HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Biol Psychiatry. 2019 April 01; 85(7): e29–e30. doi:10.1016/j.biopsych.2019.02.001.

Found in Translation: Autism Genetics and the Quest for Its Rosetta Stone

Jonathan Goldstein,
Icahn School of Medicine at Mount Sinai, New York, New York

David A. Ross,
Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut

Daniel Moreno De Luca
Division of Child and Adolescent Psychiatry, Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, Rhode Island.

> Since 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far…
>
> — Leo Kanner (1)

So begins the seminal paper by child psychiatrist Leo Kanner in which he described 11 children who, despite individual differences, displayed a common “inability to relate themselves in the ordinary way to people and situations.” Kanner believed they had “a unique ‘syndrome’, not heretofore reported, which seems to be rare enough” that he called “early infantile autism.” In many respects, his description (“autistic aloneness” and “insistence on sameness”) seems remarkably contemporary. Yet while the phenomenology was accurate, our understanding of almost every other aspect of the condition has evolved considerably.

One major shift has been from regarding autism as a relatively rare to a somewhat common condition: the earliest estimates suggested a prevalence of 2 to 4 per 10,000 children; the most recent estimates suggest that it may be as high as 1 in 59 (2). The cause of this increase is complex and may include better identification of existing cases, a possible increase in the actual frequency, and a range of social contributors [e.g., expansion of diagnostic criteria under the new rubric of autism spectrum disorder (ASD); changes to social policy, such as improving access to special education services (3); and social influence—merely living near another child with autism may increase the probability of a diagnosis].

Of course, Kanner was also interested in the cause of the disease. Relying on the main contemporary theory, psychodynamics, he and others sought to connect autism to parenting style. Based on the observation that his autistic patients lacked “warmhearted fathers and mothers,” he suggested that cold parenting may contribute to the development of autism (the “refrigerator mother theory”) (1). Painful to a modern reader, this toxic idea dominated the

Address correspondence to Daniel Moreno De Luca, M.D., MSc., Bradley Hospital, 1011 Veterans Memorial Parkway, East Providence, RI 02915; daniel_moreno_de_luca@brown.edu.

The authors report no biomedical financial interests or potential conflicts of interest.

field for more than a decade until Bernard Rimland, a psychologist and father of a boy with autism, challenged the theory in 1964 and presented autism as a neurodevelopmental disorder.

A decisive shift toward a neurobiological perspective occurred after publication of the first twin study in 1977, which suggested that the disease had a heritability greater than 80% (3). Geneticists quickly tried to follow up on these findings using the primary approach of the time: by looking at families in which multiple siblings were affected (termed multiplex families); the hope was that linkage analyses might reveal chromosomal regions that were coinherited in individuals with autism; from this, it might be possible to identify specific risk genes. While this approach had been effective for studying rare monogenic disorders, like cystic fibrosis, the work came up short with autism: although studies revealed regions of interest on chromosomes 7 and 20, they did not determine any single cause (4).

By the 1990s, geneticists had begun to think differently about the genetic basis of many disorders, including autism. Because researchers had been unable to identify single, causative mutations, they hypothesized that they were instead “complex” disorders caused by many common genetic variants acting together. In 1996, based on this shift in thinking, geneticists Neil Risch and Kathleen Merikangas suggested an alternative approach. Rather than using multiplex pedigrees to determine genetic linkage, Risch and Merikangas proposed testing large groups of participants both with and without a specific condition. They could then identify the genetic variants that were more common in those individuals with the disorder, and were, presumably, related to its cause. This new method was termed genome-wide association study.

While the proposal was theoretically sound, it took almost a decade of technological innovation for the method to become viable (i.e., to simultaneously probe millions of single nucleotide polymorphisms across the genome). For some conditions, such as irritable bowel disease and type 2 diabetes, this approach worked well. Unfortunately, for autism, the results remained disappointing and no common variants were identified. These data posed a vexing conundrum: if the heritability of autism was so high, why were the studies coming up short?

One major reason may have stretched all the way back to Kanner’s description of a “unique ‘syndrome.’” Through the years, scientists had generally treated autism as if it were a single entity—but evidence was rapidly accumulating that this might not be the case. On one hand, several rare conditions— such as fragile X, Rett syndrome, and tuberous sclerosis, disorders that were all caused by identifiable, single-gene, pathogenic genetic changes—had shown autism as a part of the phenotype. These examples illustrated that different genetic mutations could all lead to the same phenotype. Then, in a landmark paper, Thomas Bourgeron’s group was the first to start with the phenotype of autism and identify specific risk genes (*NLGN3* and *NLGN4*) in some individuals (5). Together, these data suggested that one reason previous studies had failed was that the diagnostic category of “autism” comprised a heterogeneous population.

It turned out that there was a second, perhaps more surprising reason that previous studies had failed. In 2003, the field was turned on its head by what might ordinarily have been a

routine conversation. James Simons, a wealthy philanthropist and cofounder of the Simons Foundation, asked a geneticist at Cold Spring Harbor Laboratory, Michael Wigler, to review a grant proposal. When Wigler saw that the study focused on common variation associated with ASD, he balked (6). Previous research in the field—whether through linkage studies or genome-wide association studies—was all predicated on the idea that pathological variants were passed on from one generation to the next. But Wigler's background in cancer research had led him to consider a different possibility—what if a mutation arose spontaneously?

Testing this hypothesis required a totally different methodological approach. First, researchers would need to move beyond studies of a few candidate genes and search for rare (occurring with a frequency of, <1% in the population), de novo variants that could arise anywhere in the genome. Historically, this would not have been feasible. But the timing of their work was propitious: the recent completion of the Human Genome Project paved the way for the development of genome-wide assessment and was followed by rapid drops in the cost of sequencing and other genetic assays. Second, the study population would need to be different: instead of looking at multiplex families, researchers would need to find instances in which both parents did not have autism and only a single child was affected (termed a simplex family) —the goal, after all, was to look for new cases. Soon, the Simons Simplex Collection had gathered data from hundreds (and now thousands) of families, joining other multicenter initiatives (including the Autism Genome Project and the Autism Genetic Resource Exchange) in the quest to understand the genetic landscape of autism (7).

The data that have emerged from these collaborations have revolutionized the field. The central hypothesis was correct: it now appears that rare, pathogenic variants can be identified in 20% to 40% of ASD cases (4). More than 25 high confidence and 62 strong candidate genes have been identified (8). And new research has also clarified the relevant type of variation. While early work largely focused on looking for changes within specific genes, it has now been shown that copy number variants—i.e., duplications or deletions involving a unique (nonrepetitive) genomic sequence of greater than 1000 nucleotides—play a significant role in the underlying biology of ASD (4).

This has set the stage for what has become one of the most exciting times to truly understand the biology of autism. Besides continuing to identify new types of genetic variation that may confer risk, such as noncoding de novo variation, we have also started to appreciate different ways in which genetic changes may arise and modulate that risk—for example, through somatic mosaicism or gene alterations occurring in the setting of apparently balanced chromosomal translocations, ideas that are quite familiar to the cancer world but new for neuropsychiatric disorders. Recent work has also confirmed that early genome-wide association studies failed because they were underpowered; large-scale international collaborations (e.g., the Psychiatric Genomics Consortium) are now making progress toward identifying common risk loci, and common variation is currently thought to exert an additive effect that accounts for 40% to 60% of ASD risk (4). Finally, there has been marked progress toward understanding the biological consequences of these diverse genetic changes, for example by studying where, how, and when these autism risk genes are active and transcribed (9), or using high-throughput and high accuracy genetic techniques, such as clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, to create cellular

and animal (9) models that recapitulate genetic changes observed in patients and that can spearhead the development of new therapies.

While Kanner's 1943 phenomenological description still rings true, almost every other aspect of how we understand autism has evolved immensely—including, ironically, Kanner's own role in its history. Recent evidence has emerged that decades before Kanner's seminal paper, a Russian physician named Grunya Efimovna Sukhareva had already described the syndrome (10). The story of autism continues to be written, and hopefully, recent work into the genetic architecture of the disorder may pave the road for future interventions that will help people with ASD fully achieve their potential in an era of precision medicine.

Acknowledgments and Disclosures

Clinical Commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). David A. Ross, in his dual roles as co-chair of the NNCI and Education Editor of Biological Psychiatry, manages the development of these commentaries but plays no role in the decision to publish each commentary. The NNCI is supported by the National Institutes of Health Grant Nos. R25 MH08646607S1 and R44 MH11554601.

References

1. Kanner L (1943): Autistic disturbances of affective contact. Nervous Child 2:217–250.
2. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. (2018): Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 67:1–23.
3. Lai M-C, Lombardo MV, Baron-Cohen S (2014): Autism. Lancet 383:896–910. [PubMed: 24074734]
4. Geschwind DH, State MW (2015): Gene hunting in autism spectrum disorder: On the path to precision medicine. Lancet Neurol 14:1109–1120. [PubMed: 25891009]
5. Jamain S, Quach H, Betancur C, Råstam M, Colineaux C, Gillberg IC, et al. (2003): Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nat Genet 34:27–29. [PubMed: 12669065]
6. Hall SS (2014): Solving the autism puzzle. MIT Technology Review. Available at: https://www.technologyreview.com/s/533501/solving-theautism-puzzle/#comments. Accessed December 20, 2018.
7. Fischbach GD, Lord C (2010): The Simons Simplex Collection: A resource for identification of autism genetic risk factors. Neuron 68:192–195. [PubMed: 20955926]
8. Gene SFARI (2008): Human gene module. Available at: https://gene.sfari.org/database/human-gene/. Accessed January 15, 2019.
9. Willsey AJ, State MW (2015): Autism spectrum disorders: From genes to neurobiology. Curr Opin Neurobiol 30:92–99. [PubMed: 25464374]
10. Zeldovich L (2018): How history forgot the woman who defined autism. Available at: https://www.spectrumnews.org/features/deep-dive/historyforgot-woman-defined-autism/?cn-reloaded=1. Accessed January 28, 2019.