Mitochondrial Copy Number as a Biomarker for Autism?

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Autism (AS) and autism spectrum disorders (ASD) represent a group of neurodevelopmental disorders of acute clinical and pathomechanistic heterogeneity. The serious impact of AS/ASD in families[1,2] and the alarming growth of AS/ASD in the developed world[3,4] have highlighted the pressing need both to develop new early diagnostic tools and to understand causality as a means of developing new therapeutic paradigms. In this issue of *Pediatrics*, Wong et al[5] studied mitochondrial (mt) copy number (mtCN) and the incidence of mt deletions in parents and children with autism (refs 6–8 and review in ref 9). They report an increased mtCN in patients with AS compared with matched control children, as well as an increase in the number of mt deletions, although there was no evidence of excessive mt gene loss between these 2 groups.

In addition, they found that fathers of AS children had a higher incidence of mitochondrial DNA (mtDNA) deletions (but not mtCN) compared with fathers of control children, with the converse being observed in mothers of AS children. Of note, increased maternal or paternal age did not seem to have an effect on the magnitude of this difference. Finally, because of the contributory role of p53 in mediating mtCN and possibly mtDNA integrity, the authors studied the p53 locus, where they found an increased incidence of microdeletions in both the children diagnosed with AS and their parents.

These studies touch on 2 important areas of autism research. First, it is known that several genes causing AS/ASD, such as *PTEN, CHD8,* and *CUL3*, are regulators of p53.[10–13] However, given that each of these proteins has multiple functions, the implication of p53 directly might help us focus on a subset of their activities with regard to AS-relevant pathways. Second, these studies, performed in peripheral blood monocytes, have the potential to contribute to the keenly needed search for reliable biomarkers. As such, it is tantalizing to speculate that counts of quantitative analyses, such as mtCN, together with genomics and early-infantile behavioral characteristics,[14–16] might generate matrices of diagnostic and prognostic value.

At the same time, several key questions remain. First, observational studies of heterogeneous neurodevelopmental traits, such as autism, have been notorious for generating false positives. Thus, replication of these data in a significantly larger cohort is mandated, not only for confirmation but also for a more accurate assessment of relative risk. This is particularly important in order to enable the community to assess the possibility that the mtCN/deletion phenotype might be independent of paternal age, in sharp contrast to the current thought about the mechanisms of de novo mutations (novel genetic lesion due to an error of copying of the genetic material in the germ cell of 1 of the parents or in the fertilized egg itself) in the nuclear genome.[13,17,18]

Second, the question of cause and effect remains. The observation that mt deletions did not appear to affect gene numbers argues that the observed mt

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phenotypes might be outcomes or other processes, not drivers. This does not belittle the value of these data, but focuses their utility as a marker as opposed to an AS driver. The authors highlight, appropriately, the known roles of p53 in regulating both mtCN and mtDNA integrity.[19–21] At the same time, p53 negatively regulates the proliferation and survival of adult neuronal stem cells, without affecting their differentiation potential.[22] In its absence (mouse *p53*-null, in which *p53* is no longer functional), neuronal stem cell self-renewal and the number of differentiated neurons increases. Furthermore, in the absence of both *p53* and the autism-associated gene *Pten* (mouse mutant model lacking both genes), neuronal stem cells have a higher renewal and neuronal differentiation potential.[23]

As such, it is possible that the observed mtDNA defects are a mechanistically unrelated surrogate of p53-mediated defects in the central nervous system that are potent drivers of neurodevelopmental circuitry anomalies. This is a testable hypothesis; the identification of numerous AS-associated genes from exome studies (high-throughput sequencing of all the exons of known coding genes in the human genome) is potentiating the generation of a host of new mouse models. It will be interesting to ask whether such models exhibit mtDNA number and content pathologies and whether these pathologies extend to the developing nervous system. At the same time, studies of mt function in both animal models and in AS patients might provide further illumination.

ABBREVIATIONS

AS: autism
ASD: autism spectrum disorder
mt: mitochondrial, mtCN, mitochondrial copy number
mtDNA: mitochondrial DNA

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