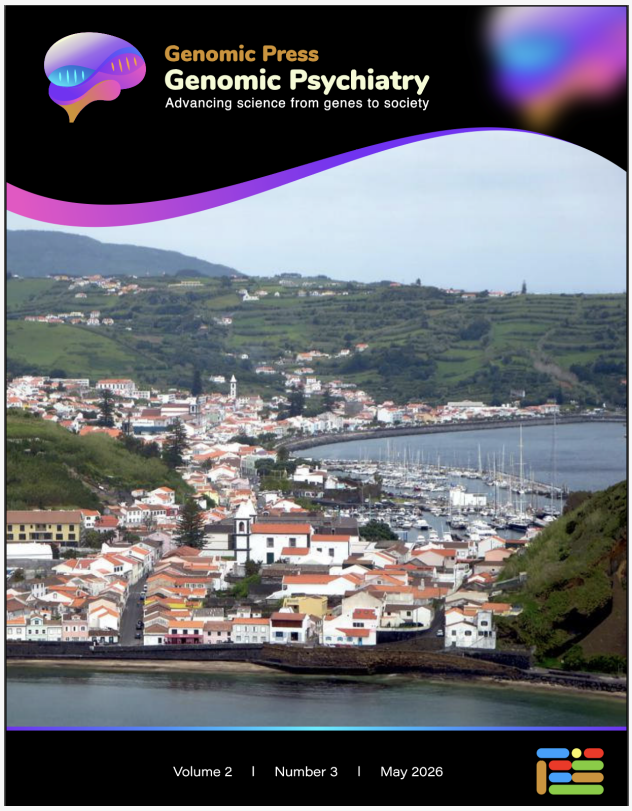
A single broken gene reads aloud in several dialects across one Portuguese island family

The same ultra-rare gene mutation appears as schizophrenia in most carriers, as autism in one sibling, and leaves their grandmother entirely well.



When the family tree outsmarts the diagnostic manual

PISCATAWAY, NJ, UNITED STATES, June 16, 2026 /EINPresswire.com/ -- For most of a century, psychiatry has kept its disorders in separate rooms. Schizophrenia in one. Bipolar disorder in another. Autism somewhere down a different corridor entirely. The arrangement was orderly, and it organized clinics and insurance codes and the words that families carried home from the appointment. It was also, as anyone who ever sat with real patients understood, a little bit of a fiction at the edges. The diagnoses were tidy. The family histories were not.

A study published today in Genomic Psychiatry walks back into those family histories and finds the walls thinner than the manuals would have us believe. Carlos N. Pato, Michele T. Pato, and a team spread across more than a dozen institutions returned to a place that geneticists prize and tourists merely photograph: the Azores and Madeira, the scattering of Portuguese islands that rise green and steep out of the open Atlantic. The cover of this issue looks down on one of them, the town of Horta on Faial, its red roofs crowded along a thin neck of land between two harbors.

These particular islands held the answer because of their soil and their centuries of relative isolation. Settlers arrived roughly six hundred years ago, a small founding population, almost entirely Portuguese, and then the place was largely left alone. The genetic deck, so to speak, was shuffled once and rarely shuffled again. That is the kind of quiet, contained ancestry that lets a rare mutation stand out from the noise the way a single lit window stands out on a dark hillside. From this population the researchers assembled the Portuguese Island Collection, a resource built patiently since the 1990s and followed across four generations of illness and recovery.

The diagnostic boxes have always leaked. The current report examines 173 multiplex families, households in which at least two members carried a serious psychiatric diagnosis. In 49 of them, just over 28 percent, the same family tree bore both psychosis and mood disorder: schizophrenia in one relative, a crushing depression or bipolar disorder in the next. In a smaller set, 12 families or roughly 7 percent, autism and intellectual disability folded into the same pedigree, the multi-generation family tree, alongside schizophrenia or mood disorder. The categories, in other words, refused to stay in their lanes. The denser the family, the more the diagnoses mixed.

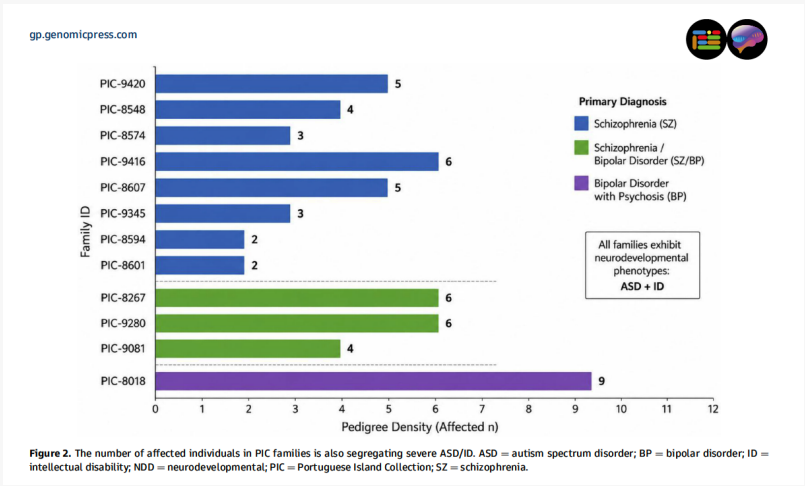


Figure 2. The number of affected individuals in PIC families is also segregating severe ASD/ID. ASD = autism spectrum disorder; BP = bipolar disorder; ID = intellectual disability; NDD = neurodevelopmental; PIC = Portuguese Island Collection; SZ = schizophrenia.

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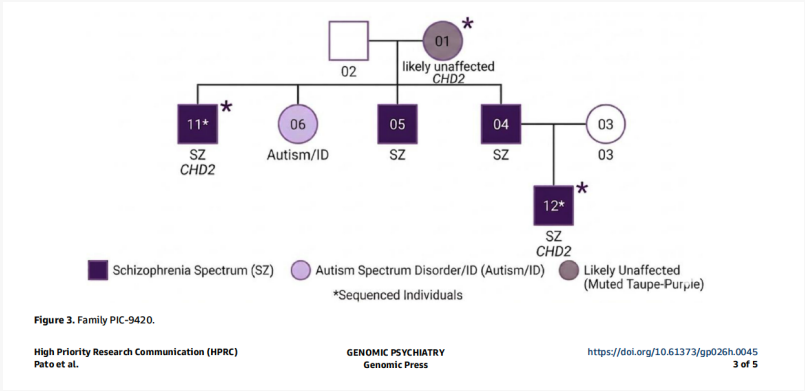


Figure 3. Family PIC-9420.

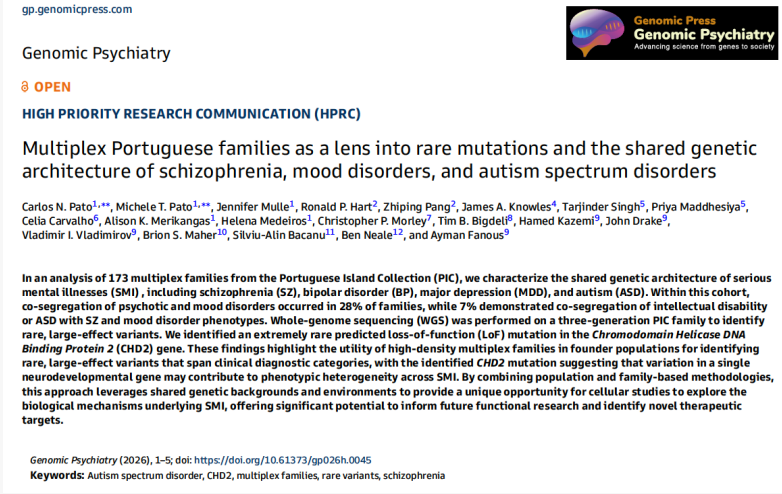
Family PIC-9420

"When you study an isolated founder population like this one, the shared ancestry and the shared environment let you see the inherited architecture that larger case-control studies tend to dilute," said Carlos N. Pato, MD, PhD, Executive Chair of the Department of Psychiatry at Rutgers, The State University of New Jersey, and corresponding author of the study.

One family, read in three different ways, is what lifts this work above careful bookkeeping. In a three-generation pedigree, the team performed whole-genome sequencing and found an ultra-rare stop-gain mutation in CHD2, a genetic change that may abruptly halt or alter the construction of the protein. CHD2 helps build chromatin architecture, the scaffolding that packages DNA, while the brain is still under construction. The gene is usually discussed in the vocabulary of childhood epilepsy and autism, and it carries the highest-confidence rating for autism risk. Here it does something stranger. It travels down three generations and surfaces, in most of the relatives who carry it, as schizophrenia. In one sibling it appears instead as autism with intellectual disability. The mutation is identical. The destination is not. A single broken gene, it turns out, can be read aloud in several dialects.

The variant itself is almost vanishingly rare. It did not appear at all in two large reference

databases for schizophrenia and bipolar disorder, and it surfaced exactly once among more than 800,000 unrelated people in a global genomic catalog. The relatives across the second and third generations who were sequenced carry it and live with schizophrenia. The father of one affected grandson is an obligate carrier, someone the family pattern shows must carry the variant, diagnosed with schizophrenia, though he himself was never sequenced.



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HIGH PRIORITY RESEARCH COMMUNICATION (HPRC)

Multiplex Portuguese families as a lens into rare mutations and the shared genetic architecture of schizophrenia, mood disorders, and autism spectrum disorders

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In an analysis of 173 multiplex families from the Portuguese Island Collection (PIC), we characterize the shared genetic architecture of serious mental illnesses (SMI) , including schizophrenia (SZ), bipolar disorder (BP), major depression (MDD), and autism (ASD). Within this cohort, co-segregation of psychotic and mood disorders occurred in 28% of families, while 7% demonstrated co-segregation of intellectual disability or ASD with SZ and mood disorder phenotypes. Whole-genome sequencing (WGS) was performed on a three-generation PIC family to identify rare, large-effect variants. We identified an extremely rare predicted loss-of-function (LoF) mutation in the *Chromodomain Helicase DNA Binding Protein 2* (CHD2) gene. These findings highlight the utility of high-density multiplex families in founder populations for identifying rare, large-effect variants that span clinical diagnostic categories, with the identified *CHD2* mutation suggesting that variation in a single neurodevelopmental gene may contribute to phenotypic heterogeneity across SMI. By combining population and family-based methodologies, this approach leverages shared genetic backgrounds and environments to provide a unique opportunity for cellular studies to explore the biological mechanisms underlying SMI, offering significant potential to inform future functional research and identify novel therapeutic targets.

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Keywords: Autism spectrum disorder, CHD2, multiplex families, rare variants, schizophrenia

"A rare variant with a large effect, sitting inside a family like this one, gives us something a database never can," said Michele T. Pato, MD, co-first author of the study. "It lets us ask why the same mutation may appear as one illness in one person and a different illness in their sibling. The answer to that question is where new treatment targets are likely to be hiding."

> We went back to the families because the families suffered with diagnoses that crossed boundaries we drew on paper."
>
> *Dr. Carlos N. Pato, Executive Chair of Psychiatry, Rutgers University*

A quieter figure in this pedigree, the woman who by every expectation should have been sick, may matter most of all. The grandmother carries the same broken gene, and she is, by every account in the record, well. The variant did not spare her grandchildren. It did not spare a relative who meets full criteria for schizophrenia yet may not carry the mutation at all, a possible phenocopy, a case that mimics the inherited illness without the genetic cause, that the authors deliberately keep in the frame rather than dismiss as an inconvenient asterisk. But it spared her. Three readings of one mutation in one family: illness with the variant, illness without it, and the variant carried in a body that never fell ill. The authors point to the work of Mayana Zatz on older people who harbor pathogenic variants and yet never develop the expected disease. Whatever held the line in that grandmother is, in a sense, the closest thing in this family to a medicine.

The authors are careful to mark the limits of what the work does and does not show. Autism was originally an exclusion criterion when the collection began, which means the 7 percent figure almost certainly undercounts autism and intellectual disability in these families. One key relative was sequenced but failed quality control, so whether that person carries the variant remains

unknown, and the pattern of inheritance is therefore less than airtight. The proposed molecular consequences of the truncation, which clips the final seventeen amino acids from the protein near a site that other molecules may chemically modify, remain, in the authors' own framing, speculative until they are tested in living cells. Pedigree size and the way families were ascertained may also shape the numbers. These are findings to build on, not verdicts to hand down.

A map of psychiatric illness drawn from family histories emerges when the two great approaches to the field meet. An accompanying editorial in Genomic Psychiatry, by Julio Licinio, frames the study as a meeting point between two opposite approaches. Large consortium studies have been dissolving the old diagnostic partitions from the top down, finding that most genetic signal is shared across disorders rather than specific to any one. Pato and colleagues arrive at the same destination from the bottom up, one family at a time. The two directions meet in the middle, and the handshake is convincing. The stated hope is that a handful of these rare variants will converge on a few downstream biological pathways, and that those pathways might one day yield treatments useful across the diagnostic spectrum rather than locked inside a single box. It is a long road. This study is a reminder that the most modern insight sometimes arrives by the oldest method we have, which is to sit down with a family and listen to who got sick, and when, and how.

The peer-reviewed research article in Genomic Psychiatry titled "Multiplex Portuguese families as a lens into rare mutations and the shared genetic architecture of schizophrenia, mood disorders, and autism spectrum disorders," is freely available via Open Access, starting on 16 June 2026 in Genomic Psychiatry at the following hyperlink: https://doi.org/10.61373/gp026h.0045

An accompanying Editorial in Genomic Psychiatry titled "When the family tree outsmarts the diagnostic manual," providing expert perspective on this research, is freely available via Open Access on 16 June 2026 in Genomic Psychiatry at the following hyperlink: https://doi.org/10.61373/gp026d.0048

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