



Recessive LAMC3 mutations cause malformations of occipital cortical development

Tanyeri Barak; Angeliki Louvi; Hande Kaymakcalan-Celebiler; Saliha Yilmaz; Mehmet Bakircioglu; Ahmet Okay Caglayan; Ali Kemal Ozturk MD; Katsuhito Yasuno; Kaya Bilguvar MD; Murat Gunel MD

Introduction

The cerebral cortex develops through a series of highly coordinated phases including proliferation of neural progenitors, migration of postmitotic cells from the germinal matrix to the newly forming cortex and organization of the mature cortical cytoarchitecture. The study of malformations of cortical development that interfere with the proper formation of the typical cortical gyration pattern in humans provides a unique opportunity to understand this elegant process.

Methods

We applied homozygosity mapping followed by whole-exome capture and sequencing to identify the underlying genetic cause in consanguineous, single-affected-member Turkish kindreds with malformations of occipital cortex gyration, notably characterized by the presence of both pachygyria and polymicrgyria.

Learning Objectives

By the conclusion of this session, participants should be able to have an insight into the genetic basis of malformations of human occipital cortical development.

Results

We have identified independent, novel homozygous and compound heterozygous deleterious mutations in LAMC3 in three such kindreds. LAMC3 demonstrated species specific expression profile during cerebral cortical development. Additionally we showed that, in humans, its expression was more prominent within the temporo-occipital lobes as compared to frontal regions and it paralleled that of genes known to be expressed during the period of dendritogenesis within visual cortex during late fetal and early post-natal periods.

Conclusions

Mutations in LAMC3 have not previously been reported. We have shown that recessive LAMC3 mutations cause human occipital cortical malformations characterized by complex gyration abnormalities. Further studies are needed to identify other molecules involved in the intricate process of cortical organization and to understand why the phenotype associated with LAMC3 mutations is restricted to the occipital lobes.

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