NEWS

Mitochondria mediate effects of PTEN mutations

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People with inherited PTEN mutations who have autism or developmental delay have more copies of mitochondrial DNA than do people with PTEN mutations who have cancer, a new **study** has found.

The findings provide clues to why mutations in the same gene can have different outcomes, says lead investigator **Charis Eng**, chair of the Genomic Medicine Institute and director of the Center for Personalized Genetic Healthcare at the Cleveland Clinic in Cleveland, Ohio.

Up to 2 percent of autistic people have mutations in **PTEN**. Mutations in the gene, a tumor suppressor, are associated with several types of cancer, including melanoma, breast cancer and thyroid cancer. But not everyone with a PTEN mutation develops cancer. About 25 percent of people with PTEN mutations have both autism and cancer.

People with PTEN mutations and autism or developmental delay are more likely to have **harmful copy number variants** than are those with PTEN mutations and cancer, Eng and her colleagues previously reported. The two groups also show differences in blood levels of 52 metabolites. This led Eng's team to explore a possible role for mitochondrial DNA, which encodes genes important for cell metabolism.

The new findings provide "additional and strong evidence for the idea that mitochondria contribute to neurodevelopmental disorders," says **Victor Faundez**, professor and vice chair of cell biology at Emory University in Atlanta, Georgia, who was not involved in the study.

Mitochondria power cellular proliferation — a process central to both cancer and neurodevelopment. “If you have a mismatch between the proliferation and the energy required for that, either too much or too little, it could cause problems,” says **Anthony Wynshaw-Boris**, professor and chair of genetics and genome sciences at Case Western Reserve University in Cleveland, who was not involved with the study.

Earlier this year, Wynshaw-Boris and his team reported that PTEN mutations **affect the growth of organoids** derived from autistic people more profoundly than those derived from neurotypical people. “Our motivation was the same in trying to find out what’s in the background that actually causes these differences,” he says. “So I think this is an exciting study.”

The findings were published in April in *HGG Advances*.

Eng and her colleagues analyzed whole-genome sequencing data from 498 people with inherited PTEN mutations, including 164 people with autism or developmental delay but not cancer, 184 people with cancer but no neurodevelopmental condition, 132 people with neither cancer nor a neurodevelopmental condition, and 18 people with cancer and a neurodevelopmental condition.

Participants with a neurodevelopmental condition and not cancer had a higher median copy number of mitochondrial DNA than did participants with neither condition and participants with cancer only, the researchers found. The findings held up when the researchers controlled for age and sex, and when they narrowed their analysis to the 213 people in the H haplogroup, which is the most common haplogroup among people of Caucasian ancestry. Haplogroups are sets of single nucleotide variants that reflect ancestry, so focusing on a single haplogroup helps control for those variants.

The researchers also identified 1,691 mitochondrial single nucleotide variants among the people in the H haplogroup. People with a neurodevelopmental condition had fewer of these variants than did people without a neurodevelopmental condition, regardless of cancer status; and people with cancer had fewer such variants than did those without cancer, regardless of neurodevelopmental status. The associations persisted when the researchers focused only on variants predicted to disrupt mitochondrial function.

The mechanisms through which mitochondrial genetic variants influence the outcome of PTEN mutations are unclear. But the ability to scour whole-genome sequencing data from a large group of people with PTEN mutations is sure to provide insights, says Wynshaw-Boris. “It’s great to see this kind of work is going with a lab that has this kind of collection,” he says.

Eng suspects the mechanism may reside in the role of the mitochondria in the energy-intensive process of DNA damage repair. “One of the roles of PTEN is guardianship of the genome,” she says. “We think that if this guardianship is disrupted, maybe it doesn’t repair so well.”

PTEN is not the only autism gene with a **cancer connection**. “We can conceive of these diseases as a continuum, where the slider might be mitochondrial function,” Faundez says.

How cells respond to DNA damage and mitochondrial dysfunction may depend on where they are — in the brain or elsewhere in the body, Eng says. She and her team plan to explore this next.

With additional reporting by Laura Dattaro.

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