Accurate detection of low-level somatic mutation in intractable epilepsy

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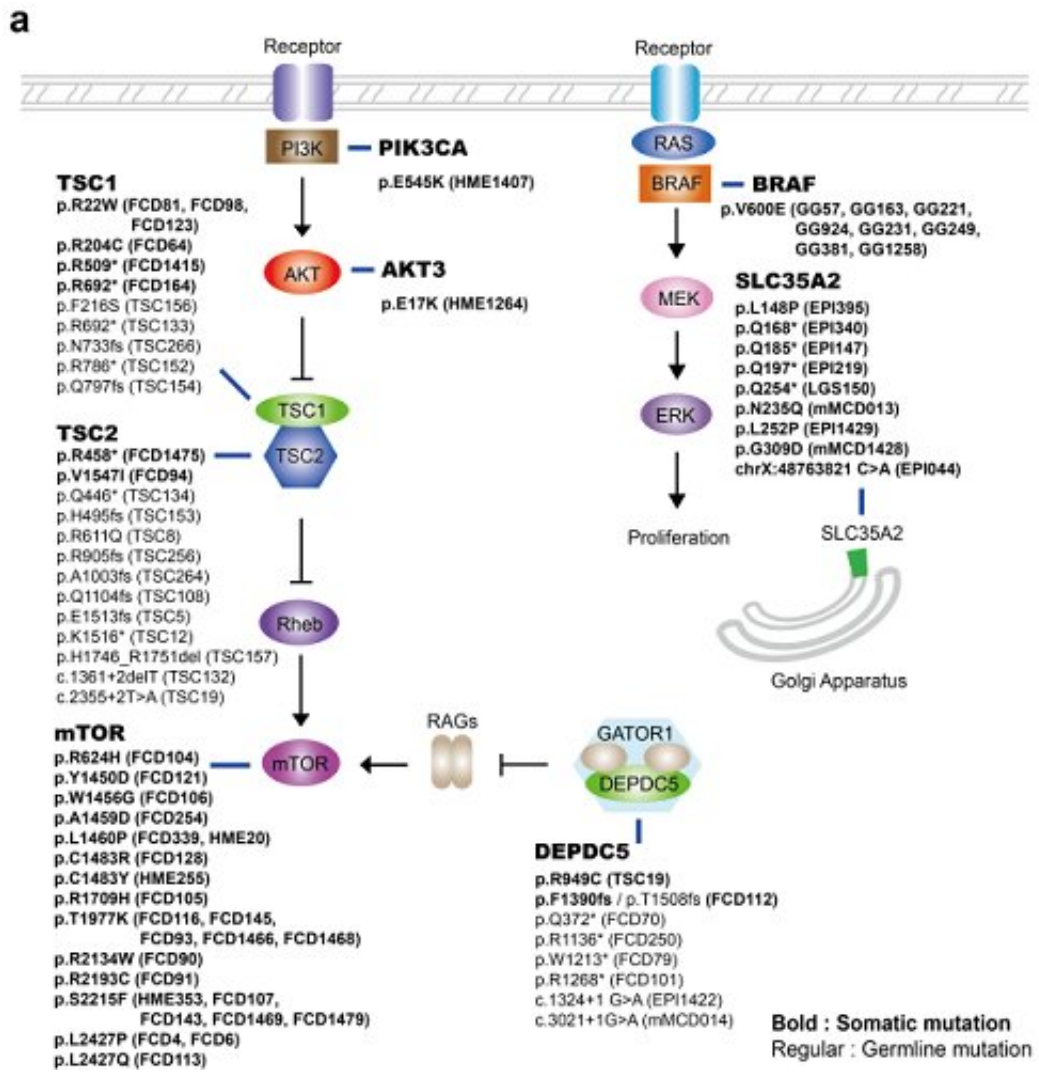

Landscape of somatic and germline mutations identified in intractable epilepsy patients. a Signaling pathways for all of the mutated genes identified in this study. Bold: somatic mutation, Regular: germline mutation. b The distribution of variant allelic frequencies (VAFs) of identified somatic mutations. c The

detecting rate and types of identified mutations according to histopathology. Yellow: somatic mutations, green: two-hit mutations, grey: germline mutations. Credit: KAIST

KAIST medical scientists have developed an advanced method for perfectly detecting low-level somatic mutation in patients with intractable epilepsy. Their study showed that deep sequencing replicates of major focal epilepsy genes accurately and efficiently identified low-level somatic mutations in intractable epilepsy.

According to the study, their diagnostic method could increase the accuracy up to 100%, unlike the conventional sequencing analysis, which stands at about 30% accuracy. This work was published in *Acta Neuropathologica*.

Epilepsy is a neurological disorder common in children. Approximately one third of child patients are diagnosed with intractable epilepsy despite adequate anti-epileptic medication treatment.

Somatic mutations in mTOR pathway genes, SLC35A2, and BRAF are the major genetic causes of intractable epilepsies. A clinical trial to target Focal Cortical Dysplasia type II (FCDII), the mTOR inhibitor is underway at Severance Hospital, their collaborator in Seoul, Korea. However, it is difficult to detect such somatic mutations causing intractable epilepsy because their mutational burden is less than 5%, which is similar to the level of sequencing artifacts. In the clinical field, this has remained a standing challenge for the genetic diagnosis of somatic mutations in intractable epilepsy.

Professor Jeong Ho Lee's team at the Graduate School of Medical Science and Engineering analyzed paired brain and peripheral tissues

from 232 intractable epilepsy patients with various brain pathologies at Severance Hospital using deep sequencing and extracted the major focal epilepsy genes.

They narrowed down target genes to eight major focal epilepsy genes, eliminating almost all of the false positive calls using deep targeted sequencing. As a result, the advanced method robustly increased the accuracy and enabled them to detect low-level somatic mutations in unmatched Formalin Fixed Paraffin Embedded (FFPE) brain samples, the most clinically relevant samples.

Professor Lee conducted this study in collaboration with Professor Dong Suk Kim and Hoon-Chul Kang at Severance Hospital of Yonsei University. He said, "This advanced method of genetic analysis will improve overall patient care by providing more comprehensive genetic counseling and informing decisions on alternative treatments."

Professor Lee has investigated low-level somatic mutations arising in the brain for a decade. He is developing innovative diagnostics and therapeutics for untreatable brain disorders including intractable epilepsy and glioblastoma at a tech-startup called SoVarGen. "All of the technologies we used during the research were transferred to the company. This research gave us very good momentum to reach the next phase of our startup," he remarked.

More information: Nam Suk Sim et al, Precise detection of low-level somatic mutation in resected epilepsy brain tissue, *Acta Neuropathologica* (2019). DOI: 10.1007/s00401-019-02052-6

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