

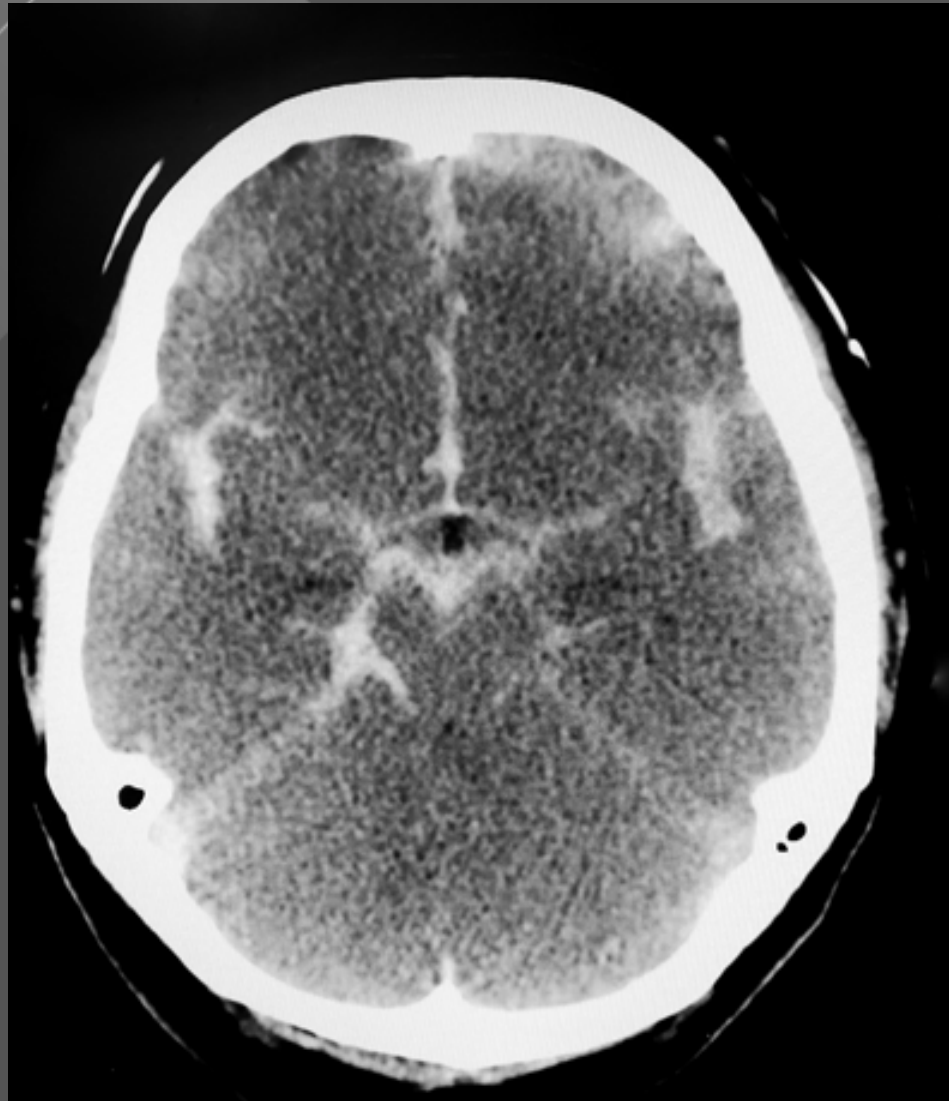
Genética y epigenética del vasoespasma y la ict en la hemorragia subaracnoidea aneurismática

II congreso anual ricor-ictus



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Barcelona (SPAIN)

ANEURISMAL SUBARACHNOID HEMORRHAGE



1

Epidemiology

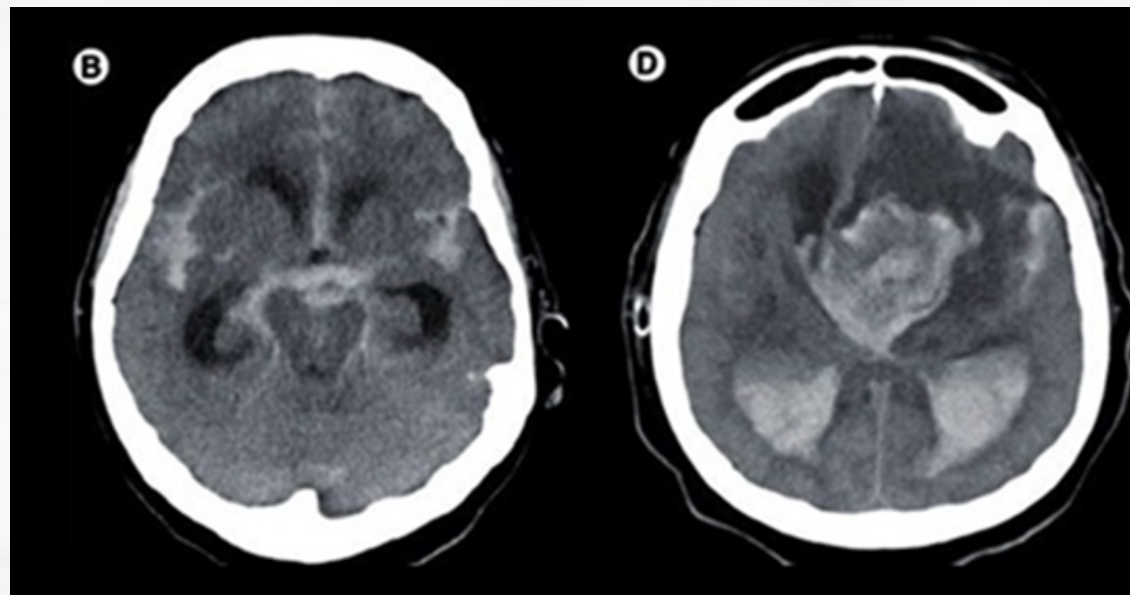
5% all stroke
mean age 50-60y

2

Prognosis

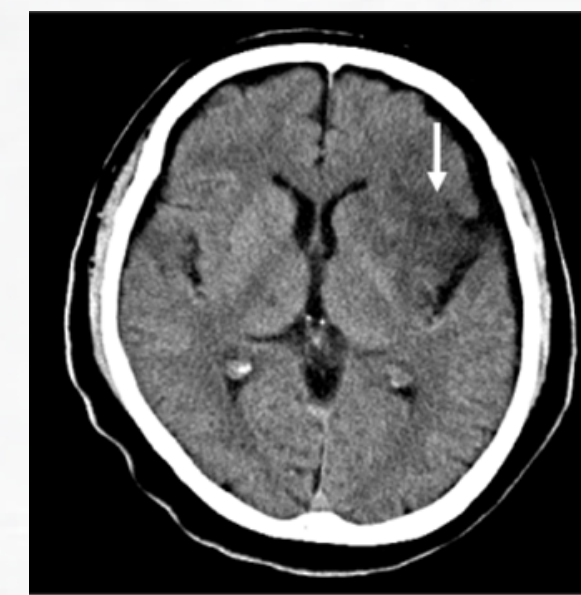
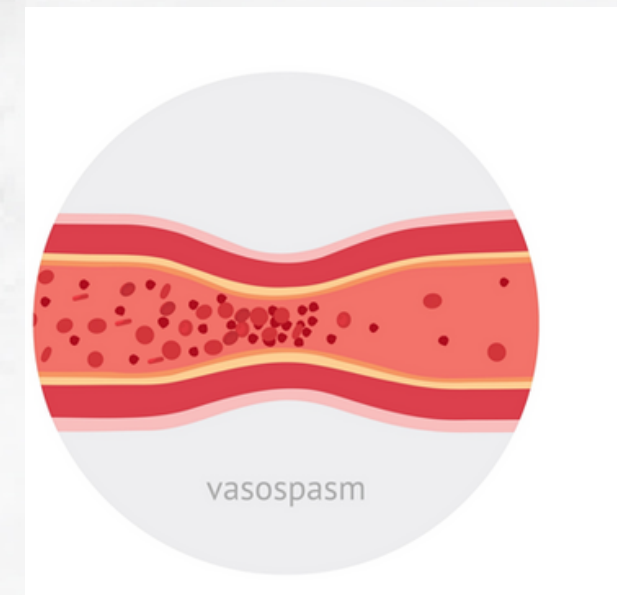
Mortality 30%
Improved in last decades

PROGNOSIS



INITIAL BLEEDING

WFNS scale
Fisher scale



COMPLICATIONS

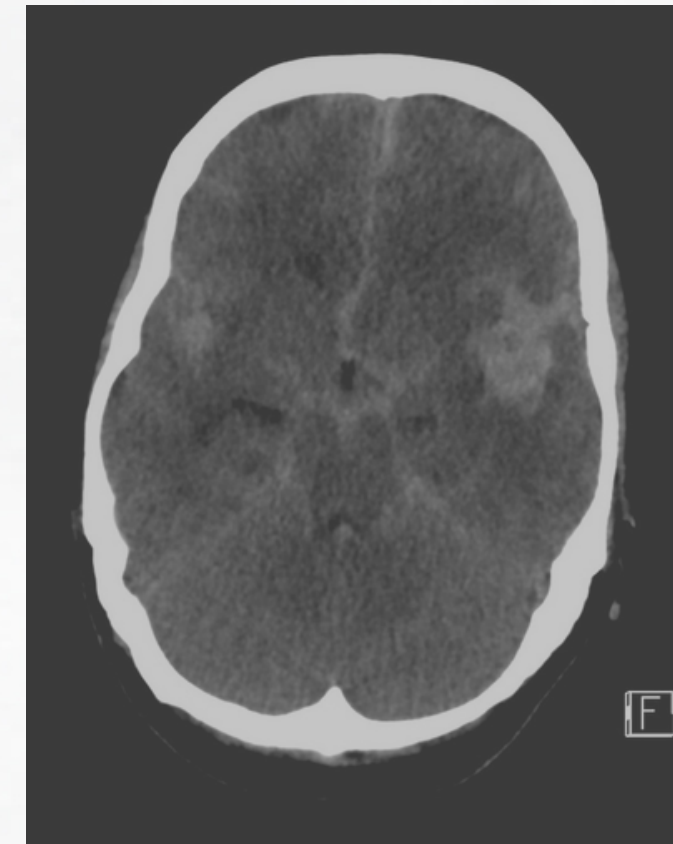
Rebleeding
Vasospasm
DCI

27 y female, right MCA ane, clipped



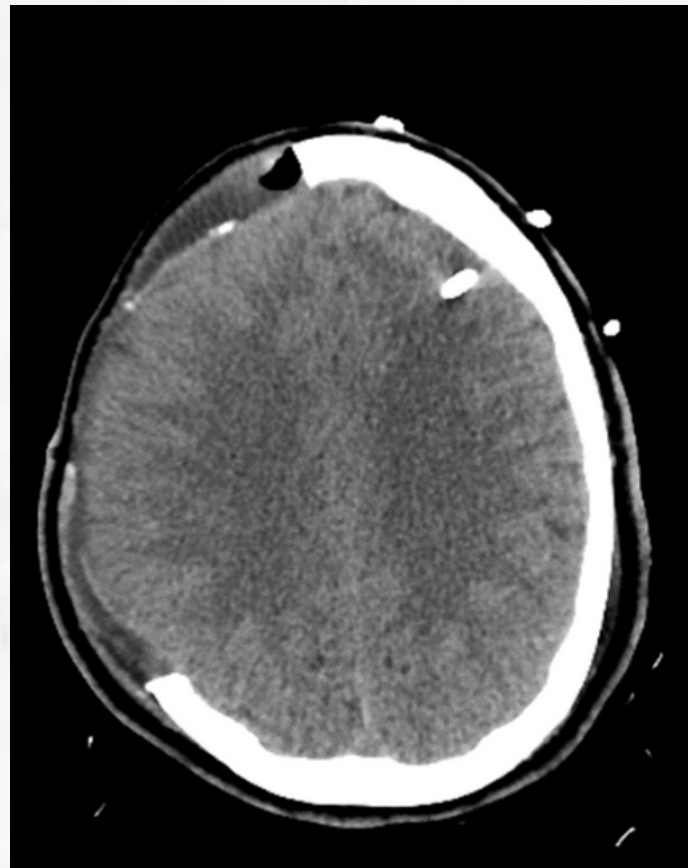
Severe Vasospasm

44y female, left MCA ane, coiled



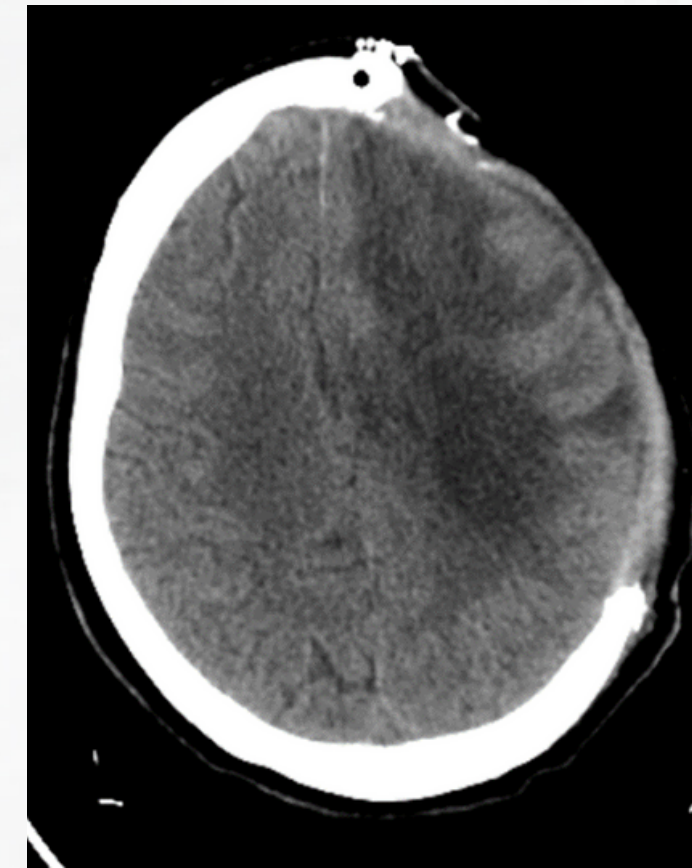
NO VASOSPASM

No DCI



Severe Vasospasm 4rd day

DCI



NO VASOSPASM

***is there a genetic
or epigenetic
predisposition to
vasospasm or
DCI?***



GENETIC STUDIES

Candidate Gene

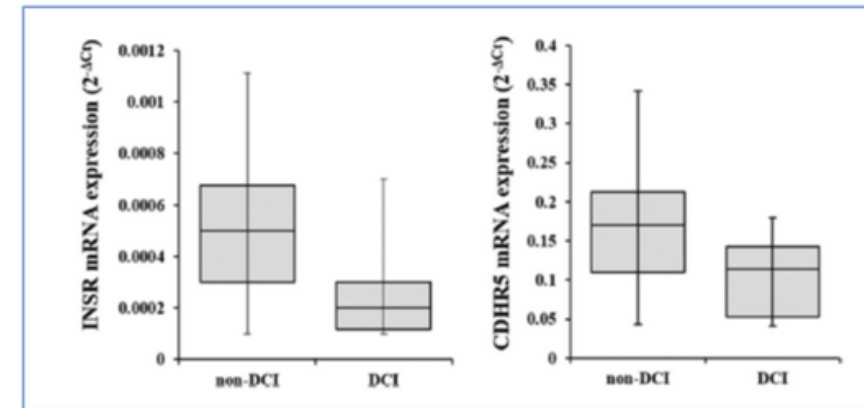
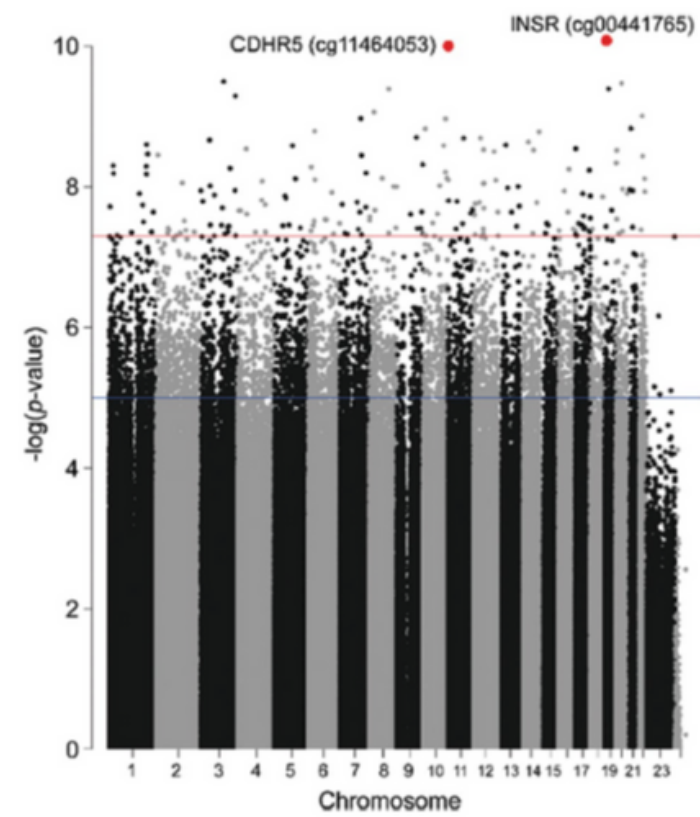
Inflammation
Endothelial dysfunction
Fibrinolytic system
Brain metabolism

GWAS

N= 245 aSAH, Rs999662 (SLC12A3) ---->TCD vasospasm in
P = 3.39 10⁻⁸
N=190 aSAH, no association in GWAS

EPIGENETIC STUDIES DCI

EWAS



EWAS

Kim BJ et al. *Sci. Reports* 2020

AIM OF OUR LINE OF RESEARCH

Identify **genetic variants** of vasospasm and/or DCI, through Genome-wide association (**GWAS**)

Identify **methylation alterations** in loci associated with vasospasm and/or DCI through Epigenome-Wide Association (**EWAS**)

Analyze the influence of the genetic sequence on DNA methylation at specific loci (**meQTLs**),

Create a **risk scale** for vasospasm/ DCI

GENETICS OF VASOSPASM AND DELAYED CEREBRAL ISCHEMIA IN ANEURYSMAL SUBARACHNOID HAEMORRHAGE

GENVADER



multicentric

1. Hospital del Mar Barcelona, Spain.
2. UCL Queen Square Institute of Neurology. University College London, UK.
3. University Medical Center Utrecht, The Netherlands.
4. University of Helsinki, Finland.
5. University of Geneva, Switzerland.
6. CHU Nantes, France.
7. CAN project investigators, France.



inclusion

1. aSAH with data on VS and DCI
2. individual level whole-genome genotype data



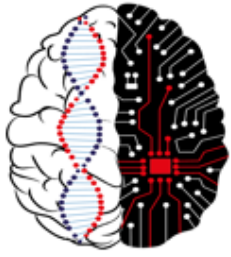
gwas

QC analyses
Controlling for population stratifications
Mixed Model GLM
VS-DCI separatedly



computing

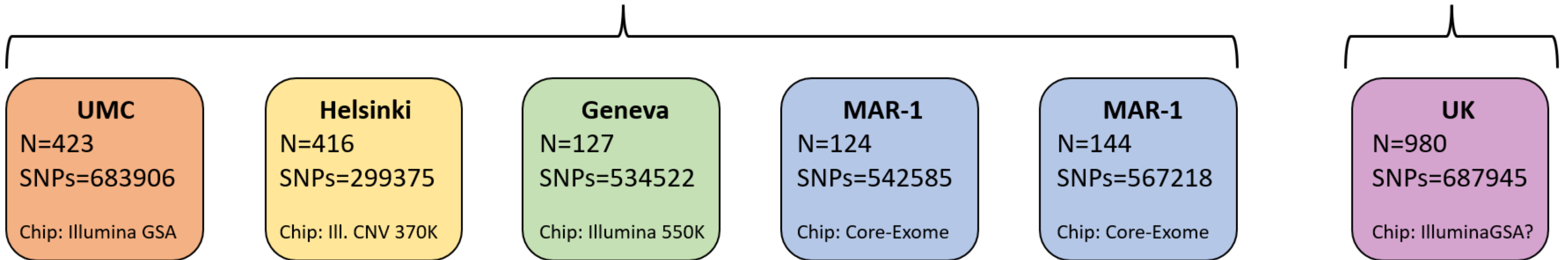
Poligenic risk score
Mediation analysis VS-DCI
Characterization of GWAS loci
Drug target enrichment

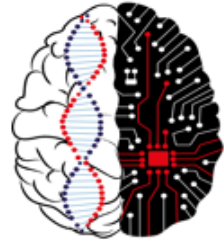


Cohorts description: Patients already included

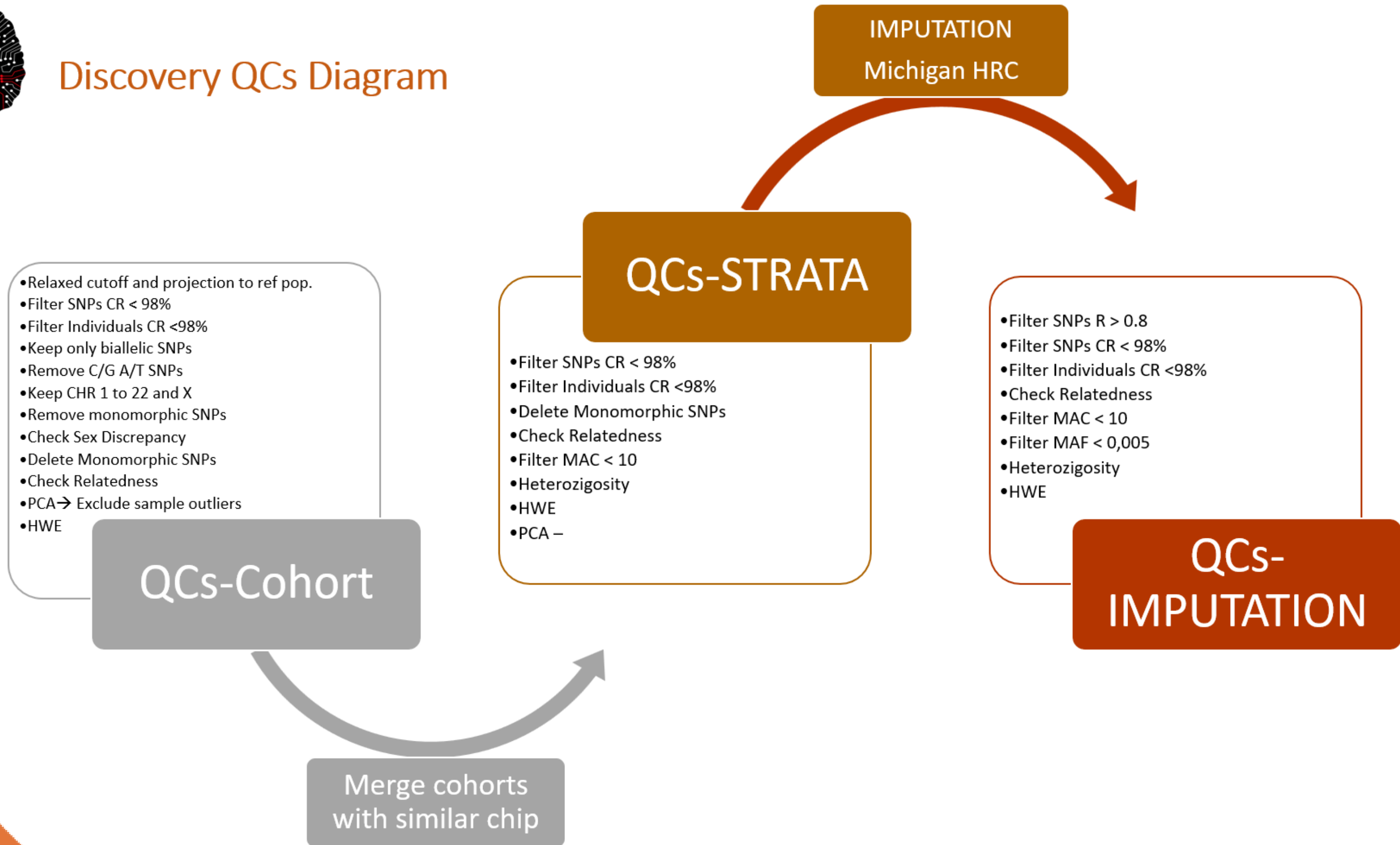
STAGE 1 –DISCOVERY (N=~1300)

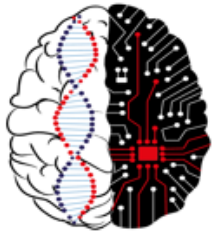
STAGE 2 - Replication



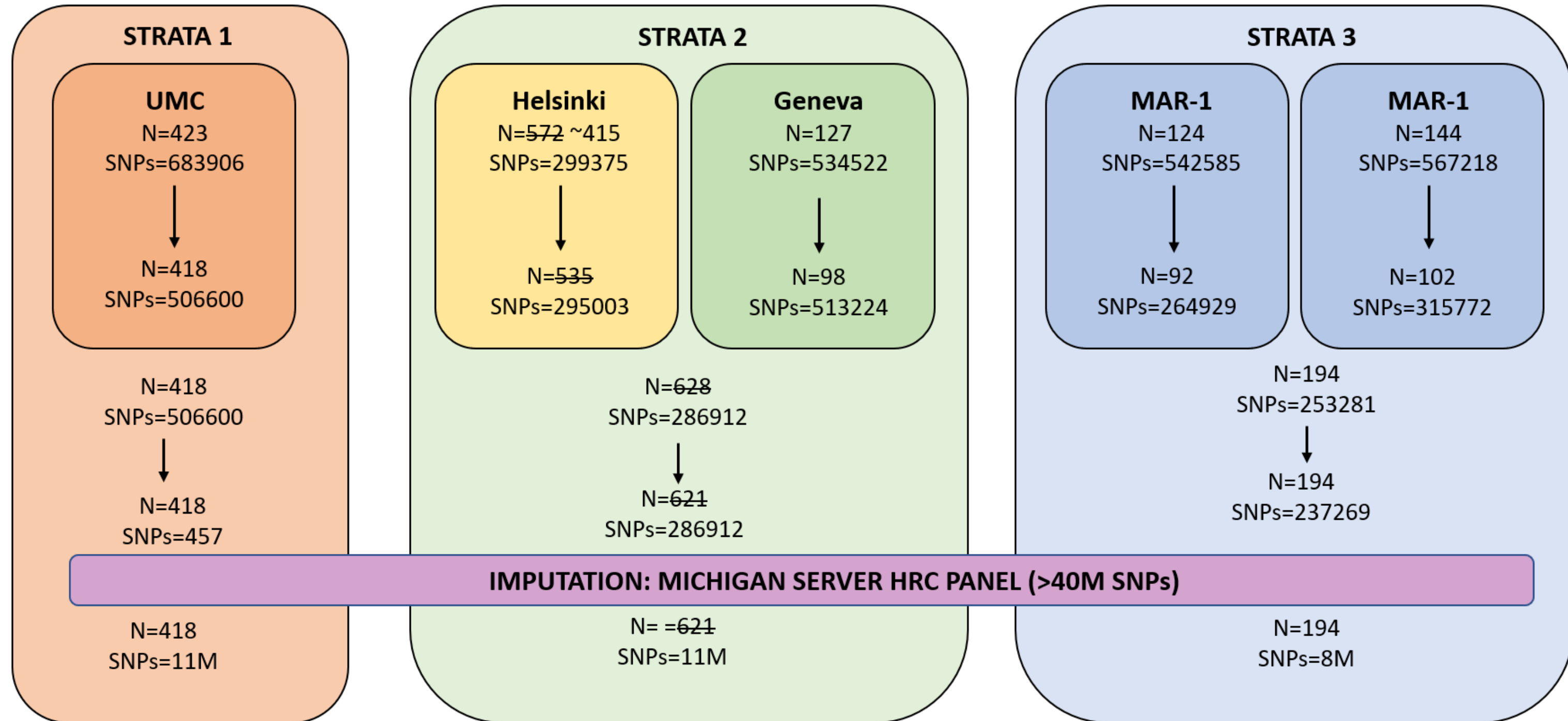


Discovery QCs Diagram





Cohorts after Merging



EPIGENETIC CHANGES IN ANEURISMAL SUBARACHNOID HEMORRAGE




mocentric

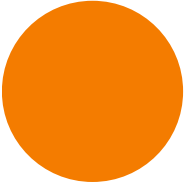
1. Hospital del Mar
Barcelona, Spain


inclusion

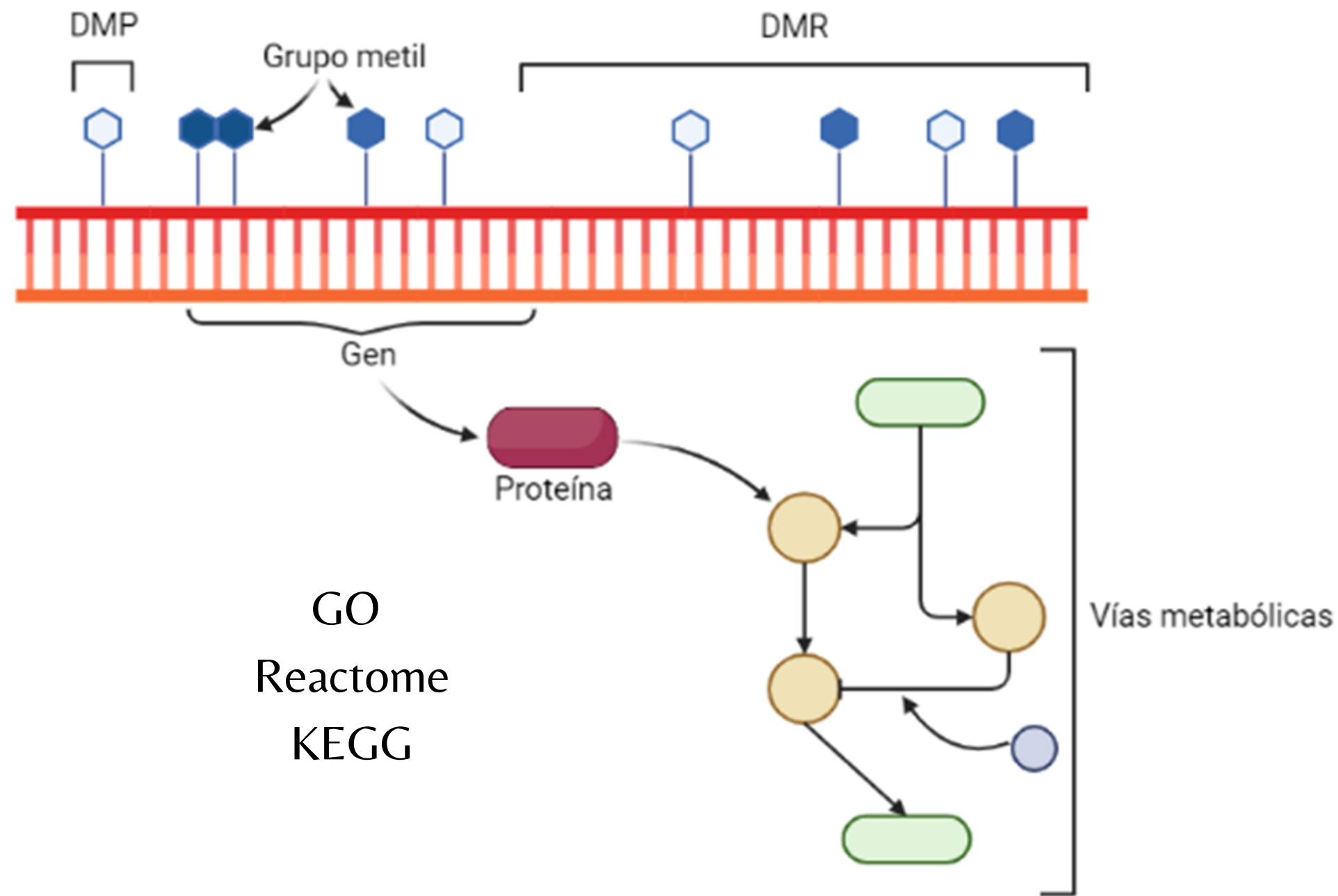
aSAH with data on VS
and DCI

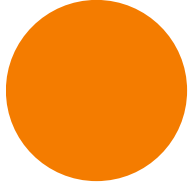

ewas

EPIC Illumina chip (>850K CpG s)
Differential methylation (DMP)
VS-DCI separatedly
Replication


computing

EPIGENETIC CHANGES IN ANEURISMAL SUBARACHNOID HEMORRAGE



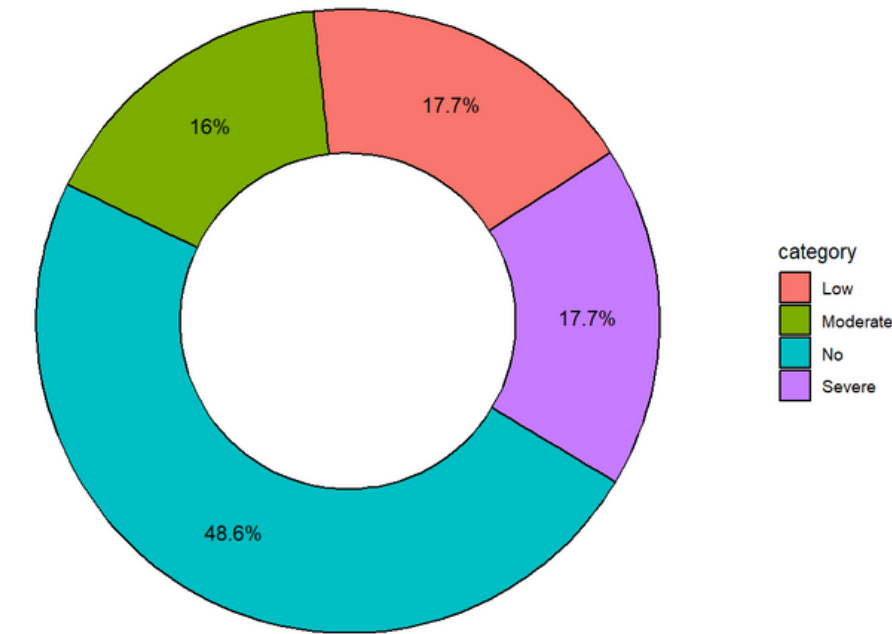

computing

RESULTS

	N=282
Edad	55.0 [17.0;88.0]
Sexo:	
Hombre	93 (33.0%)
Mujer	189 (67.0%)
Etnia:	
Caucásica	241 (85.5%)
Otra	41 (14.5%)
HTA	133 (47.2%)
Fumador	106 (37.6%)
Fisher:	
1	9 (3.19%)
2	23 (8.16%)
3	66 (23.4%)
4	184 (65.2%)
Hunt Hess:	
1	6 (2.13%)
2	152 (53.9%)
3	59 (20.9%)
4	32 (11.3%)
5	33 (11.7%)
Días hasta llegada	0.00 [0.00;32.0]

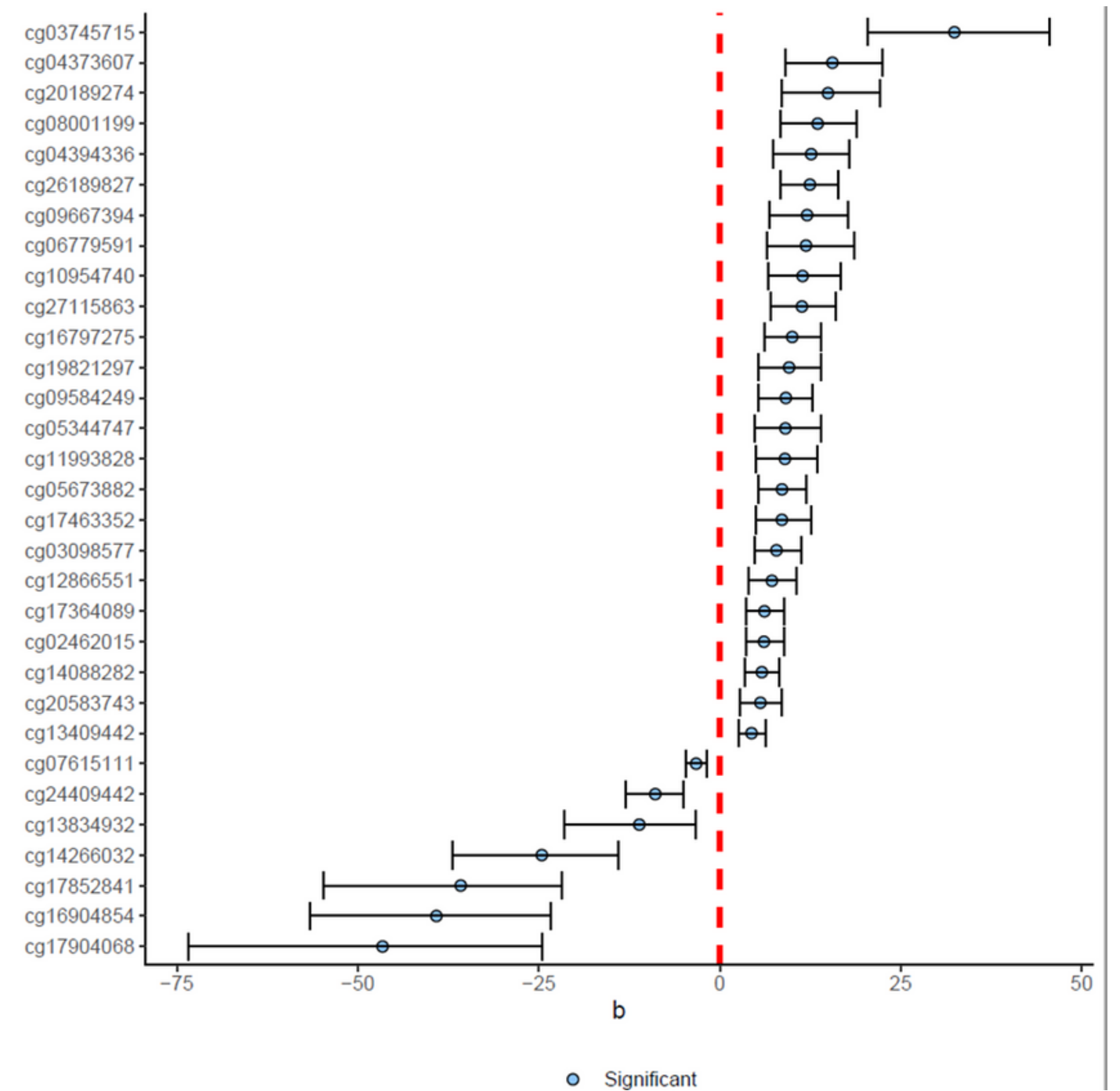
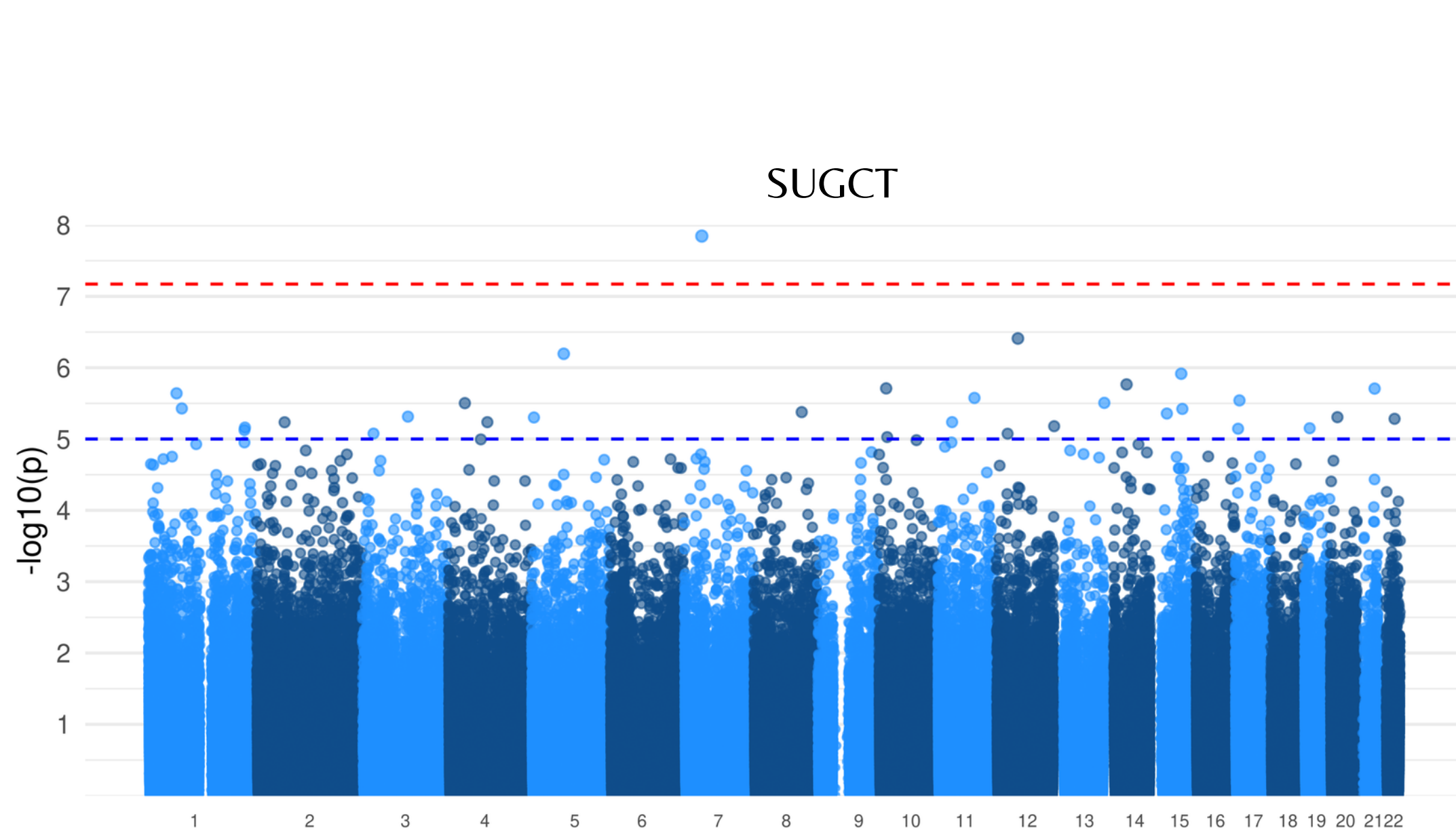
VS 145 (51.4%)

Proportion of Vasospasm Categories



DCI 71 (25.2%)

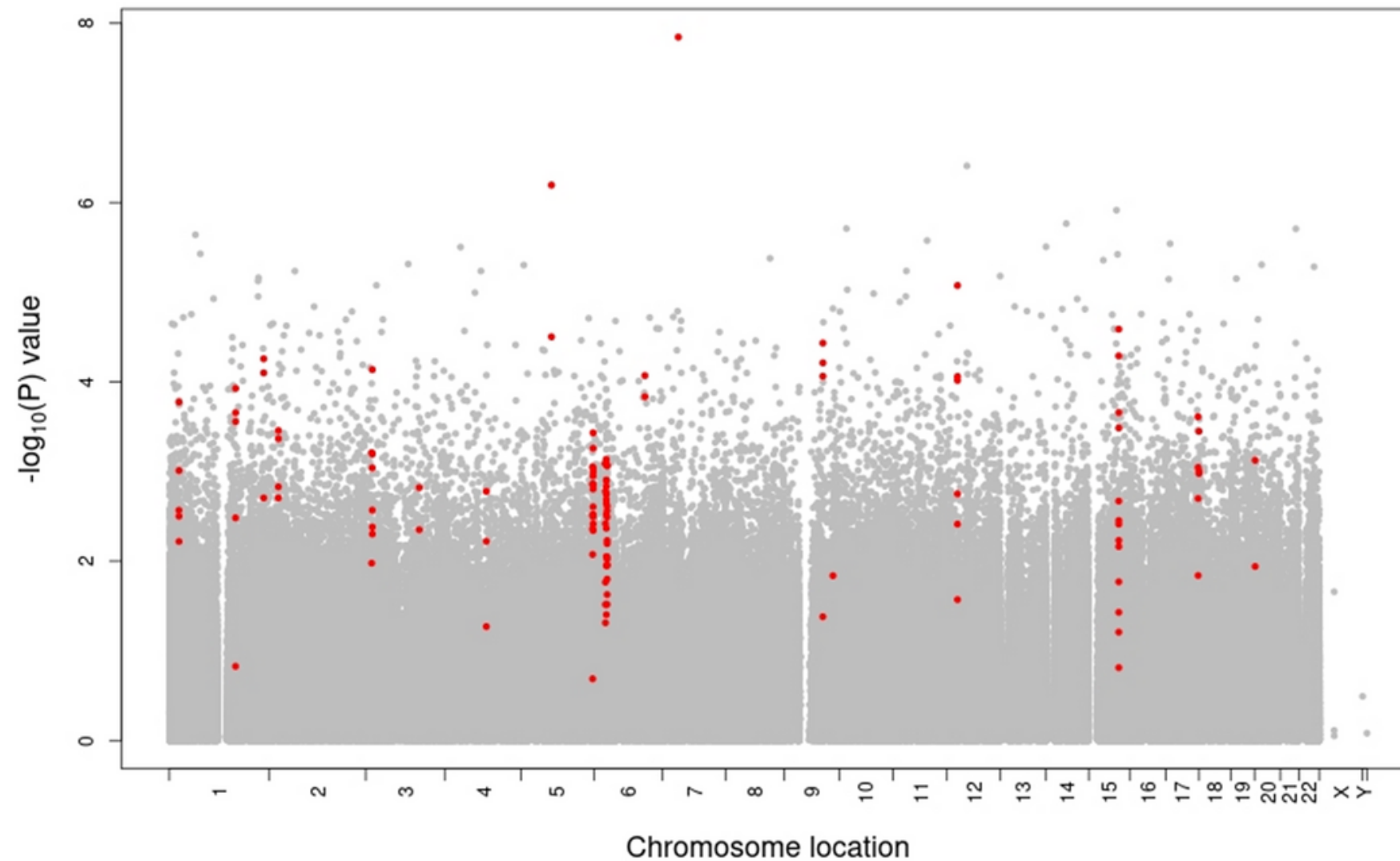
RESULTS VASOSPASM



adjusted by age + sex + smoker + ethnicity + fisher

DMR

vasospasm



* HLA-B, HLA-DPA1, COL11A2 (chr 6)

* COL23A1 (chr 5)

PATHWAYS

- GO
- Reactome
- KEGG

Óxido nítrico
endotelial

Estrés
oxidativo

Inmunidad e
inflamación

Apoptosis

LIMITATIONS

Sample size
Ewas from blood
Need replication

STRENGTH

largest GWAS and EWAS
Exhaustive study and phenotyping
Pathophysiology

Join us !!

IMIM

Parc de Salut
MAR
Barcelona

Institut Hospital del Mar
d'Investigacions Mèdiques



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Neurology Department & Neurovascular Research Group Hospital del Mar Medical Research Institute (IMIM) Barcelona (SPAIN)



J. Jiménez Conde MD, PhD



J. Jiménez Balado MSc, PhD



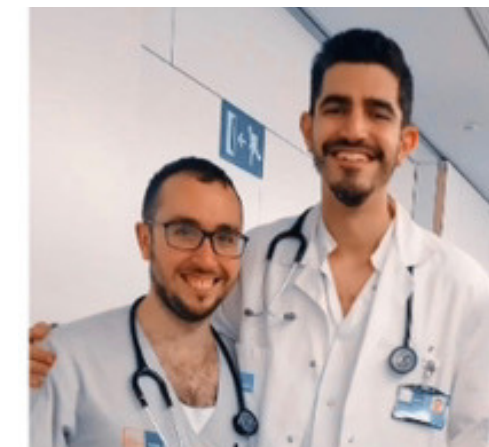
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Antoni Suàrez, MD Adrià Macias, MD



Ana Rodríguez Campello MD, PhD



Eva Giralt MD, PhD



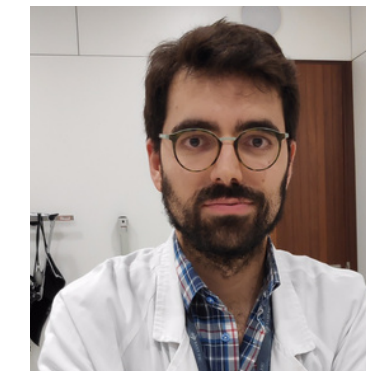
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