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The need for unbiased cognitive assessment in Rett syndrome: is eye tracking the answer?

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This commentary is on the original article by Rose et al. on pages 364–371 of this issue.

Although Rett syndrome was initially described in 1966, it was virtually unknown in the broader medical community until 1983. Since then, major advances have taken place, including the implication of the *MECP2* gene in the majority of cases of Rett syndrome, as well as the development of mouse models recapitulating the core characteristics of the disorder. Progress also has been made in understanding many aspects of the genotype-phenotype associations observed in Rett syndrome. Significant effort is being made towards developing targeted therapeutics to reverse or rescue the phenotype. Despite this impressive progress towards a complete understanding of the genetic underpinnings of the disorder, research aimed at developing a full observationally-based description of the Rett syndrome behavioral phenotype has been relatively stagnant over the last three decades (the RTT natural history study notwithstanding)[1]. As progress continues at the bench, there is a renewed need to refine (and possibly redefine) the range of therapeutic outcomes and clinical endpoints relevant to Rett syndrome. There remain relatively large knowledge gaps specific to the Rett syndrome behavioral phenotype. It is not clear what directly observable features of the syndrome may be most relevant for understanding health and behavior needs of individuals living with Rett syndrome, and how that information could be used to improve intervention/support service options. Novel and valid assessment approaches to understanding the Rett syndrome behavioral phenotype are needed.

Initial clinical descriptions of Rett syndrome in the 1980s and 1990s included scores from standardized IQ and adaptive behavior assessments that indicated that affected individuals were functioning at levels consistent with severe to profound intellectual impairment. In reporting these results, however, the researchers rarely acknowledged the bias inherent in assessing individuals with severe apraxia and ataxia using standardized assessments founded on an assumption of verbal and motoric competencies consistent with cognitive functioning. As a result, conventional wisdom has held that Rett syndrome results in severe to profound intellectual impairment. More recently, some researchers have begun to recognize the need for the development of appropriate, accessible methods of assessment for use in this population.[2] Because of the widespread belief among parents and practitioners that individuals with Rett syndrome communicate with their eyes, eye-tracking technology has quickly become the method of choice for such assessments. Three previous studies[3–5] used eye tracking as a means of assessing cognition and comprehension among young females with Rett syndrome. Among these, however, only one included a control group, making interpretation of the results nearly impossible. The results of the one study in which a control group was included[3] suggested that cognitive skills may be much more variable among individuals with Rett syndrome than had been previously thought, as some affected individuals performed at or near the level of age-matched, typically developing peers. Despite this provocative finding, over a decade passed without another study attempting to replicate or extend these results.

The research by Rose et al. represents an important step towards the development of accessible, unbiased assessments for use with individuals with Rett syn-

drome.[6] Their results suggest that at least some individuals with Rett syndrome demonstrate evidence of visual recognition, although on average they perform more poorly than their typically developing peers. Before the results of this type of assessment can be used to inform medical or educational decisions, however, more work is needed to validate the test and to develop appropriate norms. Until then, it will be impossible to interpret an individual's performance with regards to normative and atypical development. Nevertheless, the results suggest that the visual paired-comparison paradigm and similar tasks could eventually be used to assess cognition among individuals with Rett syndrome, as well as others with motoric and verbal deficits.

Rapid advances from the bench have already led to initial clinical trials of pharmacological therapies that may improve outcomes for individuals with Rett syndrome. The current lack of appropriate psycho-social assessments for this population makes outcome measurement in current and future clinical trials very challenging, and the need for unbiased, standardized assessments is urgent. It is likely that new therapeutics designed to reverse the symptoms of Rett syndrome will be forthcoming. Rose et al. have shown that relatively novel technologies, such as eye tracking, can be harnessed to create novel assessments, which are accessible to individuals with Rett syndrome, and which can provide meaningful information for use by families, educators, or as outcome measures in clinical trials. It is likely that such assessments will continue to challenge the conventional wisdom and move the field closer to fully understanding the Rett syndrome behavioral phenotype.

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Apolipoprotein E and the genetics of cerebral palsy – where to next?

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This commentary is on the original article by Lien et al. on pages 372–377 of this issue.

Lien et al.[1] describe an association study of the apolipoprotein E (APOE) gene with cerebral palsy (CP). Their results, supported by a growing body of literature, do not show a significant association. Their paper also asks the question, do genetic risk factors influence the severity of CP? a question which has received little attention in the literature to date. This question reflects an important shift in the way we think about the genetic contributors to CP. It moves the focus from CP causation to modulation, as seen in severity. Lien et al. test this hypothesis using the APOE gene as an example; however, they provide only weak evidence in a small cohort that CP severity is indeed influenced by genetic factors.

The paper begs the question, why do we continue to perform genetic association studies of CP? The literature now contains over 30 such studies, and apart from a few small initial studies, the results have been negative.[2]

One good reason for continuing the search for genetic contributors (both causal and otherwise) to CP is the body of evidence for a genetic component that remains unexplained. Male predominance, familial clusters, twin studies, and a high prevalence of co-diagnosis with other genetic conditions are all consistent with a genetic contribution to CP.[3] The few positive association studies to date do not explain all of the apparent genetic components.

When gene association studies with CP commenced, this avenue was the obvious way forward for CP genetics. Positive associations were few and even fewer associations were