rett (AFSR) and ACI Neurosciences Intégratives et Computationnelles from the French Ministry of Research.

Competing interests: None declared.

REFERENCES

- Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol* 1983;**14**:471–9.
- Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, Williamson S, Leonard H. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr* 2006;**148**:347–52.
- Percy AK. Rett syndrome. Current status and new vistas. *Neurol Clin* 2002;**20**:1125–41.
- Schanen CJ, Houwink EJ, Dorrani N, Lane J, Everett R, Feng A, Cantor RM, Percy A. Phenotypic manifestations of MECP2 mutations in classical and atypical Rett syndrome. *Am J Med Genet A* 2004;**126**:129–40.
- Schanen NC, Roth Dahle EJ, Capozzoli F, Holm VA, Zoghbi HY, Francke U. A new Rett syndrome family consistent with X-linked inheritance expands the X chromosome exclusion map. *Am J Hum Genet* 1997;**61**:634–41.
- Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;**23**:185–8.
- Wan M, Lee SS, Zhang X, Houwink-Manville I, Song HR, Amir RE, Budden S, Naidu S, Pereira JL, Lo IF, Zoghbi HY, Schanen NC, Francke U. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. *Am J Hum Genet* 1999;**65**:1520–9.

- 8 Schanen C, Francke U. A severely affected male born into a Rett syndrome kindred supports X-linked inheritance and allows extension of the exclusion map. *Am J Hum Genet* 1998;**63**:267–9.
- 9 Franco B, Ballabio A. X-inactivation and human disease: X-linked dominant male-lethal disorders. *Curr Opin Genet Dev* 2006;**16**:254–9.
- 10 Masuyama T, Matsuo M, Jing JJ, Tabara Y, Kitsuki K, Yamagata H, Kan Y, Miki T, Ishii K, Kondo I. Classic Rett syndrome in a boy with R133C mutation of MECP2. *Brain Dev* 2005;**27**:439–42.
- 11 Budden SS, Dorsey HC, Steiner RD. Clinical profile of a male with Rett syndrome. *Brain Dev* 2005;**51**:S69–71.
- 12 Couvert P, Bienvenu T, Aquaviva C, Poirier K, Moraine C, Gendrot C, Verloes A, Andres C, Le Fevre AC, Souville I, Steffann J, des Portes V, Ropers HH, Yntema HG, Fryns JP, Briault S, Chelly J, Cherif B. MECP2 is highly mutated in X-linked mental retardation. *Hum Mol Genet* 2001;**10**:941–6.
- 13 Orrico A, Lam C, Galli L, Dotti MT, Hayek G, Tong SF, Poon PM, Zappella M, Federico A, Sorrentino V. MECP2 mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett* 2000;**481**:285–8.
- 14 Klauk SM, Lindsay S, Beyer KS, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. *Am J Hum Genet* 2002;**70**:1034–7.
- 15 Kankirawatana P, Leonard H, Ellaway C, Scurlock J, Mansour A, Makris CM, Dure LS 4th, Friez M, Lane J, Kiraly-Borri C, Fabian V, Davis M, Jackson J, Christodoulou J, Kaufmann WE, Ravine D, Percy AK. Early progressive encephalopathy in boys and MECP2 mutations. *Neurology* 2006;**67**:164–6.
- 16 Villard I, Kpebe A, Cardoso C, Chelly PJ, Tardieu PM, Fontes M. Two affected boys in a Rett syndrome family: clinical and molecular findings. *Neurology* 2000;**55**:1188–93.
- 17 Lynch SA, Whatley SD, Ramesh V, Sinha S, Ravine D. Sporadic case of fatal encephalopathy with neonatal onset associated with a T158M missense mutation in MECP2. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F250–2.
- 18 Moog U, Smeets EE, van Roozendaal KE, Schoenmakers S, Herbergs J, Schoonbrood-Lenssen AM, Schrandt-Stumpel CT. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2). *Eur J Paediatr Neurol* 2003;**7**:5–12.
- 19 Ventura P, Galluzzi R, Bacca SM, Giorda R, Massagli A. A novel familial MECP2 mutation in a young boy: clinical and molecular findings. *Neurology* 2006;**67**:867–8.
- 20 Laccone F, Zoll B, Huppke P, Hanefeld F, Pepinski W, Trappe R. MECP2 gene nucleotide changes and their pathogenicity in males: proceed with caution. *J Med Genet* 2002;**39**:586–8.
- 21 Moog U, Van Roozendaal K, Smeets E, Tserpelis D, Devriendt K, Buggenhout GV, Frijns JP, Schrandt-Stumpel C. MECP2 mutations are an infrequent cause of mental retardation associated with neurological problems in male patients. *Brain Dev* 2006;**28**:305–10.
- 22 Yntema HG, Oudakker AR, Kleefstra T, Hamel BC, van Bokhoven H, Chelly J, Kalscheuer VM, Fryns JP, Raynaud M, Moizard MP, Moraine C. In-frame deletion in MECP2 causes mild nonspecific mental retardation. *Am J Med Genet* 2002;**107**:81–3.
- 23 Geerdink N, Rotteveel JJ, Lammens M, Sistermans EA, Heikens GT, Gabreels FJ, Mullaart RA, Hamel BC. MECP2 mutation in a boy with severe neonatal encephalopathy: clinical, neuropathological and molecular findings. *Neuropediatrics* 2002;**33**:33–6.
- 24 Zeev BB, Yaron Y, Schanen NC, Wolf H, Brandt N, Ginot N, Shomrat R, Orr-Urtreger A. Rett syndrome: clinical manifestations in males with MECP2 mutations. *J Child Neurol* 2002;**17**:20–4.
- 25 Leuzzi V, Di Sabato ML, Zollino M, Montanaro ML, Seri S. Early-onset encephalopathy and cortical myoclonus in a boy with MECP2 gene mutation. *Neurology* 2004;**63**:1968–70.
- 26 Ravn K, Nielsen JB, Uldall P, Hansen FJ, Schwartz M. No correlation between phenotype and genotype in boys with a truncating MECP2 mutation. *J Med Genet* 2003;**40**:e5.
- 27 Dayer AG, Bottani A, Bouchardy I, Fluss J, Antonarakis SE, Haenggeli CA, Morris MA. MECP2 mutant allele in a boy with Rett syndrome and his unaffected heterozygous mother. *Brain Dev* 2007;**29**:47–50.
- 28 Meloni I, Bruttini M, Longo I, Mari F, Rizzolio F, D'Adamo P, Denvriendt K, Fryns JP, Toniolo D, Renieri A. A mutation in the rett syndrome gene, MECP2, causes X-linked mental retardation and progressive spasticity in males. *Am J Hum Genet* 2000;**67**:982–5.
- 29 Kleefstra T, Yntema HG, Oudakker AR, Romein T, Sistermans E, Nillesen W, van Bokhoven H, de Vries BB, Hamel BC. De novo MECP2 frameshift mutation in a boy with moderate mental retardation, obesity and gynaecomastia. *Clin Genet* 2002;**61**:359–62.
- 30 Meins M, Lehmann J, Gerresheim F, Herchenbach J, Hagedorn M, Hameister K, Epplen JT. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. *J Med Genet* 2005;**42**:e12.
- 31 Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, Lugtenberg D, Bienvenu T, Jensen LR, Gecz J, Moraine C, Marynen P, Fryns JP, Froyen G. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet* 2005;**77**:442–53.
- 32 Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, Bier JA, Pai S, Simensen R, Williams C, Giampietro PF, Schwartz CE, Stevenson RE. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and Adjacent Region in Xq28. *Pediatrics* 2006;**118**:e1687–95.
- 33 Del Gaudio D, Fang P, Scaglia F, Ward PA, Craigen WJ, Glaze DG, Neul JL, Patel A, Lee JA, Irons M, Berry SA, Pursley AA, Grebe TA, Freedenberg D, Martin RA, Hsieh GE, Khera JR, Friedman NR, Zoghbi HY, Eng CM, Lupski JR, Beaudet AL, Cheung SW, Roa BB. Increased MECP2 gene copy number as the result of genomic duplication in neurodevelopmentally delayed males. *Genet Med* 2006;**8**:784–92.
- 34 Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M. Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. *Neuropediatrics* 2001;**32**:162–4.
- 35 Leonard H, Silberstein J, Falk R, Houwink-Manville I, Ellaway C, Raffaele LS, Engerstrom IW, Schanen C. Occurrence of Rett syndrome in boys. *J Child Neurol* 2001;**16**:333–8.
- 36 Maiwald R, Bonte A, Jung H, Bitter P, Storm Z, Laccone F, Herkenrath P. De novo MECP2 mutation in a 46,XX male patient with Rett syndrome. *Neurogenetics* 2002;**4**:107,108.
- 37 Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. *Lancet* 2000;**356**:830–2.
- 38 Armstrong J, Pineda M, Aibar E, Gean E, Monros E. Classic Rett syndrome in a boy as a result of somatic mosaicism for a MECP2 mutation. *Ann Neurol* 2001;**50**:692.
- 39 Kleefstra T, Yntema HG, Nillesen WM, Oudakker AR, Mullaart RA, Geerdink N, van Bokhoven H, de Vries BB, Sistermans EA, Hamel BC. MECP2 analysis in mentally retarded patients: implications for routine DNA diagnostics. *Eur J Hum Genet* 2004;**12**:24–8.
- 40 Topcu M, Akyerli C, Sayi A, Toruner GA, Kocoglu SR, Cimbis M, Ozcelik T. Somatic mosaicism for a MECP2 mutation associated with classic Rett syndrome in a boy. *Eur J Hum Genet* 2002;**10**:77–81.
- 41 Gendrot C, Ronce N, Raynaud M, Ayrault AD, Dourlens J, Castelnaud P, Muh JP, Chelly J, Moraine C. X-linked nonspecific mental retardation (MRX16) mapping to distal Xq28: linkage study and neuropsychological data in a large family. *Am J Med Genet* 1999;**83**:411–8.
- 42 Lindsay S, Splitt M, Edney S, Berney TP, Knight SJ, Davies KE, O'Brien O, Gale M, Burn J. PPM-X: a new X-linked mental retardation syndrome with psychosis, pyramidal signs, and macroorchidism maps to Xq28. *Am J Hum Genet* 1996;**58**:1120–6.
- 43 Gomot M, Gendrot C, Verloes A, Raynaud M, David A, Yntema HG, Dessay S, Kalscheuer V, Frints S, Couvert P, Briault S, Blesson S, Toutain A, Chelly J, Desportes V, Moraine C. MECP2 gene mutations in non-syndromic X-linked mental retardation: phenotype-genotype correlation. *Am J Med Genet A* 2003;**123**:129–39.
- 44 Biancalana V, Beldjord C, Taillandier A, Szpiro-Tapia S, Cusin V, Gerson F, Philippe C, Mandel JL. Five years of molecular diagnosis of Fragile X syndrome (1997–2001): a collaborative study reporting 95% of the activity in France. *Am J Med Genet A* 2004;**129**:218–24.
- 45 Miltenberger-Miltenyi G, Laccone F. Mutations and polymorphisms in the human methyl CpG-binding protein MECP2. *Hum Mutat* 2003;**22**:107–15.
- 46 Yntema HG, Kleefstra T, Oudakker AR, Romein T, de Vries BB, Nillesen W, Sistermans EA, Brunner HG, Hamel BC, van Bokhoven H. Low frequency of MECP2 mutations in mentally retarded males. *Eur J Hum Genet* 2002;**10**:487–90.
- 47 Bourdon V, Philippe C, Martin D, Verloes A, Grandemenge A, Jonveaux P. MECP2 mutations or polymorphisms in mentally retarded boys: diagnostic implications. *Mol Diagn* 2003;**7**:3–7.
- 48 Moncla A, Kpebe A, Missirian C, Mancini J, Villard I. Polymorphisms in the C-terminal domain of MECP2 in mentally handicapped boys: implications for genetic counselling. *Eur J Hum Genet* 2002;**10**:86–9.
- 49 Ylisaukko-Oja T, Rehnstrom K, Vanhala R, Kempas E, von Koskull H, Tengstrom K, Mustonen A, Onup K, Lahdetie J, Jarvela I. MECP2 mutation analysis in patients with mental retardation. *Am J Med Genet A* 2005;**132**:121–4.
- 50 Kammoun F, de Roux N, Boesplflug-Tanguy O, Vallee L, Seng R, Tardieu M, Landrieu P. Screening of MECP2 coding sequence in patients with phenotypes of decreasing likelihood for Rett syndrome: a cohort of 171 cases. *J Med Genet* 2004;**41**:e85.
- 51 Dipanda Z, Thauvin-Robinet C, Cusin V, Madinier N, Manceau E, Dizel D, Dulieu V, Mugneret F, Huet F, Teyssier JR, Faivre L. A new cohort of MECP2 mutation screening in unexplained mental retardation: careful re-evaluation is the best indicator for molecular diagnosis. *Am J Med Genet A* 2006;**140**:1603–7.
- 52 Tejada MI, Penagarikano O, Rodriguez-Revenga L, Martinez-Bouzas C, Garcia B, Badenas C, Guitart M, Minguez M, Garcia-Alegria E, Sanz-Parrá A, Beristain E, Mila M. Screening for MECP2 mutations in Spanish patients with an unexplained mental retardation. *Clin Genet* 2006;**70**:140–4.
- 53 dos Santos JM, Abdalla CB, Campos M Jr, Santos-Reboucas CB, Pimentel MM. The A140V mutation in the MECP2 gene is not a common etiological factor among Brazilian mentally retarded males. *Neurosci Lett* 2005;**379**:13–16.
- 54 Watson P, Black G, Ramsden S, Barrow M, Super M, Kerr B, Clayton-Smith J. Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. *J Med Genet* 2001;**38**:224–8.
- 55 Laan LA, Vein AA. A Rett patient with a typical Angelman EEG. *Epilepsia* 2002;**43**:1590–2.
- 56 Imessaoudene B, Bonnefont JP, Royer G, Cormier-Daire V, Lyonnet S, Lyon G, Munnich A, Amiel J. MECP2 mutation in non-fatal, non-progressive encephalopathy in a male. *J Med Genet* 2001;**38**:171–4.
- 57 Hitchins MP, Rickard S, Dhalla F, Fairbrother UL, de Vries BB, Winter R, Pembrey ME, Malcolm S. Investigation of UBE3A and MECP2 in Angelman syndrome (AS) and patients with features of AS. *Am J Med Genet A* 2004;**125**:167–72.
- 58 Beyer KS, Blasi F, Bacchelli E, Klauk SM, Maestrini E, Poustka A. Mutation analysis of the coding sequence of the MECP2 gene in infantile autism. *Hum Genet* 2002;**111**:305–9.
- 59 Mnatakanian GN, Lohi H, Munteanu I, Alfred SE, Yamada T, MacLeod PJ, Jones JR, Scherer SW, Schanen NC, Friez MJ, Vincent JB, Minassian BA. A

- previously unidentified MECP2 open reading frame defines a new protein isoform relevant to Rett syndrome. *Nat Genet* 2004;**36**:339–41.
- 60 **Poirier K**, Francis F, Hamel B, Moraine C, Fryns JP, Ropers HH, Chelly J, Bienvenu T. Mutations in exon 1 of MECP2B are not a common cause of X-linked mental retardation in males. *Eur J Hum Genet*. 2005;**13**: 523, 524).
- 61 **Amir RE**, Fang P, Yu Z, Glaze DG, Percy AK, Zoghbi HY, Roa BB, Van den Veyver IB. Mutations in exon 1 of MECP2 are a rare cause of Rett syndrome. *J Med Genet* 2005;**42**:e15.
- 62 **Quenard A**, Yilmaz S, Fontaine H, Bienvenu T, Moncla A, des Portes V, Rivier F, Mathieu M, Raux G, Jonveaux P, Philippe C. Deleterious mutations in exon 1 of MECP2 in Rett syndrome. *Eur J Med Genet* 2006;**49**:313–22.
- 63 **Erlanson A**, Samuelsson L, Hagberg B, Kyllerman M, Vujic M, Wahlstrom J. Multiplex ligation-dependent probe amplification (MLPA) detects large deletions in the MECP2 gene of Swedish Rett syndrome patients. *Genet Test* 2003;**7**:329–32.
- 64 **Ravn K**, Nielsen JB, Skjeldal OH, Kerr A, Hulthen M, Schwartz M. Large genomic rearrangements in MECP2. *Hum Mutat* 2005;**25**:324.
- 65 **Dotti MT**, Orrico A, De Stefano N, Battisti C, Sicurelli F, Severi S, Lam CW, Galli L, Sorrentino V, Federico A. A Rett syndrome MECP2 mutation that causes mental retardation in men. *Neurology* 2002;**58**:226–30.
- 66 **Winnepeninckx B**, Errijgers V, Hayez-Delatte F, Reyniers E, Kooy F. Identification of a family with nonspecific mental retardation (MRX79) with the A140V mutation in the MECP2 gene: is there a need for routine screening? *Hum Mutat* 2002;**20**:249–52.
- 67 **Cohen D**, Lazar G, Couvert P, Desportes V, Lippe D, Mazet P, Heron D. MECP2 mutation in a boy with language disorder and schizophrenia. *Am J Psychiatry* 2002;**159**:148–9.
- 68 **Lugtenberg D**, de Brouwer AP, Kleefstra T, Oudakker AR, Frints SG, Schrandt-Stumpel CT, Fryns JP, Jensen LR, Chelly J, Moraine C, Turner G, Veltman JA, Hamel BC, de Vries BB, van Bokhoven H, Yntema HG. Chromosomal copy number changes in patients with non-syndromic X linked mental retardation detected by array CGH. *J Med Genet* 2006;**43**:362–70.
- 69 **Vorsanova SG**, Yurov YB, Ulas VY, Demidova IA, Sharonin VO, Kolotii AD, Gorbachevskaia NL, Beresheva AK, Soloviev IV. Cytogenetic and molecular-cytogenetic studies of Rett syndrome (RTT): a retrospective analysis of a Russian cohort of RTT patients (the investigation of 57 girls and three boys). *Brain Dev* 2001;**51**:S196–S201.
- 70 **Hagberg B**, Goutieres F, Hanefeld F, Rett A, Wilson J. Rett syndrome: criteria for inclusion and exclusion. *Brain Dev*. 1985;**7**: 372, 373).
- 71 **The Rett Syndrome Diagnostic Criteria Work Group**. Diagnostic criteria for Rett syndrome: The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol* 1988;**23**:425–8.
- 72 **Hagberg BA**, Skjeldal OH. Rett variants: a suggested model for inclusion criteria. *Pediatr Neurol* 1994;**11**:5–11.
- 73 **Hagberg B**, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. *Eur J Paediatr Neurol* 2002;**6**:293–7.

See your work published in *Journal of Medical Genetics*

Journal of Medical Genetics is only as good as its articles, so we work hard to support the authors who trust us to publish their work. Here are just a few reasons why you should send us your article:

- **Academic credibility** – You'll be published in one of the top medical genetics journals in Europe.
- **Maximum visibility for your article** – Your work will be seen by a wide international audience, both through the print journal (C 1500 readers per issue) and the website (C 42,000 unique visitors every month).
- **Hassle free peer review** – Our fast and efficient submission process involves only the best reviewers. The entire submission and peer review process is conducted online, saving you time and shortening the wait for your paper to be published.
- **Online First** – Your article may appear on the journal website as soon as it's accepted via our 'Online First' feature. Your colleagues could be reading your paper within days of you submitting it.

For more information or to submit an article visit www.jmg.bmj.com and click the **Online Submissions** button.