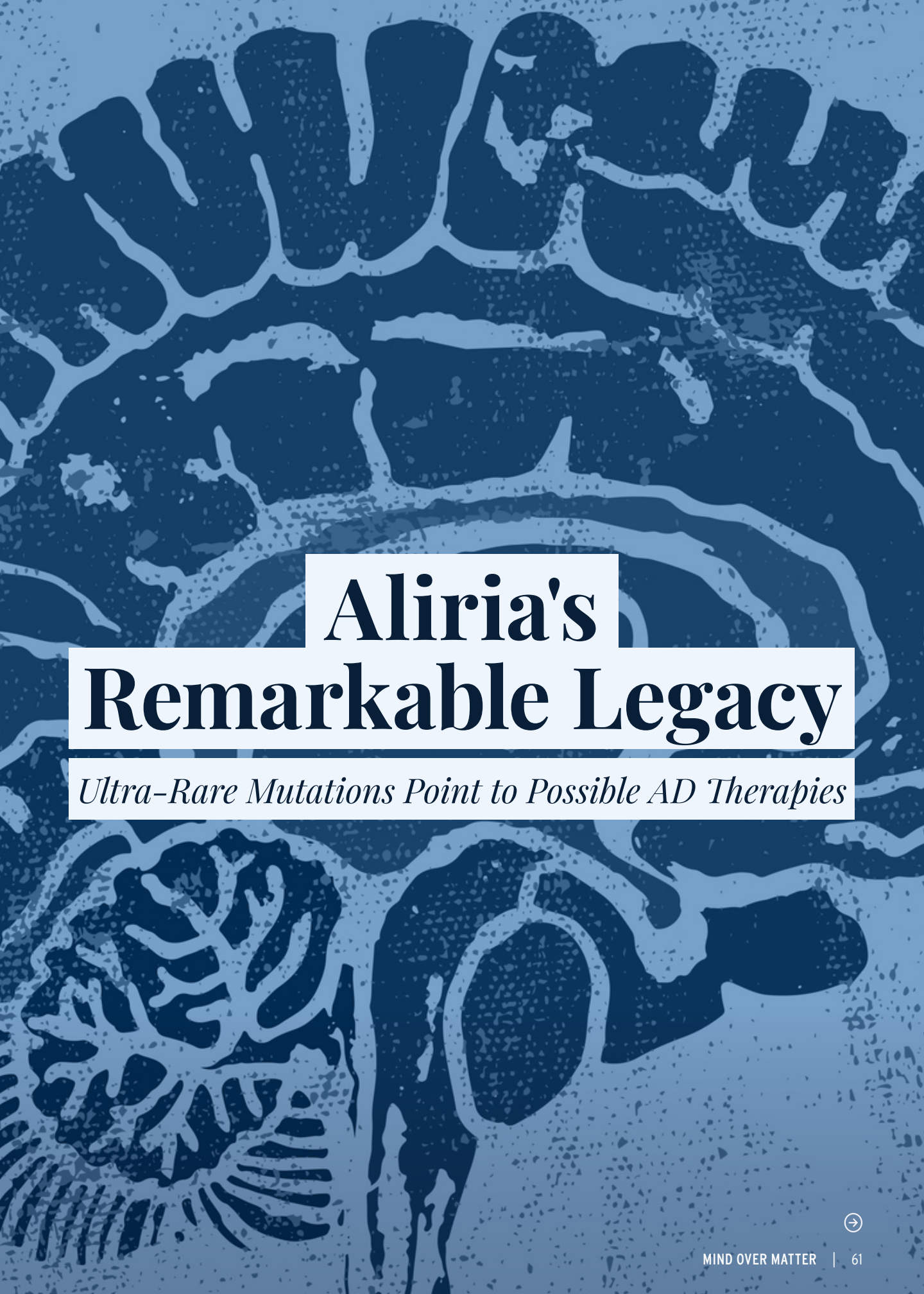

Aliria's Remarkable Legacy

Ultra-Rare Mutations Point to Possible AD Therapies

In 2017, an international group of researchers at Harvard and Massachusetts General Hospital in Boston and the University of Antioquia in Colombia encountered a tantalizing mystery. While studying a Colombian family with a genetic mutation (known as *Presenilin-1 E280A* or Paisa) that causes people who carry even a single copy to develop Alzheimer's disease (AD) in their 40s, the scientists became intrigued by one family member in particular.

Nearly 30 years after she had presumably been fated to develop early symptoms of AD, Aliria Rosa Piedrahita de Villegas, then in her early 70s, had nonetheless maintained normal cognitive function.

By unravelling the secrets of this woman's remarkable brain, scientists have discovered a potential new method of preventing AD. This could point the way to a completely new class of treatments that may not have the same drawbacks and limitations of existing drugs that remove abnormal amyloid protein from the brain.

For instance, women don't reap the already modest cognitive benefits of anti-amyloid drugs, such as lecanemab. In addition, these amyloid-targeting medications are more likely to cause side effects, such as brain swelling or bleeding in the brain in people with the strongest genetic risk factor for AD, the *APOEe4* gene.

STUDYING A TRAGIC INHERITANCE

Dr. Francisco Lopera, a Colombian neurologist, first began following Aliria's family approximately 40 years ago. Since then, researchers have gathered data on approximately 6,000 individuals in that family, roughly 1,500 of whom have been identified as having the Paisa mutation.

The Paisa mutation is autosomal dominant, meaning people who inherit just one copy can develop the disease. It's also 100% penetrant, which means that all people with the gene will develop the related disease – in this case, AD.

People with the Paisa mutation "are pretty much destined to develop mild cognitive impairment (MCI) around age 44 or 45, and dementia around 49 to 50," said Dr. Yakeel Quiroz, an associate professor in the Departments of Psychiatry and Neurology at Harvard Medical School and Massachusetts General Hospital (MGH), and Director of the Mass General Familial Dementia Neuroimaging Lab and the Multicultural Alzheimer's Prevention Program (MAPP).

> **"UNFORTUNATELY, MOST OF THEM DIE IN THEIR 60s, BECAUSE IT'S A VERY AGGRESSIVE FORM OF ALZHEIMER'S DISEASE.**

APOEε2 MAY NOT PROTECT WOMEN

A gene variant linked with a lower risk of AD may only benefit men, according to a 2023 study.

The *APOE* family of genes contain instructions for making apolipoprotein E, which plays an important role in transporting cholesterol and other fats to neurons in the brain, and is involved in regulating inflammation. There are three main variants of *APOE*, some of which influence AD risk.

Most of us have *APOEe3*, "which is neutral in terms of risk of Alzheimer's disease," explained Dr. Jennifer Rabin, Neuropsychology Lead at the Sunnybrook Research Institute Harquail Centre for Neuromodulation in Toronto and lead author of the study. On the other hand, "we've known for a long time that *APOEe2* is protective against Alzheimer's disease," she says. "*APOEe4* increases risk, and it has a more detrimental effect in females compared to males."

With that last fact in mind, Dr. Rabin investigated whether the impact of *APOEe2* on women versus men had been looked into. "There were some inklings in the literature, but it was really mixed, and the studies were small," she said.

Dr. Rabin decided to fill that gap. "We started with two big cohort studies, and we looked at sex differences as it relates to *APOEe2* in terms of cognitive decline," she said. The team used publicly available data on adults who were cognitively normal when they enrolled in large-scale observational studies.

"In both cohorts, we saw the effect where *APOEe2* was only protective in men," Dr. Rabin said. "Initially, I was skeptical. However, we successfully replicated the results in an additional cohort." The research was published in *Alzheimer's and Dementia* in October 2023.

The Paisa mutation is one of a handful of known gene mutations that cause this pattern of strongly inherited, early-onset disease, known as familial Alzheimer's (FAD), which accounts for less than 2% of total cases. The remaining more than 98% of individuals with AD are deemed as having the sporadic form of AD.

As part of the "Colombia-Boston (COLBOS)" longitudinal biomarker study of autosomal-dominant AD, Dr. Quiroz, the principal investigator, and her colleagues investigated further, examining Aliria's DNA and bringing her to Boston for brain imaging.

POSSIBLE SOURCE OF PROTECTION IDENTIFIED

The genetic analysis revealed that Aliria carried two copies of another very uncommon genetic mutation thought to protect against Alzheimer's disease – the *APOE 3 Christchurch*, or *APOECh,* variant.

HAVING ONE COPY OF *APOECH* IS RARE, TWO, VANISHINGLY SO.

Imaging of Aliria's brain differed markedly from that of individuals with the mutation whose symptoms followed the usual aggressive path.

Typically, in the earlier stages of AD, a protein called amyloid-beta begins to build up in the brain and forms plaques. Then, another protein – tau – starts to collect in neurons, eventually forming threads that tangle together.

"In Alzheimer's disease, tau accumulates in a specific pattern. It starts in the medial temporal lobes, where the hippocampus is located – an area that plays a key role in memory," noted Dr. Jennifer Rabin, Neuropsychology Lead at the Sunnybrook Research Institute Harquail Centre for Neuromodulation and assistant professor of neurology at the University of Toronto.

"This is why memory problems are often one of the earliest signs of Alzheimer's disease. From there, tau spreads to the outer part of the temporal lobes, and eventually to the frontal temporal lobes," Dr. Rabin said. "When tau accumulates, it damages brain cells, causes the brain to shrink, and leads to cognitive decline."

A SURPRISING PARADOX

Individuals with the Paisa mutation whose disease followed the expected trajectory, "have really high levels of amyloid usually around age 28 or 29, and they have fairly significant accumulation of tau pathology by their late 30s or early 40s," Dr. Quiroz explained.

"(Aliria) had very high levels of amyloid – the highest of anyone I have seen," Dr. Quiroz said of the results of a scan. However, "tau was very limited." Even more intriguing, "she didn't have any tau in the entorhinal cortex or hippocampus, which are important for memory," Dr. Quiroz added. The team first described Aliria's case in *Nature Medicine* in November 2019.

When Aliria died of cancer at 77 in 2020, having only recently developed mild cognitive impairment, "the family donated her brain, and we were able to confirm that she had high levels of amyloid and very limited levels of tau pathology and neurodegeneration," said Dr. Quiroz. (This research was published in the journal *Acta Neuropathologica* in September 2022.)

"IT WAS VERY REMARKABLE TO SEE THAT, BASED ON THE EVIDENCE WE HAVE, TAU IS MORE LINKED TO COGNITIVE DECLINE THAN AMYLOID.

But exactly how were the two copies of Christchurch protecting against these changes? The researchers discovered it impaired an interaction that's thought to help tau tangles develop. Christchurch inhibited the ability of apolipoprotein E (APOE) – a protein that transports cholesterol and other fats in the body – with a type of sugar found on the surface of brain cells – heparan sulphate proteoglycans or HSPGs.

(A body of earlier research has established "that HSPG is important for amyloid aggregation, it's important for amyloid-induced neuroinflammation, and it's important for neuronal uptake of tau," Dr. Quiroz said.)

From there, "we were able to develop an antibody that pretty much mimics the way Christchurch behaves with APOE and HSPG," said Dr. Quiroz, "inhibiting the binding between the two."

MIMICKING EFFECT OF MUTATION

The researchers next wanted to investigate whether a single copy of *APOECh* could provide people with the Paisa mutation with partial protection against AD dementia. "From about 2,000 DNA samples we had available from Colombian families, we were able to identify 121 individuals as having one copy of the Christchurch mutation," Dr. Quiroz said.

"Those who carry only one copy of Christchurch had a delay of about five years in the onset of MCI compared to non-carriers.

One of these carriers travelled to Boston twice for brain imaging. The scans showed that "the amyloid keeps accumulating very slowly, but there's definitely something happening that's limiting the tau pathology," Dr. Quiroz said. The study was published in June 2024 in *The New England Journal of Medicine*.

Of course, "something people always ask me is if what we're seeing in these families in Colombia is something we can extend to the general population," said Dr. Quiroz. Her colleagues and scientists at other institutions are working on answering that question.

PROMISE OF BROADER BENEFIT

A group of researchers led by Dr. Maxine Nelson at the Gladstone Institute of Neurological Disease in San Francisco investigated whether *APOECh* could counter the effects of the *APOEe4* gene variant.

"*APOEe4* is the most common (genetic) risk factor for Alzheimer's disease," Dr. Quiroz explained. "They showed that in a mouse model and cellular experiments, two copies of Christchurch provided protection against tau pathology and neurodegeneration as well as neuroinflammation – something very similar to what we saw in humans," Dr. Quiroz said.

As well, the researchers "observed that one copy of the mutation showed some protection against neurodegeneration and neuroinflammation," she added. The study was published in *Nature Neuroscience* in November 2023.

THIS HELD OUT THE POSSIBILITY THAT THE IMMUNE-PRODUCED PROTEIN THAT PROTECTED AGAINST THE EFFECTS OF THE PAISA MUTATION COULD POTENTIALLY HAVE A SIMILAR IMPACT ON THOSE OF *APOEE4*.

Research conducted by Dr. Quiroz's group confirmed this is the case. "We now have a more advanced antibody that mimics the effect of Christchurch, and Dr. Claudia Marino published more data on that antibody," explained Dr. Quiroz. In the study, the antibody curbed the process that forms tau tangles in mice genetically altered with the *APOEe4* gene. This work appeared in *Alzheimer's and Dementia* in February 2024.

"It would be great if we could replicate what (Aliria) had and give it to other people," Dr. Quiroz said. Currently, the antibody is being tested in animal models. "It may take a few years until we move from this phase, but it's very promising." In future, she added, the hope is "to run clinical trials with individuals at risk of sporadic Alzheimer's disease."

"We're living in an incredibly exciting time for Alzheimer's treatments," said Dr. Rabin.

LEARNING FROM GENETIC EXTREMES

Studying families that either develop a very severe form of a disease or are protected against it can help scientists decipher how specific genetic mutations exert these effects, which in turn can lead to treatments that benefit a much broader segment of the population.

For instance, the path to the discovery of PCSK9 inhibitors – a class of potent cholesterol-lowering medications that mimic the effects of genetic variants that cause carriers to have extremely low levels of LDL cholesterol – began with studies of large multigenerational families with a condition called familial hypercholesterolemia.

The work of Dr. Quiroz and her colleagues is an excellent example of how studying genetic extremes can yield important insights into the mechanisms involved in the development of AD. Two other genetic variants that cause early-onset Alzheimer's – the Uppsala and Arctic mutations – were discovered in a similar fashion.

Research into the Arctic mutation led to the development of an immunotherapy drug that targets abnormal amyloid deposits in the brain. And a team of researchers, which included Dr. Martin Ingelsson, now a senior scientist at Toronto's Krembil Research Institute, identified three ways in which the Uppsala mutation promotes higher levels of amyloid beta in the brain. They also discovered that, unlike typical amyloid deposits, those caused by Uppsala did not trigger an immune reaction in surrounding tissue.

"THERAPIES ARE NOW EMERGING THAT EFFECTIVELY TARGET THE DISEASE PROCESS – WHAT WE CALL DISEASE-MODIFYING TREATMENT – RATHER THAN MERELY MANAGING SYMPTOMS. WHILE PROMISING, THESE DRUGS ARE NOT CURES AND ARE NOT CURRENTLY APPROVED IN CANADA.

However, research led by Dr. Quiroz and her colleagues provides hope that it may be possible to prevent AD in people at genetic risk of the disease.