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Opinion

The continuing Conundrum regarding *MECP2* variants in Males

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Opinion

Rett syndrome (RTT) was first recognized by Andreas Rett nearly sixty years ago [1] and came to international attention following the landmark publication of Hagberg et al. in 1983 [2]. Subsequent studies sought to identify the molecular underpinnings of this rare neurodevelopmental disorder as a genetic etiology seemed to be the most likely mechanism regarding its causation. In 1999, Amir et al. established that RTT is caused by variants in the methyl-CpG-binding protein 2 *(MECP2)* gene located a Xq28 [3]. At present, more than 96% of individuals fulfilling the diagnostic criteria for RTT have a variant in this gene [4]. As an X-linked dominant disorder, its occurrence solely in females was expected and the presence of *MECP2* variants in males was initially regarded as lethal. Subsequently, numerous reports emerged in the decade after the gene discovery describing males with *MECP2* variants and clinical features ranging from developmental delay to significant neonatal encephalopathy [5-19]. Yet, the notion that pre-term or early neonatal male lethality is likely has remained even to the present day [20], plus two reports from rettsyndromenews.com/2021/12/15 and rettsyndromenews.com/2022/05/25. Adding to the confusion, the presence of classic RTT in males with *MECP2* variants and X-chromosome mosaicism is well-documented, either due to somatic mosaicism or in association with Klinefelter syndrome, a 47XXY chromosomal disorder. This has been documented since *MECP2* was first associated with RTT [21-23]. In both instances, males had two populations of X-chromosomes just as in females, allowing them to fulfill the established criteria for classic RTT [4].

Recently, data from the US Natural History Study (NHS) of RTT and RTT-related disorders were examined yielding 30 males with *MECP2* variants [24]. Among these males, a wide phenotypic spectrum occurred ranging from severe neonatal encephalopathy with significant respiratory instability to mild to moderate cognitive impairment. Two males had somatic mosaicism and were deemed to meet clinical criteria for classic RTT. Sixteen males had variants seen in females with RTT, nine males had likely pathogenic variants not previously seen in females with RTT, and three males had variants of uncertain pathogenesis. While fourteen of the sixteen males sharing variants seen in females with RTT did have a period of regression and could be considered to meet the first criteria for atypical RTT from that perspective, their clinical presentation and overall course was more severe and their RTT features less impressive than that observed in females with atypical RTT. As a result, it was felt that these males should be characterized or designated as a new diagnostic entity, **male RTT encephalopathy**, to distinguish them from females with atypical RTT.

To indicate the breadth of neurodevelopmental delay, two of the males with variants not seen in females with RTT, including one with the A140V variant, had relatively mild cognitive

impairment. The A140V variant, noted in the references above as well in subsequent publications, was initially described as causing developmental delay only in males. More recently, descriptions of neurologic or psychiatric manifestations have been seen in females with this variant as well [9,13,25,26].

The predominance of RTT in females is due principally to the primary occurrence of variants in *MECP2* arising as *de novo* events in rapidly dividing germinal cells, namely, in paternal sperm [27-29]. As such, these X chromosomes from paternal germinal cells could only result in female offspring, hence, resulting in the female preponderance of individuals with these variants. In contrast, males with *MECP2* variants arise from female carriers who are completely normal phenotypically or have mild developmental delays as previously described [5,19]. Males may also result from *de novo* occurrences in the ovum. Indeed, the recent US Natural History data report [24] revealed virtually equal numbers of vertical transmission and *de novo* events. Twelve of the twenty-four mothers tested demonstrated vertical transmission from the mothers to their sons; one was presumed to result by this mechanism as his sister also had the same variant. The remaining eleven were shown to be *de novo* events.

Following the US NHS report, at least an additional sixty males with *MECP2* variants were identified through the International Rett Syndrome Foundation. Many of these males were from the US, but not seen in the NHS due to their severe encephalopathy which prevented them from being seen in one of the US NHS sites. Subsequently, a more complete list, including males from international sites, has been developed. This includes as many as thirty males known through the group or from published reports with somatic mosaicism, one with Klinefelter syndrome, twelve with severe encephalopathy, and as many as thirty with male RTT encephalopathy. Currently, efforts are in progress to obtain comprehensive clinical information and genetic testing results through virtual assessments from as many of these males as possible. Genetic testing will be accomplished for those who have been evaluated previously but lack formal molecular testing.

One of the long-term concerns raised by the parents or caregivers of these affected males is that access to emerging therapies currently being evaluated in females with RTT as well as future therapies such as the proposed gene therapies may be hampered or even blocked by their failure to meet the established clinical criteria for RTT. This reflects an inherent bias that needs to be eliminated. Indeed, one of the concerns regarding gene therapy in females with RTT is the potential over-expression of the normal gene, resulting in the same situation already known to exist, predominantly in males, the *MECP2* Duplication Disorder. This disorder was predicted shortly after the identification of the genetic basis for RTT [30]. Its occurrence was established shortly thereafter through a number of different investigations [31-37]. This disorder also has very significant neurodevelopmental features. Therefore, gene replacement in the female with RTT must be modulated to as not to over-express the gene in the population of cells already expressing the normal copy of *MECP2*. As such, gene replacement treatment in males in which all cells express the variant gene would not have this limitation.

Conclusion

MECP2 variants in males, while being significantly less common than RTT in females, is a not-insignificant challenge for parents or other caregivers. It represents striking differences from RTT allowing it to escape early diagnosis. Nonetheless, its early recognition is essential to confirm the proper treatment strategy. The occurrence of male *MECP2* variants is not lethal and deserves the same level of care provided to all with neurodevelopmental disorders.

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