Study clarifies genetic autism risk in PTEN patients

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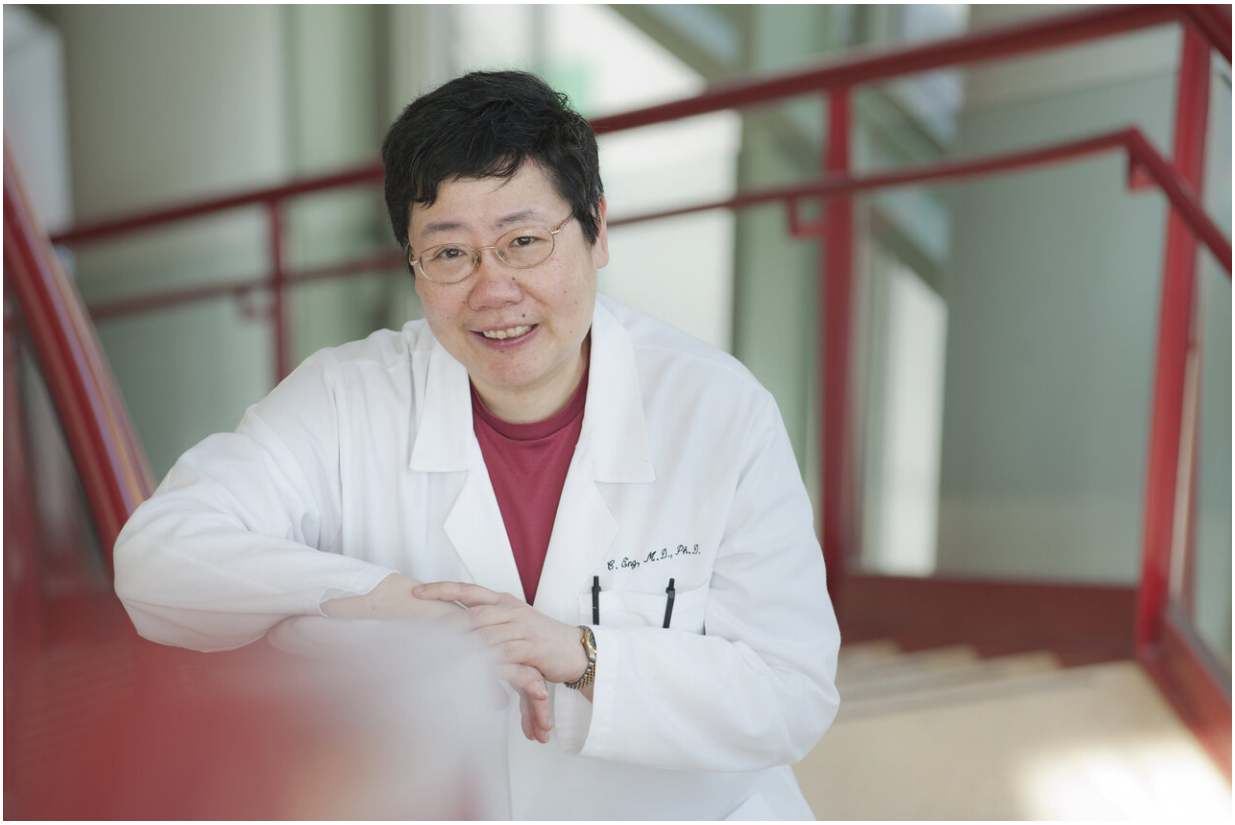

In a newly published study, a team of researchers led by Charis Eng, MD, PhD, of Cleveland Clinic's Genomic Medicine Institute, identified for the first time an explanation of why patients with identical PTEN mutations often have vastly different clinical presentations. Credit: Cleveland Clinic

Cleveland Clinic researchers have identified for the first time an

explanation of why patients with identical PTEN mutations often have vastly different clinical presentations.

In a new study published in *JAMA Network Open*, a team of researchers led by Charis Eng, MD, Ph.D., of Cleveland Clinic Lerner Research Institute's Genomic Medicine Institute, discovered that copy number variations (CNVs) may act as genomic modifiers that influence the risk of autism spectrum disorder (ASD) and/or developmental delay (DD) versus cancer risk in individuals with PTEN mutations.

Germline mutations of the tumor suppressor gene PTEN are associated with a group of genetic disorders that increase the risk of certain cancers, cognitive and behavioral deficits, benign growths and tumors (i.e., hamartomas), and macrocephaly. These disorders are known collectively as PTEN hamartoma tumor syndrome (PHTS), but they manifest as a broad, difficult-to-predict range of clinical outcomes and have been found to inexplicably result in distinct subsets of patients with either cancer or ASD/DD. In fact, PTEN is one of the most common genes associated with ASD.

Previous studies have indicated associations between CNVs, or large structural genetic changes involving the deletion and/or duplication of DNA segments, and neurodevelopmental disorders and sporadic cancers. Therefore, specific CNVs may be linked with either ASD/DD or cancer incidence in individuals with PTEN mutations.

To investigate these associations, Dr. Eng's team quantified the total number of CNVs in patients from three PHTS phenotype groups (i.e., PHTS-ASD/DD, PHTS-no ASD/DD and PHTS-cancer) with similar PTEN mutations. They demonstrated an overall increased CNV burden per individual in patients with ASD/DD compared to those without ASD/DD or those with cancer. However, they found no difference in CNV burden between patients without ASD/DD and patients with

cancer.

They also determined that 10% of the PHTS-ASD/DD patients carried CNVs associated with neurodevelopmental disorders—compared to only 2.6% of PHTS-no ASD/DD and 1.7% of PHTS-cancer patients—while no CNVs involved in known cancer-associated genes were identified in PHTS-cancer patients.

These findings suggest that CNVs operate as genomic modifiers of ASD/DD risk in individuals with PHTS, meaning they not only provide insight into the ASD/DD versus cancer phenotypes associated with PTEN mutations but also may aid in the prediction of clinical outcomes to inform PHTS medical management. Furthermore, the study demonstrates that CNV burden analysis may also be applied to other clinically heterogeneous disorders for which no outcome-specific predictors are known.

Dr. Eng was the first to link PTEN to Cowden Syndrome, which is a PHTS disorder, and subsequently to ASD. She is the inaugural chair of Cleveland Clinic Lerner Research Institute's Genomic Medicine Institute and inaugural director of the Center for Personalized Genetic Healthcare, which includes the PTEN Multidisciplinary Clinic for children and adults with a confirmed or possible diagnosis within the PHTS spectrum.

Provided by Cleveland Clinic

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