A somatic mutation is a change in the DNA sequence of a somatic cell of a multicellular organism with dedicated reproductive cells; that is, any mutation that occurs in a cell other than a gamete, germ cell, or gametocyte

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An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases.

Low-level somatic mutations have been shown to be the major genetic etiology of intractable epilepsy. The extents thereof, however, have yet to be systematically and accurately explored in a large cohort of resected epilepsy brain tissues. Moreover, clinically useful and precise analysis tools for detecting low-level somatic mutations from unmatched formalin-fixed paraffin-embedded (FFPE) brain samples, the most clinically relevant samples, are still lacking. In total, 446 tissues samples from 232 intractable epilepsy patients with various brain pathologies were analyzed using deep sequencing (average read depth, 1112x) of known epilepsy-related genes (up to 28 genes) followed by confirmatory site-specific amplicon sequencing. Pathogenic mutations were discovered in 31.9% (74 of 232) of the resected epilepsy brain tissues and were recurrently found in only eight major focal epilepsy genes, including AKT3, DEPDC5, MTOR, PIK3CA, TSC1, TSC2, SCL35A2, and BRAF. Somatic mutations, two-hit mutations, and germline mutations accounted for 22.0% (51), 0.9% (2), and 9.1% (21) of the patients with intractable epilepsy, respectively. The majority of pathogenic somatic mutations (62.3%, 33 of 53) had a low variant allelic frequency of less than 5%. The use of deep sequencing replicates in the eight major focal epilepsy genes robustly increased PPVs to 50-100% and sensitivities to 71-100%. In an independent FCDII cohort of only unmatched FFPE brain tissues, deep sequencing replicates in the eight major focal epilepsy genes identified pathogenic somatic mutations in 33.3% (5 of 15) of FCDII individuals (similar to the genetic detecting rate in the entire FCDII cohort) without any false-positive calls. Deep sequencing replicates of major focal epilepsy genes in unmatched FFPE brain tissues can be used to accurately and efficiently detect low-level somatic mutations, thereby improving overall patient care by enriching genetic counseling and informing treatment decisions [1)].

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Sim NS, Ko A, Kim WK, Kim SH, Kim JS, Shim KW, Aronica E, Mijnsbergen C, Spliet WGM, Koh HY, Kim HD, Lee JS, Kim DS, Kang HC, Lee JH. Precise detection of low-level somatic mutation in resected epilepsy brain tissue. Acta Neuropathol. 2019 Aug 3. doi: 10.1007/s00401-019-02052-6. [Epub ahead of print] PubMed PMID: 31377847.