Exploring the Genetic Basis of Focal Cortical Dysplasia Type 1

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COLLÉGIAL INTERNATIONAL SAINTE-ANNE

Abstract

Focal cortical dysplasia (FCD) Type I—a localized brain abnormality—is a poorly understood cause of pediatric drug-resistant epilepsy (DRE).[2,3,4] This study explores the potential role of *SLC35A2* gene mutations in FCD Type I and potential age and gender influences. DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) brain tissue, followed by a two-step polymerase chain reaction (PCR) and gel electrophoresis. Amplicon sequencing was then carried out on two patient samples, revealing four *SLC35A2* variants after filtering: two classified as benign and two as variants of uncertain significance (VUS). Table 1 summarizes the genetic variants, while Figure 2 presents the cohort's clinical data. Although no pathogenic variants were identified, the VUS findings remain noteworthy.

Introduction

This study aims to investigate the presence of somatic mutations in the *SLC35A2* gene in pediatric patients with FCD I.

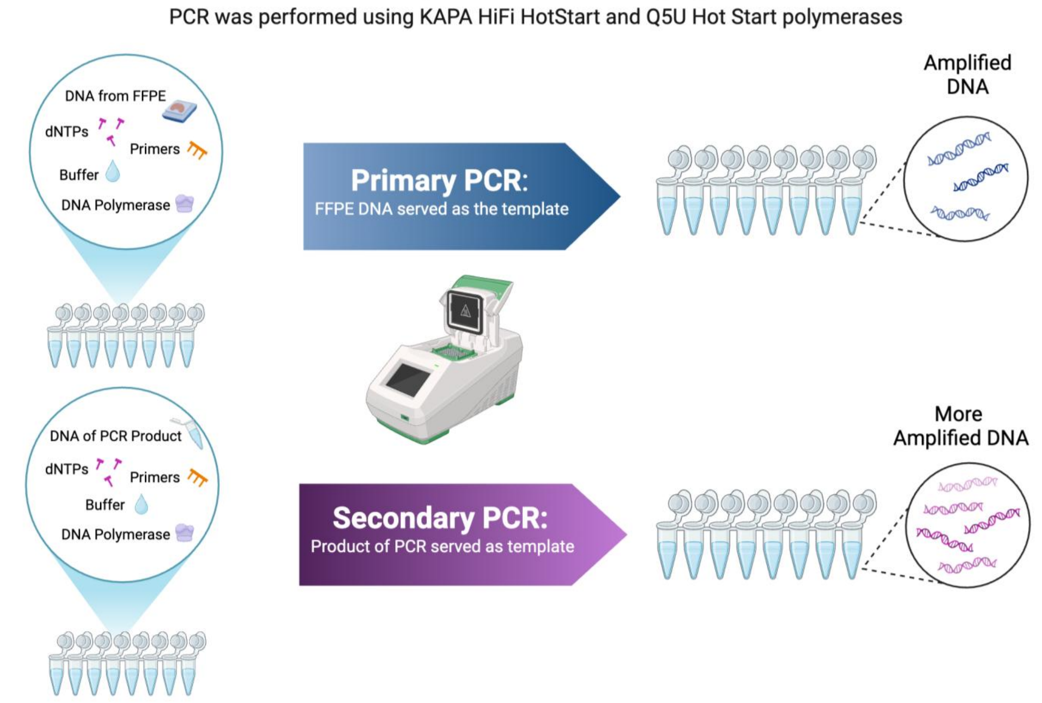
- The *SLC35A2* gene encodes a UDP-galactose translocator critical for glycosylation, a process essential for proper neuronal function and brain development.[1,6,7]
- Mutations in *SLC35A2* may disrupt glycosylation, leading to abnormal cortical organization observed in FCD I.[1,5]

Materials & Methods

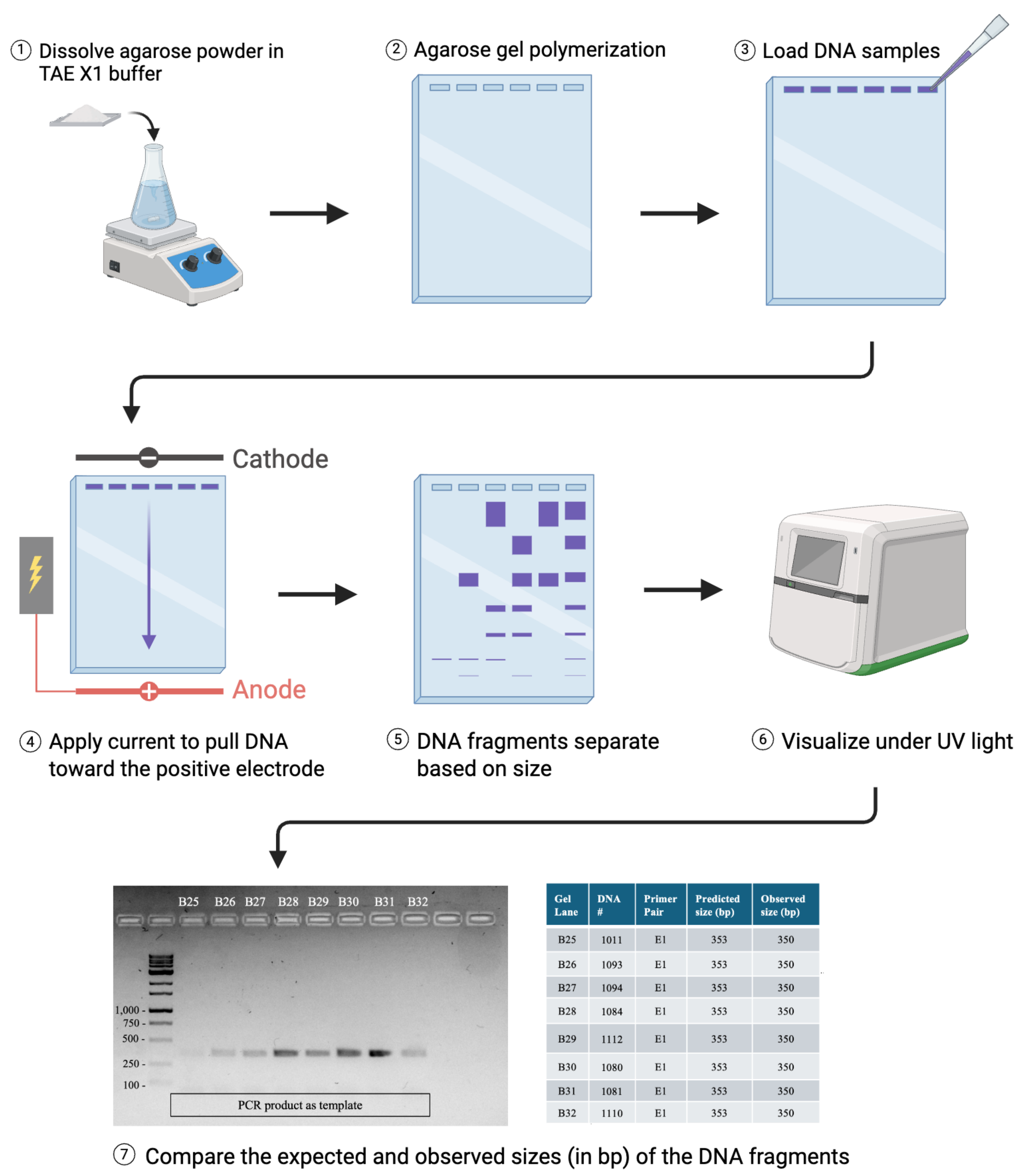
Resected brain tissue was collected from 25 pediatric DRE patients at the Montreal Children's Hospital and The Neuro between 1998 to 2022. Tissue was paraffin-embedded and sectioned at 7 µm. Genomic DNA was extracted using the QIAamp DNA FFPE Advanced Kit (Qiagen), optimized for degraded samples.

Two-step PCR Approach

PCR was performed using KAPA HiFi HotStart and Q5U Hot Start polymerases



Agarose Gel Electrophoresis



Images were generated using *BioRender* @Briana Lalla 2025

Results

Table 1. Summary of Variants Identified in the *SLC35A2* Gene using *VarSome*

DNA-ID	Position	Alleles	Sample_ Depth	Sample_ Depth_Ref	Sample_ Depth_Alt	Sample _Alt_Af	SELECT_HGVS_P	DBSNP_ID	ACMG Classification
1036-E1	chrX:48911633	C/T	48942	47724	1218	0.025	NM_005660.3:p.Ala2Thr	Rs1236879702	Likely Benign
1036-E4C	chrX:48904699	C/A	22575	21722	853	0.038	NM_005660.3:p.Gly207Val	None	Likely Benign
1036-E4C	chrX:48904888	G/T	25487	24725	762	0.03	NM_005660.3:p.Pro341Thr	None	Uncertain Significance
1037-E4C	chrX:48904736	C/A	25826	25549	277	0.011	NM_005660.3:p.Gly195Cys	None	Uncertain Significance

Variants were classified by clinical significance following ACMG guidelines, showing uncertain or likely benign impact.

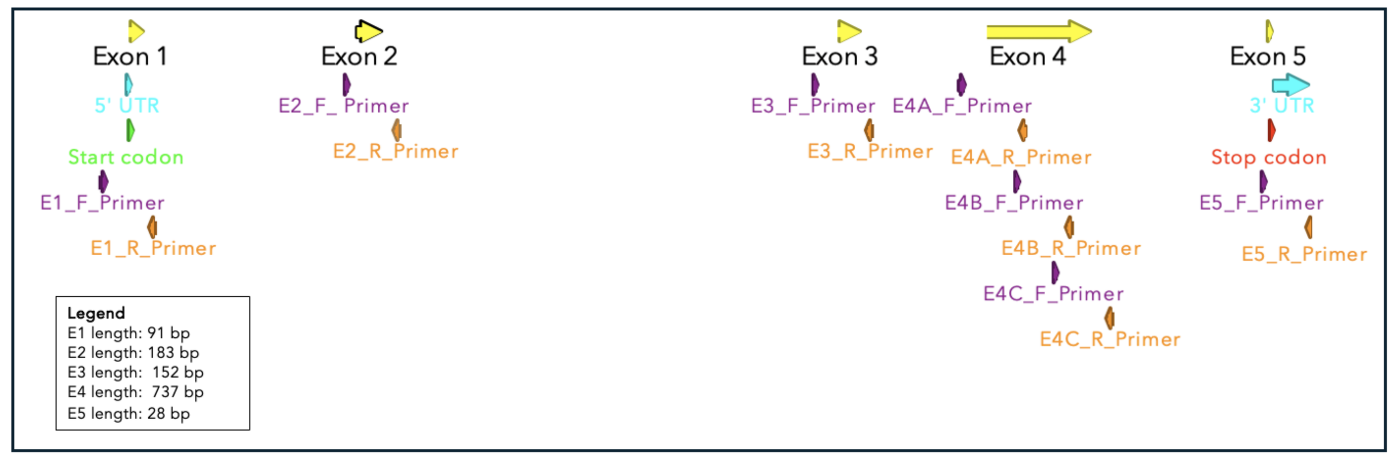


Figure 1. Annotation of the *SLC35A2* Gene Sequence. *The figure shows the SLC35A2 gene with five exons (exon 4 being the largest), 5' and 3' UTRs, start and stop codons, and primer binding sites used for PCR amplification, created with Plasmid Editor.*

Number of patients	25
Male:Female	15:10
Age at Seizure Onset	
One epilepsy surgery	25
Two epilepsy surgeries	10
Histopathology FCD1	
First surgery	16
Second surgery	6

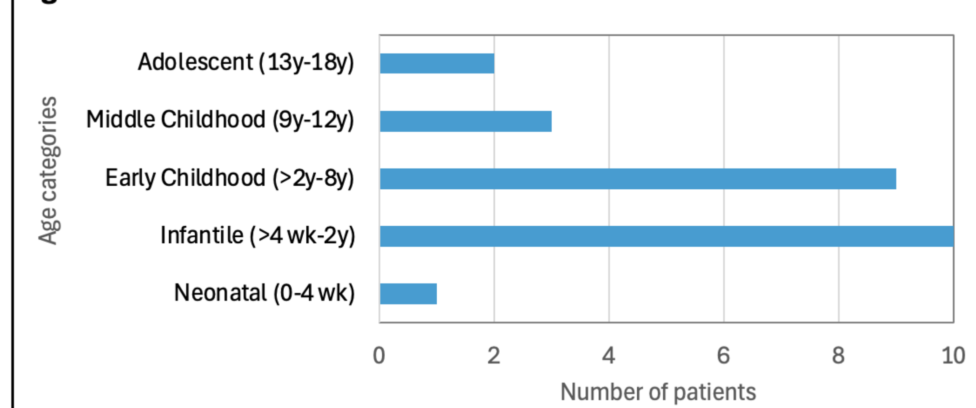


Figure 2. Clinical Information. *Inclusion criteria consisted of male and female patients with a post-surgical diagnosis of FCD 1. The average age at seizure onset was 3.3 years, and the average age at resection was 11.4 years.*

Conclusions

Two *SLC35A2* variants identified are benign, while two are of uncertain significance (VUS) with unclear impact.[9] No clinical data, including age and gender, showed any link to these variants.[3,5,10] Studying VUS remains important for improving genetic diagnosis and patient care.[8] These findings enhance understanding of *SLC35A2* in FCD Type I and highlight the need for further research to clarify their clinical relevance.

Future Works

The next phase of this project will involve sequencing the remaining patients' amplified DNA to identify mutations in the *SLC35A2* gene. This analysis will help further explore *SLC35A2* variants' contributions to the pathogenesis of FCD Type I.

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