Advances in autism research, 2021: continuing to decipher the secrets of autism

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We are proud to publish this Special Issue focused on autism, a topic that has been exceedingly important for *Molecular Psychiatry* since our inception. It is not too bold a statement to say that we were a fundamental contributor to bringing autism to the forefront of the national discourse. A Pubmed search reveals 403 articles published in *Molecular Psychiatry* since our founding in 1996. Our first autism article by Vincent et al., published in July 1996, examined the fragile X syndrome gene (FMR1) for mutations in autistic individuals, using single-stranded conformational polymorphism analysis; those authors identified three new FMR1 polymorphisms and identified specific and significant association findings with autism [1].

In late 2001–early 2002 we received four exciting papers with findings on the genetics of autism that were published together in our March 2002 issue, with an accompanying editorial [2–6]. We issued then a press release that was picked up by *Time* magazine and served as the basis for their unprecedented May 6, 2002 cover story on autism, featuring as that iconic magazine’s cover a young boy who was visibly autistic [7]. That was the first time that a person with autism was the cover of a national magazine. The magazine’s cover displayed in big yellow letters “Inside the world of autism” and it had a subtitle stating “More than one million Americans may have it, and the number of new cases is exploding. What scientists have discovered. What families should know.” The full story, by Nash [8], was entitled: “The Secrets of Autism,” with the following subtitle: “The number of children diagnosed with autism and Asperger’s in the U.S. is exploding. Why?” *Time*’s cover article was so successful that their editors expanded that from a single issue into an entire series on autism over

multiple issues. That *Time* series effectively made autism emerge as a mainstream topic of kitchen table conversations across America. As that effort was triggered by our press release and four articles on autism, it is reasonable to boast that *Molecular Psychiatry* launched the national conversation on autism.

The four papers highlighted in our March 2002 issue were within the first 20 articles that we published on this topic. Now, 383 papers later, we have a much more substantial body of work that further unravels the secrets of autism, the culmination of which is this autism Special Issue, with 26 truly superb papers on autism [9–34]. These extraordinary articles cover essentially all aspects of this disorder, from the training of specialists, to the interface with other disorders, such as polycystic ovarian syndrome and Alzheimer’s disease, and in-depth analyses of genetics, structural and functional imaging, as well as neuroscience, including postmortem brain studies, transcriptome of induced pluripotent stem cell models, assessments of the role of vitamin D, and studies highlighting the contributions of inflammatory mediators to autism.

We have had for over three decades a particular interest on the interface of immune mediators and psychiatric disorders [35]. It is very rewarding to see the interface of immune mediators and psychiatry evolve from a hypothesis, that we and others explored decades ago, into a broad and established area within psychiatric neuroscience. As we have developed a new model of analysis of the simultaneous contributions of multiple genes and environmental factors to a psychiatric phenotype [36], were also encouraged to see studies looking at the polygenic risk for autism in the context of childhood trauma, life-time self-harm, and suicidal behavior and ideation [30], as well in comparison to several other psychiatric disorders [32].

One paper in this issue, by Frye et al., is highly usual, and particularly intriguing: it investigates the role of the mitochondrion, in the influence of prenatal air pollution exposure on neurodevelopment and behavior in 96 children with autism spectrum disorder [22]. Second and third

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trimester average and maximal daily exposure to fine air particulate matter of diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was obtained from the Environmental Protection Agency's Air Quality System. Mediation analysis found that mitochondrial respiration linked to energy production accounted for 25% and 10% of the effect of average prenatal $\text{PM}_{2.5}$ exposure on neurodevelopment and behavioral symptoms, respectively. Those results suggest that prenatal exposure to $\text{PM}_{2.5}$ disrupts neurodevelopment and behavior through complex mechanisms, including long-term changes in mitochondrial respiration and that patterns of early development need to be considered when studying the influence of environmental agents on neurodevelopmental outcomes.

We are honored to have initiated the national conversation on autism twenty years ago and we believe that the 403 autism papers published to date in *Molecular Psychiatry*, including, but not limited to those highlighted in this Special Issue, report major advances in a key area of molecular psychiatry. It is particularly rewarding to see that these articles cover the full spectrum of research translation [37], from molecules to society.

In future issues, *Molecular Psychiatry* will continue to publish outstanding advances in autism research.

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