MECP2 duplication is associated with severe epileptic encephalopathy in the presence of a permissive genetic background

D Marafie[1], B Suter[1,2], V Pacheco[2], D Glaze[1,2], R Schultz[1,2], J Drabek[2], and AM Goldman[2]

1) Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA.
2) Department of Neurology, Baylor College of Medicine, Houston, TX, USA.

PURPOSE

MECP2 duplication syndrome (MDS) is a rare neurodevelopmental X-linked dominant disorder with prominent neurological phenotype that includes infantile hypotonia, severe intellectual disability, psychomotor regression, autism, and spasticity.[1] The syndrome has 100% penetrance in males and is extremely rare in female carriers due to skewed X-inactivation.[2] Epilepsy is a frequent neurological co-morbidity in MDS, affecting almost 1/2 of the patients and it is often medically intractable.[1] Yet, there is incomplete understanding of the epilepsy prevalence, spectrum, and severity in MDS patients. The *MECP2* Duplication Clinic of the Blue Bird Clinic Rett Center at Texas Children's Hospital is an important national and international referral center for children affected by MDS. In this pilot study, we aimed to utilize this unique resource, in order to analyze several clinical attributes of epilepsy in this syndrome and to perform detailed molecular analysis of MDS associated epilepsy in one family. Our goal is to inform patient care, improve diagnostic precision of MDS related epilepsy, and to aid in family counseling of this complex genetic syndrome.

METHODS

The study was approved by the Baylor College of Medicine IRB. We performed a retrospective chart review on 41 subjects with MDS followed in the *MECP2* Duplication Clinic of the Blue Bird Clinic Rett Center. There were 16/41 subjects that satisfied study enrollment criteria with respect to the quality of the clinical and diagnostic information. Charts of MDS subjects were reviewed and we performed systematic collection of data related to the patients' family and medical history with a special focus on the history of epilepsy, imaging findings, and qualitative features of the *MECP2* duplications. We performed whole exome sequencing, according to the established methods, in two siblings affected by recurrent epilepsy and MDS.

RESULTS

We identified 12 males and 4 females with MDS with sufficient clinical information for analysis (male to female ratio = 3:1). MDS was recurrent in 2 sib pairs. Duplication was inherited or *de novo* in 12 and 2 subjects, respectively. The inheritance pattern could not be assessed in 2 adopted subjects. Length of duplications on Xq28 spanned from 0.254 to 5.910 Mb. Two patients harbored *MECP2* duplication due to interchromosomal translocations, namely between the chromosomes X and Y and chromosomes X and 13. There were no appreciable differences in clinical features of patients affected by the intra- vs. inter-chromosomal *MECP2* duplications

PREVELENCE AND SEVERITY OF EPILEPSY

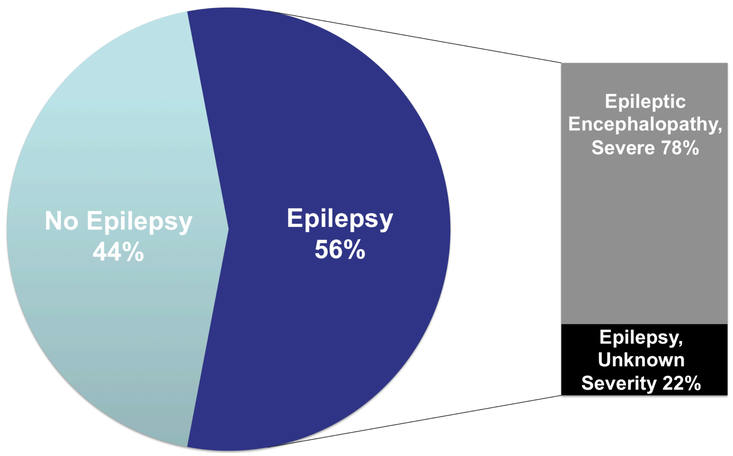

Figure 1: Nine subjects (56%) had epilepsy which was refractory in 7/9 (78%) of them. The degree of seizure control and severity could not be assessed in 2/9 subjects. Brain MRI findings included parenchymal volume loss, non-specific signal abnormalities, simplified gyral pattern, callosal hypoplasia, and cortical dysplasia.

EPILEPSY CHARESTERISTICS

Subject #	Age at epilepsy onset (years)	Current AEDs	Prior AEDs	Seizure control	Alternative therapies
1	4	VPA, RFM	LTG, CLB	Refractory	none
2	17	LEV, CLB, RFM	ZNS, VPA, CBZ, LTG, TPM	Refractory	VNS & modified ketogenic diet
3	19	LEV, CLZ, RFM	none	Refractory	Ketogenic diet
4	6	LTG, CLB, CLZ	ZNS, LEV, VPA TPM, OXC, FBM, RFM Celontin, CBZ, EZG	Refractory	VNS & ketogenic diet
5	N/A	N/A	VPA, ZNS, LEV, OXC	Refractory	none
6	3	N/A	N/A	N/A	N/A
7	N/A	N/A	LTG, VPA	Refractory	N/A
8	1.5	LEV	none	N/A	none
9	< 1	LEV, CLZ	OXC, TPM, LTG	Refractory	VNS & previously on ketogenic diet

Table 1: Age of onset of epilepsy in MDS subjects ranged from 7 days to 19 years (Average 7years 2months +/- 7years 7months). Response to antiepileptic drugs (AEDs) was variable with no AED being particularly effective. Vagal nerve simulation (VNS), used in three patients, led to improvement in the frequency of the atonic seizures in one patient, improved frequency of all seizures in one patient and was ineffective in one patient. Four patients with epileptic encephalopathy were on adjunct ketogenic diet at some point of their clinical course and parents reported modest improvement in the seizure frequency and severity in two of them.

EPILEPTIC ENCEPHALOPATHY SYNDROMES

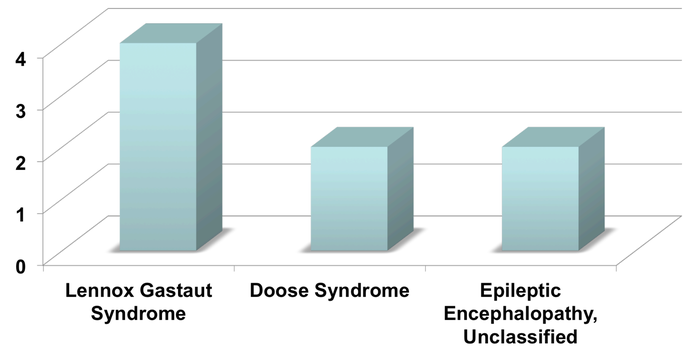

Figure 2: All seven subjects with refractory epilepsy had severe epileptic encephalopathy within the displayed syndromic spectrum. Four subjects with epileptic encephalopathy (57%) also had reflex feeding seizures. Clinical genetic analysis showed a lack of correlation between epilepsy type or severity and the *MECP2* duplication length or structural qualities (inter- vs intra-chromosomal duplications.

GENETIC ANALYSIS

Recurrent LGS in association with MDS was observed in two siblings and we performed next generation whole exome sequencing in order to better understand their susceptibility to epilepsy in the face of MDS. We uncovered multiple suspect pathogenic variants in several genes with known association with epilepsy, including *CTCL1, SUCL2, DOCK8, PIGL, ALG1, PIGO, ATIC, PGAP1, GALC, LAMC3*, and *AMK3.*

CONCLUSIONS

Review of the cohort followed at the *MECP2* Duplication Clinic of the Blue Bird Clinic Rett Center confirmed epilepsy as a frequent MDS comorbidity.

We found that the MDS related epilepsy tends to be severe, medically intractable, and without definite correlation to the qualitative features of *MECP2* duplications.

Our pilot whole exome sequencing analysis suggests that the susceptibility to epilepsy in MDS is influenced by the complex oligogenic contribution of suspect pathogenic variations in several genes with known association to human epilepsy.

References:

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