PReDICT: Pediatric stroke Rare Disorders Integrative Diagnosis and Treatment using Multi-Omics and Deep Learning

Cristòfol Vives-Bauzà

Damià Heine Suñer

13 de Junio de 2025

PReDICT Consortium

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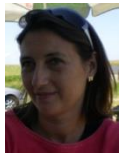

SESCAM-CHU. Albacete
Dra. Maria C. Carrascosa
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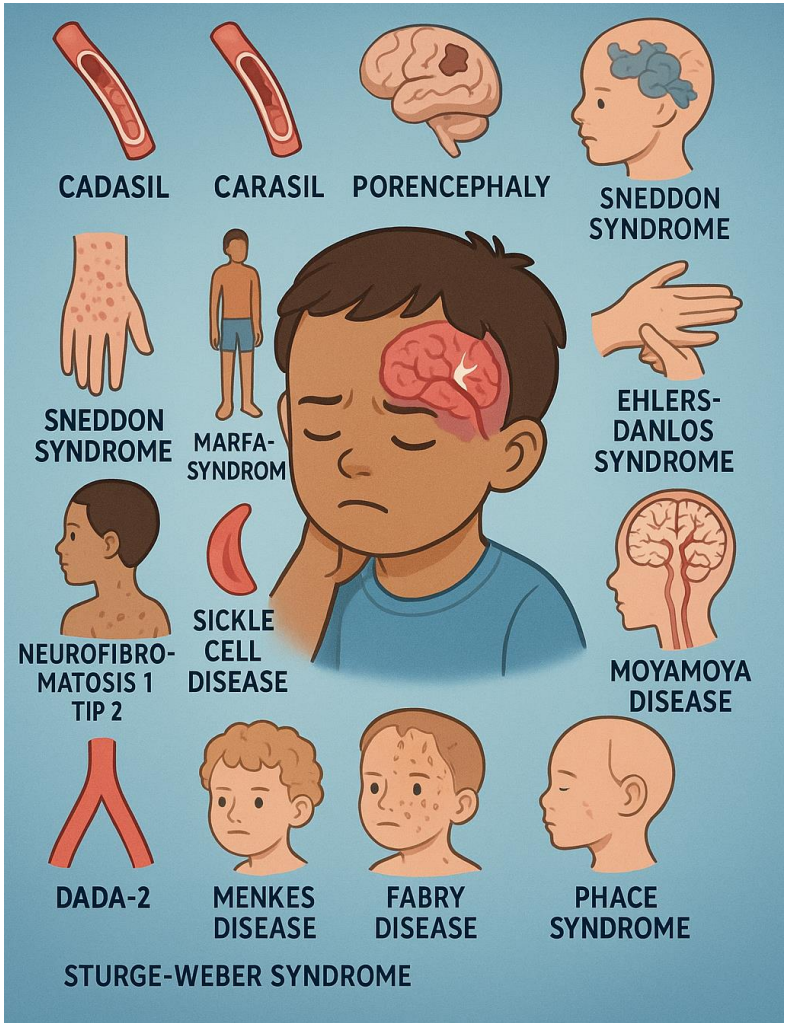
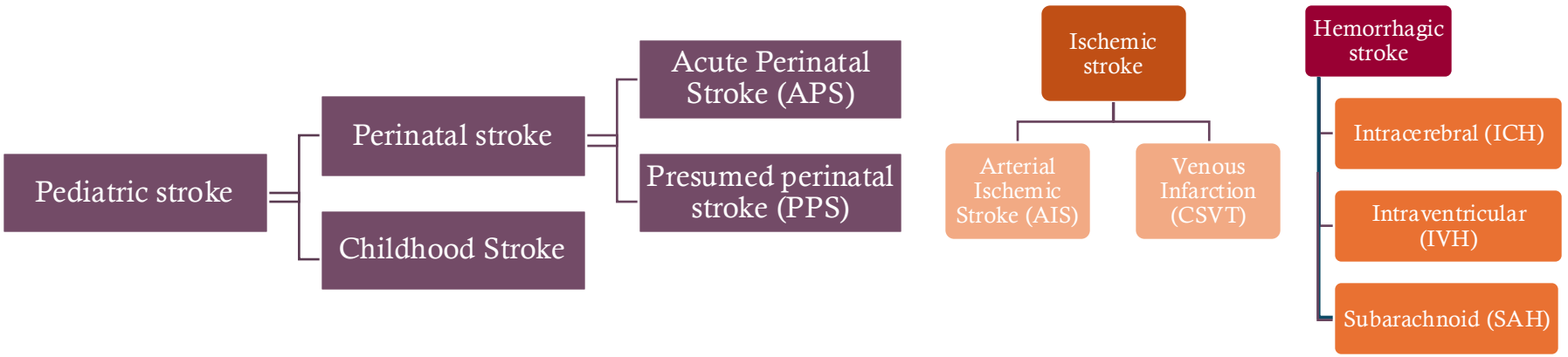
Several Rare Diseases Present with Stroke in Children



GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
Plan de Recuperación, Transformación y Resiliencia
Financiado por la Unión Europea NextGenerationEU
2024

CONVOCATORIA MISIONES CONJUNTAS PARA CONCESION DE SUBVENCIONES A PROYECTOS DE INVESTIGACION EN ENFERMEDADES RARAS

Pediatric Stroke causes Long-Term Neurological Deficits in Infants



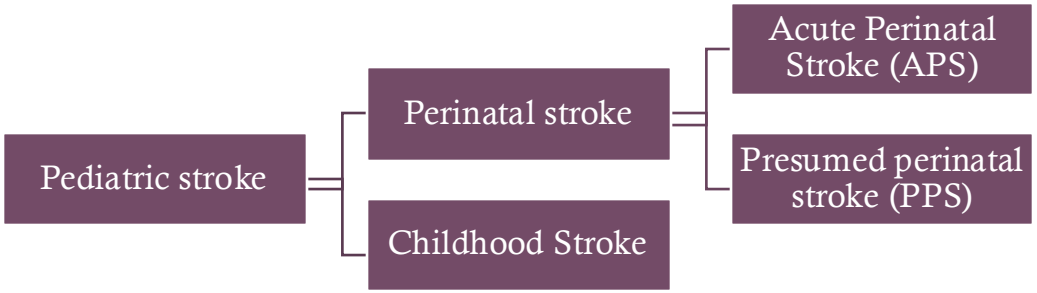
Perinatal stroke

From the 20th week of gestation until the 28th day after birth

Leading cause of hemiparethic cerebral palsy and lifelong impacts including motor, cognitive and epileptic issues

(Ferriero et al. 2019; Jankovic et al. 2022; Srivastava et al. 2022)

Pediatric Stroke causes Long-Term Neurological Deficits in Infants



Perinatal stroke

From the 20th week of gestation until the 28th day after birth

Leading cause of hemiparethic cerebral palsy and lifelong impacts including motor, cognitive and epileptic issues

Incidence

- 25 to 40 per 100,000 in neonates
- 100 per 100,000 in premature neonates

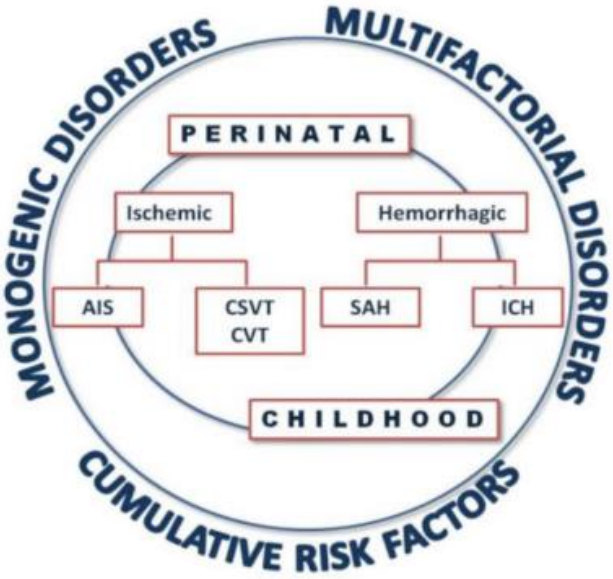
(Ferriero et al. 2019; Jankovic et al. 2022; Srivastava et al. 2022)

Pediatric Stroke Risk Factors

Neonatal factors

Thrombophilia

Congenital heart disease



Maternal conditions

Arteriopathies

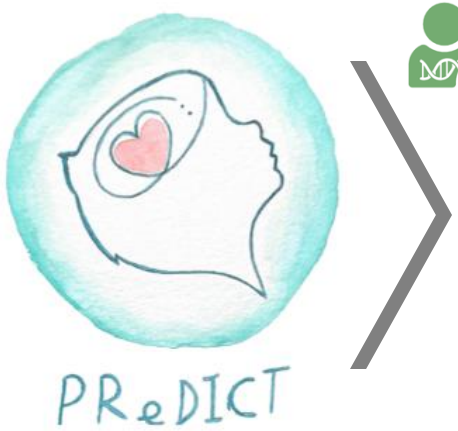
Autoimmune diseases

(Janckovic et al. 2021)

Mapping the genetic architecture of pediatric stroke

(Malone et al. 2020; Lynch et al. 2022)

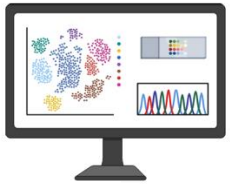
PReDICT: Pediatric stroke Rare Disorders: Integrative Diagnosis and Treatment using Multi-Omics and Deep Learning



Clinical Outcomes

Genomics

Epigenomics



Transcriptomics

Neuroimaging

Functional studies

WP1. Clinical Outcomes of Pediatric Stroke Patients (following COSMIN guidelines)

Dra. Ana M. Domínguez

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HUVM
Hospital Universitario
Virgen Macarena

CLINICAL VARIABLES:

Global Performance: Pediatric Stroke Outcome Measure (PSOM) and Pediatric Stroke Recurrence and Recovery Questionnaire (psRRQ)

Motor Function: Gross Motor Functional Measure (GMFM)

Adaptive Functioning and Behavior: Child and Adolescent Scale of Participation (CASP)

Quality of Life: Pediatric Stroke Quality of Life Measure (PSQLM)

Mood: Revised Children's Anxiety and Depression Scale (RCADS)

Cognition: NIH Toolbox

Memory: California Verbal Learning Test (CVLT-C)

Executive Function: Behavior Rating Inventory of Executive Function

Speech and Language: Focus on the Outcome of Communication Under Six

REDCap
Research Electronic Data Capture

DEMOGRAPHIC VARIABLES: Prematurity, primiparity, birth weight, cardiac disorders, congenital thrombophilia, infections, maternal diseases and cigarette smoking, placental disorders, occurrence of birth asphyxia, APGAR score.

WP2. Neuroimaging Analysis: Connectome's signature associated with Pediatric Stroke

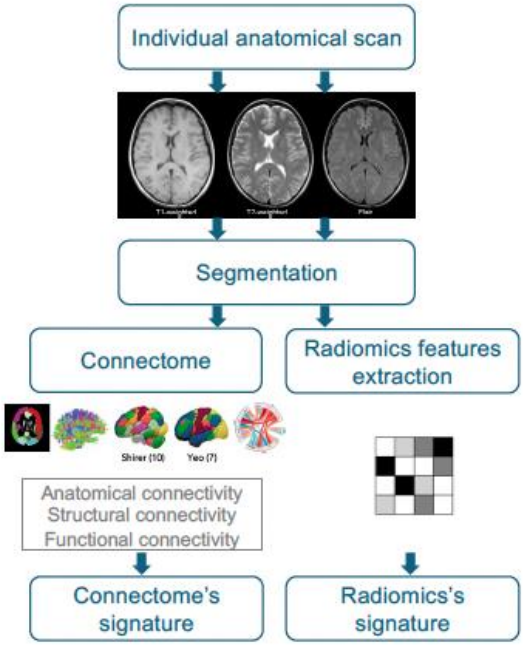
REDCap

Clinical data

MRI-CT scan

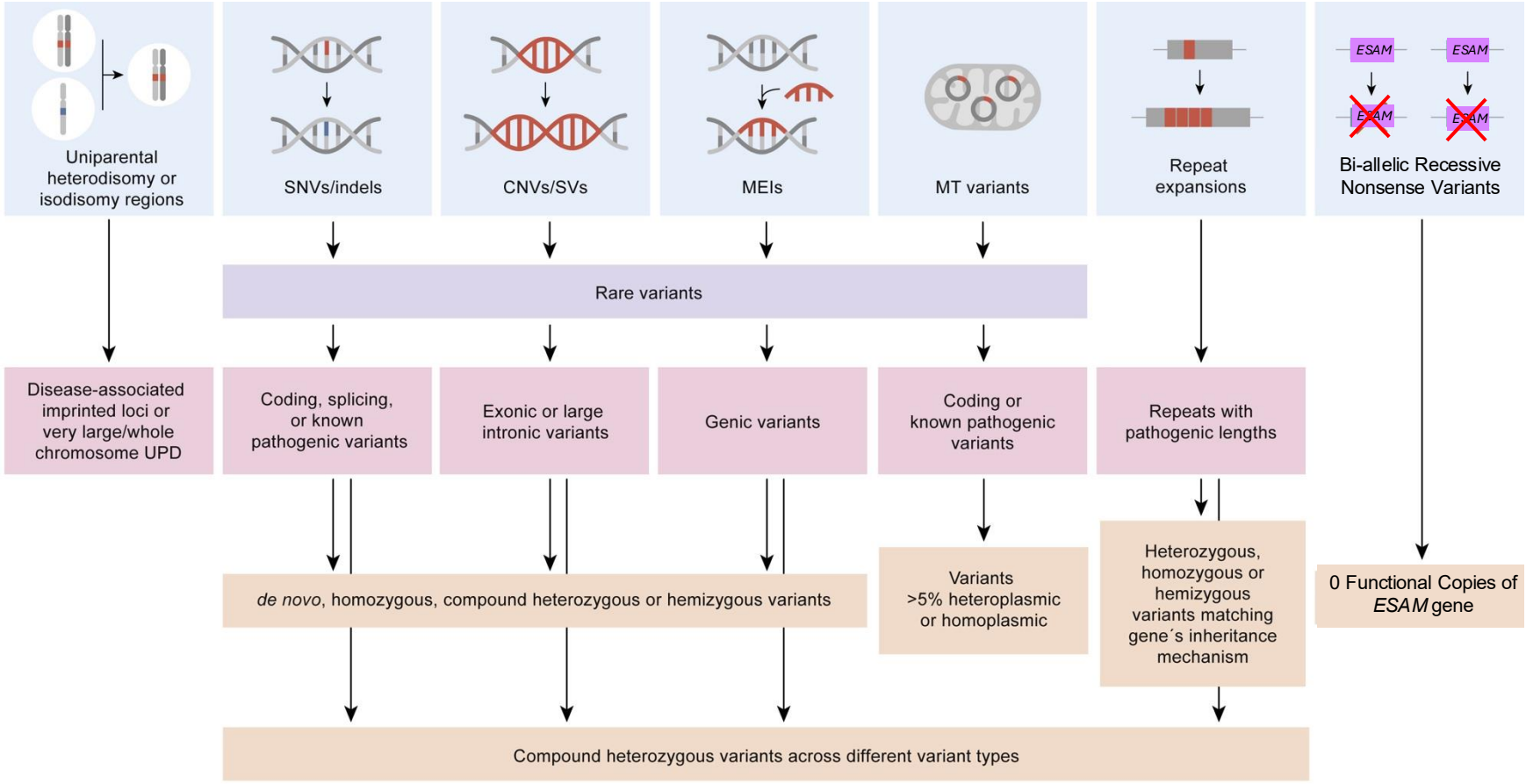
VPN connection

NAS Server (IRBLleida)



Dr. Francisco Purroy
Dra. Gloria Arqué

WP3. Trio-WGS and RNASeq to identify rare bi-allelic and *de novo* variants, CNVs, and regulatory non-coding variants as a cause of Pediatric Stroke.



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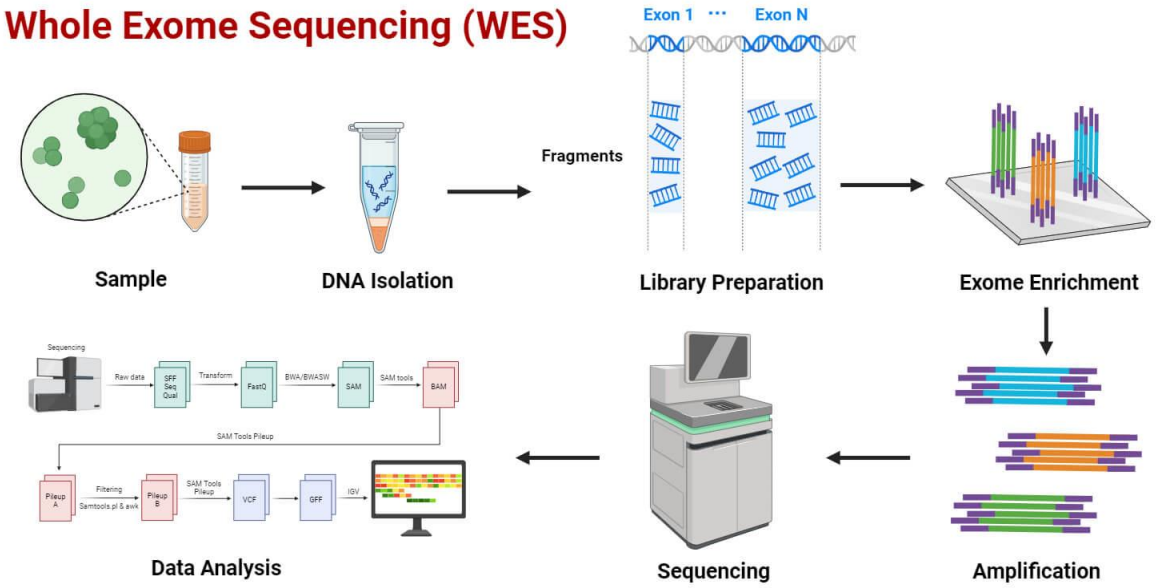
Son Espases hospital universitari

Trio-Exome Sequencing for Variant Analysis



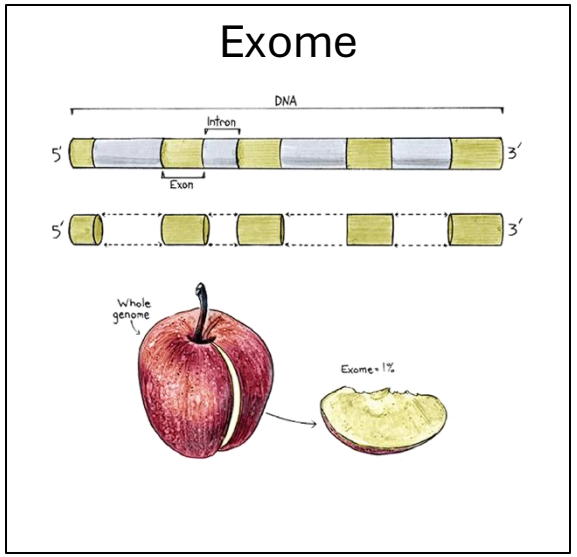
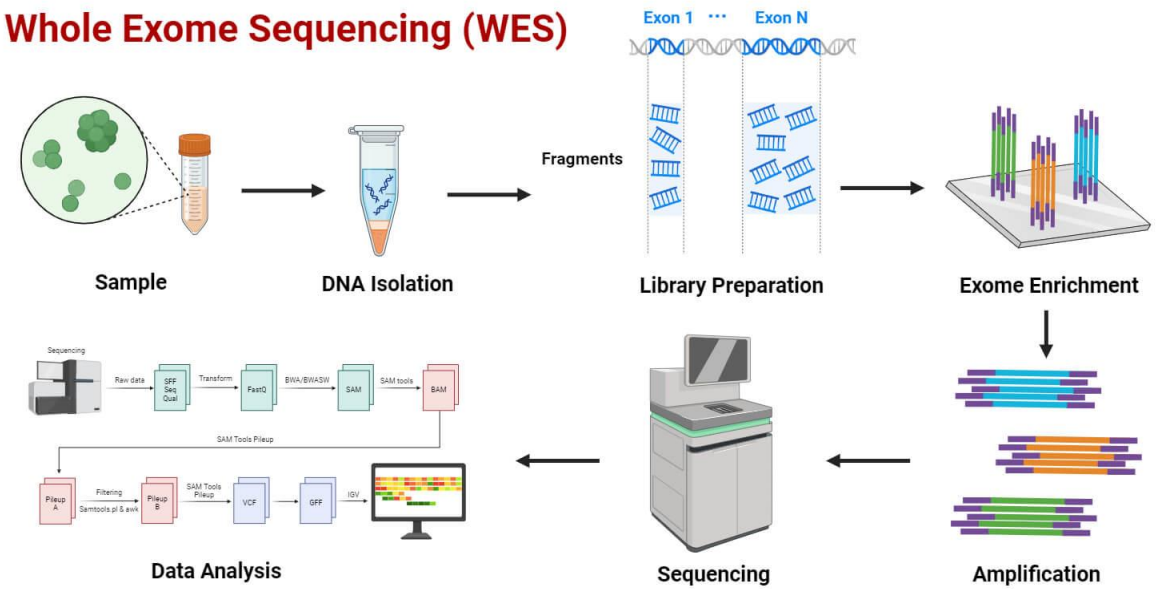


Image source: Sanju Tamang, 2024

Trio-Exome Sequencing for Variant Analysis



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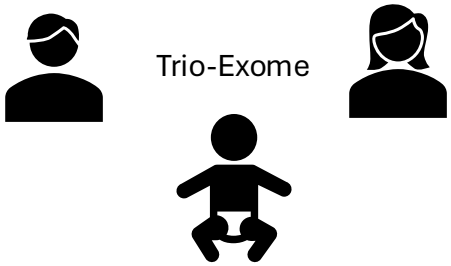


Advantages of trio-exome sequencing:

- *De novo* variants
- Recessive compound
- Inherited pathogenic variants

Pilot Study: Cohort of 34 Patients
H. Virgen Macarena & H. Son Espases

	Haemorrhagic		Ischemic		
	ICH/IVH	SAH	AIS	CSVT	*Total*
Perinatal					
Acute PS	6	4	6	-	
Presumed PS	-	2	10	-	
Postnatal	-	-	4	2	
Males	5	3	8	1	17
Females	1	3	12	1	17
Total	6	6	20	2	N = 34

Variant Analysis Using Virtual Genomic Panels

Bleeding disorders

(e.g., F7, F13A1)

Cerebral vascular malformations

(e.g., ACVRL1, CCM2)

Ischemic stroke risk

(e.g., PDE4D, NOTCH3)

Vascular development

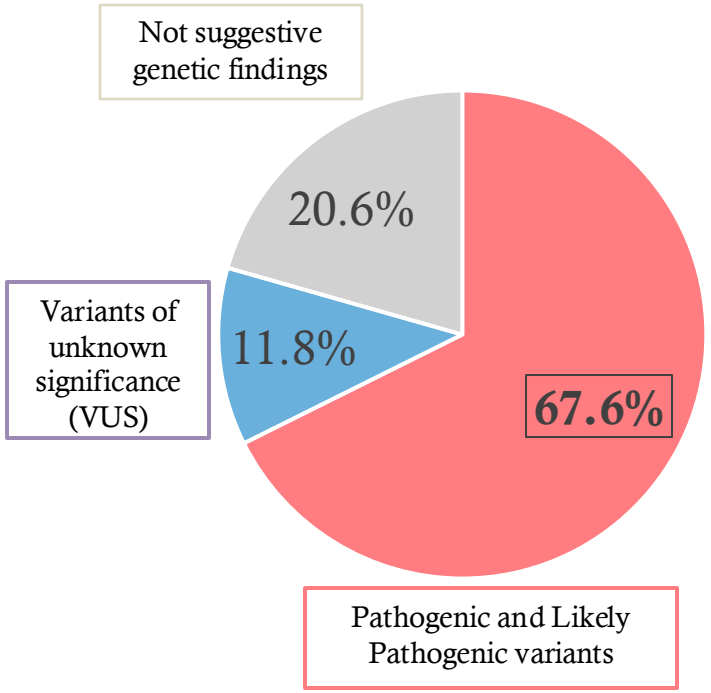
(e.g. NOTCH1, TGFBR2)

Vascular structure: cell polarity, cell-cell and cell-matrix interactions

(e.g. JAM3, PECAM1, COL1A1)

Variants with global allele frequency **<1%**

Almost 70% of Patients Harbored Pathogenic or Likely Pathogenic Rare Variants



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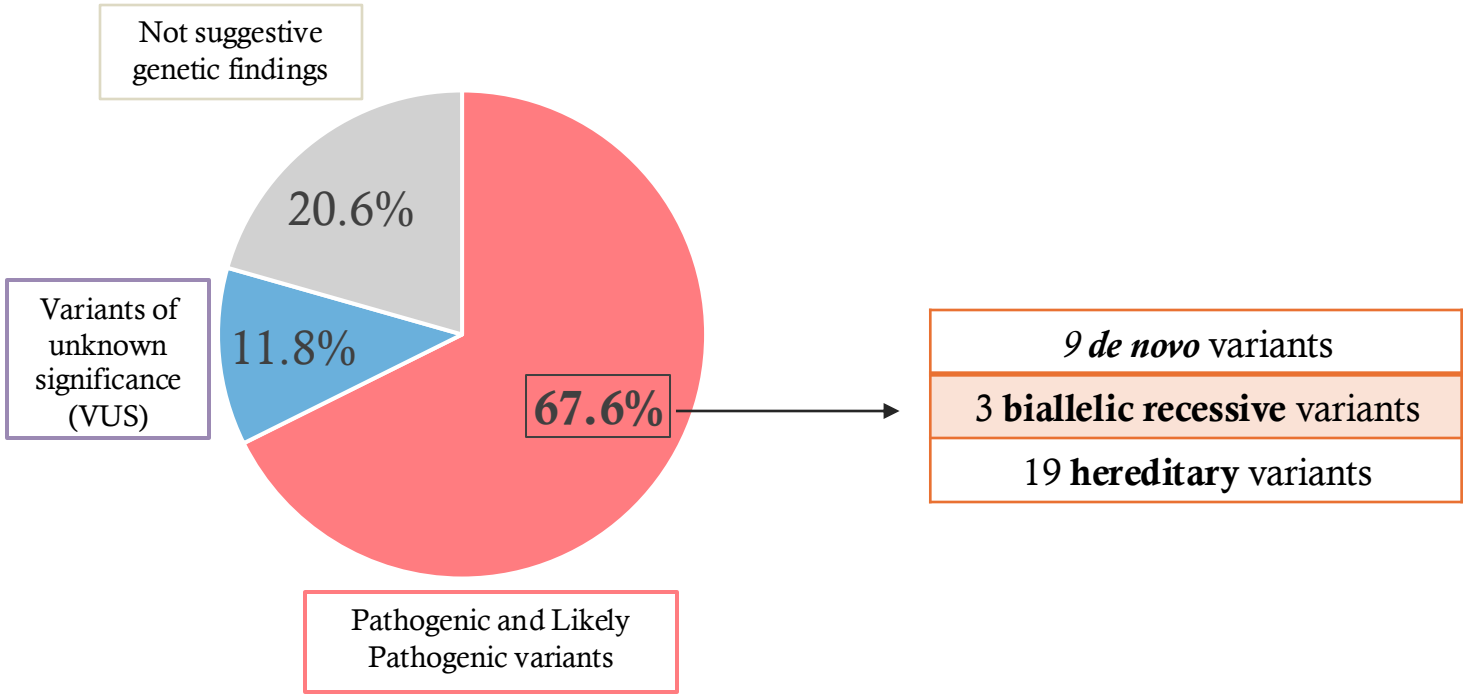


19 Genes Harboring Inherited Variants

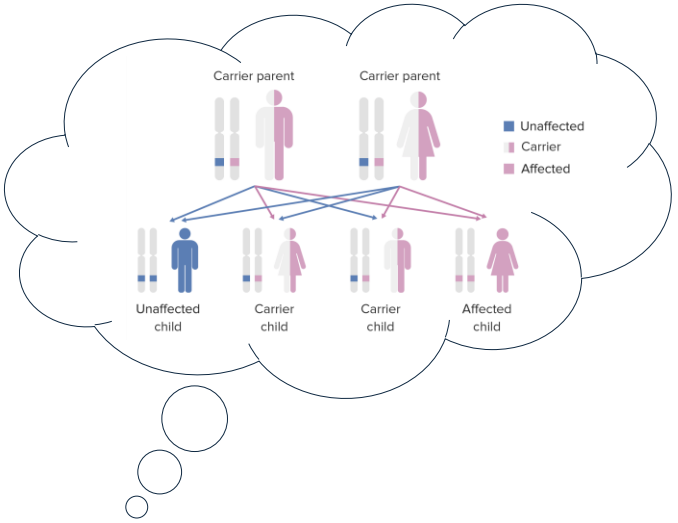
Gene	Main Associated disorders
AARS1	Charcot-Marie-Tooth Disease Type 2N and Leukoencephalopathy
ABCC6	Pseudoxanthoma Elasticum
ABCC8	Diabetes Mellitus, Hyperinsulinemic Hypoglycemia familial
APOB	Familial Hypercholesterolemia
ATM	Ataxia-Telangiectasia syndrome
F11	Factor XI deficiency
GP1BA	Bernard-Soulier Syndrome
HPS6	Hermansky-Pudlak Syndrome
INSR	Donohue Syndrome (Severe Insulin Resistance)
JAG1	Alagille syndrome

Gene	Main Associated disorders
KCNH2	Long QT Syndrome Type 2
KCNMA1	Epilepsy, Paroxysmal Dyskinesia and Liang-Wang syndrome
MPZ	Charcot-Marie-Tooth Disease Type 1B
NDUFAF7	Leigh Syndrome (Mitochondrial Complex I Deficiency)
ROBO4	Aortic Valve Disease 3 and Ascending Aortic Aneurysm
RP1	Retinitis Pigmentosa
SCN3A	Developmental and epileptic encephalopathy
SERPINC1	Antithrombin III Deficiency
SLC5A2	Renal glucosuria

(NCBI Gene, GeneCards)

3 Genes Harboring Biallelic Recessive Variants

Gene	Main Associated disorders
ASPM	Microcephaly, Lissencephaly, various cancers
EPRS1	Leukodystrophy, Microcephaly with Seizures And Cerebral And Cerebellar Atrophy
HPS1	Hermansky-Pudlak Syndrome



(NCBI Gene, GeneCards)

9 Genes Harboring *de Novo* Variants

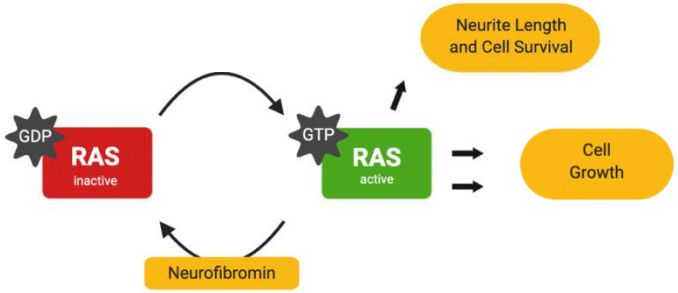
Gene	Main Associated disorders
CBL	Juvenile myelomonocytic leukemia (JMML), Moyamoya Syndrome
TIE1	Angiosarcoma, Inflammatory Breast Carcinoma
TCF12	Craniosynostosis, Intellectual Disability, Skeletal Development Syndromes
NF1	Neurofibromatosis type 1 (NF1), Juvenile Myelomonocytic Leukaemia
SEMA5A	Cri-Du-Chat Syndrome, Autism spectrum disorder (ASD), various cancers
KAT6A	Arboleda-Tham Syndrome, Syndromic Intellectual Disability
CAMK2A	Intellectual Developmental Disorder, Cortical Dysplasia With Other Brain Malformations
ENC1	Sandhoff Disease, Neuroblastoma, various cancers
RPA1	Disorders of DNA Repair (non-specific)

(NCBI Gene, GeneCards)

de Novo Rare Variants

RELATED TO STROKE RISK AND VASCULAR MALFORMATIONS

Gene	Functional effect of the mutation	Function	Main Associated Pathologies (non-stroke)	Potential Link to Arterial Ischemic Stroke (AIS)	Source
NF1 (Neurofibromin 1)	missense	Ras-GAP protein; tumour suppressor controlling cell growth/differentiation.	Neurofibromatosis type 1 (NF1), juvenile myelomonocytic leukaemia, Watson syndrome, gliomas and learning disabilities	As a RASopathy can affect the vascular formation and influence various cellular processes that determine the brain injury	PMID: 12432832; PMC11303248; PMC5873857

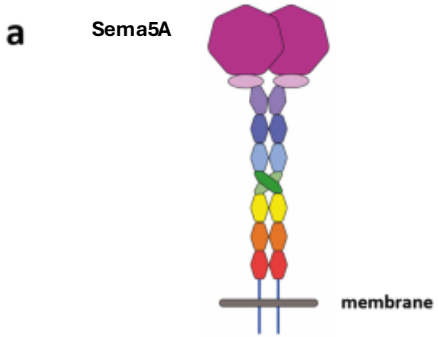


Modified from PMID: 32026187

de Novo Rare Variants

RELATED TO VASCULAR DEVELOPMENT

Gene	Functional effect of the mutation	Function	Main Associated Pathologies (non-stroke)	Potential Link to Arterial Ischemic Stroke (AIS)	Source
SEMA5A (Semaphorin 5A)	missense	Semaphorin family guidance cue; roles in axon guidance, angiogenesis and cell migration	Cri-Du-Chat Syndrome, Autism spectrum disorder (ASD), cancers (lung, pancreas)	Contributes to the remodelling of cranial blood vessels and the progression of stroke	PMC486745; PMC8957939; PMID: 25651171; PMC1061610; PMID: 38548715

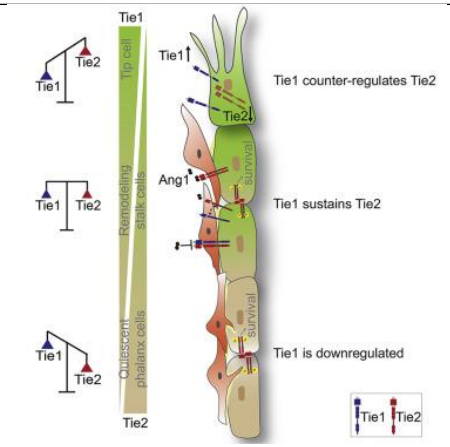


Modified from PMC10978931

de Novo Rare Variants

RELATED TO VASCULAR DEVELOPMENT

Gene	Functional effect of the mutation	Function	Main Associated Pathologies (non-stroke)	Potential Link to Arterial Ischemic Stroke (AIS)	Source
TIE1 (Tyrosine kinase with immunoglobulin-like and EGF-like domains 1)	missense	Endothelial receptor kinase involved in angiogenesis and vessel stability	Angiosarcoma, Inflammatory Breast Carcinoma, Malignant Renovascular Hypertension	Impairment of endothelial stability and cerebrovascular maturation	PMID: 38820174 PMC9508414; PMC6309948

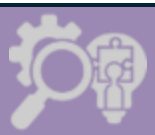


PMID: 26344773

TAKE-HOME MESSAGES

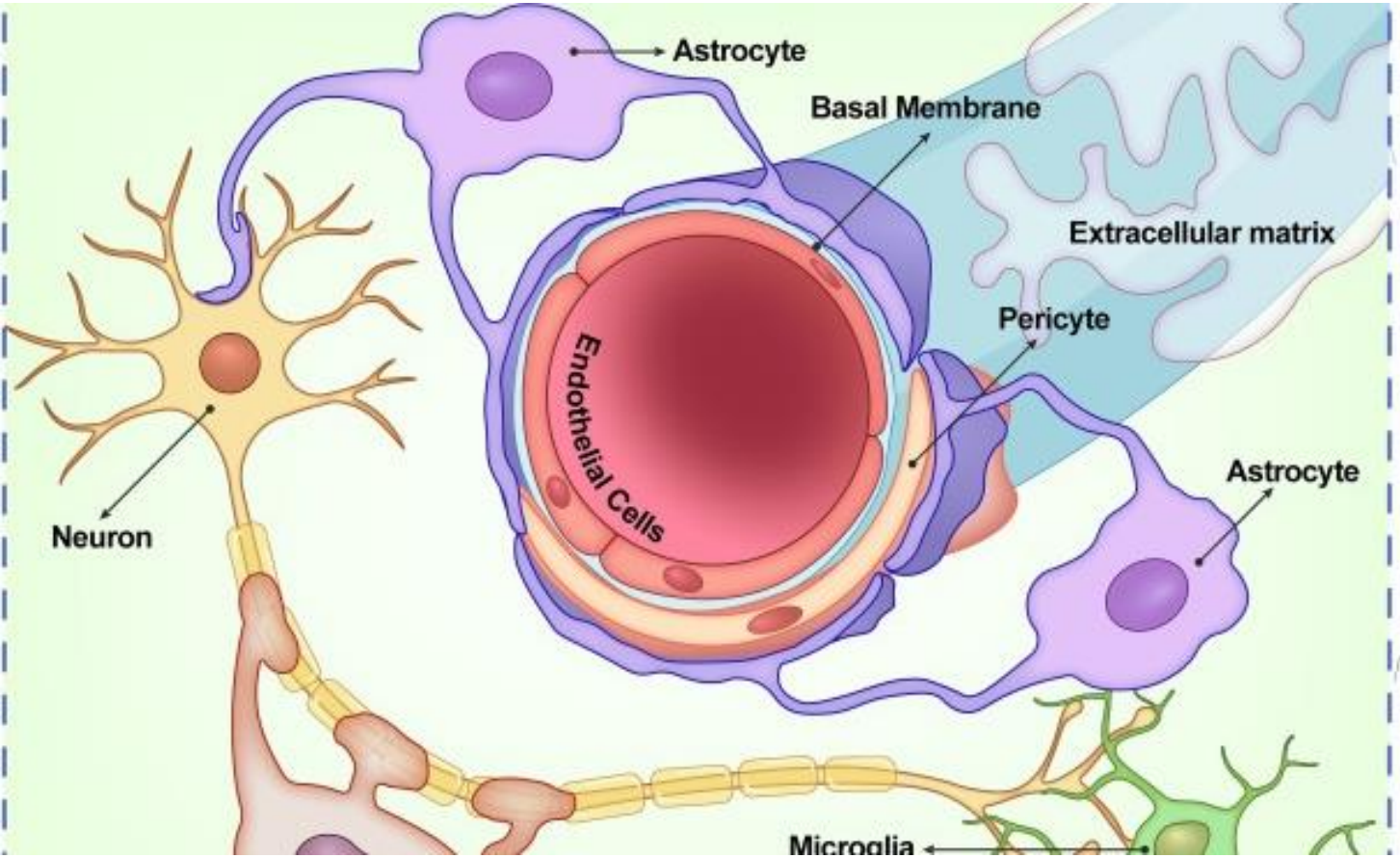
Perinatal stroke results from a broader spectrum of genetic abnormalities than previously thought

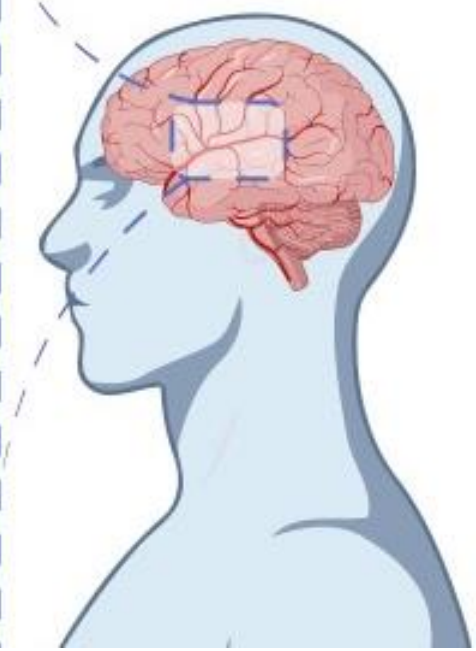
Trio-exome sequencing was highly effective in diagnosing pediatric stroke



Need for deeper investigation into rare genetic contributors to stroke

WP4. 3D-models of NVU-derived from patients to confirm variant's pathogenicity and to model BBB dysfunction, Inflammation & Angiogenesis





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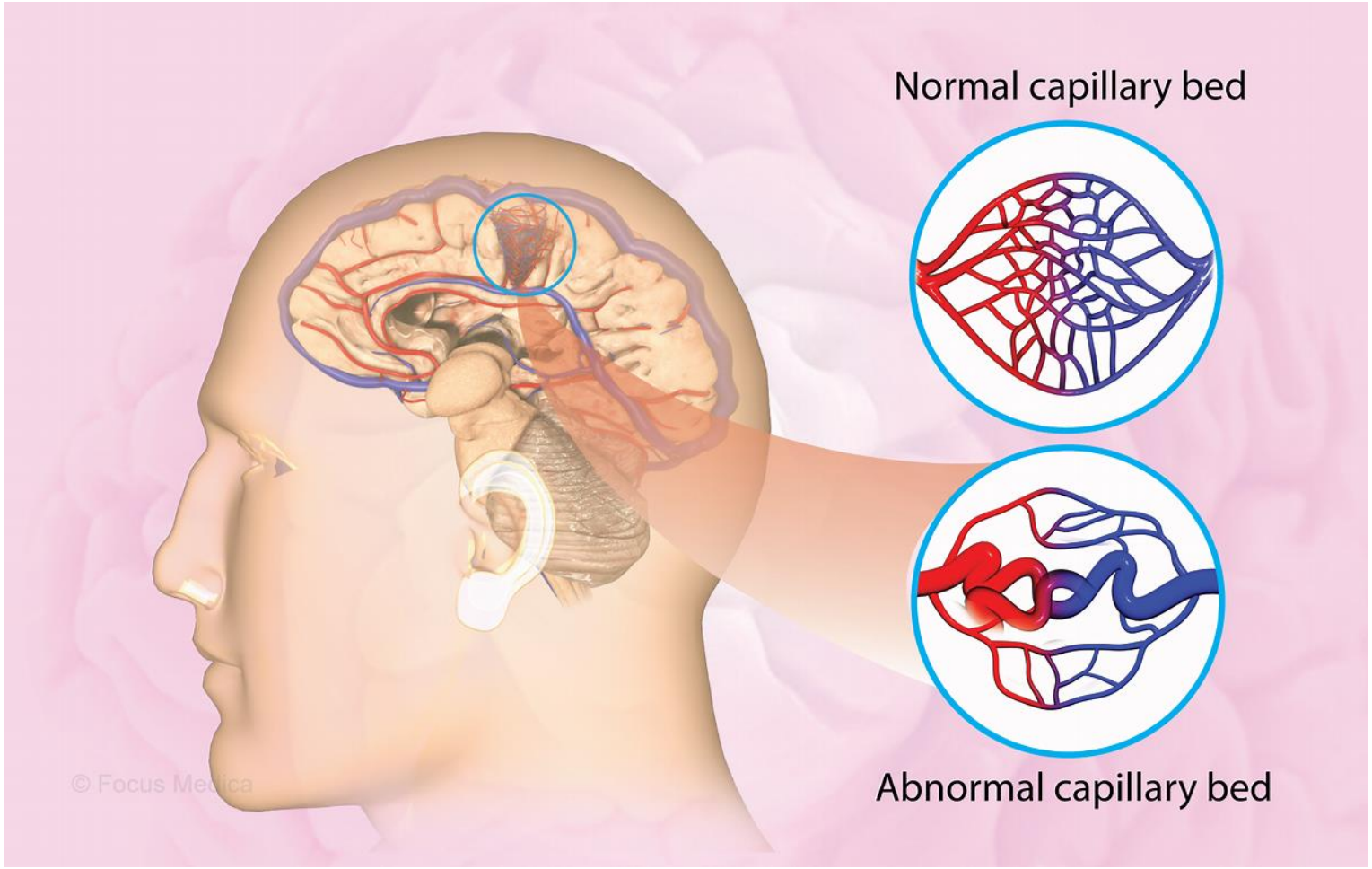
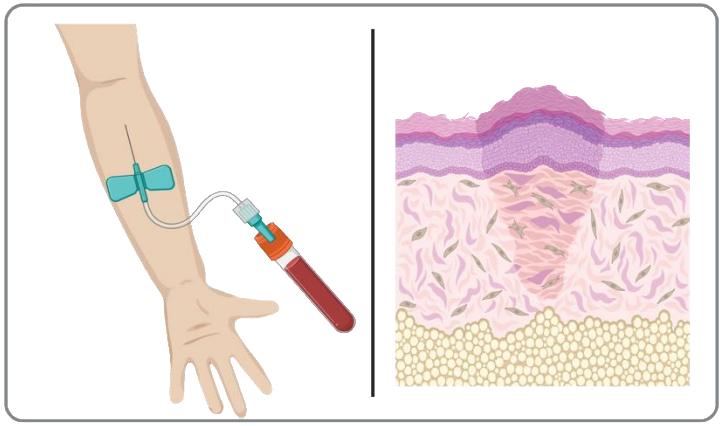
3D models of brain capillary beds

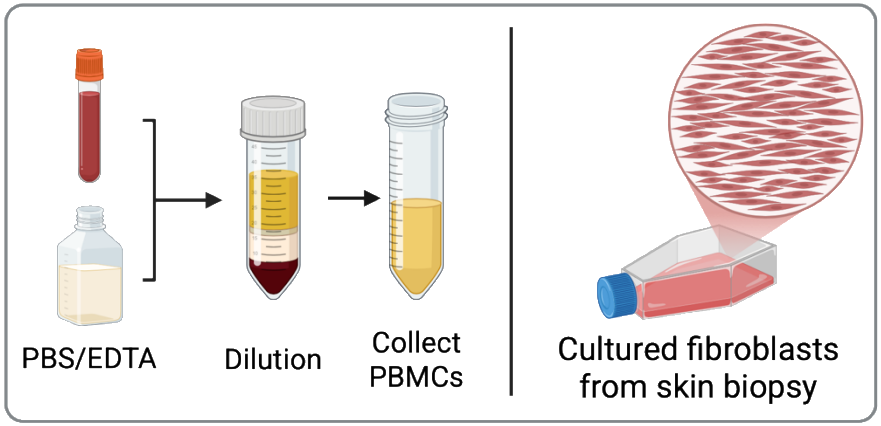


Generation of 3D-NVU Models from iPSCs Derived from Patients' PBMCs or Skin Fibroblasts

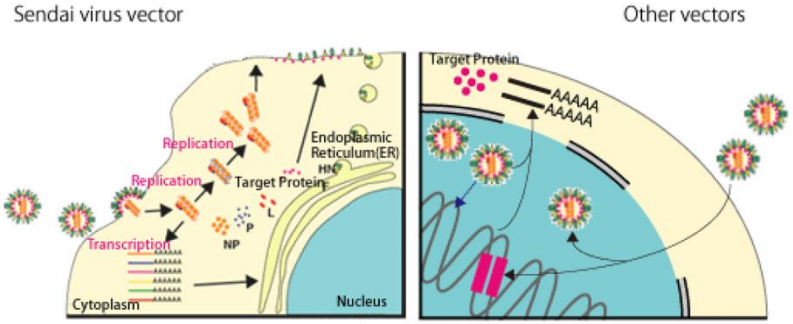
1 Blood collection or skin biopsy from patients



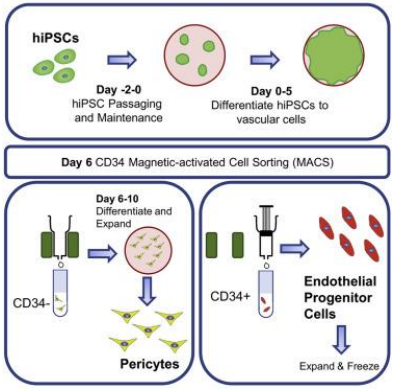
2 Harvest PBMCs or culture fibroblasts

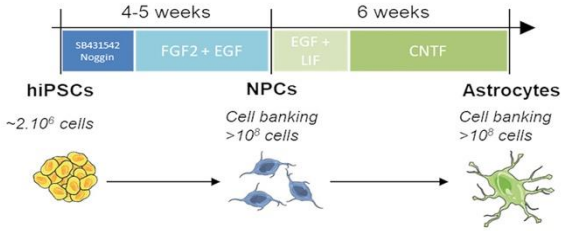


3 Reprogram PBMCs or skin fibroblasts to iPSCs

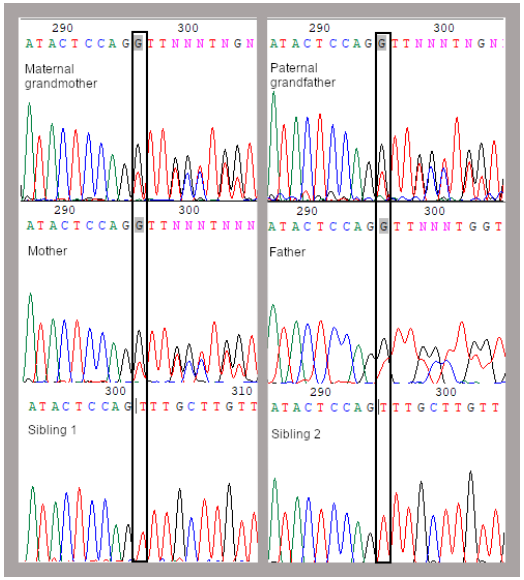


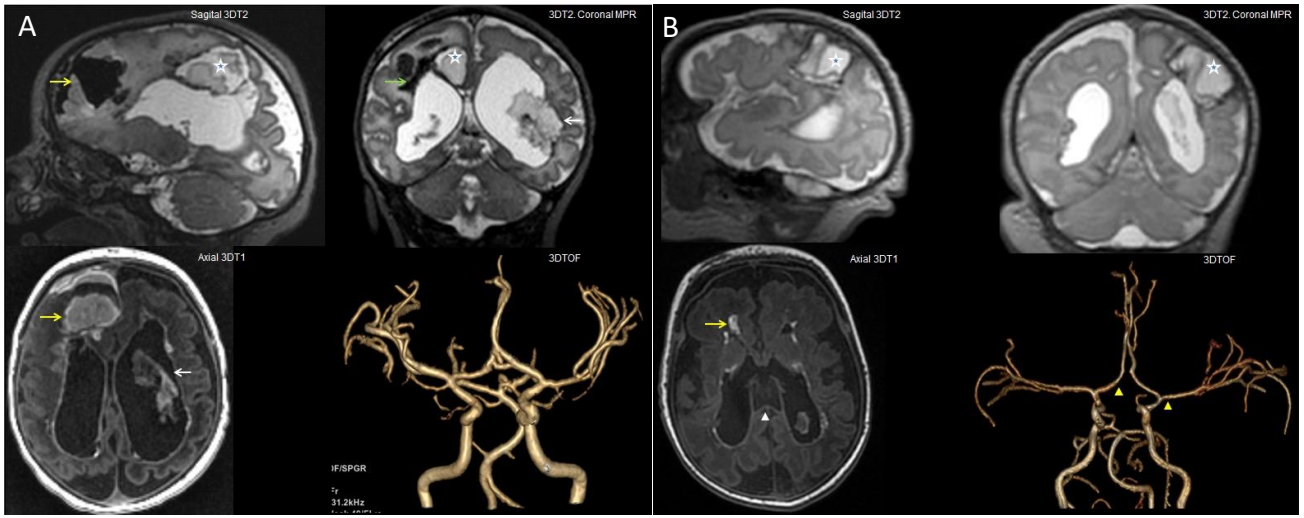
4 Differentiate patients-derived iPSCs to endothelial cells, pericytes and astrocytes





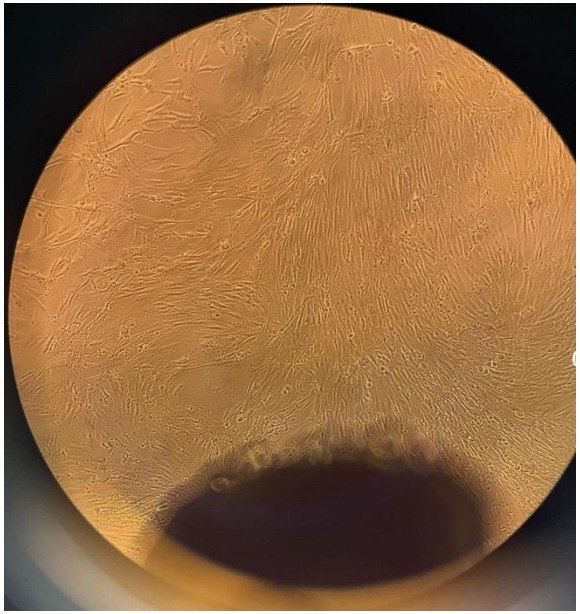
ICH associated with a biallelic recessive nonsense variant in the ESAM gene

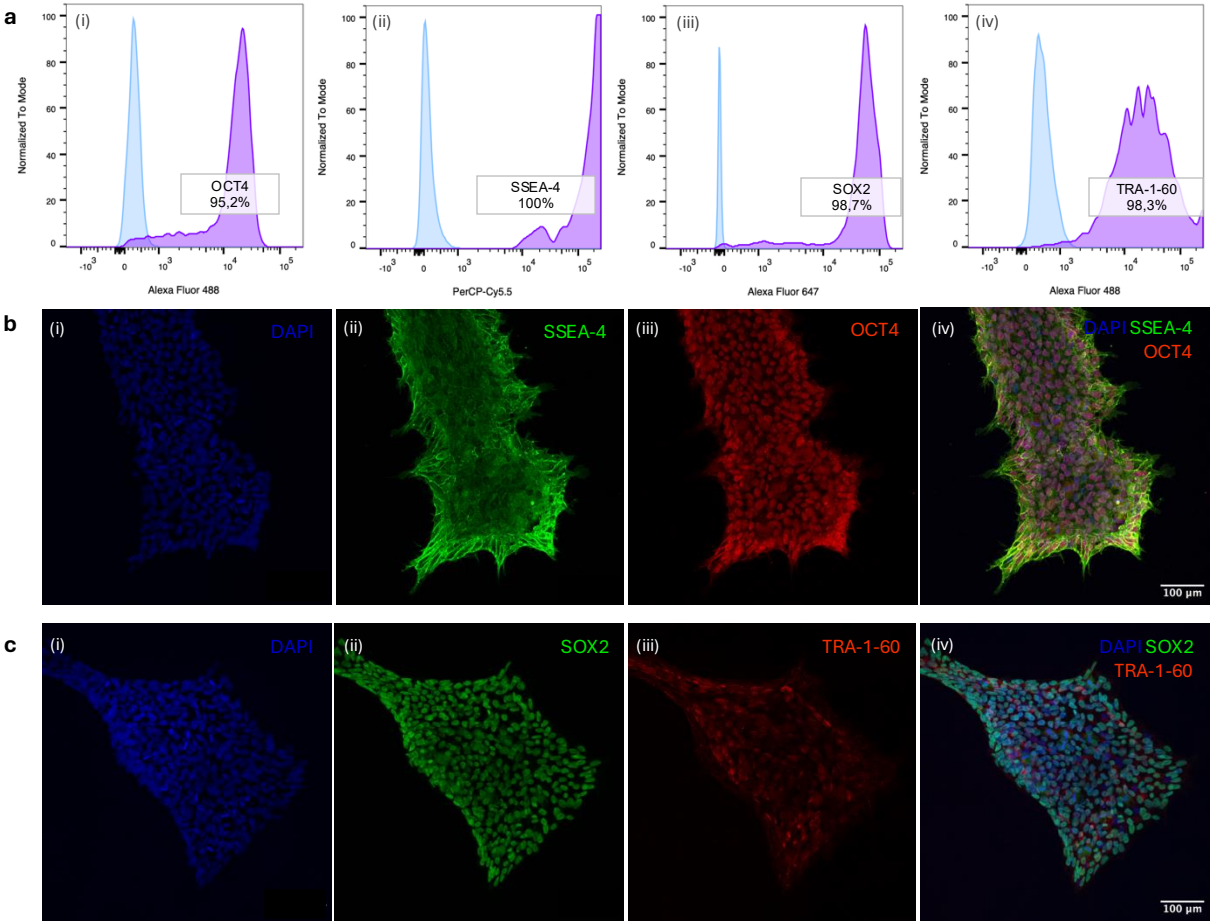




Lecca M, et al. *Am J Hum Genet*. 2023;110(4):681-690.

Generation of iPSCs from Skin Fibroblasts of two siblings harboring a biallelic recessive nonsense variant in the *ESAM* gene





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Denise G. Gornatti
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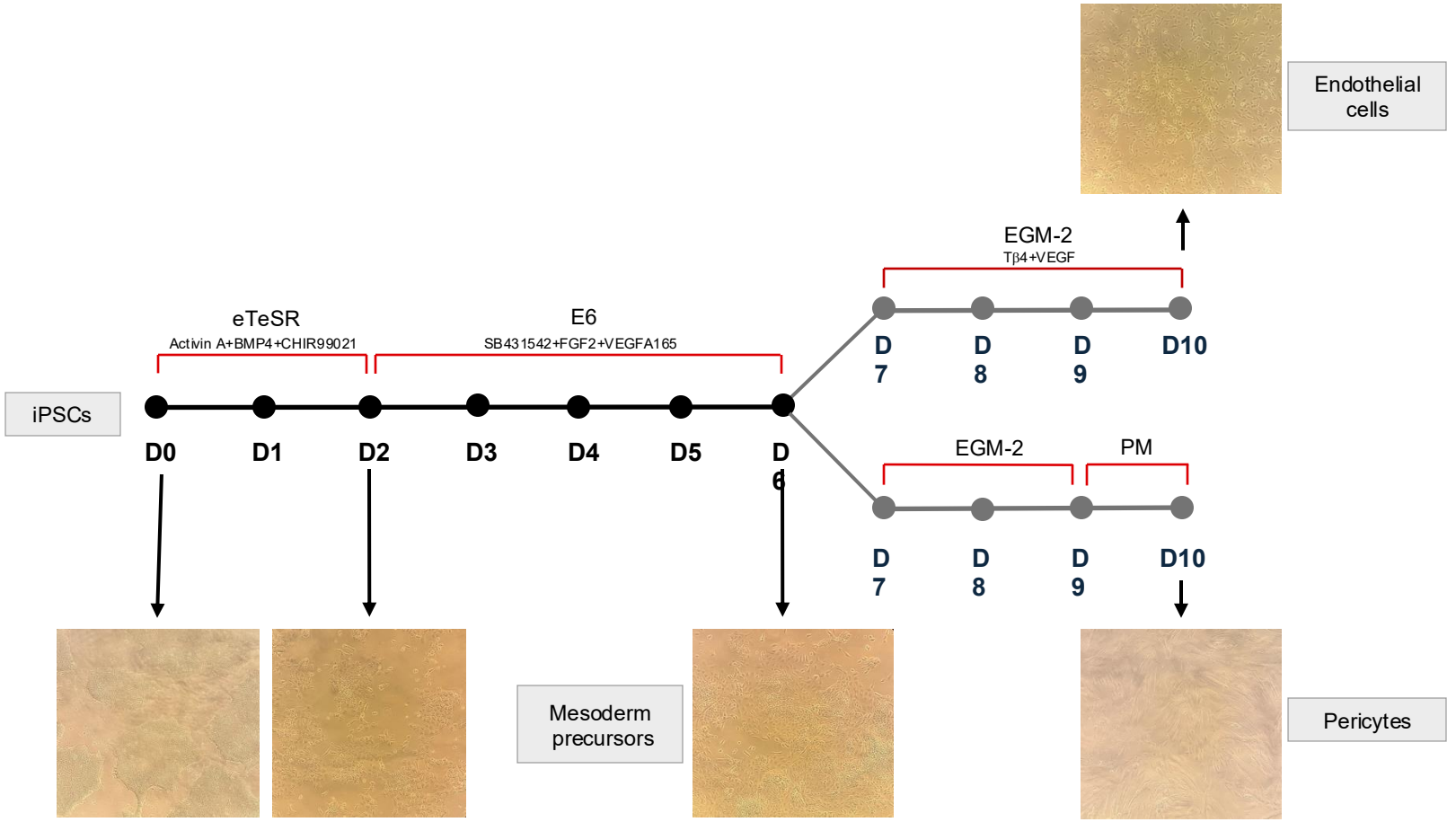
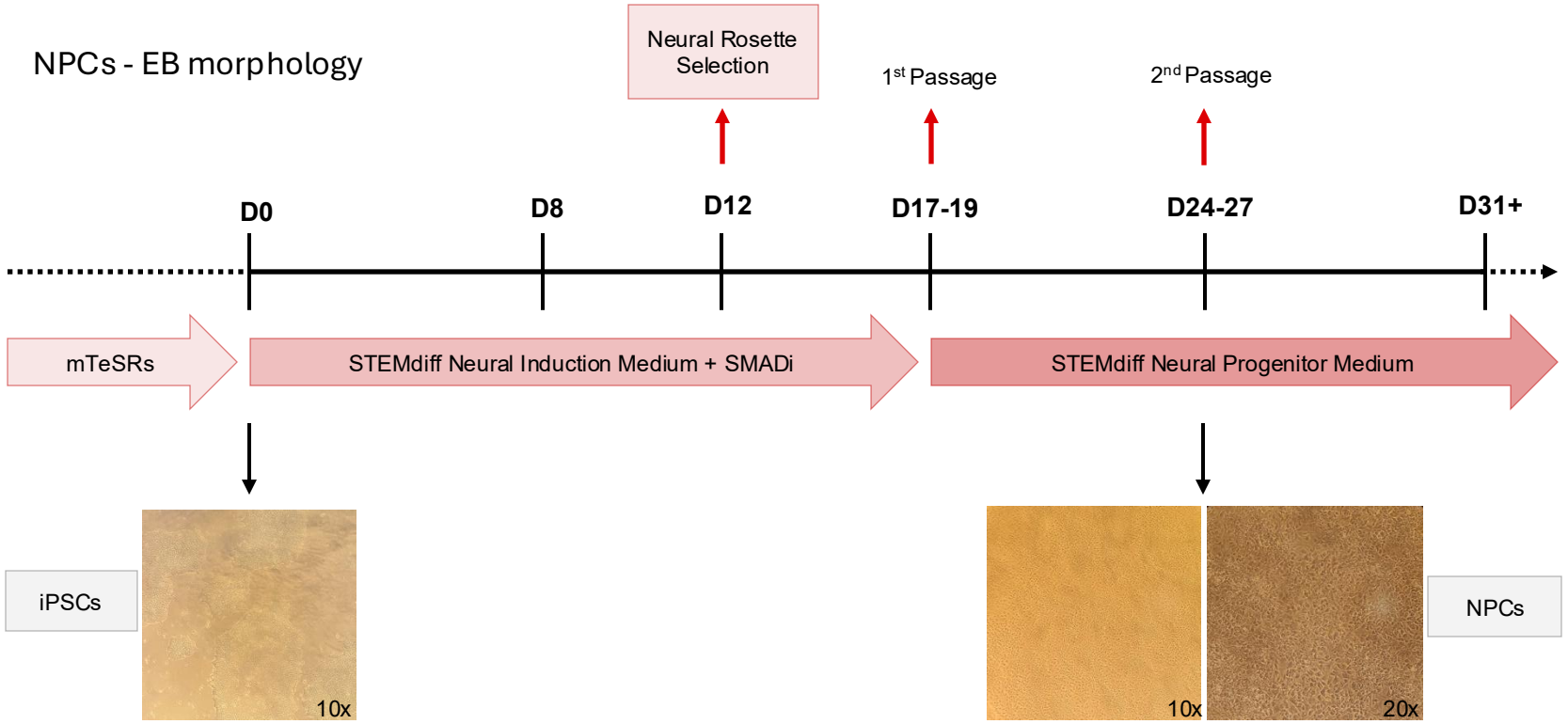
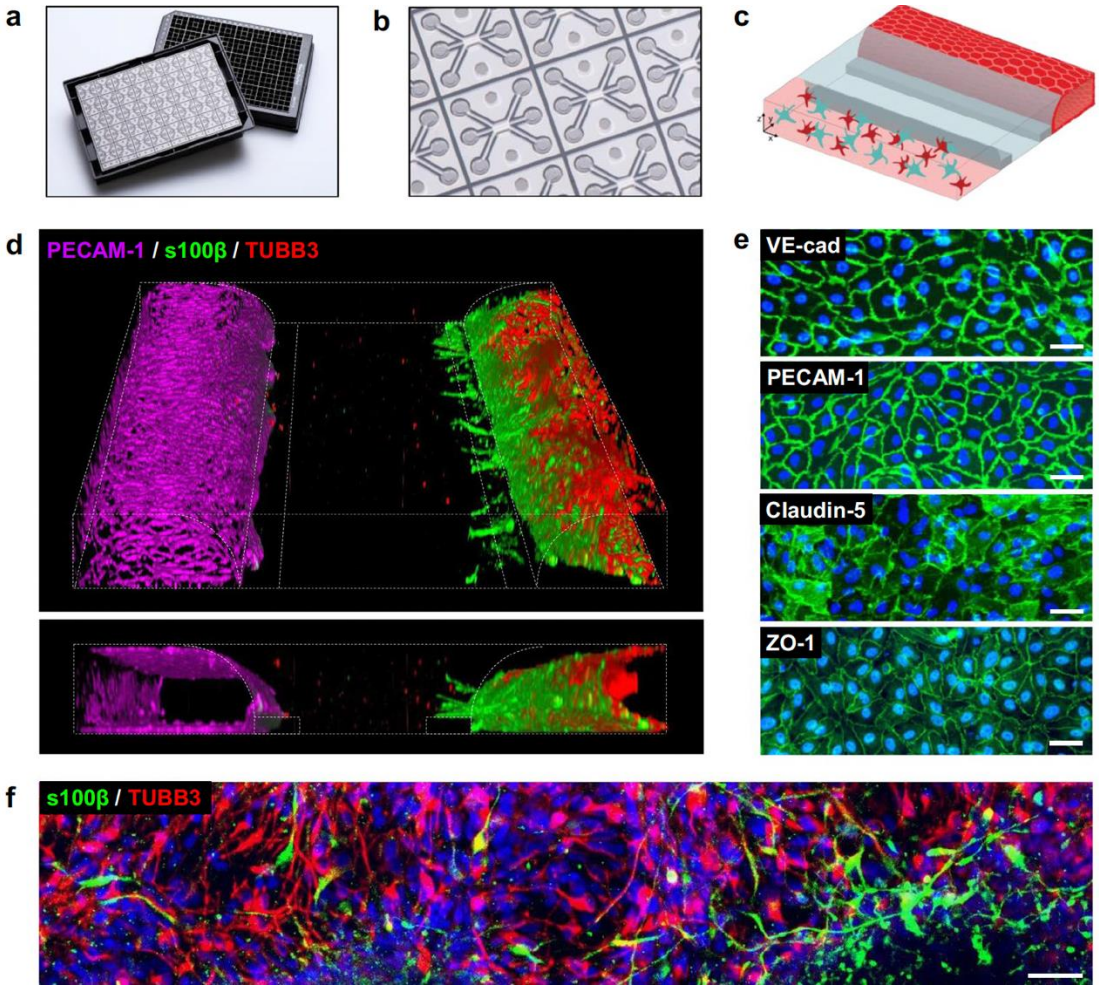
Differentiation of iPSCs to Endothelial Cells and Perycites



Differentiation of iPSCs to Neural Progenitors Cells and Astrocytes



Brain endothelial cells, astrocytes, and neurons in a 3D NVU on-a-chip



Wevers et al. *Fluids and Barriers of the CNS* (2021) 18:59

PReDICT Consortium

Thanks for your attention!

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