Genetics of perinatal stroke

Bi-allelic nonsense mutations at *ESAM* gene associated with fetal intracranial hemorrhage

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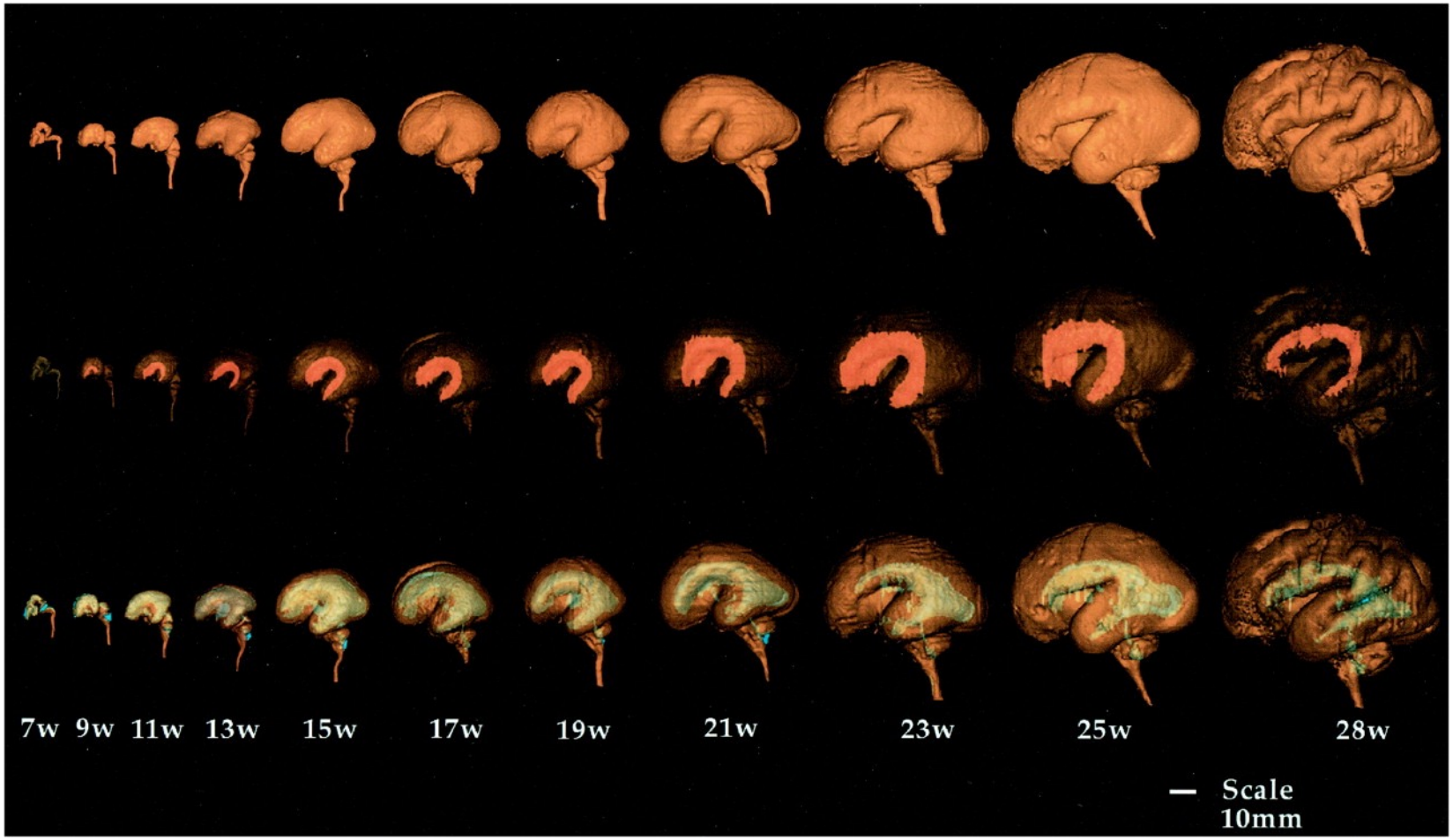
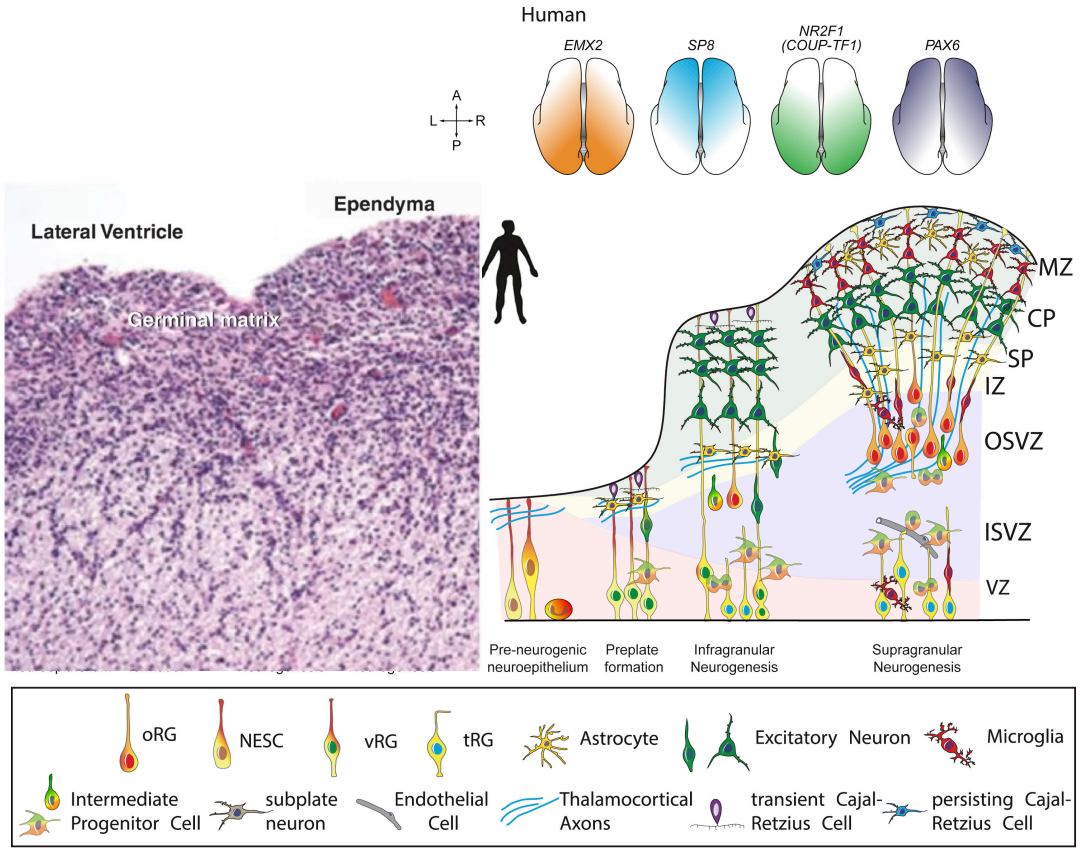
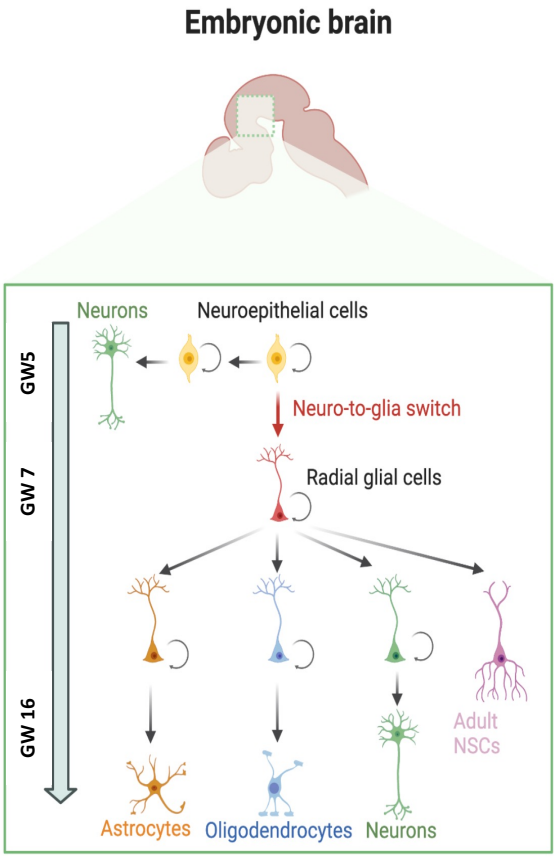
Developmental changes of lateral configuration of brain, germinal matrix, and ventricular system



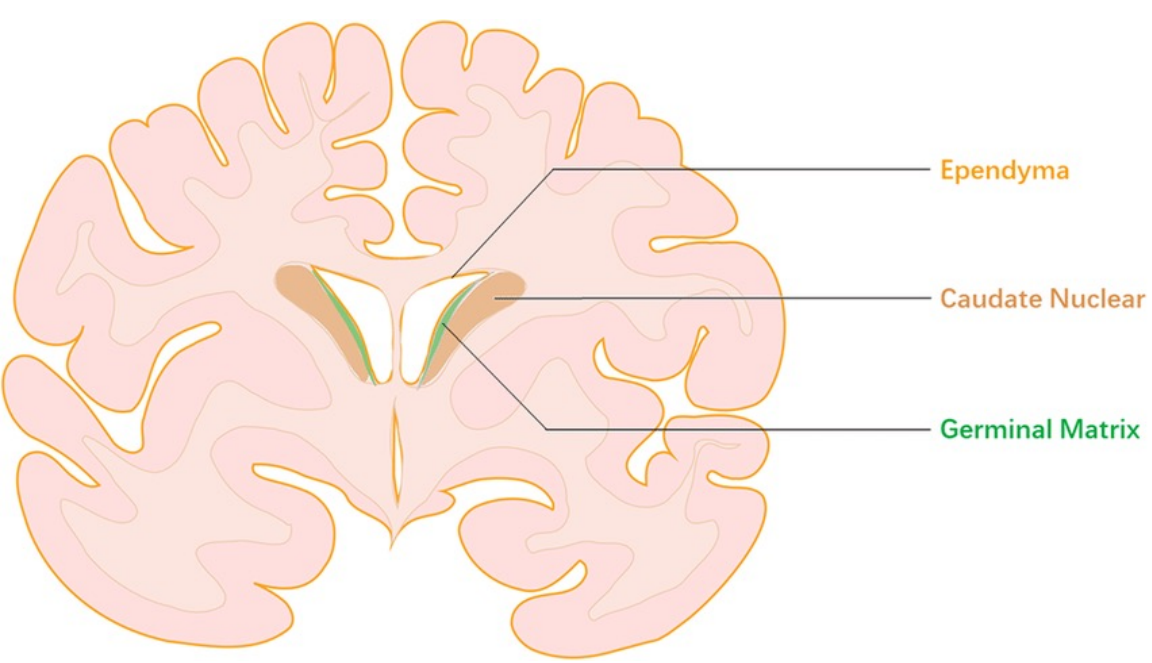
Yoshimasa Kinoshita et al. *AJNR Am J Neuroradiol* 2001;22:382-388

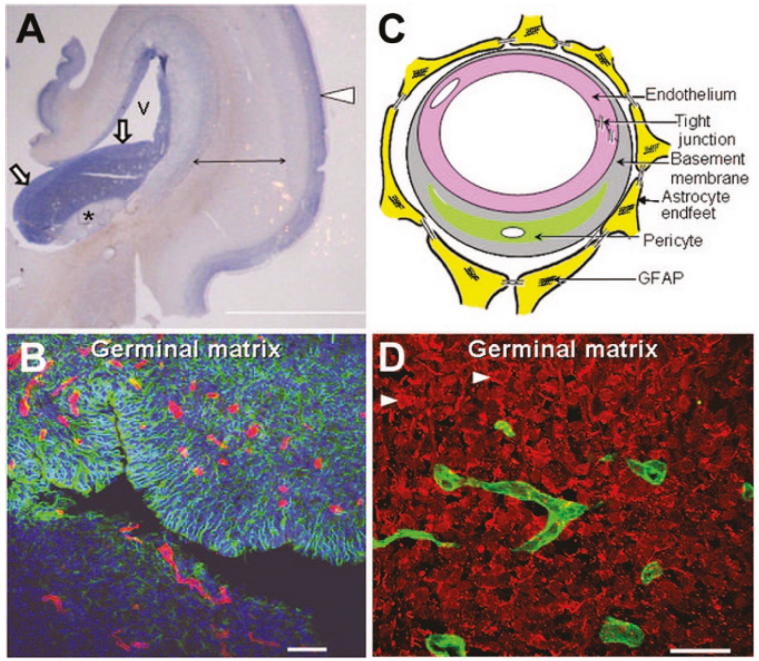
GM neurogenesis highly active from weeks 7-26. From week 26-32, GM gliogenesis takes over





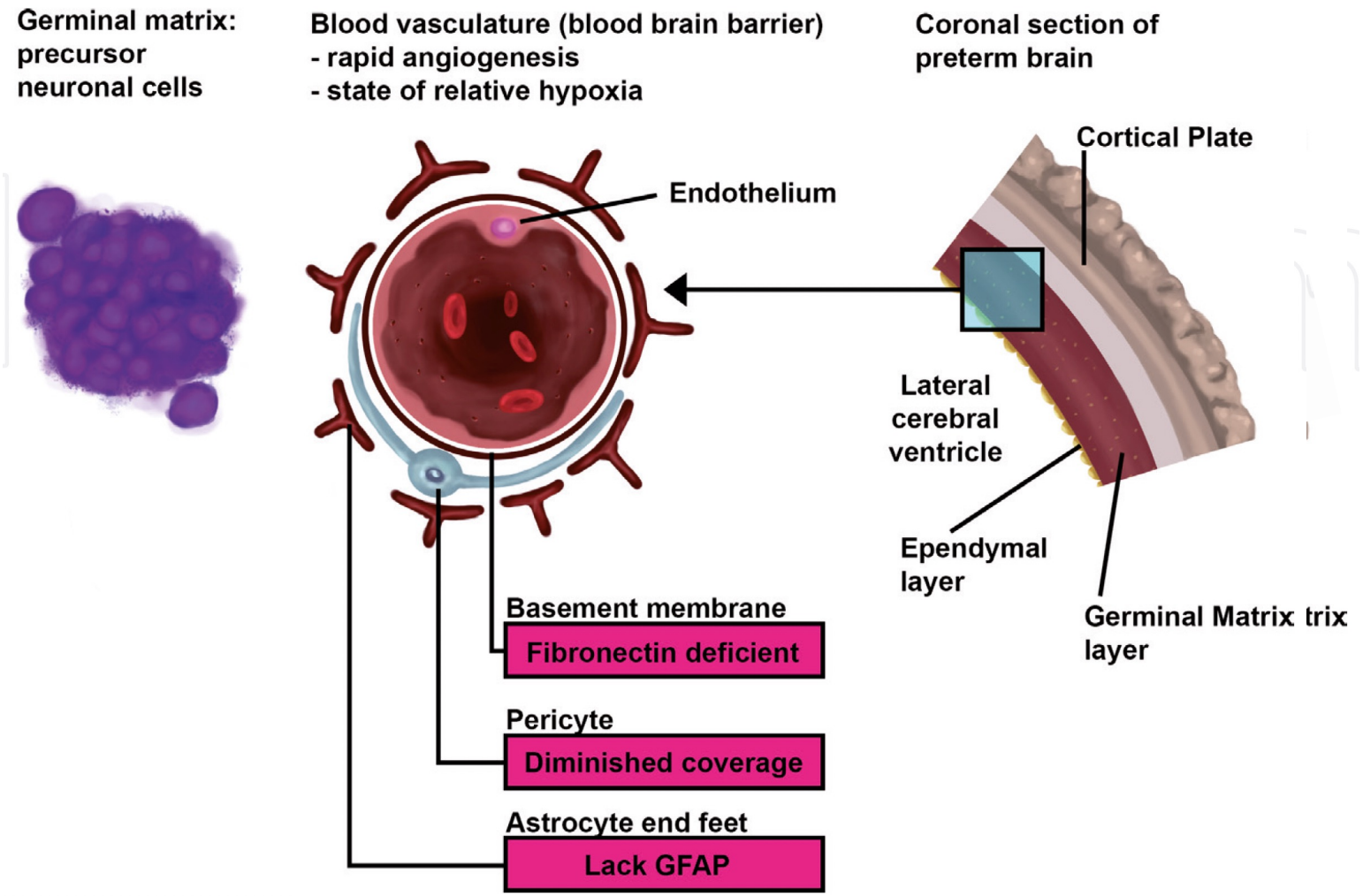
The germinal matrix is a thin layer of gray matter located beneath the ependyma, full of matrix cells and immature vasculature





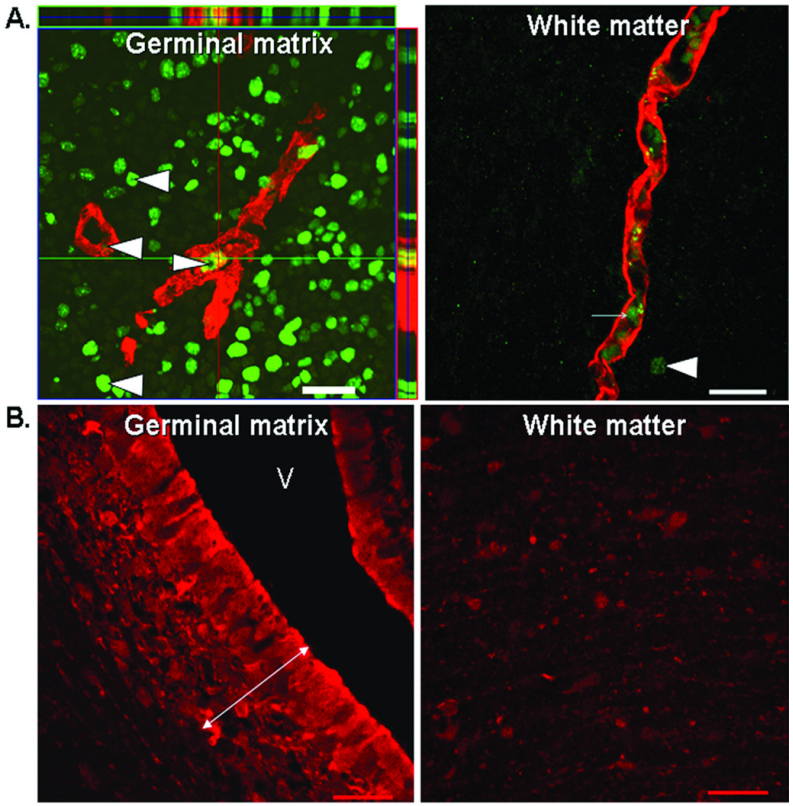
Adapted from: Cellular and Molecular Neurobiology (2019) 39:1–10

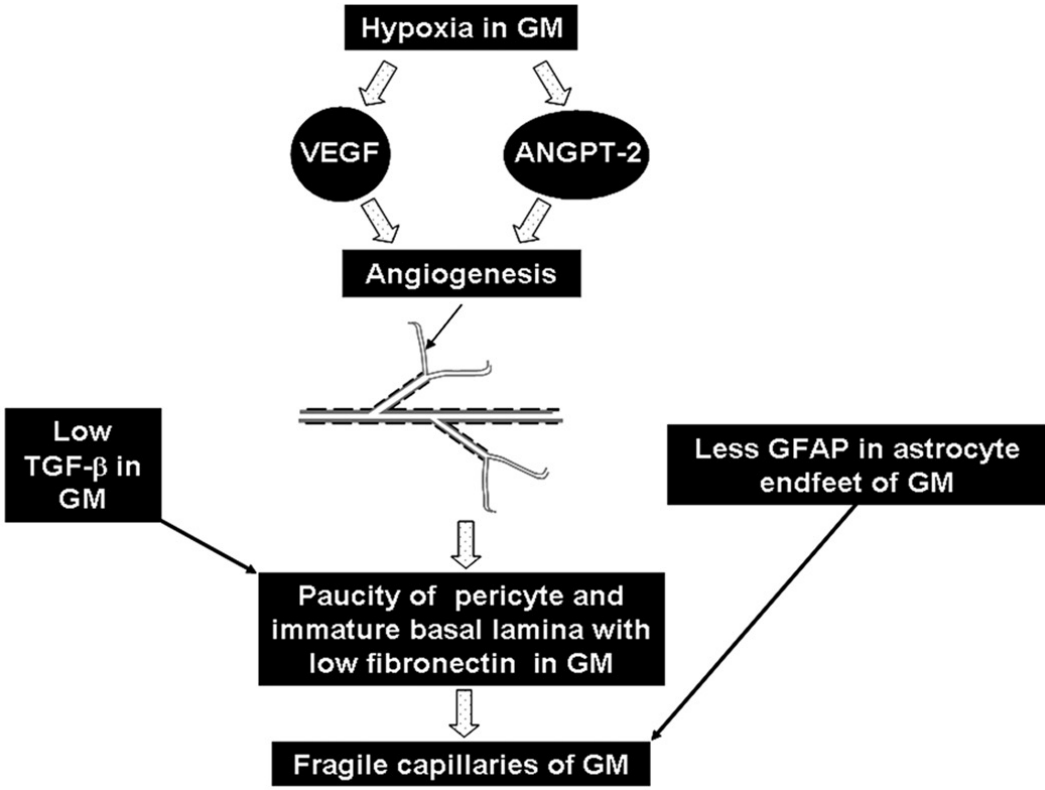
Factors contributing to the labile structure of the Blood Brain Barrier in the germinal matrix



Germinal Matrix-Intraventricular Hemorrhage: Current Concepts and Future Direction, in Cerebrospinal Fluid, B. 2021, IntechOpen: Rijeka. p. Ch. 7

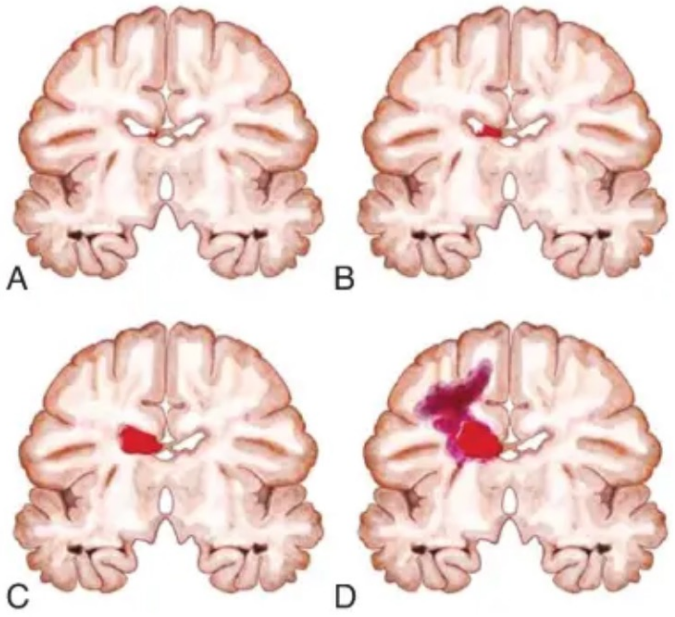
Highly rapid endothelial proliferation in the hypoxic germinal matrix

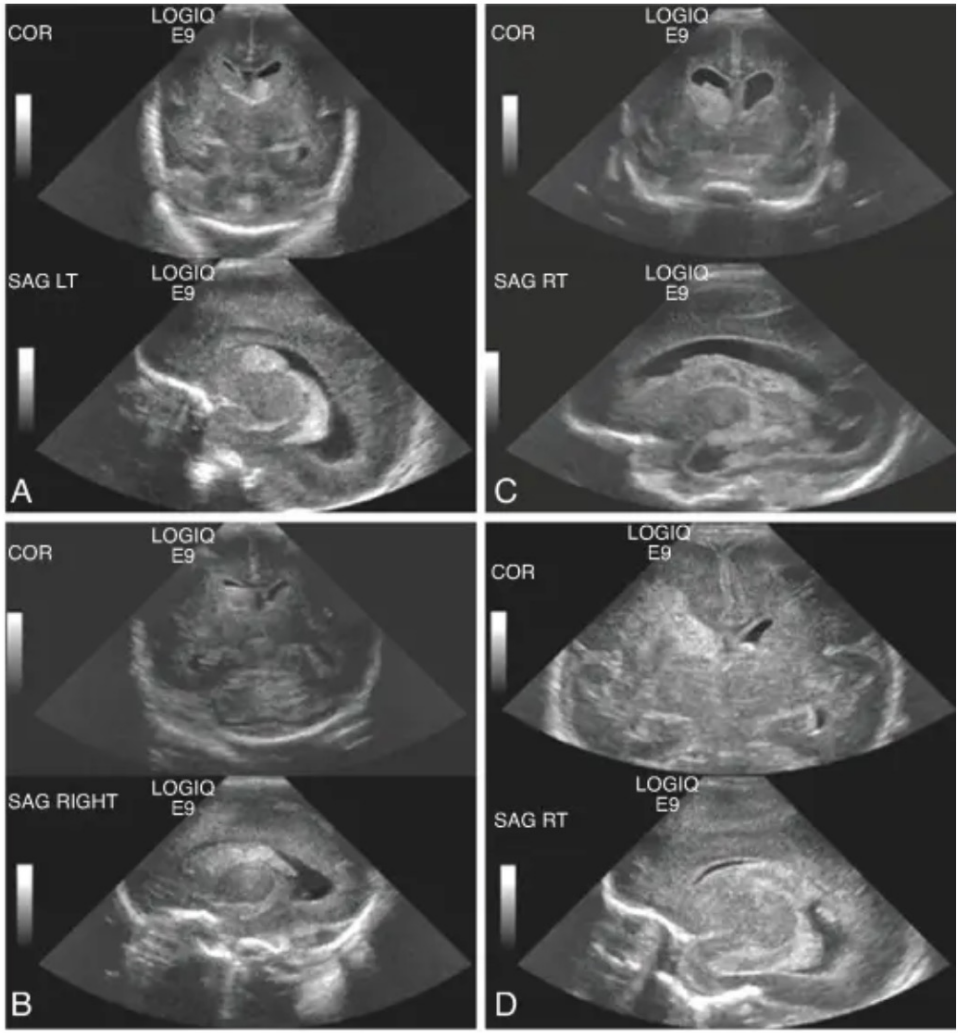




Ballabh P, et al. *Pediatr Res*. 2010; 67(1): 1–8.

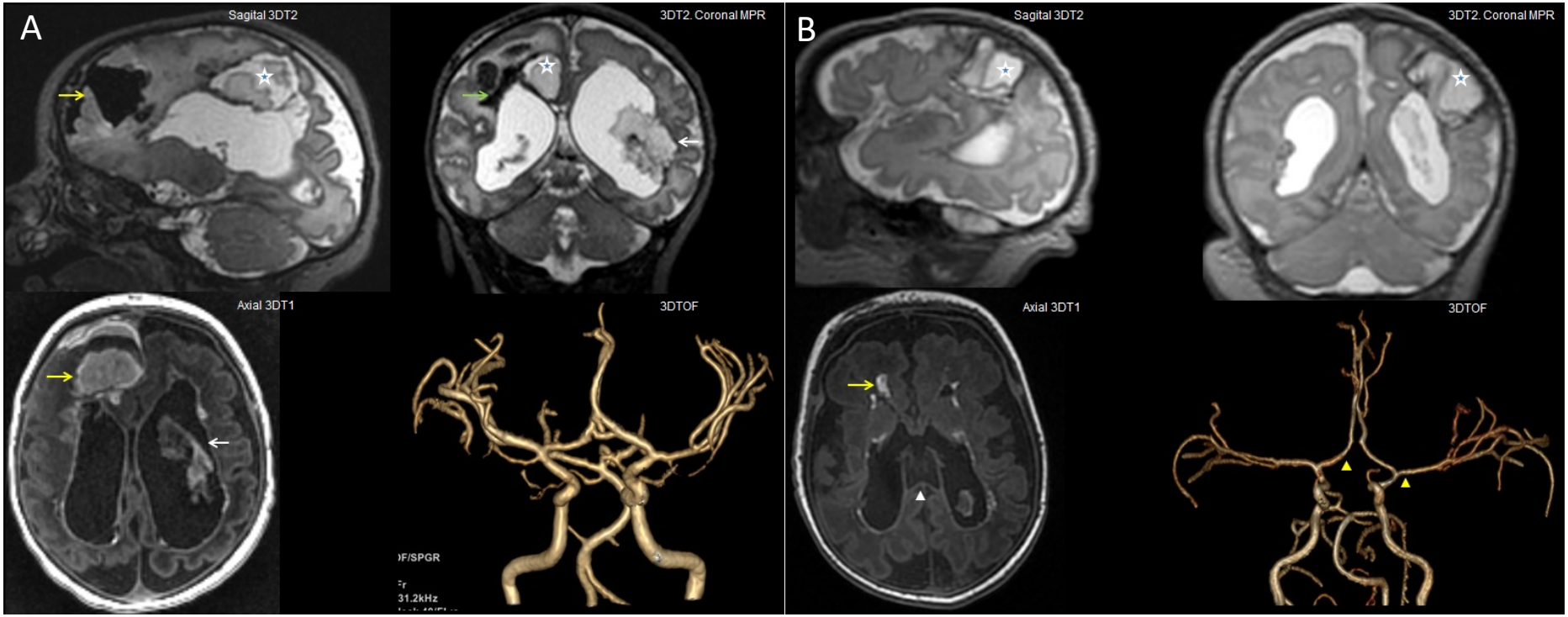
Classification of GM-IVH grades





GM-IVH: Current Concepts and Future Direction, in *Cerebrospinal Fluid*, B. 2021, IntechOpen: Rijeka. p. Ch. 7

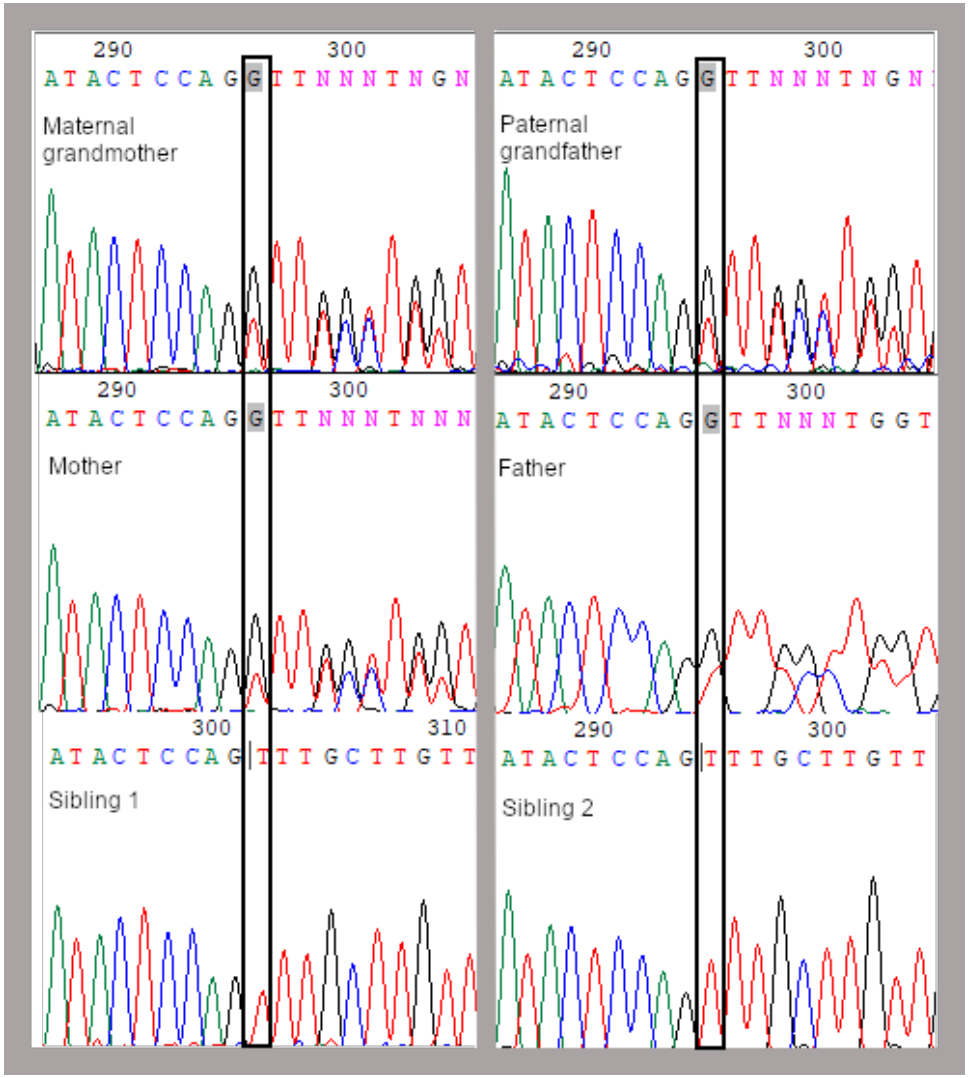
Neuroimaging abnormalities found in the siblings



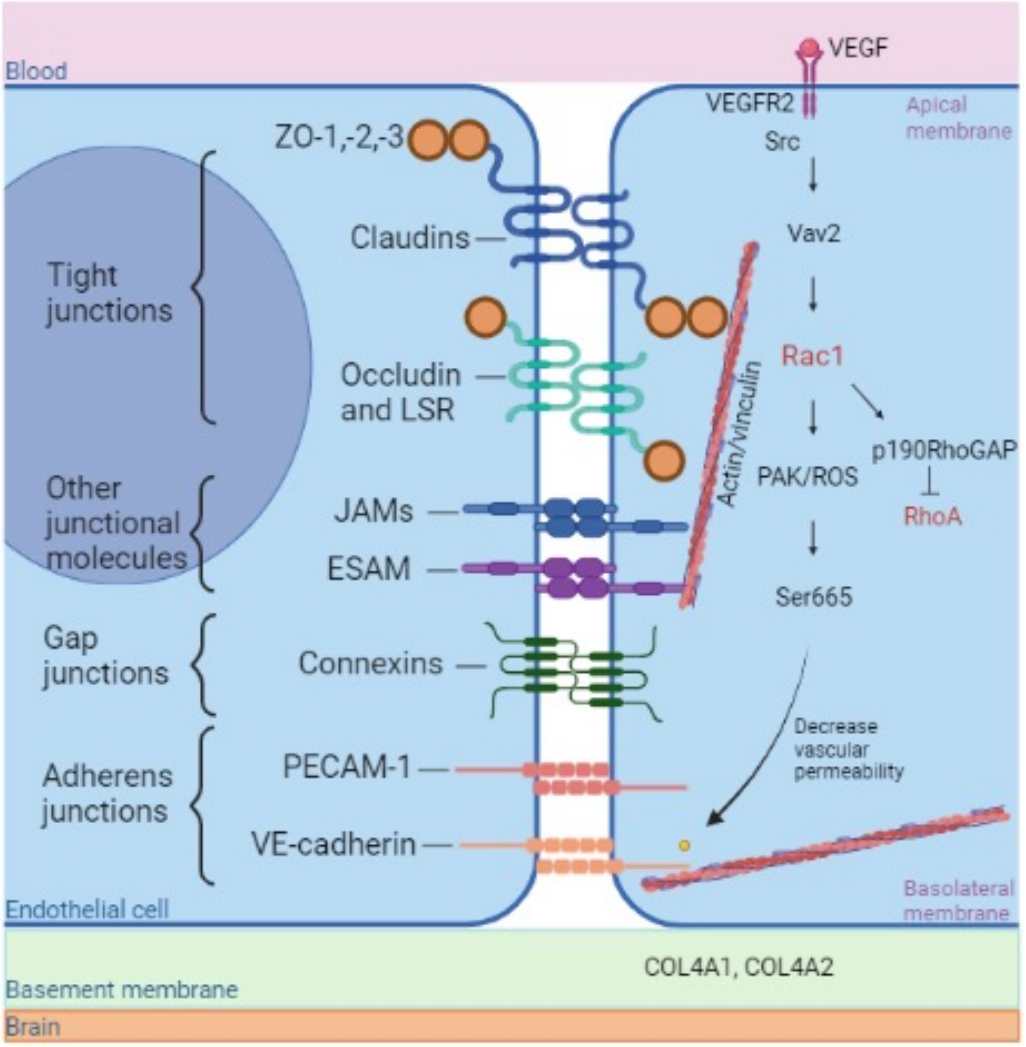
Whole-exome sequencing identified a bi-allelic nonsense mutation at *ESAM* gene in both siblings

Chr (GRCh37)	Position	Gene	Exon	Position	rs	Protein Impact	aa Change	GENEYX	GoESP	gnomAD	1000G
11	g.124626600delC	ESAM	3	c.287delC	N/A	NONSENSE	P96Lfs*32	Pathogenic	NA	NA	NA
11	g.124619754delC	VSIG2	4	c.435delC	rs762379538	NONSENSE	P310Sfs*18	Pathogenic	0.00072	0.00013	0.00062

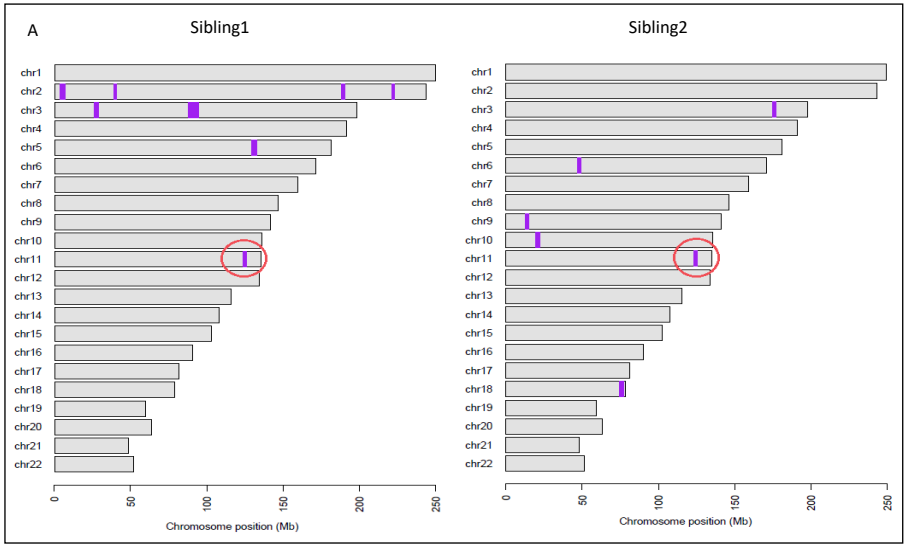
Whole-exome sequencing identified a bi-allelic nonsense mutation at *ESAM* gene in both siblings

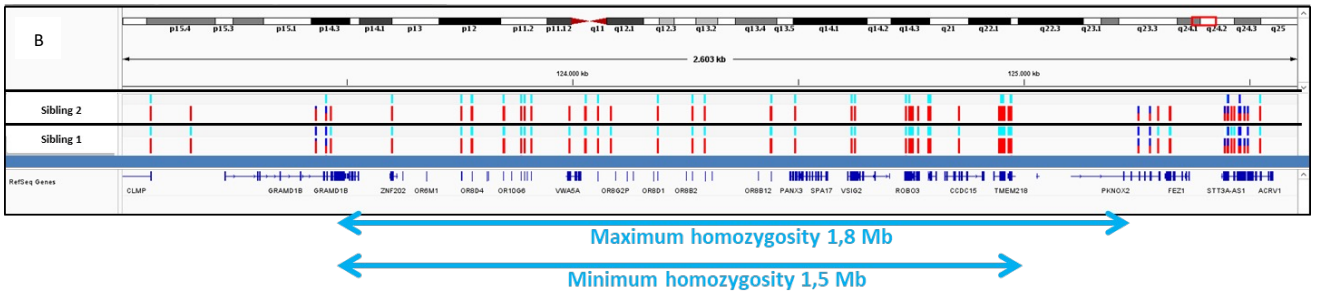


ESAM encodes an Endothelial Adhesion Molecule involved in cell-cell interaction



Both siblings share a 1.8Mb homozygosity region in chromosome 11

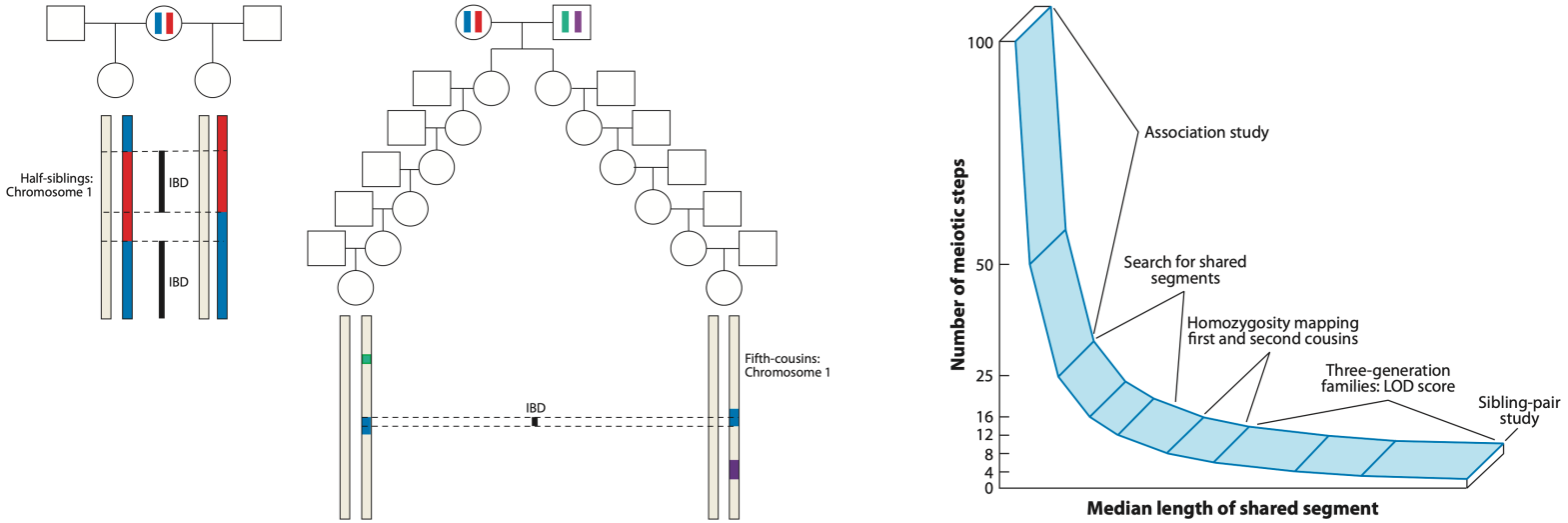




*Ligth blue bars indicate homozygous markers, dark blue or red and dark blue bars indicate heterozygous markers

Hernández J *et al*. 2024. Unpublished data.

Siblings progenitors shared a common ancestor between 560-700 years ago



Browning SR & Browning BL. (2012). Identity by descent between distant relatives: Detection and applications. *Annual Review of Genetics*, *46*, 617–633

2 cM (~2 Mb)
1,8 Mb ~ 28 generations (56 meiosis)
20-25 years/generation ~ 560-700 years

Hernández J *et al*. 2024. Unpublished data.

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Submissions | Gene Search | Diagnosis Search | Reports | Match Outcomes

Gene Search

Gene symbol : ESAM

☐ Submissions must match all gene symbols

Genomic coordinate : chr11:124,623,019-124,632,223

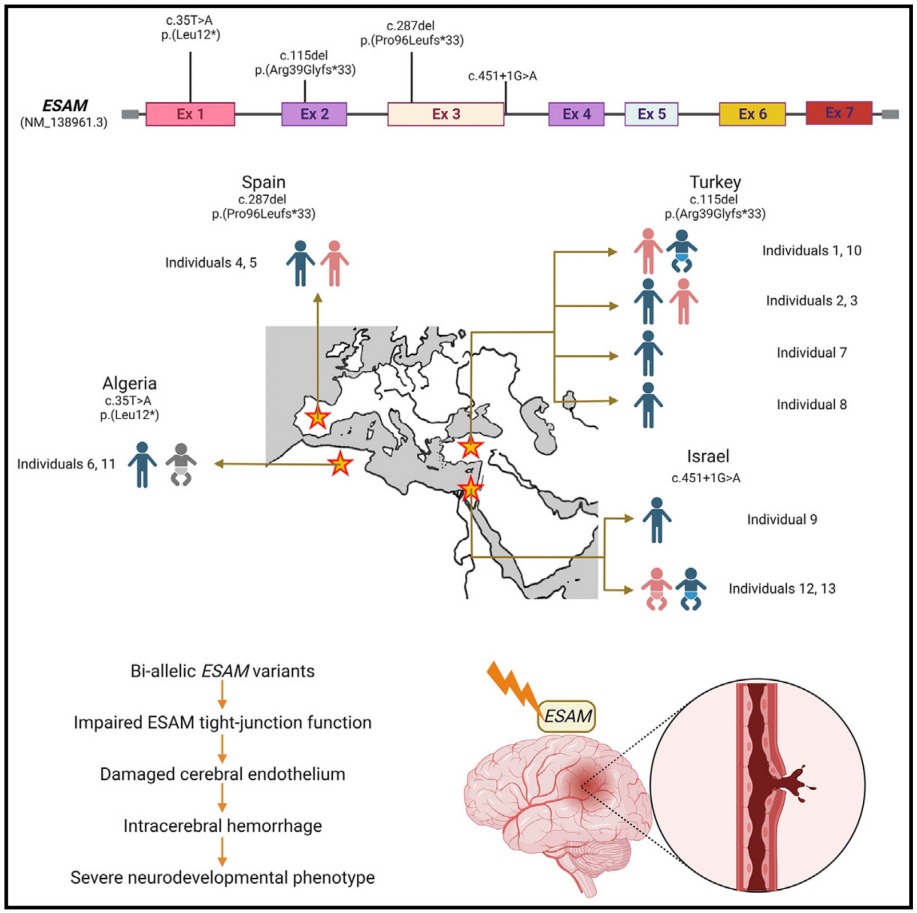
☐ Submissions must match all genomic coordinates

Assembly : GRCh37 (default)

Search

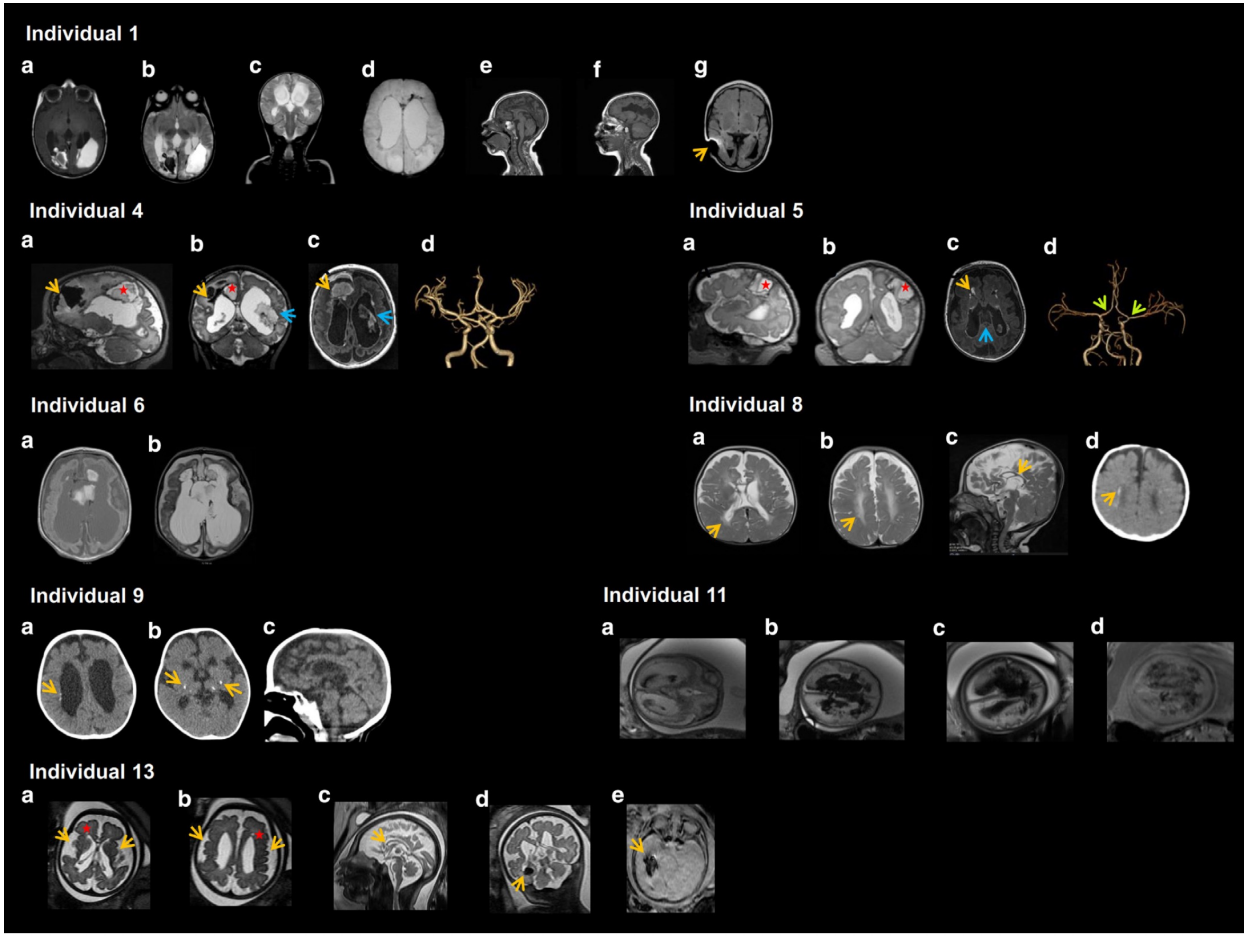
Note that this searches across your submissions ***only***, you cannot search for other submitters' entries (See FAQ 3 to see why).

Bi-allelic variants in the *ESAM* tight-junction gene cause a neurodevelopmental disorder associated with fetal intracranial hemorrhage



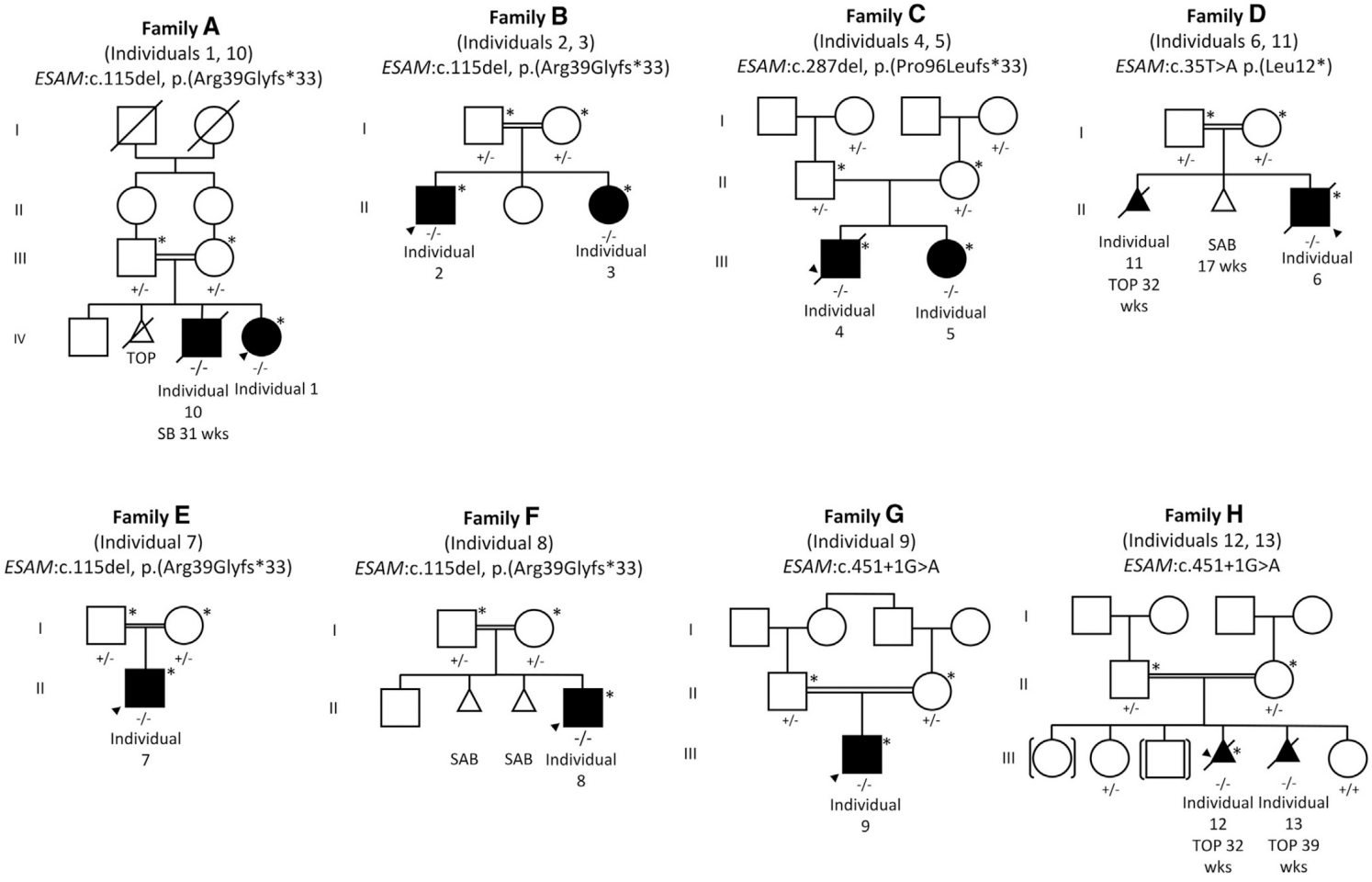
Lecca M, et al. *Am J Hum Genet*. 2023;110(4):681-690.

Neuroimaging abnormalities in individuals with homozygous ESAM variants



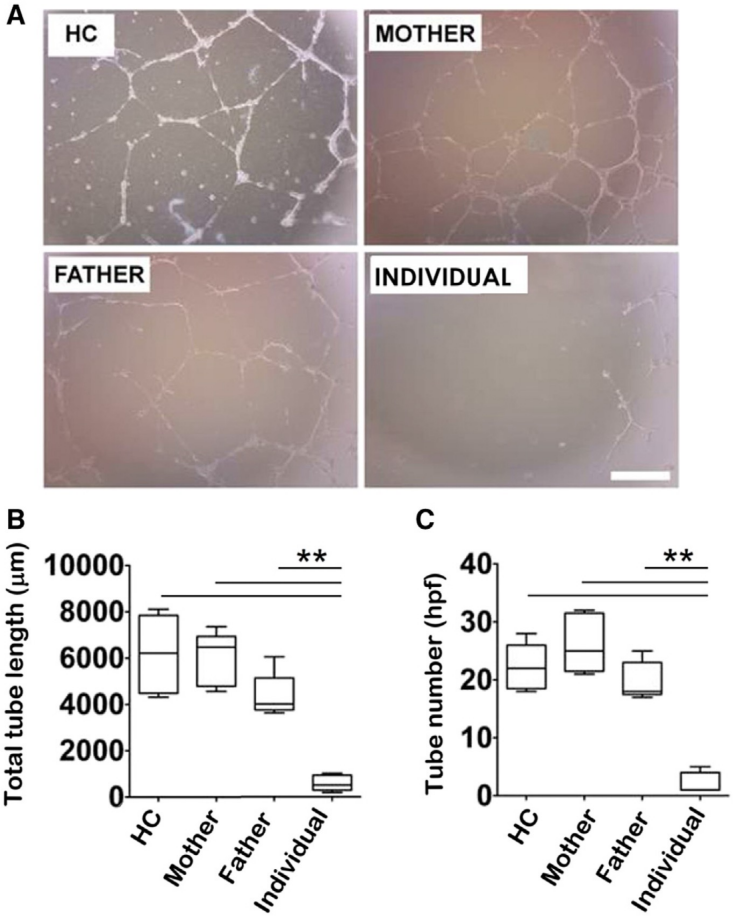
Lecca M, et al. *Am J Hum Genet*. 2023;110(4):681-690.

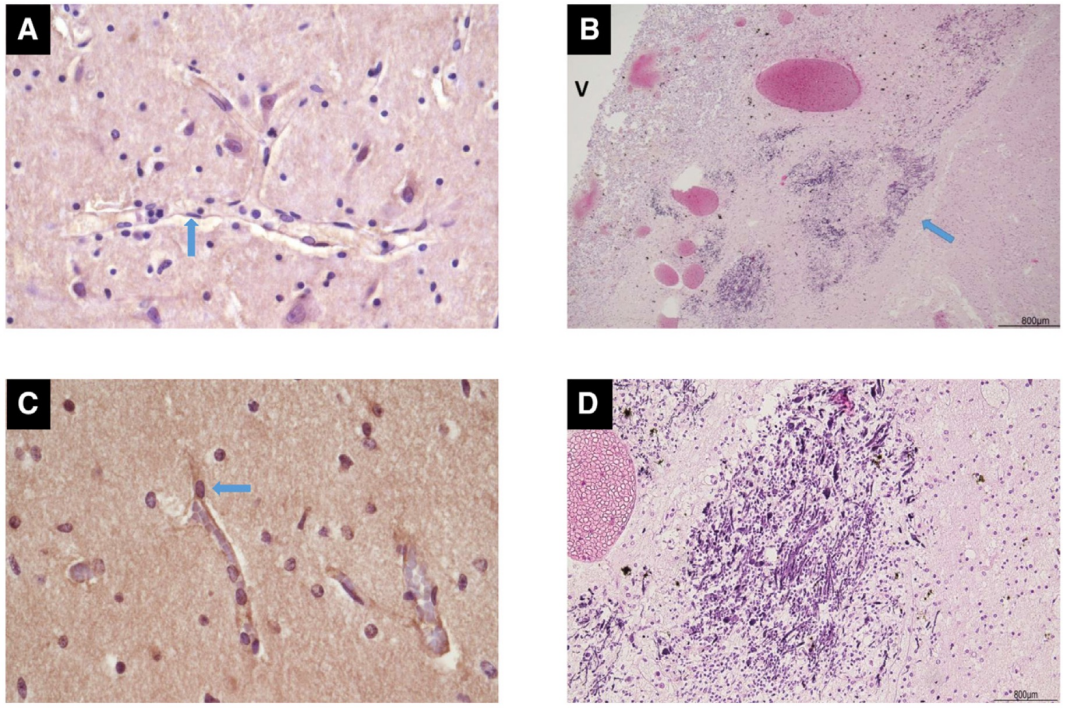
Family pedigrees and genetic findings



Lecca M, et al. *Am J Hum Genet*. 2023;110(4):681-690.

ESAM-deficient ECFC loose tubulogenesis capacity. Periventricular leukomalacia-multiple areas of calcification





Lecca M, et al. *Am J Hum Genet*. 2023;110(4):681-690.

Table 1. Phenotypic comparison of individuals with bi-allelic variants in *JAM2*, *JAM3*, *OCLN*, and *ESAM*

Clinical features	*JAM2*	*JAM3*	*OCLN*	*ESAM*
Head and neck				
Microcephaly	no	yes	yes	yes
Cataracts	no	yes	yes (rare)	no
Facial dysmorphisms	no	no	yes: long philtrum, microretrognathia, low-set ears, anteverted nares, high arched palate	yes: bitemporal narrowing, highly arched eyebrow, bulbous nasal tip, long eyelashes, high narrow palate, wide nasal bridge, upslanted palpebral fissures, microretrognathia, anteverted nares
Neurologic				
Developmental delay	yes	yes (severe)	yes (severe)	yes (severe)
Seizures	yes (rare)	yes	yes	yes
Spasticity	yes	yes	yes	yes
Hypotonia	no	yes	yes	yes
Neuroimaging findings				
Intracranial calcifications	yes	yes	yes	yes
Intracranial hemorrhage	no	yes	no	yes
Ventriculomegaly	no	yes	yes	yes
Corpus callosum anomalies	no	yes	yes	yes
Abdomen				
Hepatomegaly	no	yes	yes	no
Genitourinary				
Renal anomalies	no	yes (rare)	yes (rare)	yes (rare) (renal medullary hemorrhage)
Disease onset	adulthood	neonatal	neonatal	antenatal/neonatal

Cen Z, et al. (2020). *Brain* 143, 491–502.
Schottlaender LV, et al. (2020). *Am. J. Hum. Genet.* 106, 412–421.
Mochida GH, et al. (2010). *Am. J. Hum. Genet*. 87, 882–889
Akawi NA, et al. (2013). *Hum. Mutat.* 34, 498–505.
O'Driscoll MC, et al. (2010).. *Am. J. Hum. Genet.* 87, 354–364.
Abdel-Hamid MS, et al. (2017). *J. Hum.Genet.* 62, 553–559

Genetic findings found in perinatal hemorrhagic stroke patients

Patient	Sex	Intelectual disability	Sizures	Dysmorphic Disorder	Affected brain region	Pathogenic Variants	VUS	Observacions	
HUSE1	Male	1	1	1	Intraventricular	COL3A1	MYLK, AKAP6, RNF213, HDAC5		trio OK
HUSE2	Male	1	0	1	Intraventricular	RUNX1	DAB2IP		trio OK
ICP103	Female	0	1	0	Intraventricular	COL4A2 (Dupl. 8kb)	GDAP1, RYR1, COL22A1, CAV3, RNF213, COL4A2, CLDN6		no parents
ICP077	Female	0	0	0	Intraventricular	NOTCH1	NONE		no trio
HUSE4	Female	1	1	1	Intraventricular	KAT6A (de novo)	HRG	Arboleda-Tham	trio OK
ICP008	Male	0	1	0	Talamus	SCN3A	FLNC, TGFBR1, SH2B3	Epileptic Encephalopathy	trio OK
ICP066	Female	1	1	0	Frontal - occiptal	TRPM4	C7 , INSR, SLC8A3, TSC1, LOX, ATM		trio OK
ICP076	Male		0	0	Occipital	PRDM16	APOE, MCD		no trio
ICP079	Male	0	0	0	Frontal	PDCD10 de novo)	RYR2, TJP3, PRO1	Cavernous Malformation	no trio
ICP084	Female	0	1	0	Temporal	PTEN	NTN1, FLNC, TLR3, PKD1		no parents
ICP101	Male	0	0	0	Parietal	RANGRF	PIEZO1		no trio
ICP103	Female	0	1	0	Parietal	COL4A2 (Dupl. 8kb)	GDAP1, CMT2k, RYR1, COL22A1, CAV3, RNF213, CLD6		no parents
HUSE3	Male					HPS1	PALS1, FBN1	Hermansky-Pulak	no parents

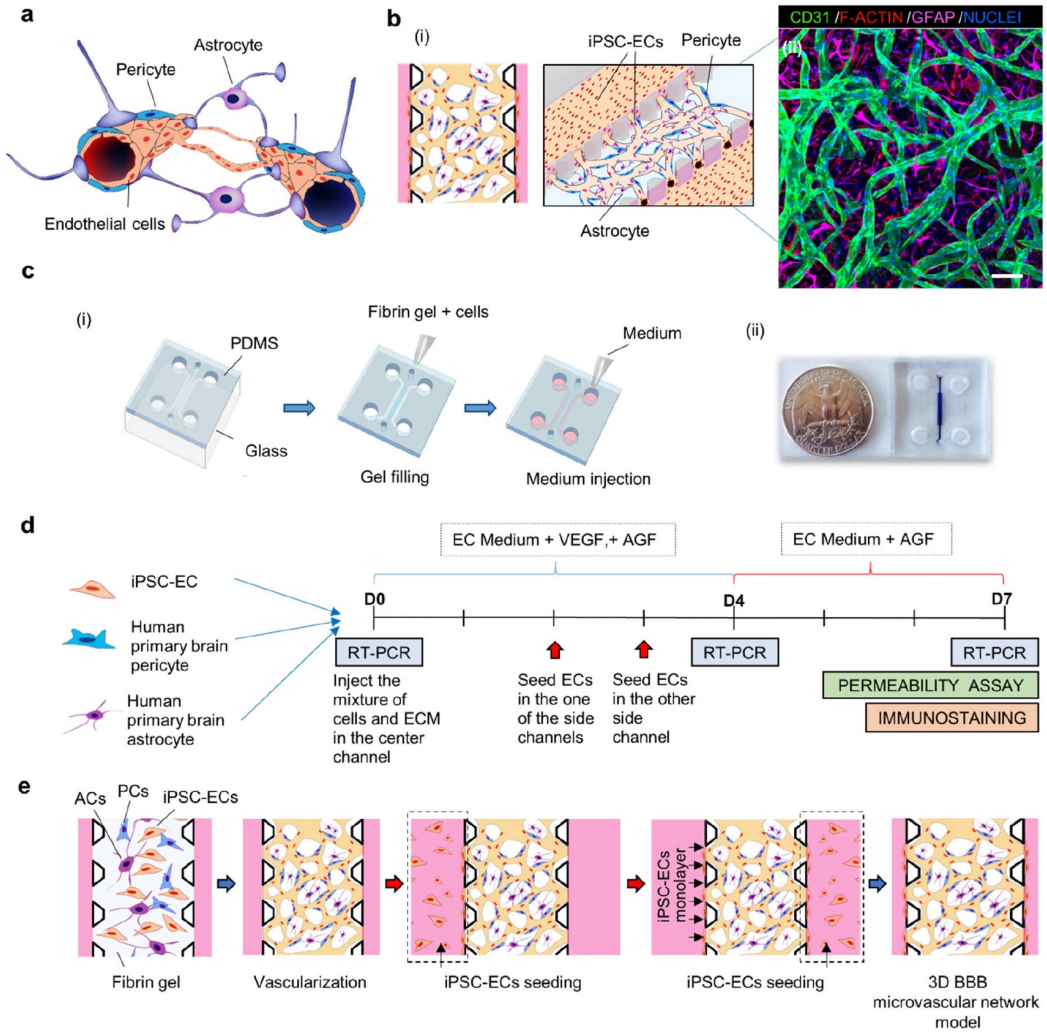
Heine-Suñer, D.*et al*. 2024. Unpublished data.

Genetic findings found in perinatal ischemic stroke patients

Patient	Sex	Intelectual disability	Sizures	Dysmorphic Disorder	Affected brain region	Pathogenic Variants	VUS	Observacions
HUSE5	Male					RNF213	MYLK, CRP, VCL, PSTPIP1, CARD14	no parents
ICP005	Male	0	0	0	parieto-temporal & occipital	ASPM (BIALLELIC)	ANK2, LQT, FHOD3, MCH, PPARG	none
ICP011	Male	1	1	0	Hemiprotuberancia	EPRS1 (BIALLELIC)	ABCC8, DCP, VCL, SRC, KNG1, NOTCH3, RNF213	no father
ICP017	Male	1	1	0	Frontal	AARS1, CAMK2A (de novo)	LRRK2, SEMA3E, KCNH2, RNF213, PDGFRB	CAMK2A intellectual disability (de novo)
ICP020	Female	0	0	0	Parietal	SLC5A2	NONE	
ICP023	Female	1	1	1	Fronto-parietal	CBL (de novo)	MLX, ARL6IP6, NPPA, COL5A2, TJP3, ITGA2	Noonan CBL de novo
ICP026	Female	0	1	0	Temporo-parietal	NONE	KLK1, MYLK, TMPO, PUBB1, ANGPTL6, JAG1	3 genes without asssigned disease de novo
ICP029	Female	1	1	0	Fronto-parietal	CMT, KCNMA1, CPA6, NDUFAF7	TNNI3K, ANKRD1, SERPINC1, SLC2A10	
ICP032	Female	0	0	0	Tlalamus	NONE	NOS3, BAG3, RNF213, IRAG1	none
ICP035	Female	0	0	0	Frontal	NONE	F9, HMCN1, MAPK15	none
ICP038	Male	0	0	0	Corona radiata	GP1BA	TNXB, C9, SNTA1, TJP3	none
ICP041	Female	1	1	0	Frontal-parietal	TCF12 (de novo)	TGFB2, F5, ALPK1	de novo LP TCF12
ICP044	Female	0	1	0	Temporoparietal frontal & insula	RPA1 (de novo)	CITED2, HDAC5	
ICP047	Male	0	1	0	Frontoparietal & insular	TIE1 (de novo)	MYH6, DTNA, HMCN1	Lymphatic malformation-hemorrhage/angiogenesis
ICP053	Male	0	0	0	Temporoparietal	NF1 (de novo)	DNM2, AR, MICAL2	

Heine-Suñer, D.*et al*. 2024. Unpublished data.

Currently working on: GM Blood-Brain Barrier *in vitro* microvascular network model



Biomaterials. 2018; 180: 117–129.

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