REVIEW

MECP2 mutations in males

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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.

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 indicationg 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 X-linked dominant disorders (see Franco, Ballabio[9] 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.

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

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

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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 *et al*[10]
S134C	MBD	12	No	None	Atypical RTT	98:2		Budden *et al*[11]
E137G	MBD	0	No	MR	None	Random	Unclassified variant	Couvert *et al*[12]
A140V	MBD	0	No	Severe MR	Mild MR	Random	Unclassified variant	Orrico *et al*[13]
	MBD	0	No	Severe MR	None	Random	Unclassified variant	Couvert *et al*[12]
	MBD	0	No	PPM-X	Mild MR	Random	Unclassified variant	Klauck *et al*[14]
F157I	MBD	0	Yes				Unclassified variant	Kankirawatana *et al*[15]
T158M	MBD	191	No	SNE	RTT	99:1		Villard *et al*[16]
	MBD	191	Yes					Lynch *et al*[17]
R167W		0	No	Moderate MR	None	Random	Unclassified variant	Couvert *et al*[12]
P225L	TRD	0	Yes				Unclassified variant	Moog *et al*[18]
P322S		0	No	None	MR	Random	Mother has mild MR Unclassified variant	Ventura *et al*[19]
R344W		0	NA	NA	NA	NA	Unclassified variant	Laccone *et al*[20]
P405L		0	No	None	MR	NA	Mother has mild MR Unclassified variant	Moog *et al*[21]
K417M		0	No	None	None	Random	Unclassified variant	Kankirawatana *et al*[15]
R453Q		0	NA	NA	NA	NA	Unclassified variant	Couvert *et al*[12]
In-Frame deletions								
P387del80		0	No	Mild MR	None	100:0		Yntema *et al*[22]
Frameshifts and nonsense mutations								
G163fs		1	No		RTT	NA		Geerdink *et al*[23]
G252fs	TRD	3	No	None	RTT		Germline mosaicism	Zeev *et al*[24]
G269fs	TRD	9	No	None	RTT	Skewed	Mother has mild MR	Wan *et al*[7]
	TRD	9	Yes					Leuzzi *et al*[25]
	TRD	9	Yes					Kankirawatana *et al*[15]
R270fs	TRD	3	Yes					Kankirawatana *et al*[15]
G273fs	TRD	0	Yes					Ravn *et al*[26]
L386fs		7	No	None	None	95:5		Dayer *et al*[27]
Q406X		0	No	Severe MR	None	Random	Mild MR in a carrier female	Meloni *et al*[28]
E472fs		0	Yes					Kleefstra *et al*[29]
Large duplications								
430 kb		0	No	None	None	90:10	Duplication of AVPR2 to FLNA	Meins *et al*[30]
0.4–0.8 Mb		0	No	Severe MR	None	>85:15	4 duplications	Van Esch *et al*[31]
0.4–0.8 Mb		0	No	Severe MR	None	>90:10	6 duplications	Friez *et al*[32]
0.2–2.2 Mb		0	U	None	None	Skewed	6 duplications and 1triplication	Del Gaudio *et al*[33]
Abnormal karyotypes								
Y141X/XXY	MBD	6	Yes					Schwartzman *et al*[34]
T158M/XXY	MBD	191	Yes				76% of XXY cells	Leonard *et al*[35]
E455X/XX		1	Yes				Heterozygous male	Maiwald *et al*[36]
Somatic mosaicism								
P56fs		0	Yes					Clayton-Smith *et al*[37]
R133H	MBD	3	Yes					Armstrong *et al*[38]
T158M	MBD	191	Yes				25% mutant cells	Kleefstra *et al*[39]
R270X	TRD	146	Yes				40% mutant cells	Topcu *et al*[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 49–52] 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),[54 55] 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

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(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 patient[56] 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 chromatography[47] or single-strand conformation polymorphism screening[52] 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 PCR[30] and dosage-sensitive Southern blots[33] 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] R133C[10] 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 MR[12] 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 MR[56] 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 mutation[21] 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

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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
Missense mutations									
R133C	Yes	Yes	Yes	Yes	Yes	11 years	S	Rigidity of four limbs, dystonic posture, early convulsions	Geerdink *et al*[10]
S134C	Yes	Yes	Yes	Yes	Yes	10 years	S	Axial and peripheral hypotonia, rigidity of four limbs, seizures	Budden *et al*[11]
E137G	U		No		U	21–56 years	Mi to S	No neonatal hypotonia, speech handicap (U)	Gendrot *et al*[41]
A140V	No		No			27–40 years	S	Resting tremor, slow movements	Orrico *et al*[13]
A140V							Mi to S	No details given	Couvert *et al*[12]
A140V	No		No		U	11–41 years	Mo to S	Psychosis, pyramidal signs, macro-orchidism, short stature (U)	Lindsay S *et al*[42]
F157I	Yes	Yes				25 months	SNE	Limb rigitity, axial hypotonia, movement disorder, head growth deceleration	Kankirawatana *et al*[15]
T158M		Yes				9–11 months	SNE	Pepper and salt hair	Villard *et al*[16]
T158M	Yes	Yes	Yes		Yes	14 months	SNE	Limb spasticity, choreiform movements	Lynch *et al*[17]
R167W	Yes		No			17–55 years	Mi	Four cases, obesity, poor motor coordination, resting tremor	Couvert *et al*[12]
P225L	No	Yes			Yes	21 years	S	Abnormal temperature control, spastic tetraplegia, dystonia, epilepsy until 7 years	Moog *et al*[18]
P322S	No				Yes	6 years	Mo	Adiposity, uncontrolled seizures, hypotonia, lower limb weakness, intention tremor, ataxia	Ventura *et al*[19]
R344W								Rett-like phenotype (no details given)	Laccone *et al*[20]
P405L	No	No	No	Yes	No	29 years	S	No spasticity, can walk, generalised epilepsy	Moog *et al*[21]
K417M	Yes	Yes				14 months		Head growth deceleration, movement disorder	Kankirawatana *et al*[15]
R453Q								No details given	Couvert *et al*[12]
In-frame deletions									
P387del80			No			24–55 years	Mi to S	No tremor	Gomot *et al*[43]
Frameshifts and nonsense mutations									
G163fs	Yes	Yes				13 months	SNE	Pepper and salt hair, limb rigidity, seizures	Geerdin *et al*[23]
G252fs	Yes	Yes		Yes		17 months	SNE	Severe hypotonia, recurrent infections	Zeev *et al*[24]
G269fs	Yes	Yes				9 months	SNE	Axial hypotonia, severe gastro-oesophageal reflux, intermittent tremor	Schanen *et al*[8]
G269fs	Yes	Yes	Yes			28 months	SNE	Uncontrolled seizures, axial hypotonia, limb rigidity	Leuzzi *et al*[25]
G269fs	Yes	Yes		Yes		27 months	SNE	No limb rigidity, axial hypotonia, movement disorder	Kankirawatana *et al*[15]
R270fs	Yes	Yes				14 months	SNE	Axial hypotonia, no limb rigidity	Kankirawatana *et al*[15]
G273fs	Yes		Yes		Yes	11 years	S	Ataxia, spasticity, uncontrolled seizures	Lugtenberg *et al*[26]
L386fs	Yes		Yes	Yes	No	4 years	S	Intention tremor, axial hypotonia, seizures	Dayer *et al*[27]
Q406X	No	Yes				34 years	S	Ataxia, spasticity, convulsions, macrocephaly, death at 39 from pneumonia, recurrent infections	Meloni *et al*[28]
E472fs	Yes	Yes				10 years	Mo	Obesity, gynaecomastia, hypotonia	Kleefstra *et al*[29]
Large duplications									
430 kb	No	No	Yes	Yes	No	8 years	S	Uncontrolled generalised epilepsy, no spasticity	Meins *et al*[30]
0.4–0.8 Mb	U	Yes				3–35 years	S	Recurrent infections, early death (U), progressive spasticity, axial hypotonia (U), seizures (U)	Van Esch *et al*[31]
0.4–0.8 Mb	U	Yes				3–25 years	S	Recurrent infections, early death (U), neonatal hypotonia, childhood spasticity, seizures (U)	Friez *et al*[32]
0.2–2.2 Mb	U	No		U		3 months–16 years		Recurrent infections (U), axial hypotonia, childhood spasticity, genital abnormalities (U)	Del Gaudio *et al*[33]
Abnormal karyotypes									
Y141X/XXY			Yes	Yes		5.5 years	S	Hypotonia	Schwartzman *et al*[34]
T158M/XXY	No		Yes	Yes	Yes	9 years	S	A brother with del22q11	Leonard *et al*[35]
E455X/XX	Yes		Yes			2 years	S	SRY translocated on one X chromosome	Maiwald *et al*[36]
Somatic mosaicism									
P56fs	No	Yes	Yes	No	Yes	6 years	S	Seizures, truncal hypotonia, ataxic gait	Clayton-Smith *et al*[37]
R133H						14 years	S	Typical RTT phenotype (no details given)	Armstrong *et al*[38]
T158M	Yes		Yes	Yes	Yes	11 years	S	Convulsions and diffuse EEG abnormalities	Kleefstra *et al*[39]
R270X	Yes	No	Yes	Yes	Yes	12 years	S	Poor lower limb musculature, hypertonia	Topcu *et al*[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.

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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 Y141X[34] 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.

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