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The *MECP2* Duplication Syndrome

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Abstract

In this review, we detail the history, molecular diagnosis, epidemiology, and clinical features of the *MECP2* duplication syndrome, including considerations for the care of patients with this X-linked neurodevelopmental disorder. *MECP2* duplication syndrome is 100% penetrant in affected males and is associated with infantile hypotonia, severe to profound mental retardation, autism or autistic features, poor speech development, recurrent infections, epilepsy, progressive spasticity, and, in some cases, developmental regression. Most of the reported cases are inherited, however, *de novo* cases have been documented. While carrier females have been reported to be unaffected, more recent research demonstrates that despite normal intelligence, female carriers display a range of neuropsychiatric phenotypes that pre-date the birth of an affected son. Given what we know of the syndrome to date, we propose that genetic testing is warranted in cases of males with infantile hypotonia and in cases of boys with mental retardation and autistic features with or without recurrent infections, progressive spasticity, epilepsy, or developmental regression. We discuss recommendations for clinical management and surveillance as well as the need for further clinical, genotype-phenotype, and molecular studies to assist the patients and their families who are affected by this syndrome.

Keywords

MECP2; Xq28; mental retardation; autism; recurrent infections; epilepsy; *FLNA*; *IRAK1*

INTRODUCTION

Mutation of the X-linked methyl-CpG-binding protein 2 gene (*MECP2*; OOMIM:300005) was identified as the cause of Rett syndrome in 1999 [Amir et al., 1999]. A suspected human gain-of-function disorder was predicted by the observation that mice engineered to overexpress human *MECP2* from its own promoter develop a progressive neurological disorder which includes stereotyped and repetitive movements, epilepsy, spasticity, hypoactivity, and early death [Collins et al., 2004]. A second mouse model engineered with a *Mecp2* transgene targeted to the endogenous *tau* locus, and which overexpressed *Mecp2* four to six-fold in the homozygous state, exhibited profound and progressive motor dysfunction [Luikenhuis et al., 2004]. The striking phenotypes of these mouse models provide the strongest evidence to date that *MECP2* duplication causes the neurological disorder observed in affected males.

The identification of submicroscopic *MECP2* duplications was described in 2004 when quantitative polymerase chain reaction studies were designed to specifically screen children with clinical features of Rett syndrome but who were *MECP2* mutation negative. The initial

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report described a girl with the preserved speech variant of Rett syndrome; however, in this case the methodology failed to distinguish between partial and complete duplication of the *MECP2* locus and therefore between loss and gain of MeCP2 function [Ariani et al., 2004]. Subsequently, a 430 kb duplication encompassing the entire *MECP2* locus was identified in a boy with hypotonia, mental retardation, lack of speech, loss of purposeful hand use, and the acquisition of stereotyped hand movements [Meins et al., 2005]. Sanlaville et al., reviewed 19 cases of functional disomy of the Xq28 region due to Xq-Yq translocation, Xq-Xp rearrangements, and X-autosome translocations and found that individuals in this group shared distinctive facial features, axial hypotonia, severe feeding difficulties, abnormal genitalia, developmental delay, and susceptibility to infection [Sanlaville et al., 2005]. The use of multiplex ligation-dependent probe amplification (MLPA) and the clinical implementation of high resolution human genome analysis by array comparative genomic hybridization (array-CGH) led to the identification of additional males with duplication of Xq28 that includes the *MECP2* locus and the following common phenotypes: infantile hypotonia, severe to profound mental retardation, poor speech development, recurrent infections, epilepsy, and progressive spasticity [Van Esch et al., 2005; del Gaudio et al., 2006; Friez et al., 2006; Lugtenberg et al., 2006; Smyk et al., 2007; Clayton-Smith et al., 2008; Prescott et al., 2008; Echenne et al., 2009; Kirk et al., 2009; Lugtenberg et al., 2009; Velinov et al., 2009; Ramocki et al., In press]. In this review, we detail the molecular diagnosis, epidemiology, and clinical features of the *MECP2* duplication syndrome, including considerations for the care of patients with this X-linked neurodevelopmental disorder.

MOLECULAR DIAGNOSIS AND EPIDEMIOLOGY

Many diagnostic laboratories now offer clinical testing for *MECP2* duplication using quantitative real-time PCR, MLPA, and/or array-CGH methodologies, and most use one method for primary detection and a second method for diagnostic confirmation. Large, cytogenetically visible duplications of Xq28 including the *MECP2* locus have been identified in affected males [Sanlaville et al., 2005], but most reported duplications are submicroscopic and span 0.3 to 4 Mb in size [Van Esch et al., 2005; del Gaudio et al., 2006; Smyk et al., 2007; Clayton-Smith et al., 2008; Carvalho et al., 2009; Ramocki et al., In press].

There have been no unbiased studies to assess the incidence and/or prevalence of the *MECP2* duplication syndrome or of *MECP2* duplication carriers in the population; however, several relatively large studies provide some insight. Duplication of Xq28 including the *MECP2* gene was discovered to be the most common submicroscopic telomeric rearrangement identified in clinical testing of 5380 consecutive patients referred for chromosome microarray testing [Shao et al., 2008]. A recent study identified *MECP2* duplications in 2/122 (1.6%) neurodevelopmentally delayed male patients specifically referred for *MECP2* gene rearrangement studies [del Gaudio et al., 2006]. Lugtenberg and colleagues identified *MECP2* duplication in 3/134 (2.2%) males with severe encephalopathy similarly referred for intragenic *MECP2* mutation analysis and in 3/283 (1.1%) males with X-linked mental retardation who had normal karyotype and fragile X studies [Lugtenberg et al., 2009]. The clinical diagnostic laboratory at our institution performed array-CGH analysis on 4683 male individuals over a three year period with typical referral indications that included developmental delay, mental retardation, dysmorphic features, multiple congenital anomalies, autism, epilepsy, short stature, failure-to-thrive, or other similar diagnoses, and identified 19 males (0.41%) with duplication of the *MECP2* locus and one individual with deletion. Similar duplications of the *MECP2* locus were not identified in more than 600 control parental samples (mothers of boys with *MECP2* duplication excluded) tested during the same period by array-CGH (Sau Wai Cheung, personal

communication). Smaller studies with more specific inclusion criteria had a much higher detection rate. Van Esch and colleagues screened 17 males with mental retardation and progressive spasticity and identified 3 males (17.6%) with *MECP2* duplication [Van Esch et al., 2005]. Friez and colleagues screened 17 males with X-linked mental retardation (all had linkage to Xq28 or had a phenotype consistent with Xq28 functional disomy) and identified 2 males (11.8%) with *MECP2* duplication [Friez et al., 2006]. Collectively, these data suggest that *MECP2* duplication syndrome may explain approximately 1% of cases of X-linked mental retardation; however, when males with mental retardation who also demonstrate other features of *MECP2* duplication are screened, the likelihood of detecting duplication of the *MECP2* locus appears to approach 15%.

Submicroscopic Xq28 duplications encompassing *MECP2* are considered nonrecurrent events because the breakpoint location and rearrangement size vary among affected individuals. Many genomic disorders (e.g. Charcot-Marie-Tooth disease, hereditary liability to pressure palsies, Smith-Magenis syndrome and Potocki-Lupski syndrome on chromosome 17, or the 22q11.2 related conditions (DiGeorge velocardiofacial syndrome) are caused by recurrent reciprocal deletion and duplication events which are initiated by double-strand DNA break repair followed by non-allelic homologous recombination (NAHR) between flanking low copy repeats (LCRs) [Stankiewicz and Lupski, 2002]. While the Xq28 region that is prone to genomic instability does contain multiple LCRs, duplication of *MECP2* does not appear to be mediated by a NAHR mechanism [del Gaudio et al., 2006; Bauters et al., 2008; Carvalho et al., 2009]. Bauters and colleagues proposed a non-homologous end joining followed by break-induced repair mechanism but they could not exclude fork stalling and template switching (FoSTeS) as a mechanism for such rearrangements [Lee et al., 2007; Bauters et al., 2008; Carvalho et al., 2009].

The FoSTes model was recently implicated as a mechanism to explain nonrecurrent rearrangements of the proteolipid protein-1 gene (*PLP1*) that occur in Pelizaeus-Merzbacher disease [Lee et al., 2007; Hastings et al., 2009]. This model is based on long-distance template switching during DNA replication initiated by collapsed forks. FoSTeS uses base pair microhomologies to prime DNA replication on the switched template which can occur over long distances producing rearrangements [Lee et al., 2007]. Nonrecurrent rearrangements produced by FoSTeS can display breakpoint grouping and, in some cases, varying levels of complexity since multiple template switches may occur yielding complex rearrangements [Lee et al., 2007]. Due to the previous report of a patient with a complex rearrangement that included both duplicated and triplicated genomic regions [del Gaudio et al., 2006], Carvalho and colleagues hypothesized that the FoSTeS mechanism may mediate the Xq28 rearrangements observed in individuals with *MECP2* duplication and triplication syndromes. They used a tiling path oligonucleotide microarray to study the rearrangements in 30 affected individuals and determined that at least 8/30 (minimally 27%) rearrangements are complex (regions of duplicated sequence interspersed with normal sequence or triplicated sequence and triplications), that there is non-random grouping of the distal breakpoints into two LCR clusters, and that most of the sequenced breakpoints contain microhomologies [Carvalho et al., 2009]. These data are most consistent with the FoSTes model for the *MECP2* duplication syndrome.

CLINICAL FEATURES OF *MECP2* DUPLICATION SYNDROME

Now that more than 100 individuals have been described (Table I), the *MECP2* duplication syndrome has emerged as a clinically recognizable entity in many instances. The core phenotypes of this X-linked neurodevelopmental syndrome include infantile hypotonia, mild dysmorphic features (brachycephaly, large ears, midface hypoplasia, depressed nasal bridge, and/or slightly upturned nares, refer to Fig 1), developmental delay/severe to profound

mental retardation, and absent to minimal speech. Affected males may manifest a combination of variable phenotypes including recurrent infections, progressive spasticity with the lower limbs affected to a greater extent than the upper limbs, ataxia, autism or autistic features, and focal onset or generalized epilepsy. We propose that if specifically assessed, progressive lower extremity spasticity and autistic features or autism will prove to be core phenotypes in affected males.

In our comprehensive clinical study of males with *MECP2* duplication syndrome (age range of 3-15 years), we observed abnormal movements in all nine subjects including choreiform movements characterized by intermittent, spontaneous writhing movements of the arms, hands, fingers, head, or tongue in most, as well as stereotyped midline hand movements that were present in all of the subjects examined [Ramocki et al., In press]. Some subjects also experienced developmental regression that manifested as loss of purposeful hand use, speech, self-help skills, and/or ambulation, but none had normal development prior to regression [Ramocki et al., In press]. The onset of regression correlated with seizure onset in two of the patients in our study. Recovery to their prior level of function did not occur despite initiation of seizure medications, and in fact they manifest medically-refractory epilepsy. The third patient who experienced developmental regression did not have epilepsy. The electroencephalograms (EEGs) in all nine of the affected males in our series were abnormal and characterized by slowing of the background EEG activity, slowing of the occipital dominant rhythm, and/or absence of the occipital dominant rhythm. Paroxysmal rhythmic slow (theta) activity was also recorded in the posterior regions of four patients. Typically, these abnormal findings are considered indicative of a diffuse disturbance in brain function. The epileptiform patterns that were captured included multifocal spike discharges, generalized spike and slow wave activity, and clinical (atonic) and multifocal EEG seizure discharges. These findings are very similar to the observations documented and reviewed in the case series of Echenne and colleagues [2009]. They note that polymorphic crises typified by absences, partial, and generalized seizures, and generalized status epilepticus are common in reports of patients with well-characterized epilepsy, as is myoclonic or myoclonic-astatic epilepsy [Echenne et al., 2009]. Despite treatment with epilepsy medications, vagus nerve stimulation, and the ketogenic diet, a subset of patients with *MECP2* duplication manifest medication/treatment-refractory epilepsy [Echenne et al., 2009; Ramocki et al., in press] (unpublished data). Males with *MECP2* duplication should be referred to a pediatric neurologist for evaluation, treatment of epilepsy and spasticity, anticipatory guidance, and long-term management. Upper airway congestion and obstructive sleep apnea have improved in some boys who underwent adenoidectomy and/or tonsillectomy procedures (unpublished data). Polysomnography and evaluation by a pediatric sleep specialist are helpful to document and treat obstructive sleep apnea, sleep-related hypoxemia, or other sleep-related phenomena in the appropriate clinical setting. Physical medicine and rehabilitation specialists are also very skilled at managing the physical needs of affected boys. Early referral to a pediatric ophthalmologist is also important to treat strabismus or amblyopia that is frequently noted in boys with this syndrome. Referrals to the early childhood intervention program unique to each U.S. state or the overseas equivalent should be made as soon as abnormal development is identified, and patients should continue to receive year round occupational, physical, and speech therapies as well as behavioral support. These therapies are often beneficial even if the patient's skills plateau in order to prevent regression.

In terms of prognosis, we found that the majority of subjects in our series started walking between the ages of 18 months and 2.5 years, although the three males who exhibited developmental regression lost the ability to ambulate independently [Ramocki et al., in press]. Overall, 72% of patients reported in the literature achieved ambulation. The males that we studied demonstrated cognitive abilities ranging from a developmental age of 3-25

months, and 56% of the boys used words at one time. Usually the first meaningful words were spoken between the ages of 18 months and 4 years of age, although 80% of affected males who initially used words subsequently regressed and never regained speech. Some subjects who are non-verbal can communicate their needs by non-verbal means such as gestures or bringing their caregiver to their need. The majority have not yet achieved independence in toileting. Some males are able to feed themselves finger foods, however, most have difficulty with using utensils.

Almost 40% of males with *MECP2* duplication reported to date died before their 25th birthday usually from respiratory infections, however, this statistic likely under-estimates the true percentage of early deaths because most of the patients reported to date are young children. Approximately 75% of males experience recurrent infections, including recurrent upper respiratory infections, pneumonia, otitis media, and sinusitis. The oldest surviving males in the reported kindreds include a 45-year-old man with medically controlled epilepsy and lower extremity spasticity who remained able to ambulate with an ataxic gait and a 33-year-old man with recurrent infections, epilepsy, and spasticity who required tracheostomy placement at age 30 years[Friez et al., 2006; Kirk et al., 2009]. Similarly, 4 out of 5 patients who survived past the age of 15 in one series also required tracheostomy [Friez et al., 2006]. Triplication of the *MECP2* locus has also been reported and appears to cause phenotypes similar to those observed with the duplication but more severe [del Gaudio et al., 2006].

Interestingly, genotype-phenotype correlation studies have clearly demonstrated that the minimal region of duplication that is sufficient to cause the core phenotypes involves the *MECP2* and Interleukin-1 receptor-associated kinase 1 (*IRAK1*; OOMIM:300283) genes [del Gaudio et al., 2006; Carvalho et al., 2009; Lugtenberg et al., 2009; Ramocki et al., In press]. Given these data and the data from mouse models, we posit that *MECP2* is the primary dosage-sensitive gene contributing to the neurological phenotypes observed in affected boys. Lugtenberg and colleagues reported two brothers with duplication limited to the *MECP2* and *IRAK1* genes. The brothers shared infantile hypotonia and developmental delay, and both achieved some expressive language as well as ambulation with a gait described as ataxic, yet only one of the brothers developed spasticity, recurrent infections, and epilepsy, suggesting that genetic modifiers exist to explain the variable expressivity of some phenotypes [Lugtenberg et al., 2009]. There is a precedent for such variable expressivity in a genomic duplication disorder since identical twins with Charcot-Marie-Tooth disease type 1A due to *CMT1A* duplication have been reported with discordant clinical phenotypes [Garcia et al., 1995]. While *MECP2* is the primary dosage-sensitive gene responsible for the neurological phenotypes in the Xq28 duplications described above and is worthy of the syndrome bearing its name, certainly further studies will demonstrate that the size, extent, and gene content of each rearrangement make at least subtle contributions to clinical phenotypes. One important example (discussed below) is the discovery that filamin A (*FLNA*; OOMIM:300017) gene duplication is associated with at least one distinct clinical phenotype [Clayton-Smith et al., 2008]. The possibility that Xq28 rearrangements contribute to or modify clinical phenotypes through the disruption of the regulatory regions of nearby genes also needs to be explored.

While the *MECP2* duplication syndrome appears to represent a new form of syndromic immunodeficiency, further characterization of the immune system in boys with *MECP2* duplication is necessary. At this point, it is unclear if the immune system phenotype occurs secondary to duplication of *MECP2*, *IRAK1*, a combination of increased dosage of both genes, or to the disruption of nearby regulatory regions. *IRAK1* is a member of the toll-like receptor signaling pathway [Gottipati et al., 2008]. Toll-like receptors are essential for host recognition of microbial invasion, the activation of innate immunity, and the control of adaptive immune responses [Gottipati et al., 2008]. Many members of the highly conserved

toll-like receptor signaling pathway have been implicated in primary immunodeficiency syndromes [Notarangelo et al., 2004].

To our knowledge, increased gene dosage has never been reported as a cause of an immunodeficiency syndrome. Friez and colleagues identified low serum IgA and IgM, elevated serum IgG, poor response to polysaccharide antigen, and poor T-cell response to *Candida* (<20% in 2 individuals) in several individuals with *MECP2* duplication and recurrent infections [Friez et al., 2006]. While these findings are nonspecific, they do provide evidence of impaired immune system function. Further work is necessary to characterize the pathophysiology of immune system dysfunction in males with *MECP2* duplication in hope that specific therapies can be identified to decrease the morbidity and mortality associated with recurrent infections in these boys. Anecdotally, we know of one male with *MECP2* triplication whose recurrent respiratory infections appear to have benefitted greatly from the weekly administration of sub-cutaneous immunoglobulins. Males with *MECP2* duplication syndrome should be referred to a pediatric allergy and immunology specialist for evaluation, treatment, anticipatory guidance, and long-term follow-up care. As previously recommended, males who manifest any signs or symptoms of illness should be evaluated promptly to detect infections as early as possible, and aggressive therapy with pathogen-specific antibiotics should be initiated [Friez et al., 2006]. If respiratory status is declining, then early referral to a pulmonary specialist is indicated.

Patients with *MECP2* duplication syndrome often manifest mild, moderate, or severe constipation, gastro-esophageal reflux, aspiration risk and difficulty with oral feeding due to swallowing dysfunction, and/or failure-to-thrive. The presence of any of these concerns should trigger referral to a pediatric gastroenterology specialist for evaluation, treatment (which may include referral to a surgeon for temporary or permanent gastric or intestinal feeding tube placement and/or Nissen fundoplication), anticipatory guidance, and long-term management. Interestingly, recent work suggests that it is duplication of the *FLNA* gene that is responsible for the severe, and often fatal, chronic intestinal pseudo-obstruction phenotype observed in some males with Xq28 duplication [Clayton-Smith et al., 2008]. It is possible that Xq28 duplications that include *MECP2* but not *FLNA* somehow alter *FLNA* regulatory regions and therefore contribute to the gastrointestinal problems in affected individuals. Chronic idiopathic intestinal pseudo-obstruction (CIIP, OOMIM:300048) is a clinical syndrome characterized by severe gastrointestinal dysmotility or amotility caused by a heterogeneous group of enteric neuromuscular diseases [Gargiulo et al., 2007]. CIIP may present at any age including infancy and is diagnosed by radiological, surgical, or manometric evidence of bowel dysmotility leading to intestinal obstruction in the absence of mechanical occlusion [Gargiulo et al., 2007]. Gargiulo and colleagues previously reported a case of X-linked CIIP associated with a 2 base pair deletion in the *FLNA* gene [Gargiulo et al., 2007]. Alterations in the *FLNA* gene also cause X-linked periventricular nodular heterotopia and epilepsy (PVNH, OOMIM:300049) as well as otopalatodigital spectrum disorders, gastric immotility, thrombocytopenia, and cardiovascular anomalies including aortic dilatation, patent ductus arteriosus, bicuspid aortic valve, vasculopathy and/or coagulopathy leading to stroke, arterial dissection, and ruptured aneurysm [Fox et al., 1998; Robertson et al., 2003; Hehr et al., 2006; Parrini et al., 2006; Zhou et al., 2007]. The full extent of genotype-phenotype correlations associated with alterations in *FLNA* are beyond the scope of this manuscript and are yet to be fully ascertained. However, from a clinical and genetic counseling perspective, it is important to determine the extent and character of the Xq28 rearrangement in boys who are found to have *MECP2* duplication. The patients who also have duplication of the *FLNA* locus should be referred to pediatric cardiology, gastroenterology, and hematology specialists for evaluation, treatment, anticipatory guidance, and long-term care or surveillance. Of note, cardiac abnormalities including structural anomalies have been reported in boys with Xq28 duplication that does not include

duplication of the *FLNA* locus (or the involvement of *FLNA* was not assessed), and therefore a low threshold for referral for cardiovascular evaluation should be maintained when caring for these patients [del Gaudio et al., 2006; Friez et al., 2006]. Furthermore, we know of two patients with *MECP2* duplication who require medical management for supraventricular tachycardia; one boy is also diagnosed with Wolff-Parkinson-White syndrome (unpublished information).

All affected individuals and their families with the X-linked *MECP2* duplication or triplication syndrome should be referred to a clinical genetics professional for counseling. The vast majority of affected males reported to date inherited the duplication from their mother; however, *de novo* cases have been reported and appear to be more common in the case of functional disomy resulting from X-Y and X-autosome translocations [Sanlaville et al., 2005; Smyk et al., 2007; Clayton-Smith et al., 2008]. Fifty percent of the sons of a carrier female will be affected and 50 percent of the daughters will be carriers. Carrier females may seek the assistance of reproductive technology to select unaffected embryos obtained through *in vitro* fertilization for *in utero* implantation. Prenatal testing of at-risk pregnancies is also available. It is likely that affected females exist with significant manifestations of the *MECP2* duplication or triplication syndrome in the context of X-autosome translocations or with disadvantageous skewing of X chromosome inactivation. Affected females should be treated and screened similarly to affected males. *MECP2* duplication syndrome is 100% penetrant in affected males, but there is variable expressivity of some phenotypes. As more affected males and their genomic rearrangements are studied, additional genotype-phenotype correlations may be elucidated. The patient's primary pediatrician as well as a neurologist or geneticist should oversee the multi-disciplinary care of affected patients to make sure that all needs are being met. The patients would benefit from a comprehensive psychological evaluation as well. This evaluation should include cognitive testing, an assessment of receptive and expressive language, an evaluation of fine and gross motor skills, an assessment of functional skills, and an assessment for autism/autism spectrum disorder (including skills pre/post regression). It is important that all family members receive appropriate emotional support and a social worker can be of great assistance in identifying resources when needed. We have found that the web-site http://www.mecp2duplication.com, created by the mother of two affected sons, is a great source of support and information for affected families.

AUTISM AND *MECP2* DUPLICATION SYNDROME

Autism is a neurodevelopmental disorder characterized by deficits in communication and reciprocal social interaction accompanied by repetitive/stereotyped behaviors and/or restricted areas of interest. Autism disproportionately affects males, and some researchers have therefore searched for the involvement of X-linked loci [Jamain et al., 2003; Gauthier et al., 2005; Gong et al., 2008], including searches for *MECP2* mutations in cases of idiopathic autism [Lam et al., 2000; Vourc'h et al., 2001; Beyer et al., 2002; Carney et al., 2003; Lobo-Menendez et al., 2003; Coutinho et al., 2007]. These studies demonstrated that mutations in the coding region of *MECP2* are a rare cause of idiopathic autism. A more recent study demonstrated that polymorphisms in non-coding regions of *MECP2* may confer a significant association/increased risk of autism [Loat et al., 2008].

Rett syndrome is grouped under the same broader category of autism spectrum disorders, and impaired language, stereotyped behaviors, regression, anxiety, and social avoidance are features that are common both to RTT and to autism. Studies in mouse models demonstrate that both loss and gain of MeCP2 function can result in abnormal social behavior [Collins et al., 2004; Moretti et al., 2005; Samaco et al., 2008](Samaco and Zoghbi, unpublished data). Although previous studies of boys with *MECP2* duplication syndrome indicated the

presence of autistic features [del Gaudio et al., 2006], these features had not been objectively characterized. In our clinical characterization of patients with this syndrome, we noted that the majority had prior diagnoses of autism and that autism was often the reason for referral for genetic testing and further evaluation. In cases where regression was observed, symptoms of autism (i.e. repetitive language, language delays, restricted interests) preceded the onset of regression. On formal assessment, all affected individuals met criteria for autism (using the ADOS and the ADI-R), and overlapping features that were noticeable included: difficulties with eye gaze, gaze avoidance, stereotyped hand movements, a limited range of facial expressions, sensory interests/aversions, and fixations on objects/activities of interest (refer to Videos 1 **and** 2 which have been made available on-line with parental consent). Taken together, our data suggest that *MECP2* duplication syndrome is another cause of syndromic autism in males. There are now many precedents for overlapping neurodevelopmental disorders caused by gain or loss of function of the same gene/protein [Ramocki and Zoghbi 2008]. For example, Smith-Magenis syndrome (OMIM:182290) and Potocki-Lupski syndrome (OMIM:610883) are caused by heterozygous deletion or duplication of chromosome region 17p11.2 inclusive of the Retinoic acid-induced gene 1 (*RAI1*;OMIM:607642) gene respectively, and share overlapping clinical phenotypes including congenital anomalies, hypotonia, mental retardation, and behavioral disturbances including autism [Potocki et al., 2007; Elsea and Girirajan 2008]. Furthermore, there are now many examples of specific copy number variations (CNV) and their accompanying dosage-sensitive genes that are linked to autism and other neuropsychiatric disorders, as well as data to suggest that the overall burden of CNV in the genome may contribute to such disorders [Sebat et al., 2007; Cook and Scherer 2008; Marshall et al., 2008; Walsh et al., 2008; Glessner et al., 2009].

In the past, many studies stated that female carriers of *MECP2* duplications are unaffected due to the near 100% skewing of X chromosome inactivation observed in most individuals with the abnormal X chromosome preferentially inactivated in the assayed blood. Indeed, in our clinical characterization, we found that all female carriers exhibited cognitive abilities that ranged from the average to the superior range [Ramocki et al., In press]. Upon further examination, however, we found that the majority of women exhibited a range of neuropsychiatric abnormalities (e.g. depression, anxiety, compulsions) that predated the birth of a son with the duplication. Many women also espoused features of the broad autism phenotype, including a strong preference for structure/routine (many of these traits may be considered advantageous in many societal settings). Some women also described a preference for interaction in small groups, social anxiety, and some difficulties with reciprocal conversation. These traits in female carriers mirror the difficulties noted in the males with *MECP2* duplication syndrome (albeit to a much lesser degree). How *MECP2* duplication confers susceptibility to neuropsychiatric symptoms or to the broad autism phenotype in female carriers despite nearly 100% skewing of X chromosome inactivation (XCI) in the blood is unclear but may be related to expression from the abnormal X chromosome in select nuclei within the brain. Further studies of female carriers and controls are necessary to confirm our preliminary findings. It is also possible that polymorphisms that alter *MECP2* expression slightly above or below “normal” levels contribute to such neuropsychiatric phenotypes and/or personality traits within the greater population as a whole.

SUMMARY AND FUTURE CHALLENGES

MECP2 duplication syndrome should be included in the differential diagnosis when presented with a hypotonic male infant. In addition to infantile hypotonia, mildly dysmorphic features (brachycephaly, large ears, midface hypoplasia, depressed nasal bridge, and/or upturned nares), developmental delay/severe to profound mental retardation, absent

to minimal speech, recurrent infections, progressive spasticity with the lower limbs affected to a greater extent than the upper limbs (usually observed after age 3 years), autism or autistic features, and focal onset or generalized epilepsy represent the most common phenotypic presentations of the disorder. Developmental regression is also observed in some affected boys. Chromosome microarray analysis is currently the best initial clinical test when *MECP2* duplication syndrome is suspected because it will provide some information regarding the size, extent, and gene content of the duplication. Individuals with *MECP2* duplication syndrome should be referred to genetics, neurology, ophthalmology, physical medicine and rehabilitation, psychology, gastroenterology, and allergy and immunology specialists (and any others as needs arise) for management of their multi-disciplinary problems and for routine surveillance for the development of problems common to the syndrome. They should receive year round occupational, speech, physical and behavioral support therapies to maximize function and prevent regression. Those who have duplication of *FLNA* should also be referred to cardiology and hematology specialists.

Given that the neurological features of *MECP2* duplication syndrome are caused by the overexpression of normal MeCP2 protein, we would suggest that the potential for therapeutic intervention appears hopeful. Ongoing genotype-phenotype correlation studies are sure to reveal additional, clinically relevant information. It will be essential to elucidate the mechanism by which duplication of *MECP2* and/or *IRAK1* lead to recurrent infections as well as how to prevent the morbidity and mortality associated with these infections. Research designed to understand the molecular function of MeCP2 in Rett syndrome and *MECP2* duplication syndrome is important to understand the role of the MeCP2 protein in different neuronal populations and to identify treatments that bypass MeCP2 function and alleviate some of the phenotypes associated with the disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1.

Eight photos of boys affected by the *MECP2* duplication syndrome are published with parental consent. These photos are representative of the facial features typical of boys with the syndrome and include: brachycephaly, large ears, midface hypoplasia, depressed nasal bridge, and/or slightly upturned nares. The color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.

Table I

Phenotype[a]	Meins	Sanlaville	Van Esch	Friez	del Gaudio	Lugtenberg	Smyk	Clayton-Smith	Prescott	Ramocki[b]	Velinov	Echenne	Kirk	Total
Mental retardation	1/1	19/19	12/12	23/23	7/7	13/13	3/3	15/16	2/2	14/14	1/1	5/5	3/3	118/119 (99%)
Hypotonia	1/1	18/18		17/20	7/7	13/13	3/3	12/16		9/9	1/1	5/5		86/93 (92%)
Absent speech	1/1		10/12	18/19	6/7	10/13	3/3		2/2	7/9	1/1	5/5		63/72 (88%)
Lack ambulation			7/12	7/19	1/7	0/13	3/3		0/2	1/9	0/1	1/5		20/71 (28%)
Recurrent infections		14/15	5/9	22/23	4/7	3/13	3/3	15/16	2/2	12/14	0/1	0/5	2/3	82/111 (74%)
Breathing abnormalities					0/7				1/2	5/9				6/18 (33%)
Stereotyped hand movements	1/1				1/7			4/16		9/9				15/33 (45%)
Autistic features/autism	1/1				3/7					9/9				13/17 (76%)
Epilepsy	1/1	5/13	4/9	15/23	1/7	7/13	1/3	8/16	1/2	9/14	0/1	3/5	2/3	57/110 (52%)
GU abnormalities	1/1	15/17			2/7	1/13	3/3	4/16		3/9	0/1			29/67 (43%)
Death before 25 years			6/11	12/23		1/13			0/2	5/14			1/3	25/66 (38%)
Spasticity			9/9	7/10		6/13	3/3	4/16	1/2	8/9	0/1	2/5	2/3	42/71 (59%)
Ataxia				4/19		9/9					1/1	3/5	3/3	20/37 (54%)
GER				13/16						2/9				15/25 (60%)
Swallowing difficulty	1/1			14/16		3/13	2/3			2/9			1/3	23/45 (51%)
IPO or constipation	0/1	5/5						14/16	1/2	5/9				25/33 (76%)
Dysmorphic features	1/1					13/13	3/3	16/16	2/2		1/1	5/5		41/41 (100%)

Abbreviations used: GU, genito-urinary system; GER, gastroesophageal reflux; IPO, intestinal pseudo-obstruction

[a] Not all phenotypes were assessed in all subjects or in each study. The first author of each study is listed for ease of reference.

[b] One subject was previously published in the del Gaudio *et al.* series but is included here due to the additional phenotypes identified in the latter study.

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