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SLC35A2 somatic variants in drug resistant epilepsy: FCD and MOGHE

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Abstract

De novo somatic (post-zygotic) gene mutations affecting neuroglial progenitor cell types in embryonic cerebral cortex are increasingly identified in patients with drug resistant epilepsy (DRE) associated with malformations of cortical development, in particular, focal cortical dysplasias (FCD). Somatic variants in at least 16 genes have been linked to FCD type II, all encoding components of the mechanistic target of rapamycin (mTOR) pathway. FCD type II is characterized histopathologically by cytomegalic dysmorphic neurons and balloon cells. In contrast, the molecular pathogenesis of FCD I subtypes is less well understood, and histological features are characterized by alterations in columnar or laminar organization without cytomegalic dysmorphic neurons or balloon cells. In 2018, we reported somatic mutations in Solute Carrier Family 35 member A2 (SLC35A2) linked to DRE underlying FCD type I and subsequently to a new histopathological phenotype: excess oligodendrocytes and heterotopic neurons in subcortical white matter known as MOGHE (mild malformation of cortical development with oligodendroglial hyperplasia). These discoveries opened the door to studies linking somatic mutations to FCD. In this review, we discuss the biology of SLC35A2 somatic mutations in epilepsy in FCD and MOGHE, and insights into SLC35A2 epilepsy pathogenesis, describing progress to date and critical areas for investigation.

Keywords

Glycosylation; Somatic; Cortical malformations; Focal cortical dysplasia; Epilepsy

De novo somatic (post-zygotic) gene mutations affecting a limited number of neuroglial progenitor cell types in the embryonic cerebral cortex are increasingly identified in patients with drug resistant epilepsy (DRE) associated with malformations of cortical development (MCD), in particular, focal cortical dysplasias (FCD). Somatic variants in at least 16 genes

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encoding components of the mechanistic target of rapamycin (mTOR) pathway have been linked to FCD type II and hemimegalencephaly (HME) (Bedrosian et al., 2022). More recently, pathogenic somatic variants in *NF1*, which is part of the Ras/MAPK pathway, have been identified in FCD type II (Lopez-Rivera et al., 2023). FCD type II is characterized histopathologically by cytomegalic dysmorphic neurons and balloon cells according to the International League Against Epilepsy classification system (Najm et al., 2022). In contrast, the molecular pathogenesis of FCD subtypes Ia-Ic is less well understood and the histological features are distinct from FCD type II i.e., alterations in columnar or laminar organization without cytomegalic dysmorphic neurons or balloon cells. Somatic mutations in Solute Carrier Family 35 member A2 (SLC35A2) were first linked to DRE (Winawer et al., 2018) in association with FCD type I and subsequently with a new histopathological phenotype characterized by excess numbers of oligodendrocytes and heterotopic neurons in the subcortical white matter known as MOGHE (mild malformation of cortical development with oligodendroglial hyperplasia; see below). The identification of SLC35A2 as causative in FCD type I opened the door to new studies linking somatic mutations in other genes to FCD I (Lai et al., 2022).

1. SLC35A2 biology

SLC35A2 (OMIM300896) is located on chromosome Xp11.23 and encodes the protein UGT-1. SLC35A2 is part of the larger SLC35 family of nucleotide sugar transporters (NSTs) such as the UDP-GlcNAc (NGT) and UDP-galactose transporters (UGT) that shuttle sugar moieties (N-and O-glycans) across subcellular membranes into subcellular organelles i.e., the Golgi apparatus and endoplasmic reticulum. N-and O-glycans contribute to the structural integrity of cells, protect glycoproteins against proteolysis, enable correct polypeptide and protein folding, and direct the correct subcellular location of glycoproteins. SLC35A2 is an 8.8 kb transcript (with up to 8 spliced transcripts), encoding 396 amino acids in UGT-1 (~41kD). UGT-1 is a uridine diphosphate (UDP)-galactose translocator located within the Golgi apparatus membrane as a transmembrane protein, and depending on the transcript variant, is predicted to have 1–8 transmembrane regions (Fig. 1). Immunocytochemical studies show predominantly cytoplasmic and Golgi membrane localization of UGT-1 (Olczak et al., 2013). Specifically, UGT-1 functions to transport galactose bound to UDP into the Golgi lumen so that galactose moieties may be added post-translationally to newly synthesized proteins and lipids. The addition of galactose to individual proteins has pivotal effects on cellular transport, localization, and protein binding. SLC35A2 RNA can be detected at low to moderate levels ubiquitously across organ systems and in the brain (Figs. 2 and 3). UGT-1 protein is expressed at highest levels in neurons, and lowest levels in glial cells.

2. Role of SLC35A2 in epilepsy

Recessive disorders involving N-glycosylation defects in humans (e.g., *PMM2-, ALG6-,* and *SRD5A3*-linked conditions) typically lead to severe neurologic abnormalities including DRE, hypotonia, epileptic encephalopathy, and intellectual disability (Paprocka et al., 2021) as well as non-neurological issues such as cardiomyopathy, liver disease, craniofacial dysmorphism, and scoliosis (see Lipinski and Tylki-Szymanska, 2021). Germline SLC35A2

variants (loss-of-function) have been linked to a congenital disorder of glycosylation (SLC35A2-CDG) characterized clinically by a broad neurological phenotype including intellectual disability, hypotonia, epileptic spasms, and DRE. Brain MRI in SLC35A2-CDG individuals may show cerebellar atrophy, thinning of the corpus callosum, abnormal myelination, cerebral atrophy and ventriculomegaly. Cortical visual impairment, retinitis pigmentosa, nystagmus and strabismus are reported. Other affected organ systems include the liver, spleen, and kidney. Because SLC35A2 is an X-linked gene, most affected individuals are female and many males die from seizures or other causes. Indeed, a majority (83%) of SLC35A2-CDG patients have infantile onset epilepsy, hypotonia, intellectual disability, as well as cardiac and skeletal abnormalities (Ng et al., 2019); in this case series, all SLC35A2 variants localized to regions within one of the ten hydrophobic transmembrane domains suggesting a key disruption of transmembrane domain organization and likely, membrane transport of galactose by UGT-1.

Based on the postulated pathogenic mechanism of defective galactose transport for SLC35A2-CDG, supplementation with galactose seems a logical therapeutic consideration for SLC35A2-CDG individuals. A single case report in genotype confirmed SLC35A2-CDG patients ($n = 10$) showed improvement in the Nijmegen CDG rating scale score including a reduction in seizures in response to oral D-galactose supplementation (1.5 g/kg/day) (Witters et al., 2020). Galactose supplementation improved the glycosylation profile of fully formed glycans and fully galactosylated N-glycans suggesting a biochemical effect of galactosylation. Clearly, larger and studies are needed to assess the effectiveness of galactose therapy in SLC35A2-CDG patients and potentially for individuals with seizures resulting from somatic SLC35A2 variants.

3. Somatic SLC35A2 mutations and FCD

Somatic mutations occurring in neuroglial progenitor cells during embryonic cortical development have been shown to result in formation of FCD type II and HME. Previous studies identified somatic mutations in mTOR pathway genes (MPG) e.g., *PI3kinase, AKT3,* and *MTOR* in FCD IIA and IIB and HME specimens at low to medium allelic frequency (Lim and Lee, 2016; Talos et al., 2012). Somatic mutational analysis in resected brain FCD II and HME tissue specimens provided the experimental paradigm to investigate FCD I.

Somatic SLC35A2 variants were identified for the first time in resected brain tissue from children and adults with DRE using next-generation sequencing approaches (Winawer et al., 2018). Pathogenic SLC35A2 variants were detected in 5/56 individuals with DRE who underwent epilepsy surgery. SLC35A2 variants found in brain in these patients were not present in leukocyte DNA confirming the somatic nature of the variants. Five distinct variants were reported with mutational burden (variant allele frequency, VAF) varying from 3 to 46%; two were missense variants, and one each insertion, deletion, and duplication mutations. Software analysis posited all SLC35A2 mutations as loss-of-function mutations that would reduce or abolish UGT-1 function and disrupt intracellular transport of UDP-galactose. Histopathological analysis in this cohort showed FCD Ia in two cases, excessive gliosis in 2 cases, and normal cytoarchitecture in 1 case. These findings were completely novel and provided for the first time a causative genetic link as well as a molecular

mechanism to account for FCD Ia. Subsequently, nonsense and splicing site SLC35A2 variants were reported in 6 individuals with DRE where histopathology showed mild MCD (mMCD) and gliosis similar to findings reported by Winawer et al. (Sim et al., 2018). Biochemical glycosylomic analysis of the resected tissue in this cohort showed aberrant N-glycosylation profiles in the SLC35A2 cases supporting the idea that SLC35A2 mutations resulted in altered UGT-1 function. In another analysis, 4 of 14 patients (29%) with DRE and neuropathological findings of mMCD or FCD I were found to have a somatic loss of function SLC35A2 variant (Baldassari et al., 2019). In this cohort, somatic mutations in the mTOR pathway predominated in samples revealing FCD II, underscoring the importance of SLC35A2 mutations in malformations characterized by FCD I or mMCD. Though a small clinical sample size, patients with a higher VAF seemed to exhibit a more severe clinical phenotype i.e., more severe epilepsy and more expansive structural abnormalities on neuroimaging.

In a single 3 year old male with infantile spasms and tonic seizures, targeted sequencing of 12 brain regions following surgical resection spanning left temporal lobe, left amygdala, left hippocampus, left inferior parietal lobe, and left occipital lobe revealed a pathogenic, previously reported SLC35A2 variant (NM_005660.3:c.634_ 635delTC; p. Ser212LeufsTer9) with variant allele frequency across the resected tissues of 4.2%–19.5% (Miller et al., 2020). In this case, the proportion of the SLC35A2 variant correlated with severity and location of EEG and neuro-imaging abnormalities for each tissue region analyzed. Interestingly, histopathological analysis of areas containing the SLC35A2 variants revealed FCD Ic (combination of type Ia and Ib features). This study demonstrated that there may be high regional variability to SLC35A2 VAF detection and likely a “dose” effect of variant enrichment and severity of pathology.

4. SLC35A2: FCD and MOGHE

In the original paper linking SLC35A2 variants with DRE (Winawer et al., 2018), while 3/5 cases did not exhibit radiographic abnormalities suggestive of FCD, 2/5 cases were interpreted as “possible FCD”. Furthermore, subsequent histopathological analysis revealed FCD Ia in 2 cases and either “no lesion” or “gliosis” in the remaining 3 specimens. Interestingly, up to 25% of epilepsy surgery specimens are histopathologically classified as non-lesional i.e., no evidence for structural abnormality to account for seizures. In a histopathological series of 1381 resected epilepsy surgery brain specimens, 52 frontal lobe epilepsy cases could not be histopathologically classified and were considered non-lesional (3.7%; Schurr et al., 2017). Interestingly, an increase of Olig2-, and PDGFR-alpha-immunoreactive oligodendroglia was observed in white matter and deep cortical layers in 22 of these patients (42%) as well as heterotopic neurons in white matter. These findings were characterized histopathologically as “mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE).”

Subsequent studies have indicated that MOGHE is a new MCD subtype (Najm et al., 2022) with histopathological hallmarks including increased numbers of oligodendroglial cells within deep cortical layers and white matter, and patchy areas of hypomyelination, occurring most commonly in the frontal lobe. MOGHE is also characterized by the presence

of numerous heterotopic neurons in the subcortical white matter. Radiographically, MOGHE can be divided into 2 subtypes on brain MRI: subtype I exhibits increased laminar T2 and fluid attenuated inversion recovery (FLAIR) signal at the corticomedullary junction, and subtype II shows reduced corticomedullary differentiation because of increased signal of the adjacent white matter (Hartlieb et al., 2019). Interestingly, distribution of subtypes was found to be age-related, with subtype I occurring in patients between 1.5 and 5.1 years and subtype II occurring between 3.4 and 20.7 years of age, suggesting that MRI characteristics of MOGHE patients change from subtype I to II with age, likely due to neurodevelopmenal maturation of myelination.

Neuropathological analysis of brain tissue resected from somatic SLC35A2-associated individuals across cohorts (Sim et al., 2018; Winawer et al., 2018; Baldassari et al., 2019) consistently shows FCD Ia, mMCD, and/or excessive gliosis, even when pre-operative brain MRI was unremarkable. Histologically, FCD Ia is classified by abnormal radial organization of cortical neurons, where there are visible ‘chains’ of neurons aligned radially within the cortex as opposed to dispersed appropriately within the cortical layers. In contrast, mMCD shows much more subtle changes in lamination. On retrospective consideration, the glial cells observed in these cases may represent oligodendrocytes, and thus a MOGHE phenotype. To further assess this possibility, a recent cohort (Bonduelle et al., 2021) was assembled comprised of 20 pediatric patients with DRE following epilepsy surgery carrying a histopathological diagnosis of MOGHE and an international sample of 43 patients classified as either mMCD, FCD, unclassified FCD, or inconclusive cases ascertained at several sites in the EU between 2013 and 2019. MOGHE was defined histopathologically using 3 criteria: 1) clusters of increased oligodendroglial cell density, 2) patchy areas of hypomyelination, and 3) heterotopic white matter neurons. Among the 20 patients within the MOGHE cohort, 9 patients exhibited preoperative MRI characteristics consistent with MOGHE (subtype I with an increased laminar T2 and FLAIR signal at the corticomedullary junction or subtype II with reduced corticomedullary differentiation because of increased signal of the adjacent white matter). These 9 patients (5 M, 4 F) of the MOGHE cohort were identified as having somatic SLC35A2 variants with VAFs ranging from 7 to 52%. Within the 43 patients from the international MCD cohort in this report, 18 patients were found to have brain somatic variants in SLC35A2 and these cases underwent neuropathological reassessment, blind to initial histopathology and genetic diagnosis (by review of hematoxylin/eosin, and immunohistochemical staining for NeuN and Olig2). In 17/18 of these cases with a brain somatic SLC35A2 variant, the pathology was confirmed to be MOGHE. In the non-SLC35A2 cases, MOGHE was not identified. Importantly, laser capture droplet digital PCR was performed on single microdissected neurons and oligodendrocytes from MOGHE tissue from a single patient and revealed that clusters of glial cells (average of 36.5%) as well as heterotopic neurons (average of 8.7%) expressed a higher SLC35A2 VAF when compared to normal neurons. In fact, nearly half of Olig2+ cells that were found in clusters within the white matter carried the SLC35A2 variant.

Recent case reports have bolstered the link between MOGHE as a new pathologic entity linked to SLC35A2 variants. For example, a 17-year-old male was found to have two areas of brain abnormality (blurred gray-white matter) seen on 7 T MRI that corresponded to areas of ictal onset (Xu et al., 2023). Sequencing analysis of one resected brain region identified a

previously unreported missense variant in exon 1 of SLC35A2 gene (p.Glu24Gly) while analysis of the other resected regions did not reveal a SLC35A2 variant. Histological analysis of the SLC35A2-containing lesion revealed MOGHE. Two patients with “temporal-plus” epilepsy and biopsy-proven MOGHE have been reported demonstrating that MOGHE need not be limited only to the frontal lobe (Garganis et al., 2019). They suggested that when “temporal-plus” epilepsies present with normal hippocampi or subtle T2/FLAIR abnormalities only on MR, and refractory epilepsy, MOGHE should also be considered.

A recent study provided important insights into the genotype-phenotype associations in SLC35A2 somatic mutations (Barba et al., 2023). This retrospective, multicenter analysis of 47 patients who underwent surgery for DRE associated with somatic SLC35A2 variants (including the initial cohort of 5 individuals reported by Winawer et al., 2018 revealed wide phenotypic variability. The cohort was comprised of 47 patients (18 F), with an average age at seizure onset of 3 years (range of 3 months-24 years). The study assessed the general clinical phenotypes of subjects i.e. sex, age during surgeries/surgery history, neurological examination, cognitive assessment, seizure types, interictal and ictal scalp EEG findings, results of intracranial EEG recordings (if available), neuroimaging findings, surgical treatment history, histopathology, follow-up duration, postoperative interictal scalp EEG, postoperative seizure outcome, anti-seizure medication (ASM) history, cognitive outcome at follow up, and genetic findings on brain tissue i.e., SLC35A2 variant type and pathogenicity. In this series, patients with brain somatic SLC35A2 variants were identified as either epileptic encephalopathy (EE) or drug-resistant focal epilepsy (DR-FE). The 39 patients that were classified as early EE patients also exhibited epileptic spasms and moderate to severe intellectual disability, whereas 8 patients were identified with DR-FE with normal/borderline normal cognitive function and deficits in specific neuropsychological areas such as visuospatial, memory, or executive function. Individuals classified as EE exhibited abnormal MRIs and interictal EEGs showed slowing and/or disorganized background activity. About half of patients with DR-FE exhibited abnormal MRIs, and most DR-FE patients showed lateralized focal or multifocal, epileptiform abnormalities on interictal EEGs (along with normal background activity). Most of the patients (39/47, 83%) had an EE with early age at onset (3 months–3.5 years) characterized by epileptic spasms and possibly other seizure types. The DR-FE (8/47, 17%) had seizure onset in adolescence or adulthood. There were a spectrum of brain MRI findings including normal imaging (without an identified abnormality thought to be responsible for the patient’s seizures), focal cortical thickening, blurring of the gray/white matter junction, and laminar subcortical white matter hyperintensities on T2/fluid-attenuated inversion recovery (FLAIR) sequences. Nearly all patients had some degree of cognitive impairment, but it was mild in patients with DR-FE and moderate or severe in half of those with EE. Most of the participants (33/47, 70%) had a lobectomy whereas others had a either hemispherectomy or in contrast, a more limited resection. Post-surgical seizure freedom was achieved in 61.5% of patients with EE and 37.5% of patients with DR-FE, although post-operative cognitive performances remain unchanged in most patients; at 3 year follow up, 30/47 (64%) patients were deemed Engel class I. Among the cohort, histopathological analysis showed MOGHE in 44/47 patients. 42 patients expressed distinct mosaic SLC35A2 variants, (14 missense, 13 frameshift, 10 nonsense, 4 in-frame deletions/duplications, and 1 splicing variant) with VAFs ranging

from 1.4%–52.6%. However, histopathological or genetic differences between the 2 clinical subgroups (EE and DR-FE) were not identified.

5. SLC35A2 epilepsy pathogenesis

Currently, studies assessing SLC35A2 somatic mosaic brain variants have focused on gene discovery and the clinical phenotype of individuals with DRE. Unfortunately, the molecular pathogenesis of SLC35A2-associated DRE remains poorly understood. Studies examining expression of *Slc35a2* variants in murine N2a cells in vitro show aberrant glycosylation profiles and Golgi localization of UGT-1 (Li and Mukhopadhyay, 2019), although some do not (Kodera et al., 2013). SLC35A2 mutations engineered in CHO-Lec8 cells in vitro result in in deficiencies in galactose and sialic acid residues on proteins (Ng et al., 2019). To date, there is little understanding of how changes in N-glycosylation of proteins or lipids lead to the formation of an epileptic network. Clearly, in germline CDG, the effects of altered N-glycosylation on neural synchrony and firing are profound and likely result from changes in post-translational modification of proteins that modulate neural activity i. e., ion channels, neurotransmitter receptor subunits, that often are post-translationally modified by glycosylation, phosphorylation or other moieties. There are thousands of proteins relevant to neural activity that could be affected by loss of UGT-1 function and thus, a more thorough glycomics investigation will be necessary. In cohort of 15 SLC35A2-CDG individuals, CDG screening showed abnormal glycosylation for nine out of 15 patients (60%) (Vais et al., 2019). Mass Spectroscopy showed a characteristic loss of galactose in seven patients but interestingly, the N-glycosylation profiles were normal in some individuals even with known pathogenic SLC35A2 variants. In DRE caused by somatic SLC35A2 variants, there is the added effect of alterations in cortical structure i.e., FCD type I or MOGHE. SLC35A2 variants induce a range of histopathology from FCD I to MOGHE and very likely these changes in cortical cytoarchitecture could affect circuitry and network integrity. One curious feature of MOGHE is the apparent proliferation of oligodendrocytes in the sub-cortical white matter beneath the FCD. Laser capture microdissection and subsequent gene sequencing has identified SLC35A2 variants in oligodendrocytes suggesting that cell autonomous effects of loss of UGT1 might contribute to oligodendrocyte overgrowth. A key area of research will be to define the population of progenitor cells in which somatic SLC35A2 mutations occur. Furthermore, establishing how oligodendrocyte proliferation is linked to establishment of the epileptic network and how this pathological finding is additive to the detection of heterotopic neurons or FCD I remains a critical area of investigation.

6. Future implications

SLC35a2 variants have been identified as a common cause of neocortical epilepsy associated with FCD1A and MOGHE (Fig. 4). Several key questions remain that might have direct implications for patient care. First, more work will be needed to determine if *SLC35a2* variants can be detected in a clinical setting prior to surgical resection i. e., from a patient's explanted sEEG electrodes, blood or cerebrospinal fluid samples. If so, this would inform the molecular cause of a patient's epilepsy and could be used to predict clinical course, response to ASMs, and potentially, surgical outcomes. Pre-surgical diagnosis could also allow the application of directed therapies for those with *SLC35a2* variants, including

clinical trials, without the need for surgical resection and brain biopsy. Second, since the function of UGT-1 is known as a galactose transporter, it seems logical to consider whether oral or parenteral supplementation with galactose might mitigate seizure frequency or severity and serve as a potential disease modifying therapy in clinical trials. In children or adults prior to onset of epilepsy, the clinical identification of *Slc35a2* variants might prompt preventive treatment i. e., galactose supplementation. Finally, a key direction for research will be defining the effects of dysfunctional galactose transport on post-translational protein modification and the establishment of the epileptic network.

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Data availability

No data was used for the research described in the article.

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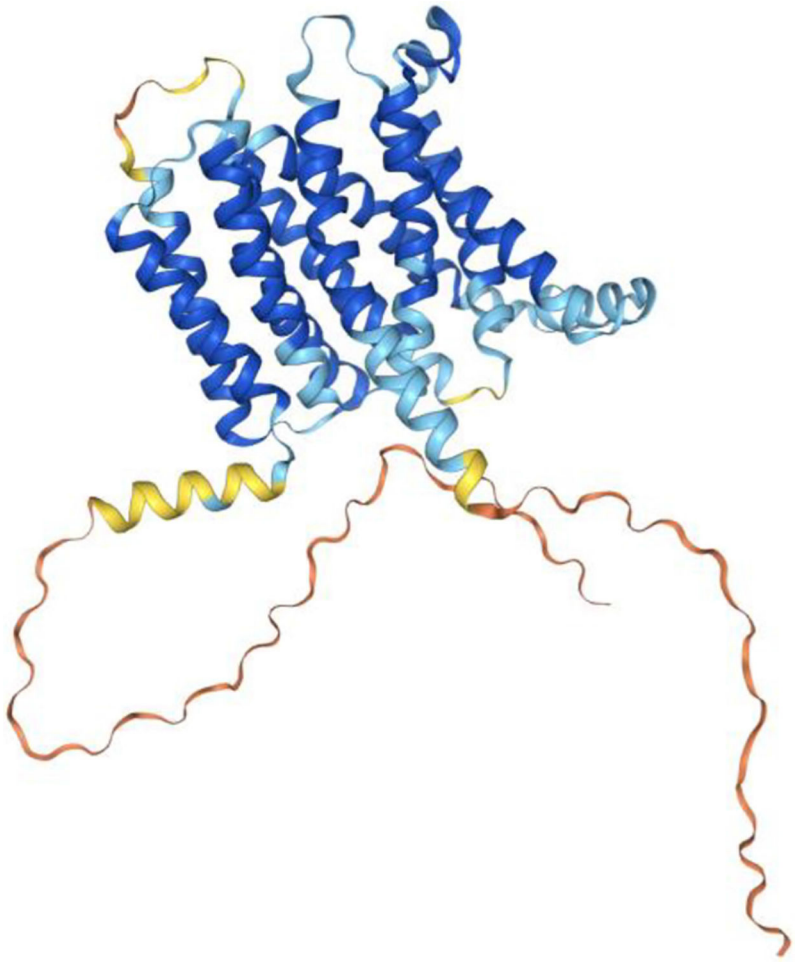

Fig. 1.
Predicted protein structure of UGT-1. In light and dark blue, are the predicted transmembrane domains.

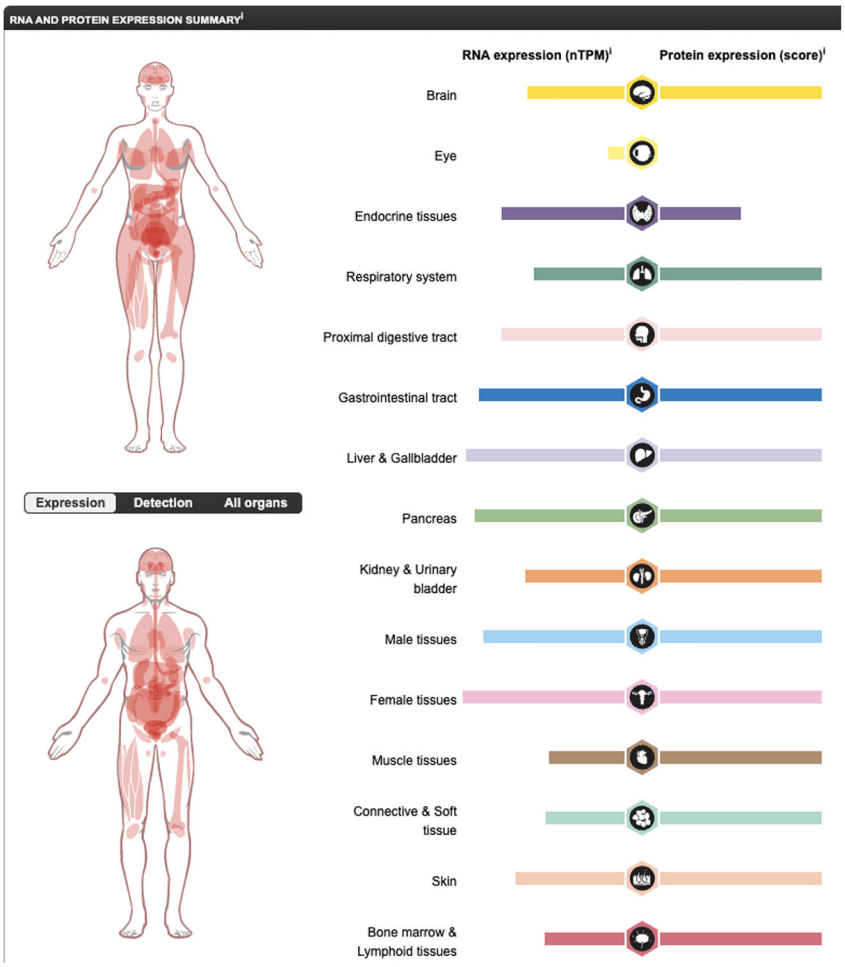

Fig. 2.
SLC35A2 mRNA and protein expression (Protein Atlas).

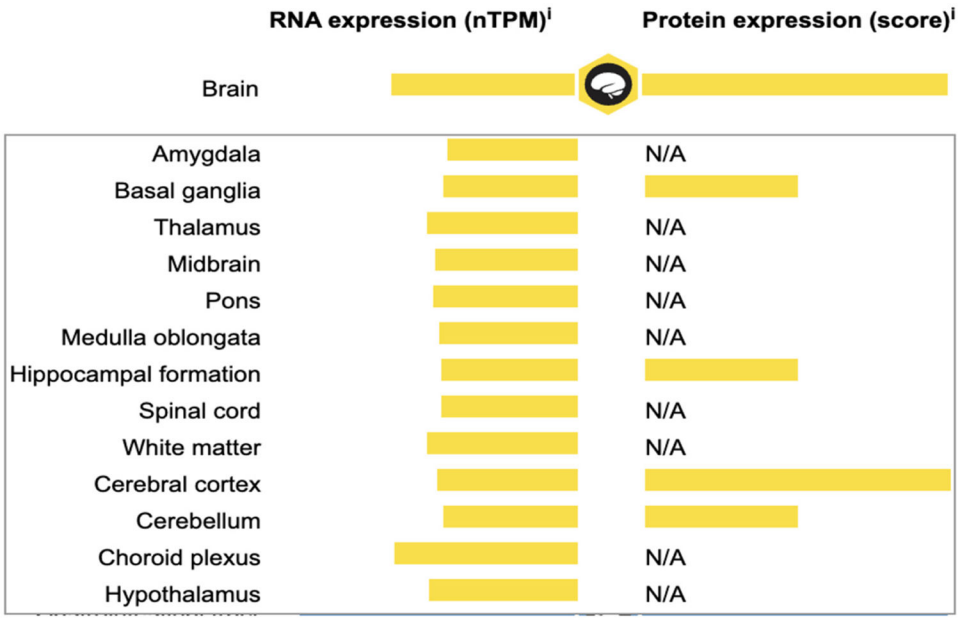

Fig. 3.
SLC35A2 mRNA and Protein Expression in the brain (Protein Atlas).

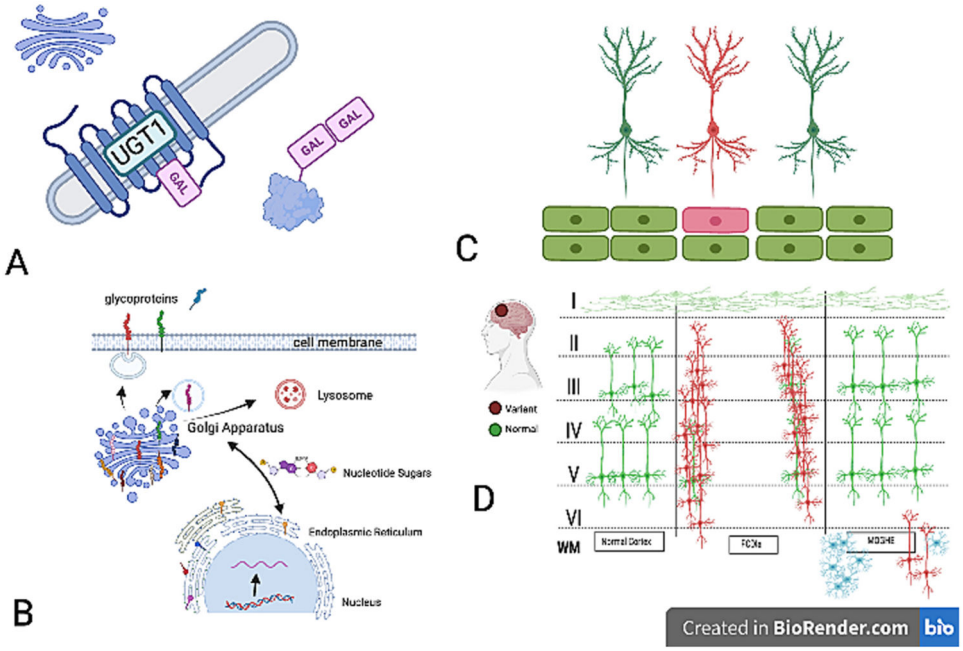

Fig. 4.

Schematic depiction of SLC35A2 and UGT-1 biology. (A), UGT-1 is located within the Golgi membrane, tethered via multiple transmembrane domains. UGT-1 adds galasctose residues (GAL) to synthesized proteins. (B) Following galactosylation, proteins exit the Golgi into the cytoplasm to enter the membrane, lysosomes, or other cellular destinations. (C) Somatic mutations in SLC35A2 occurring in a single neuroglial progenitor cell (red) among progenitors with normal genotype (green) yields a population of daughter progeny cells (D) expressing the SLC35A2 variant (D, neurons in red). Neurons (green) derived from progenitors with normal genotypes do not express SLC35A2 mutations. The focal nature of the SLC35A2 somatic mutation yields a focal MCD either FCD I or MOGHE.