破解頭痛之謎

發現血液指標助攻精準醫療

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研究團隊

臺北榮總、陽交大醫學院、中研院、國衛院

*Corresponding



王署君醫師

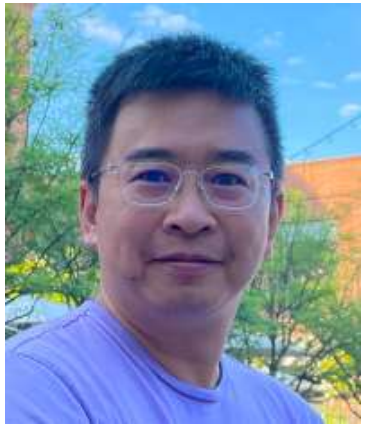
臺北榮總副院長
陽明交大醫學院院長



陳世彬醫師

臺北榮總醫學研究部
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題中心研究員



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與基因醫學研究所助
理研究員



王嚴鋒醫師

臺北榮總神經醫學中
心一般神經科主任

頭痛 是

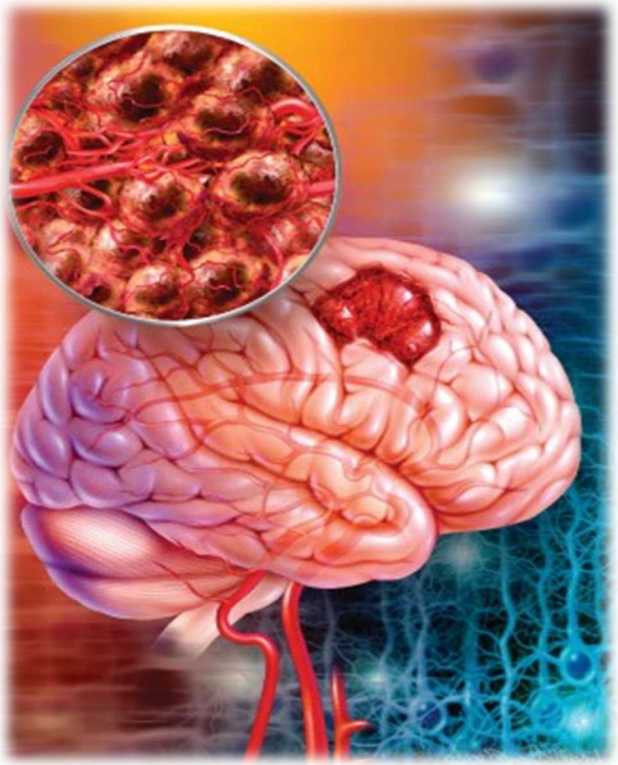
頭裡面長東西?

血管堵住? 血管要爆了?

頸椎長骨刺、眼壓高、
或鼻竇炎造成的？

心理因素?

SARS-CoV-2?





https://heho.com.tw/archives/24578

International Headache Society

Since 2005 台灣頭痛學會 Taiwan Headache Society

國際頭痛疾病分類

The International Classification of Headache Disorders

第三版 (ICHD-3)

頭痛疾病的分類

Since 2005 台灣頭痛學會 Taiwan Headache Society

Part 1. 原發性頭痛

1. 偏頭痛
2. 緊縮型頭痛
3. 三叉自律神經頭痛
4. 其他原發性頭痛疾病

Part 2. 次發性頭痛

5. 歸因於頭部及/或頸部外傷或傷害之頭痛
6. 歸因於頭及/或頸部血管疾患之頭痛
7. 歸因於非血管性顱內疾患之頭痛
8. 歸因於物質或物質戒斷之頭痛
9. 歸因於感染之頭痛
10. 歸因於體內恆定疾患之頭痛
11. 歸因於頭顱、頸、眼、耳、鼻、鼻竇、牙齒、口腔或其他顏面或頸部結構疾患之頭痛或顏面痛
12. 歸因於精神疾病之頭痛

Part 3. 疼痛性顱神經病變、其他顏面痛和其他頭痛

13. 顱頭神經疼痛性病變和其他顏面痛
14. 其他頭痛疾病

偏頭痛

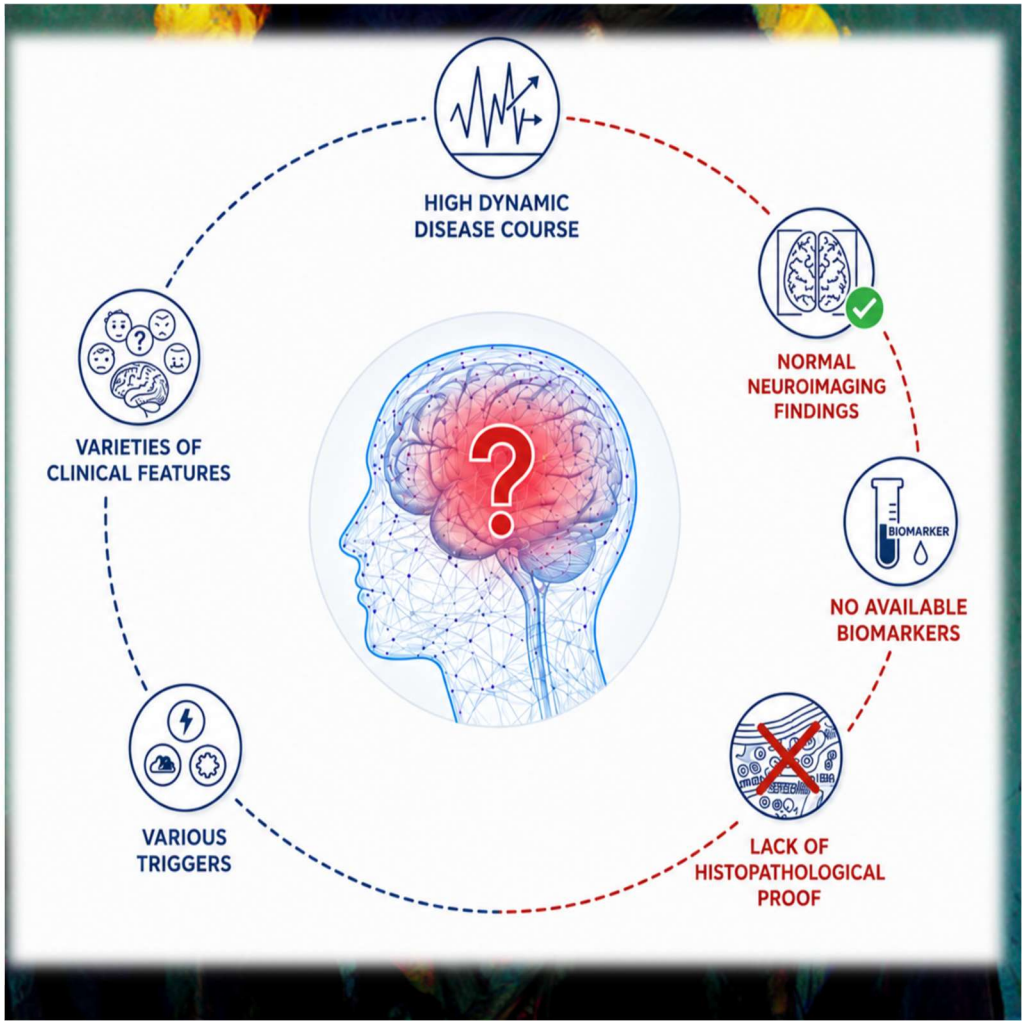


- 影響全球10億人口
- 全世界第二大致失能疾病
- 台灣近200萬病患

嚴重偏頭痛發作造成失能相當於



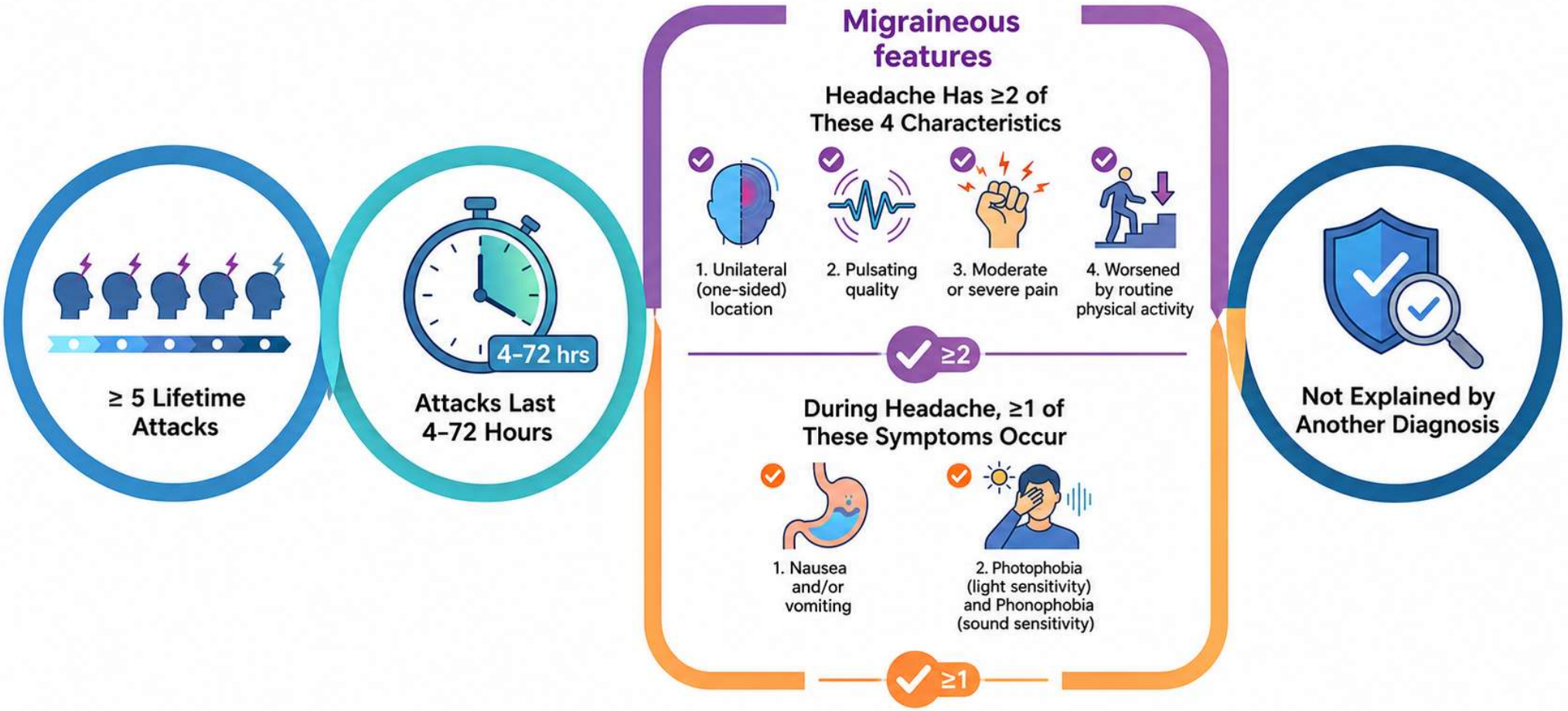




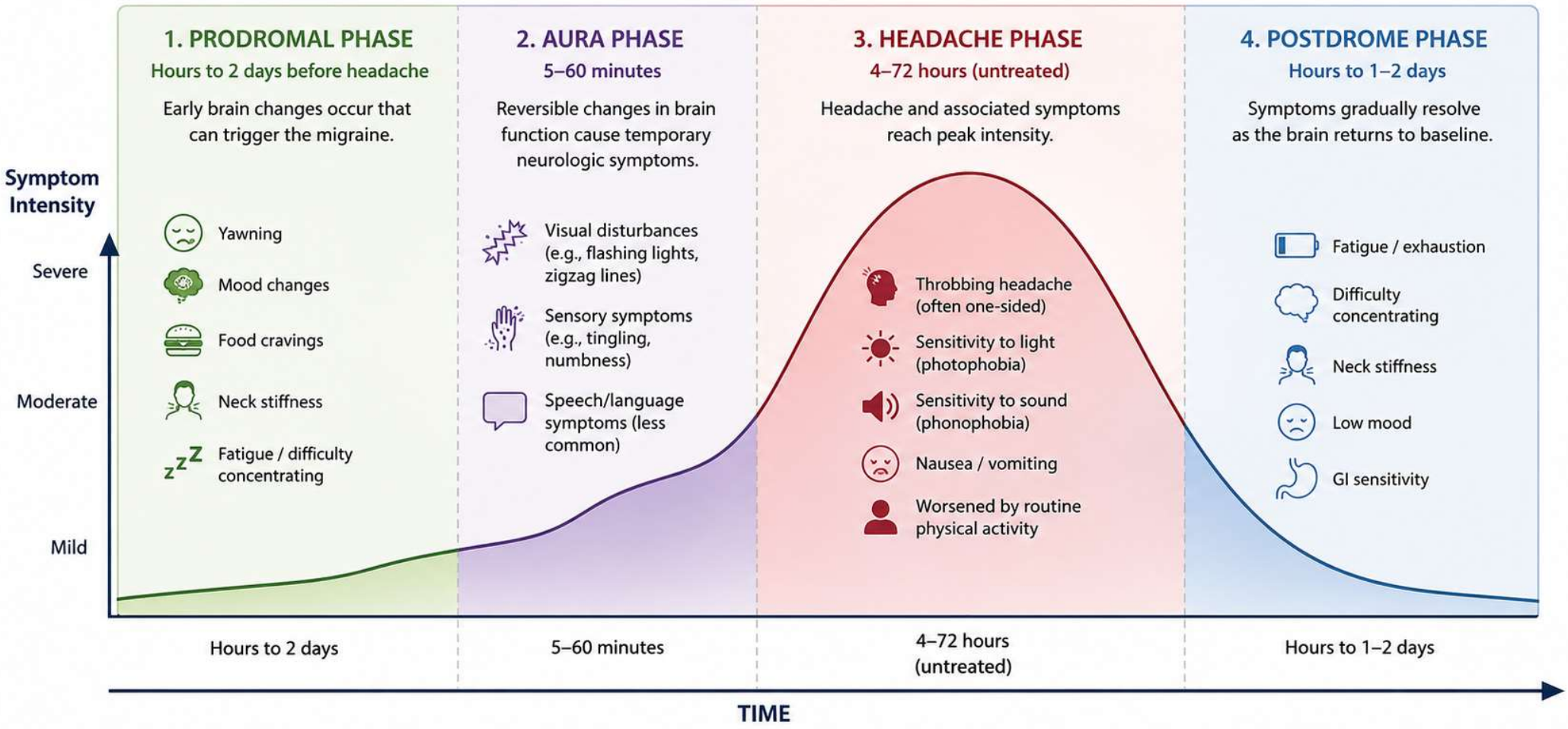
Created with Midjourney



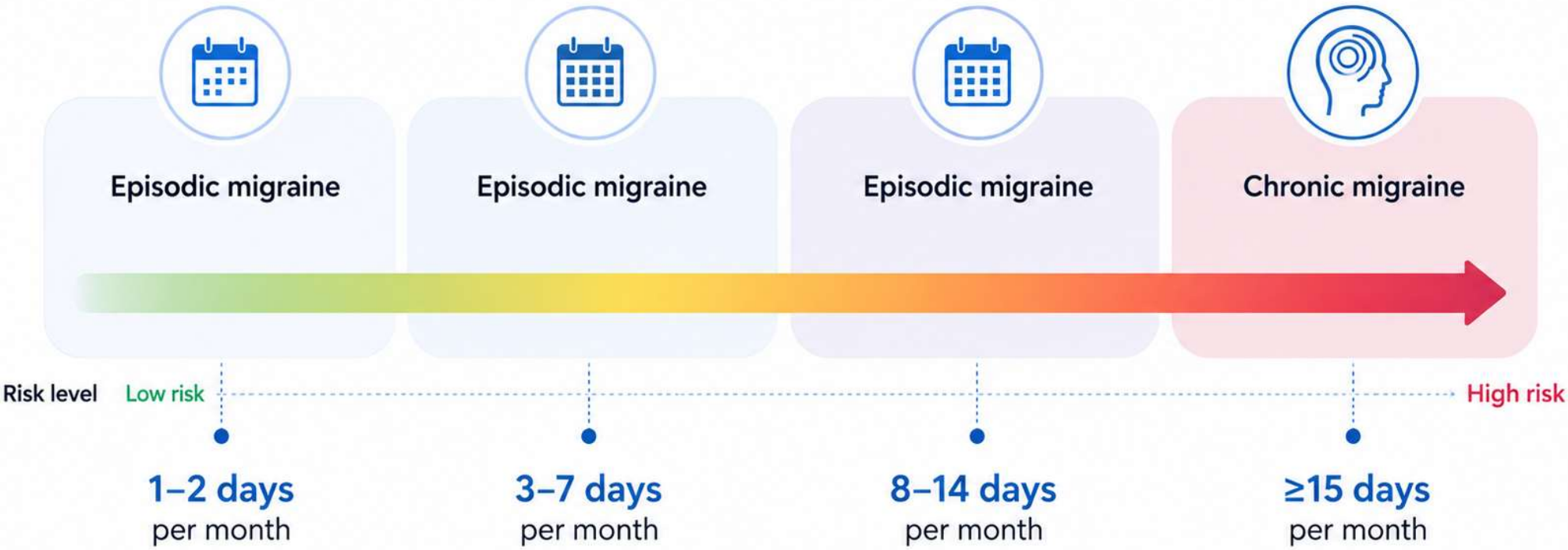
ICHD-3 Criteria 1.1 Migraine without aura



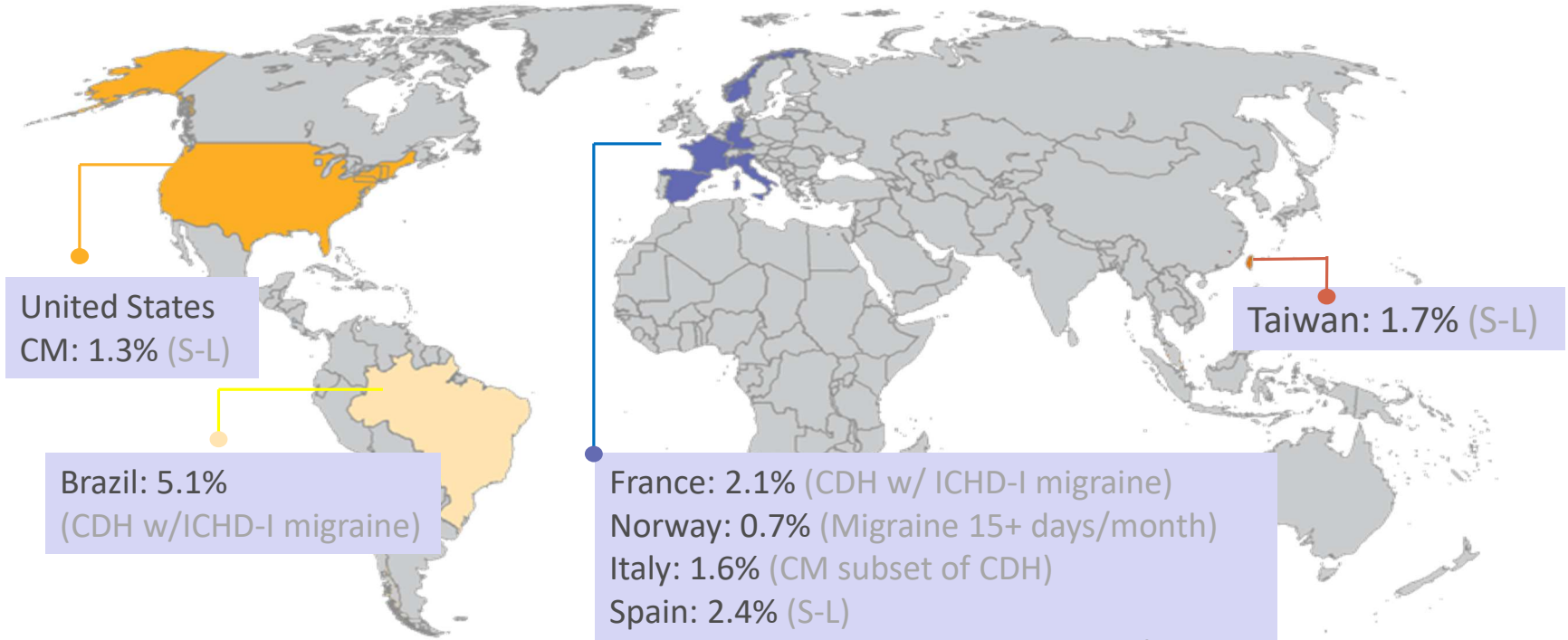
The Dynamic Course of a Migraine Attack



Migraine Progression



Chronic Migraine: Global Prevalence

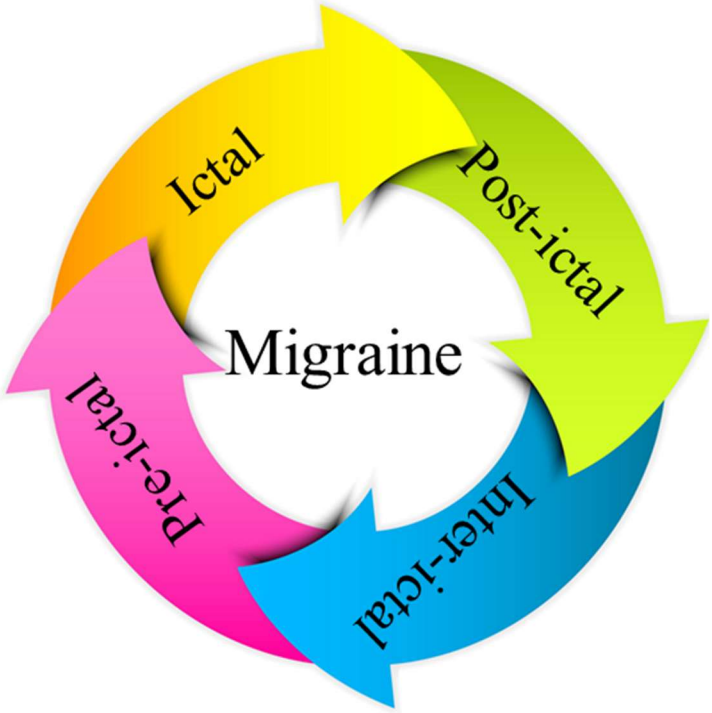


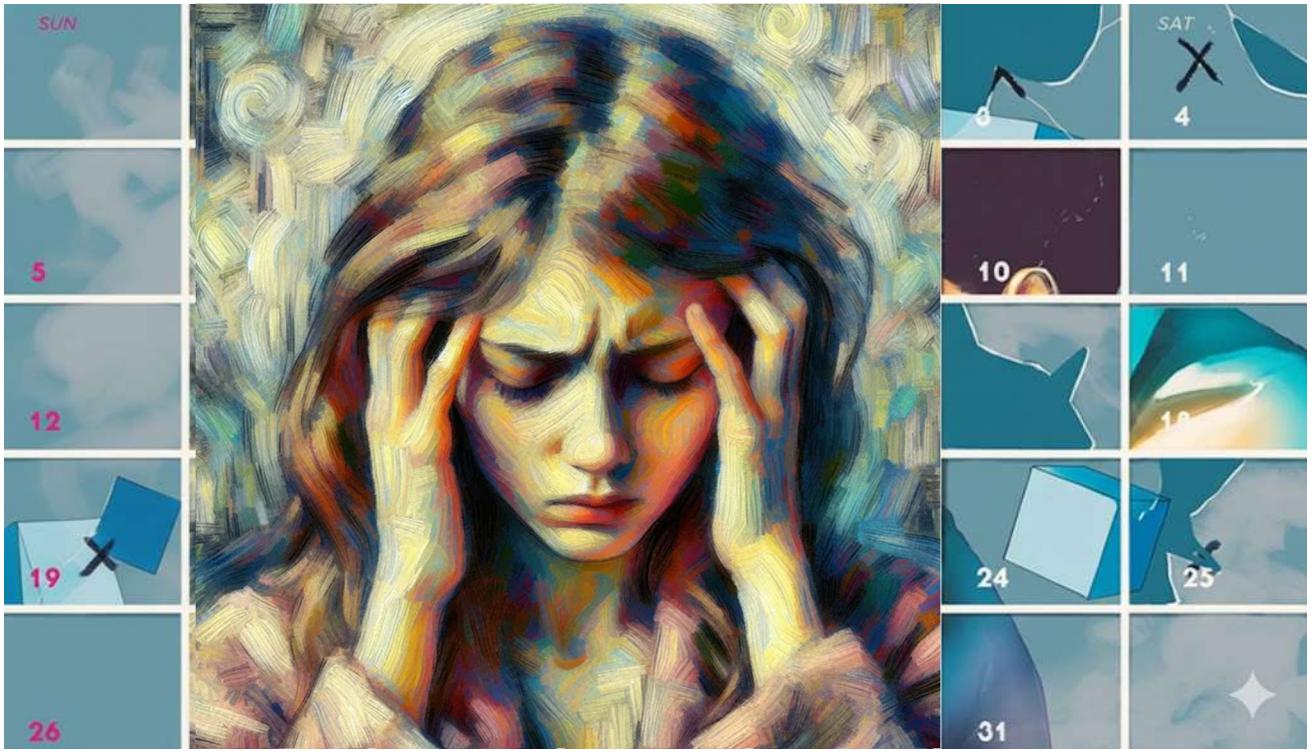
*Due to the heterogeneity of studies, some variation in definitions of chronic migraine exists.
CDH = chronic daily headache; S-L = Silberstein-Lipton definition of chronic migraine.

Natoli J et al. *Cephalalgia.* 2009. E-pub ahead of print.
Silberstein SD et al. *Neurology*. 1996;47:871-875.

Medication Overuse Headache

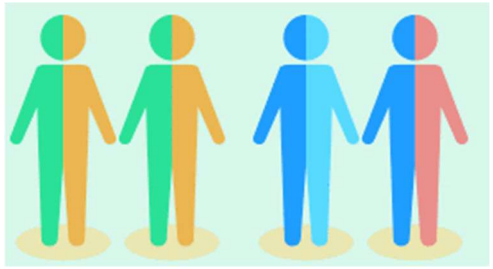



Ictal
Post-ictal
Migraine
Pre-ictal
Inter-ictal


SUN
SAT
5
10
11
12
19
24
25
26
31

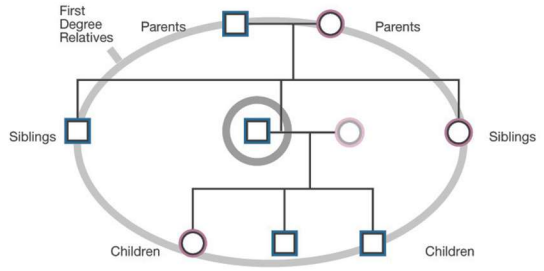

體質？

Epidemiology Suggests a Genetic Basis



MZ > DZ twins

concordance 0.68 vs. 0.22



↑ in 1st-degree relatives

RR: 1.5 to 19.3



Higher rate of family history

MA: x4; MO: x1.9

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2}$$

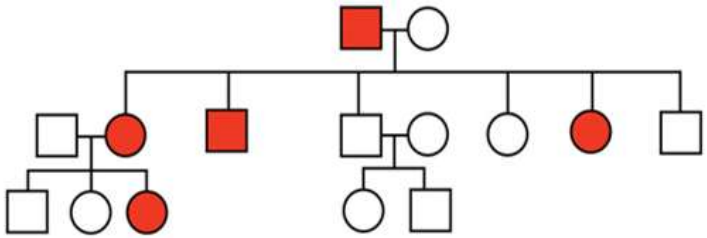
Heritability: 0.34-0.81

Neuroepidemiology. 1992; 11:46-49; *Neurology*. 1993:43:1369–73; *Cephalalgia*.1996;16:431-435; *Ann Neurol*. 1997;41:166-172; *BMJ*. 1995;311:541-544; *Hum Mol Genet*. 1998;7:459-463; *Eur J Neurol*. 2003;10:421-427; Neurology. 2006;66:344–348; Hum Genet 2009; 125:591–604; Neurology 2010;74;288-294

Rare familial form

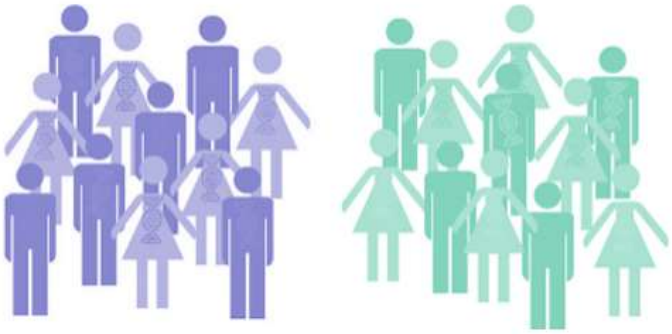
Familial hemiplegic migraine

Monogenic migraine syndrome



Common migraine

Migraine with aura Migraine without aura



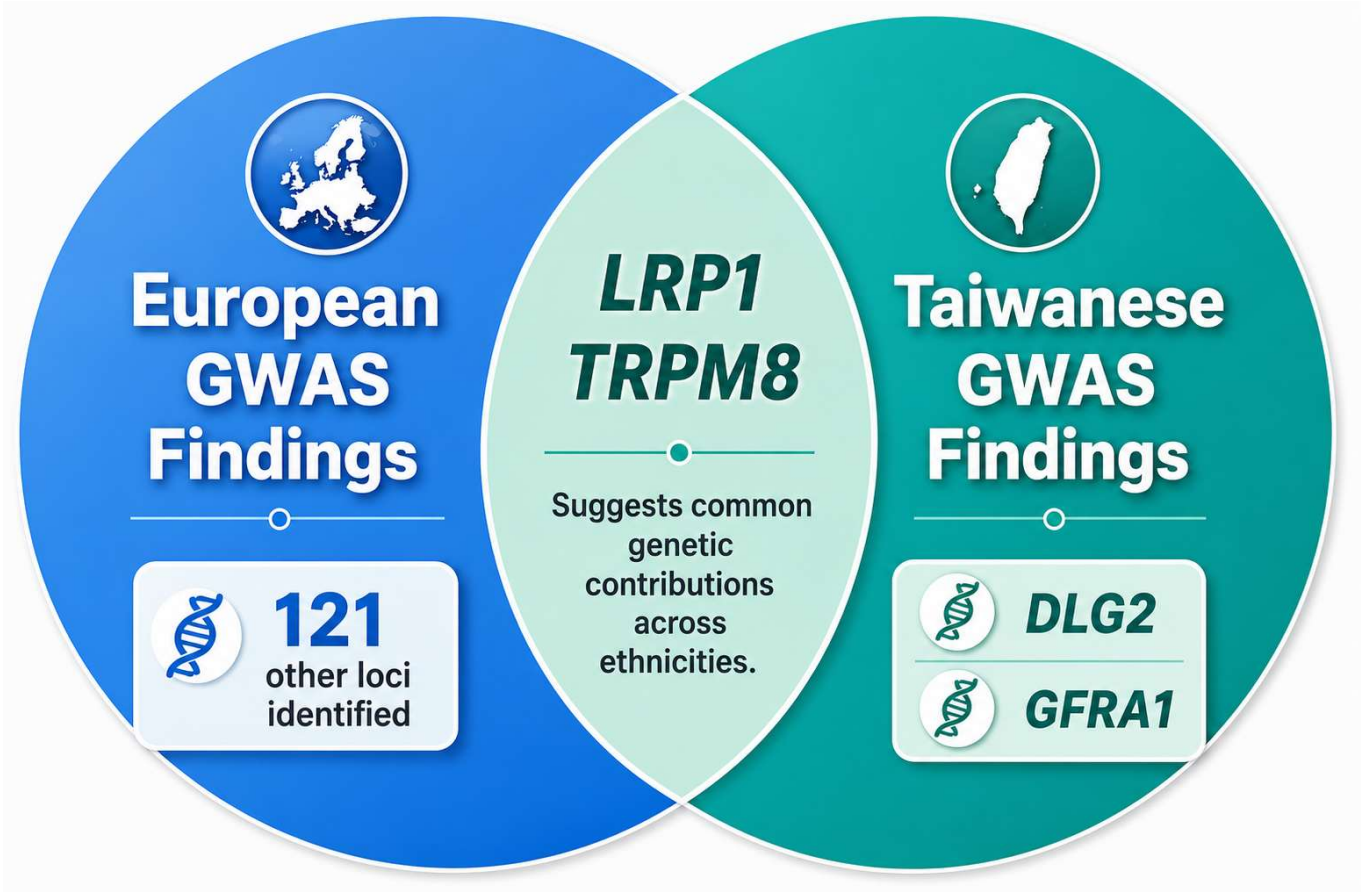
Heritability

Prevalence

Allele effect size

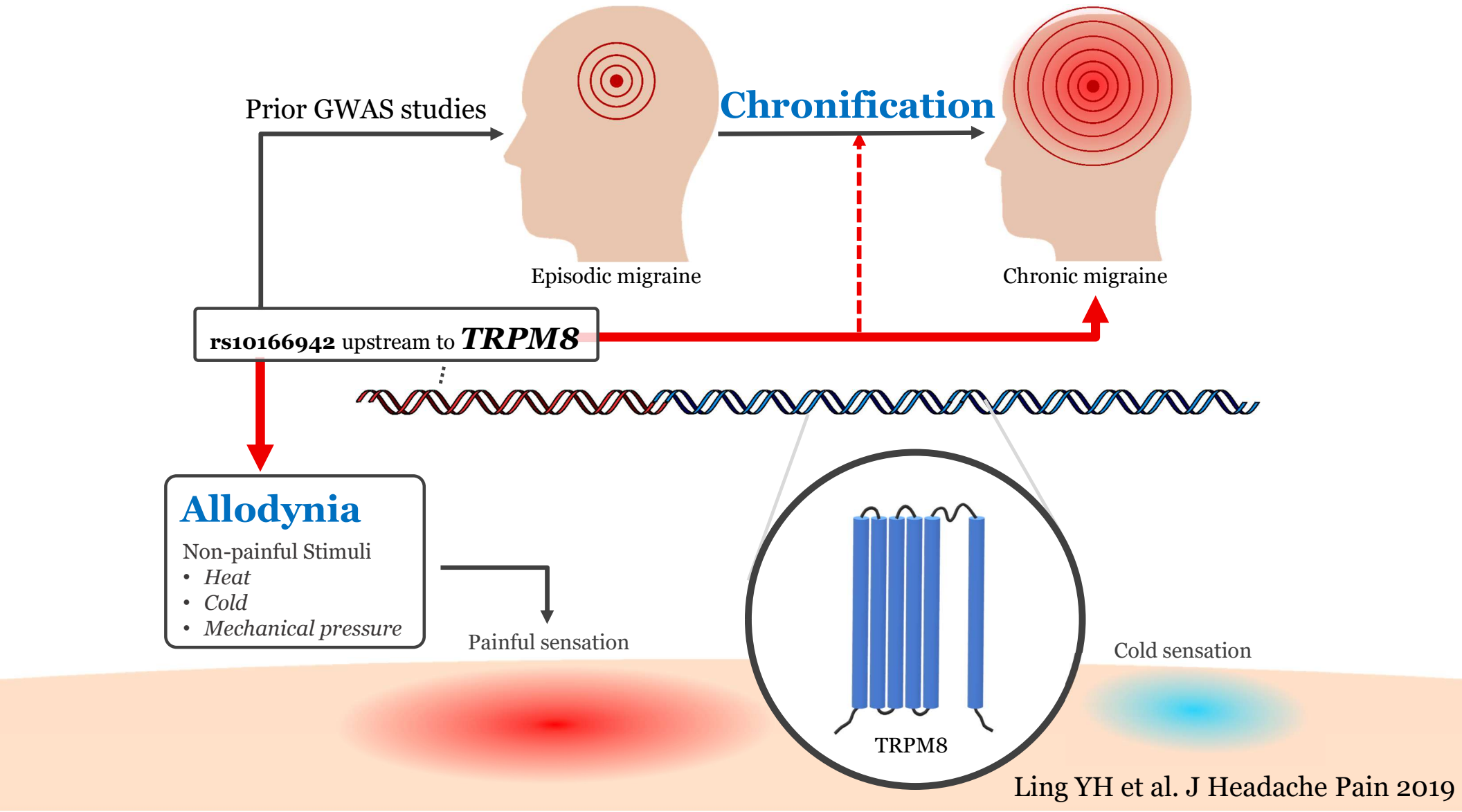
Allele frequency

Genome-wide Association Study (GWAS) of Migraine



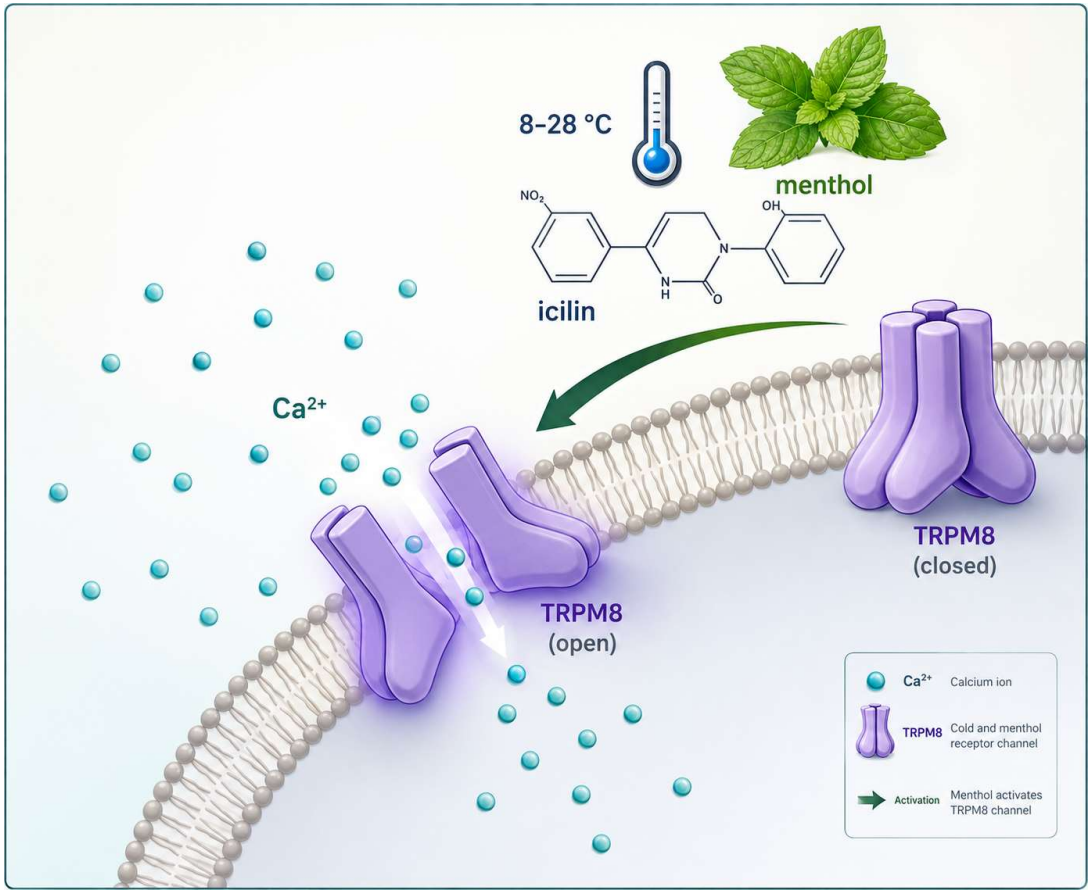
Hautakangas et al. Nature Genetics 2022

Chen et al. Cephalalgia 2018



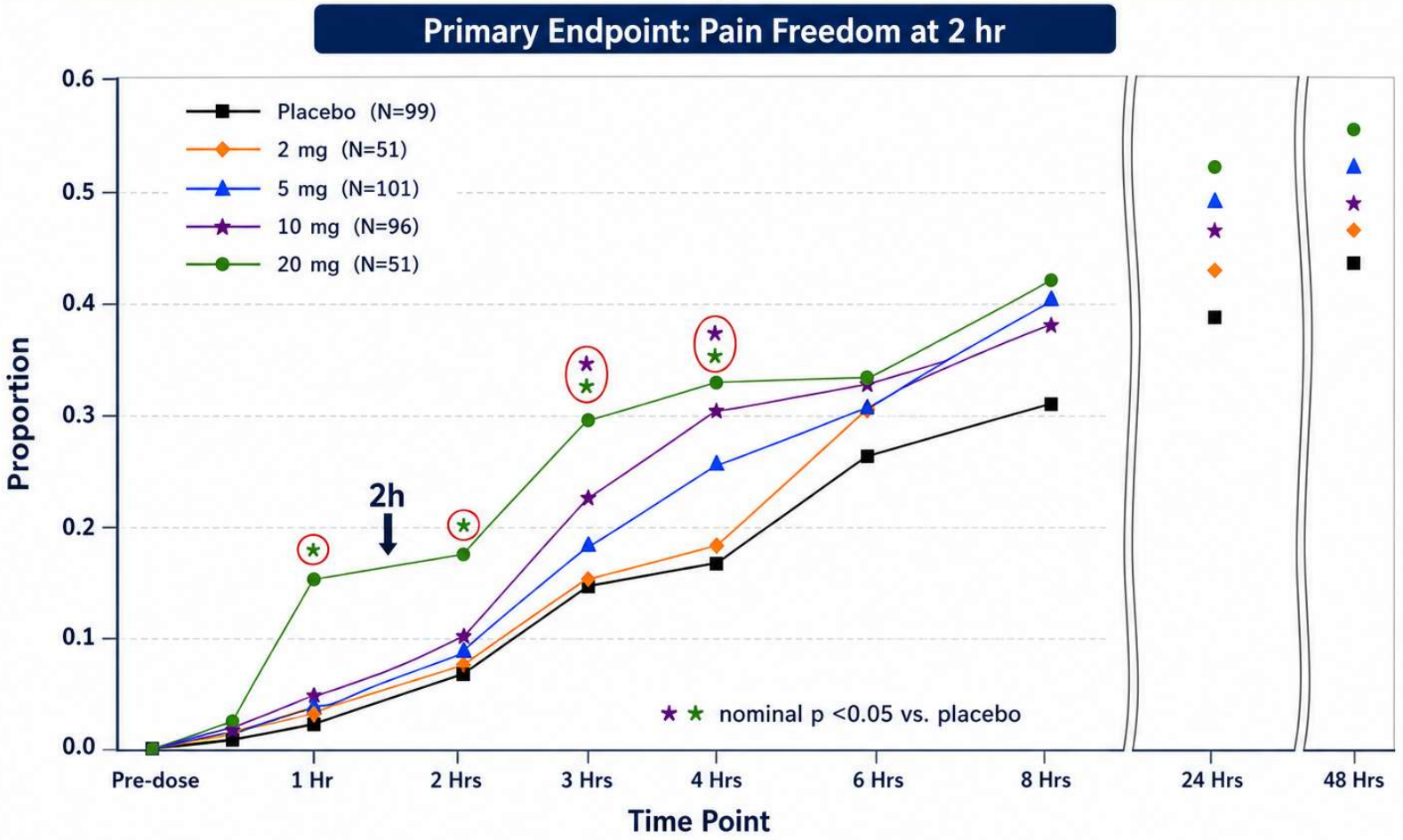
Ling YH et al. J Headache Pain 2019

Menthol: Ligand of TRPM8 receptor





Phase 2b Trial of the TRPM8 Antagonist Elismetrep in Migraine Treatment



Kallyope Inc. @ 2026 AAN



Erenumab **Galcanezumab** **Fremanazumab** **Eptinezumab**

CGRP mAb
CGRPR mAb









Ubrogepant (A) Zavegepant (A) **Rimegepant (A+P)** **Atogepant (A+P)**

CGRP antagonist (Gepants)
A: acute
P: preventive

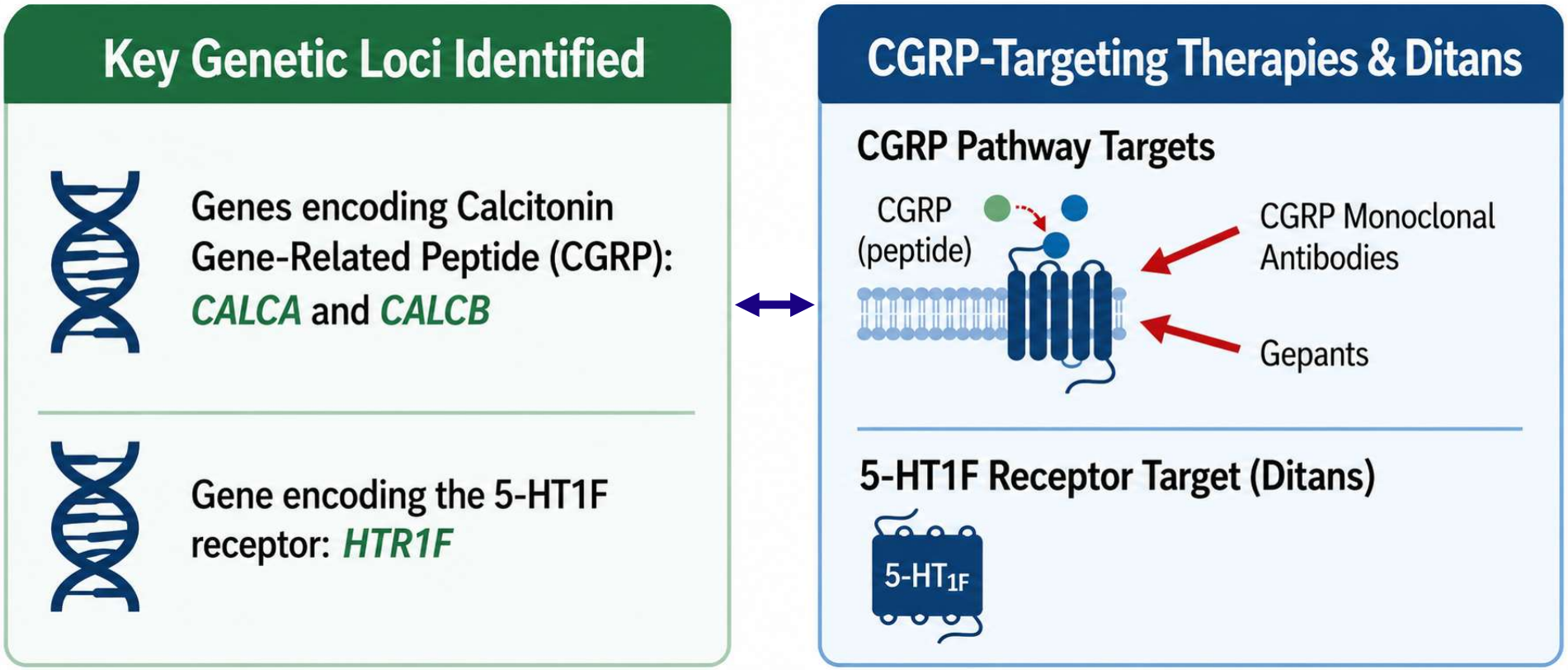








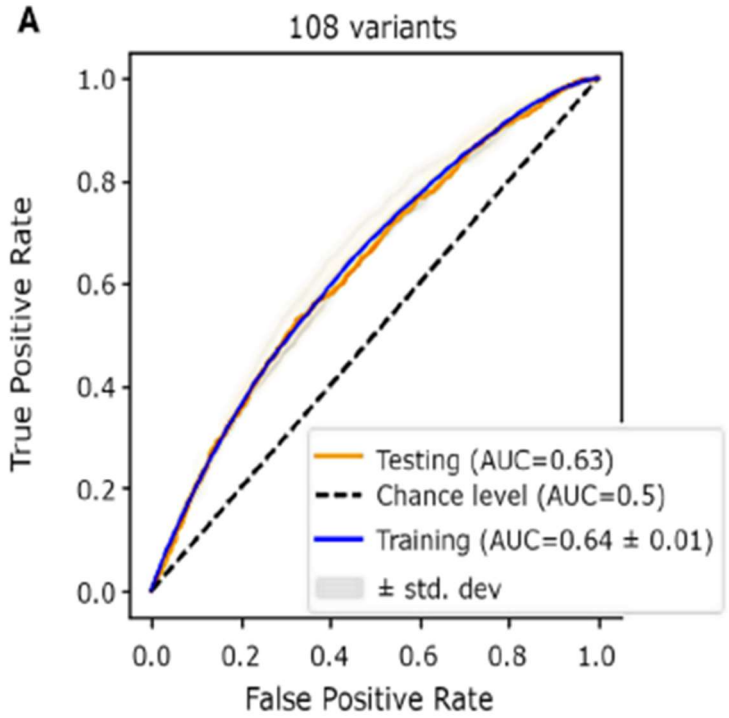
GWAS identified targets of novel migraine therapeutics



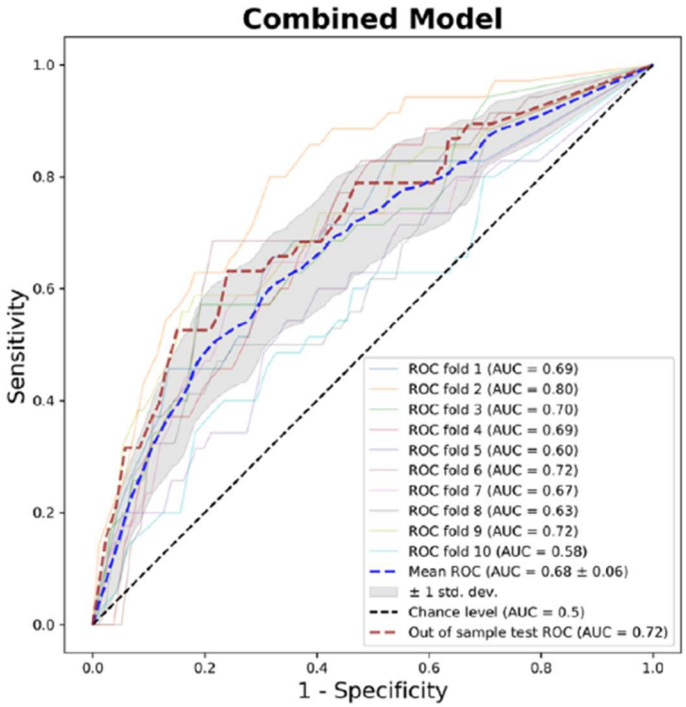
Reference: Hautakangas et al. Nature Genetics 2022

Diagnosing and predicting migraine from genotyping data using machine learning

(Norwegian HUNT-2 & HUNT3 cohorts)



Danelakis et al. Brain 2025

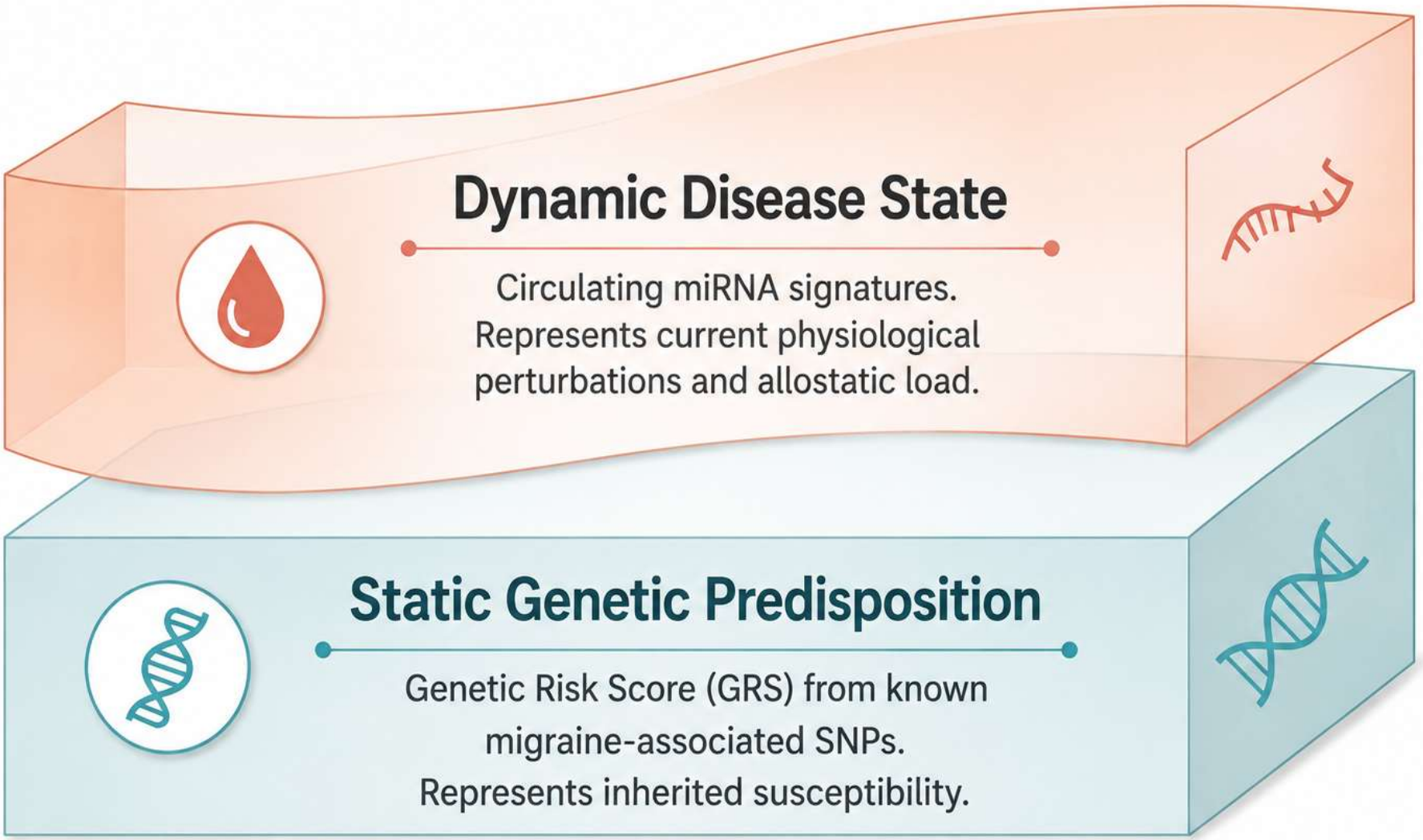


Faisal et al. TJHP 2025

Genotype model
AUC 0.56

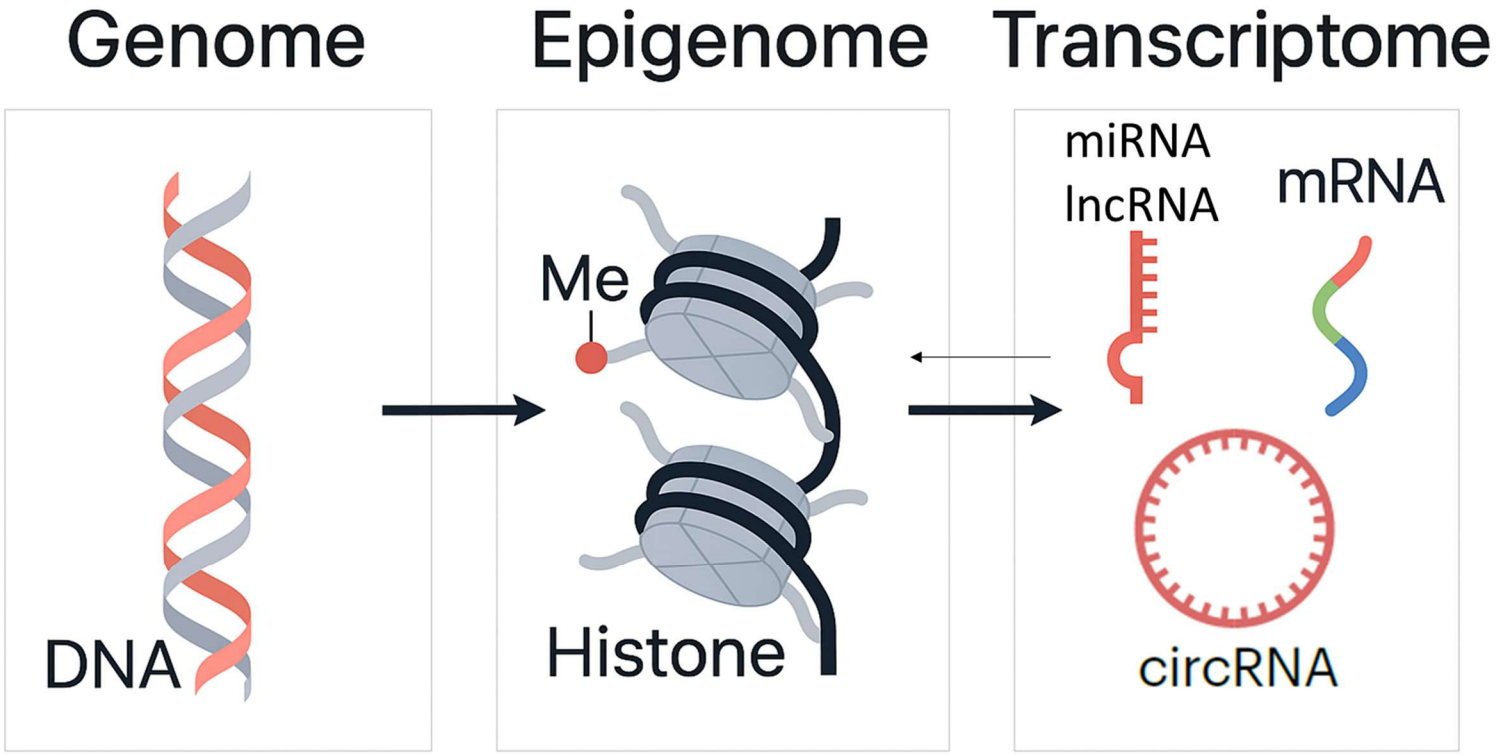
Phenotype model
AUC 0.68

Combined model
AUC 0.72

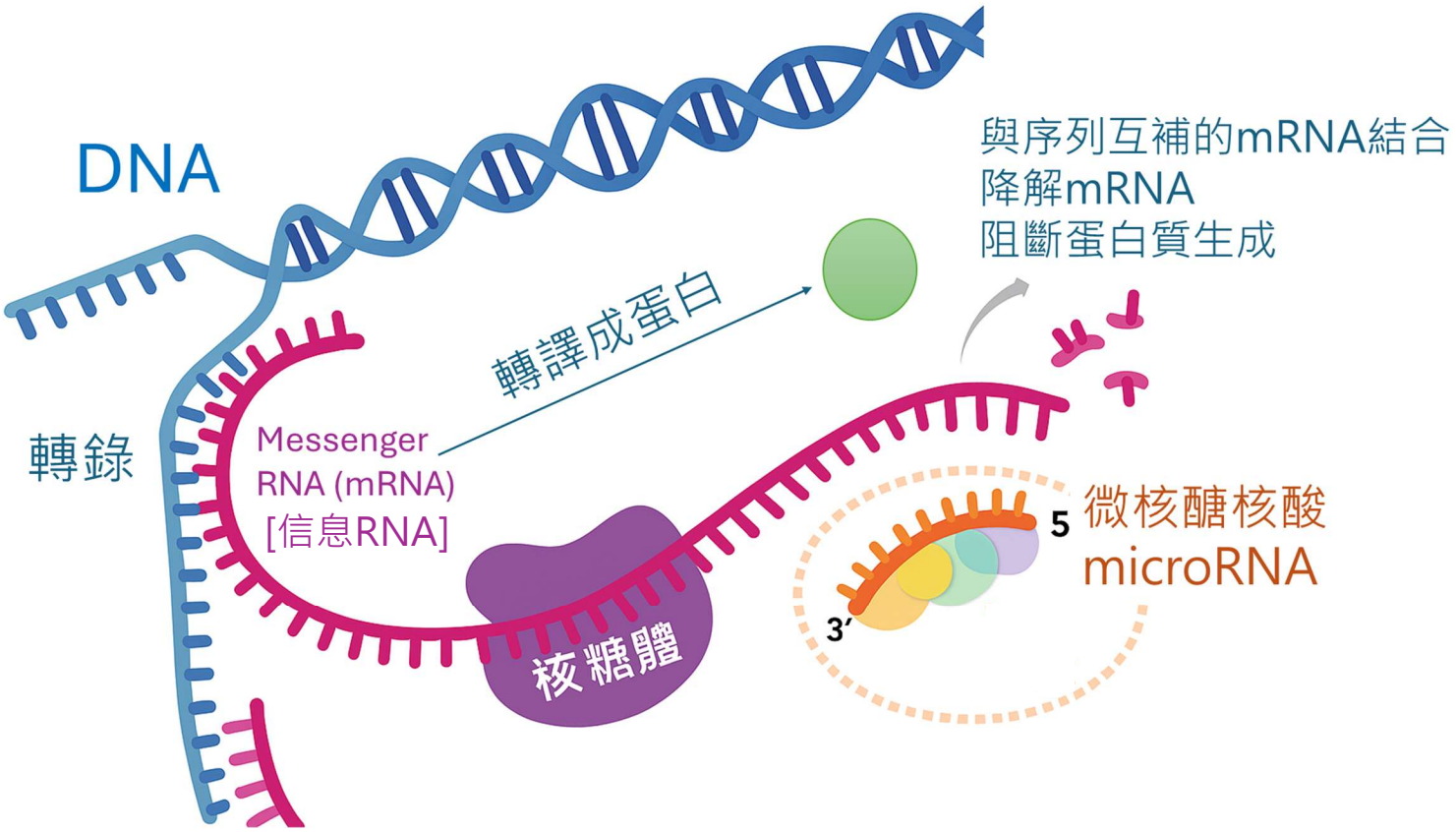

Dynamic Disease State
Circulating miRNA signatures.
Represents current physiological
perturbations and allostatic load.
Static Genetic Predisposition
Genetic Risk Score (GRS) from known
migraine-associated SNPs.
Represents inherited susceptibility.

Static
Inherited

Dynamic
Interact with environment



微核醣核酸(microRNA)



Limitations of Previous Migraine microRNA Studies



Small sample sizes



Lack of **systematic** profiling



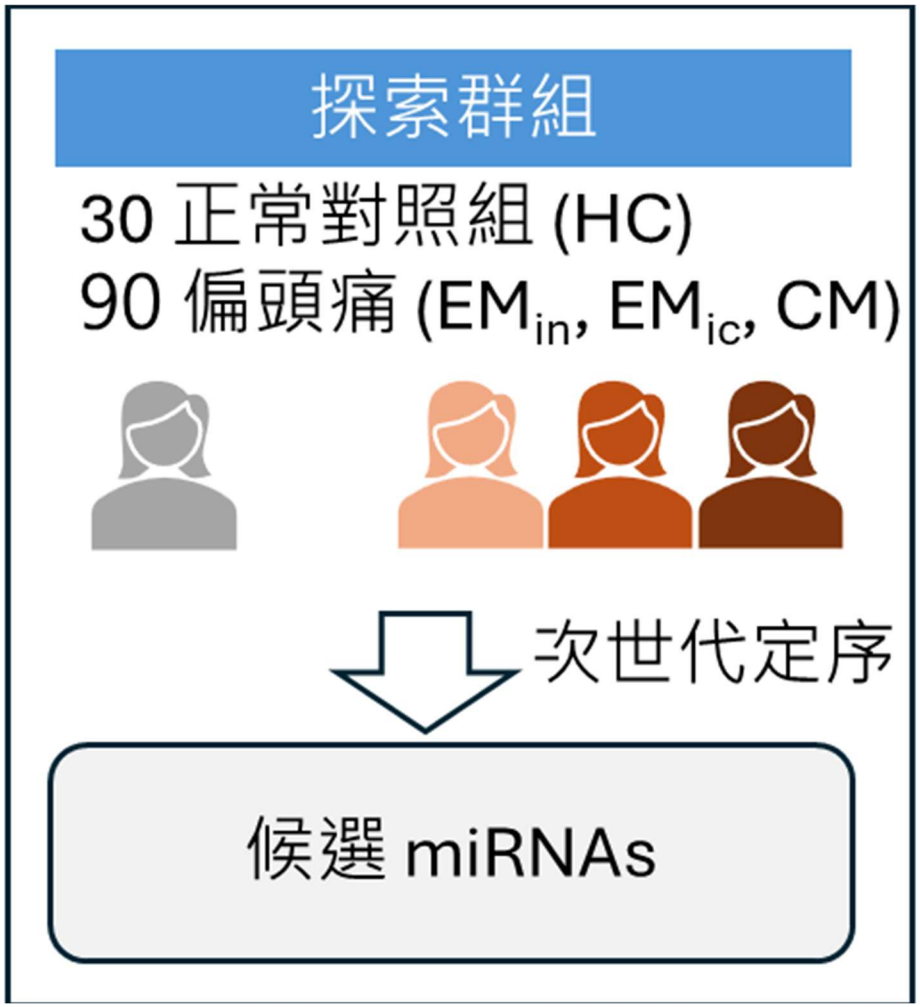
Limited independent validation

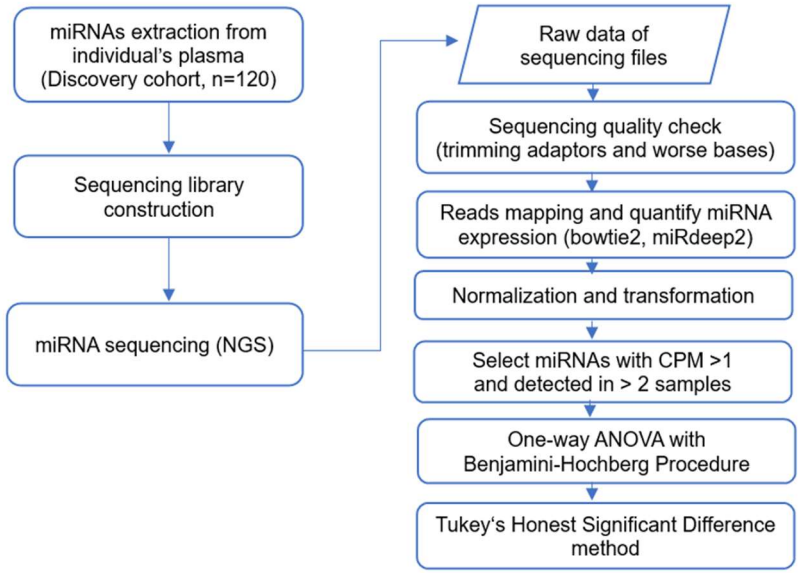


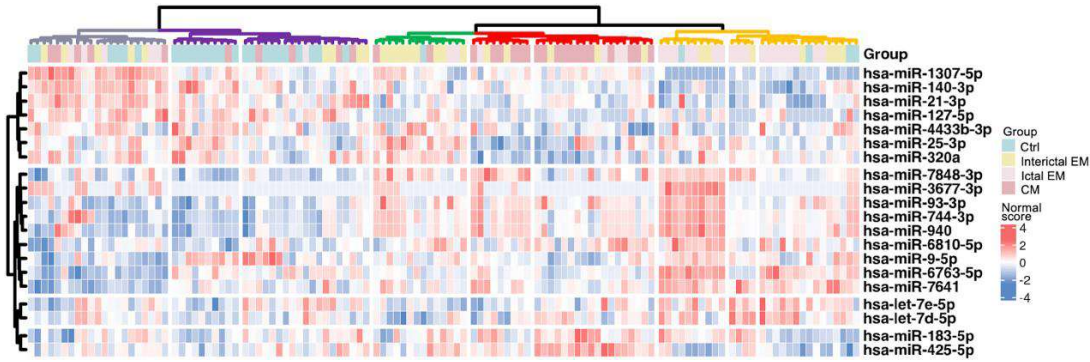
Failure to distinguish disease activity from migraine subtypes



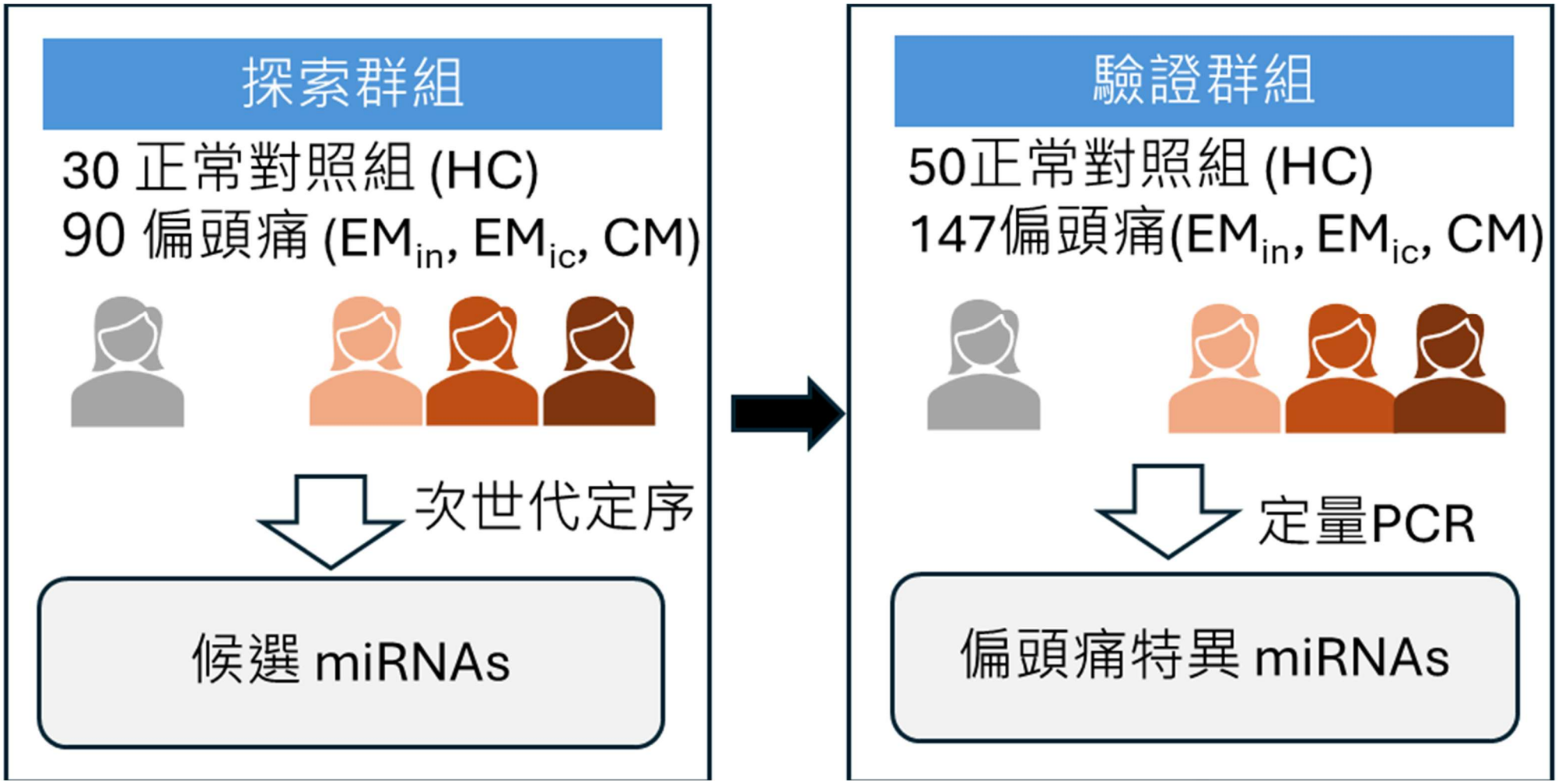
Unclear biological functions



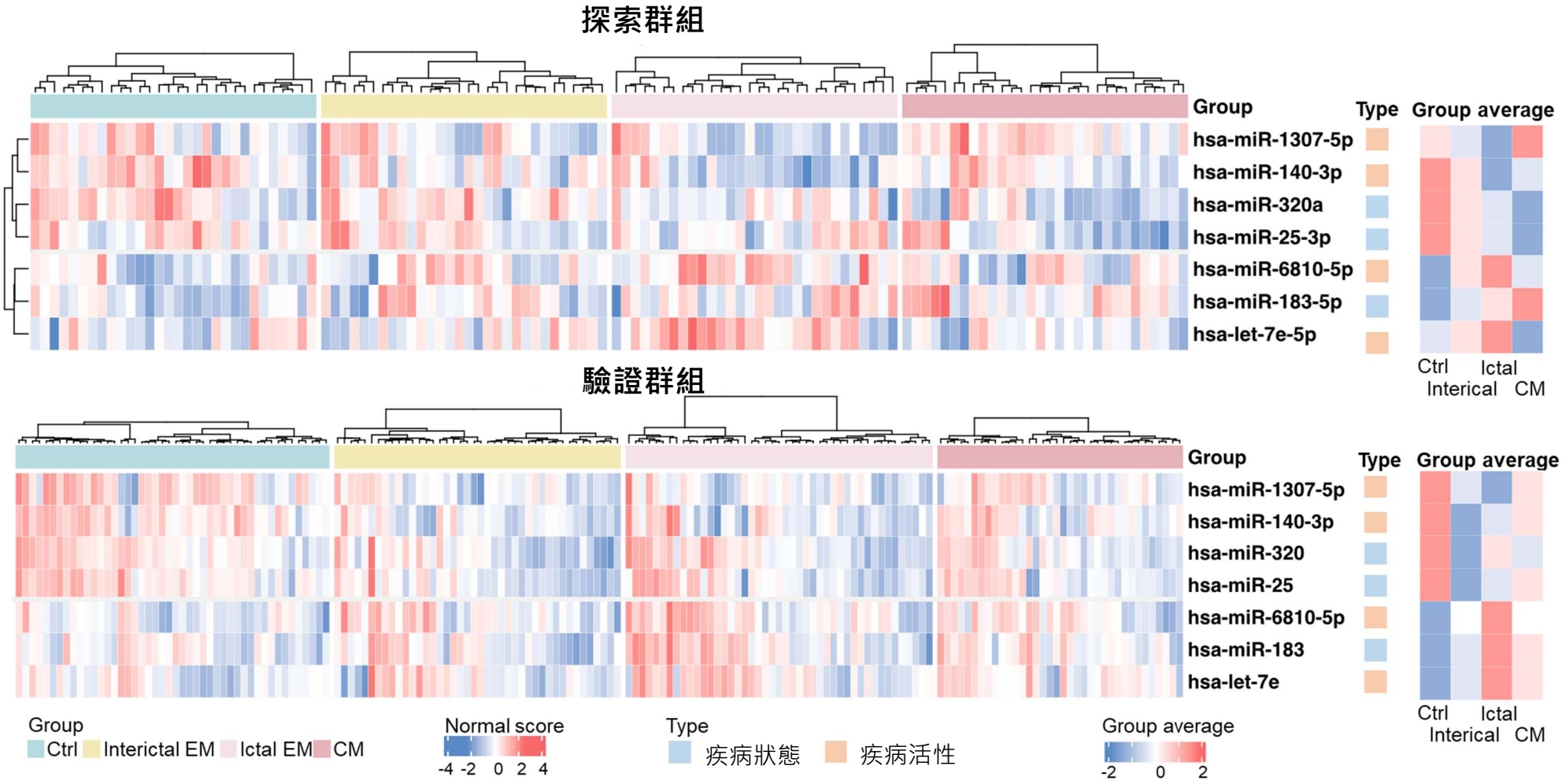




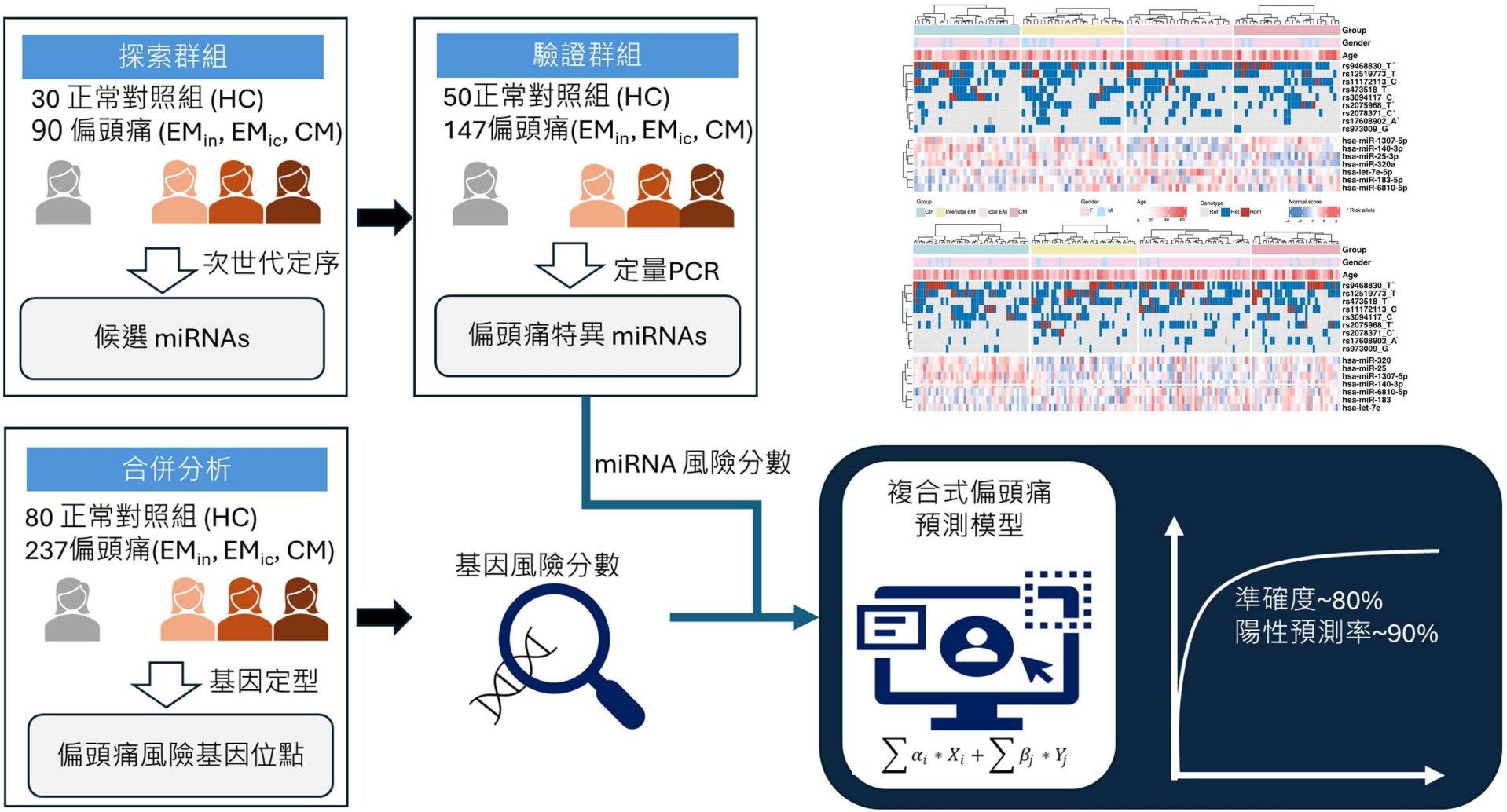
EM_{in} : 陣發性偏頭痛發作間期; EM_{ic} : 陣發性偏頭痛發作期; CM : 慢性偏頭痛



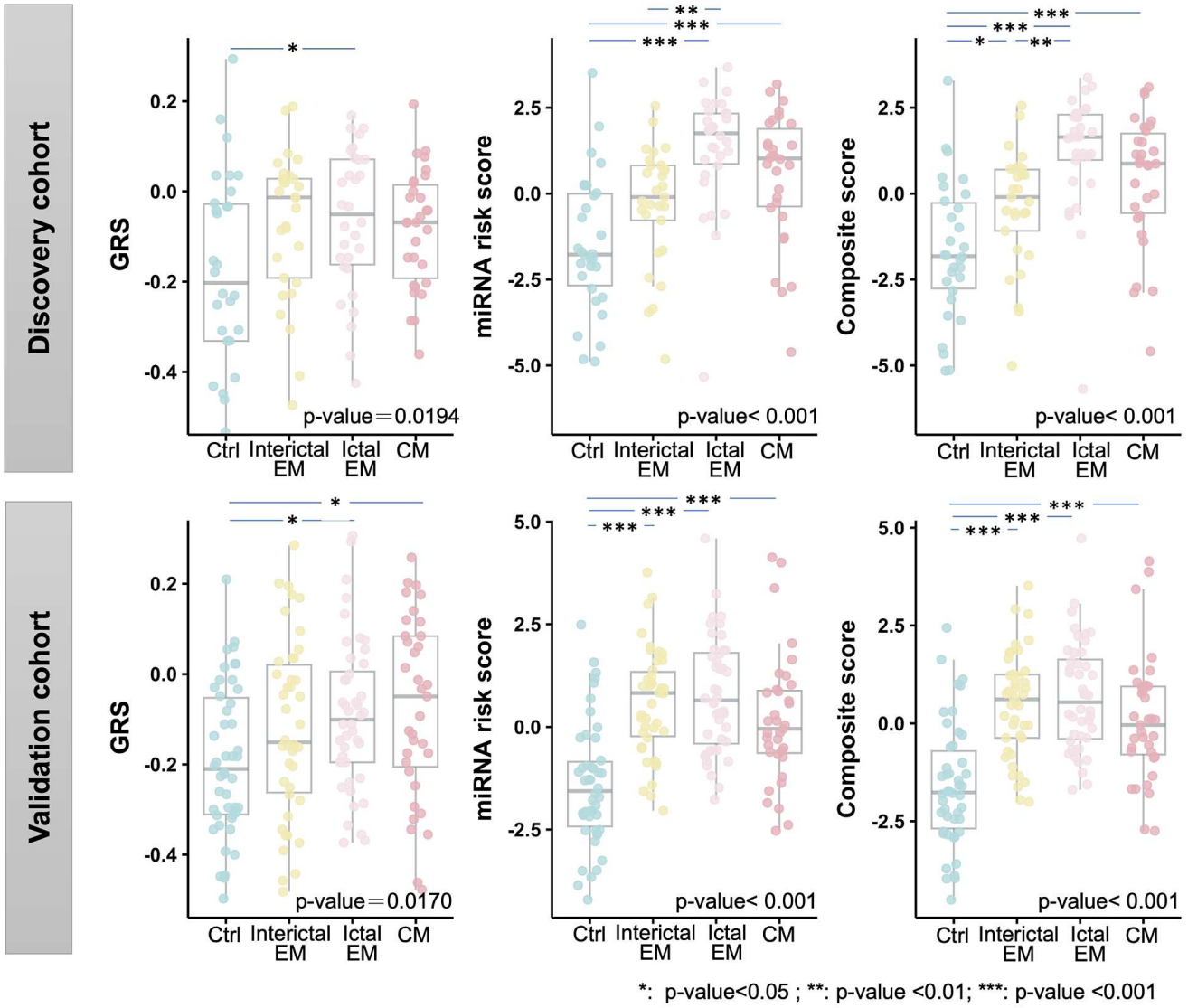
EM_{in} : 陣發性偏頭痛發作間期; EM_{ic} : 陣發性偏頭痛發作期; CM : 慢性偏頭痛



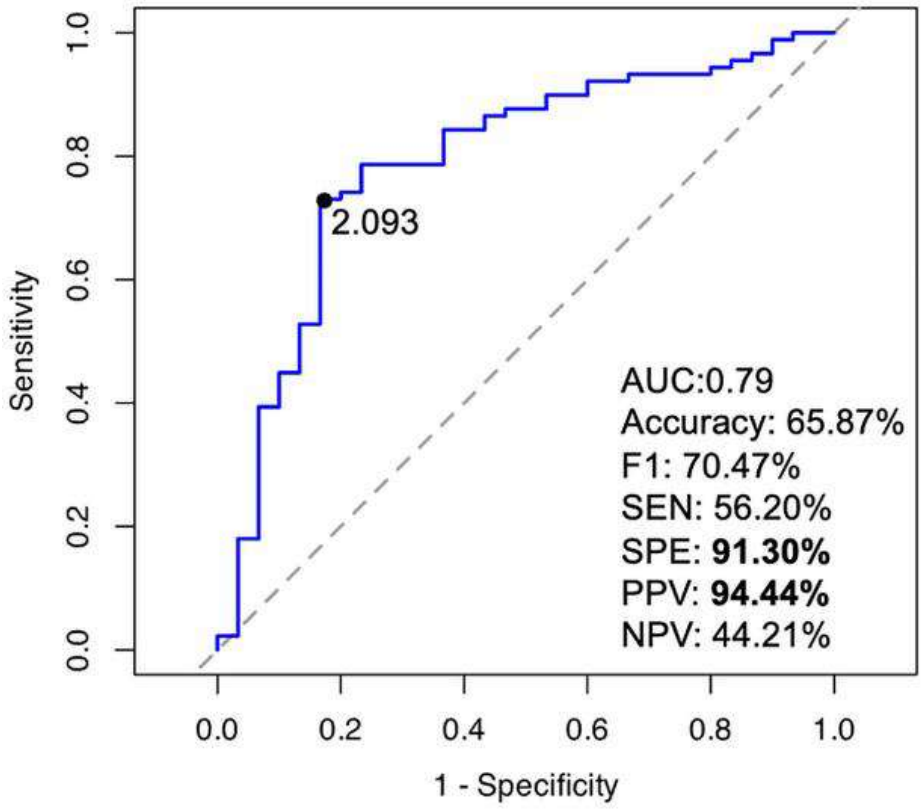
Ctrl: 正常對照組; Interictal EM: 陣發性偏頭痛發作間期
Ictal EM:陣發性偏頭痛發作期; CM: 慢性偏頭痛



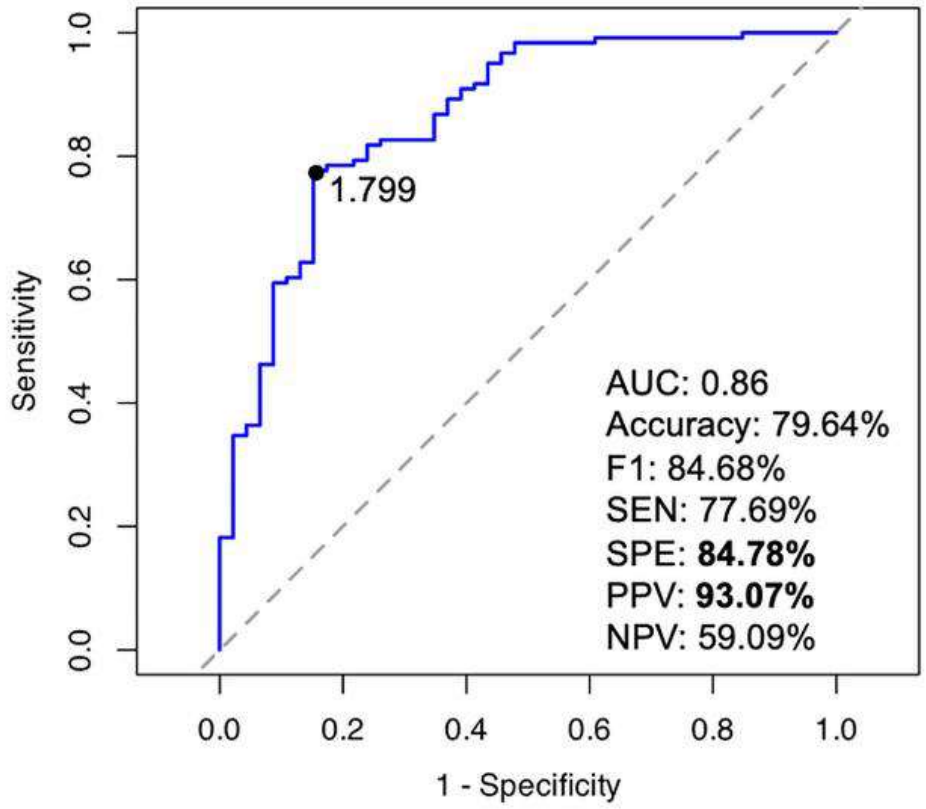
EM_{in} 陣發性偏頭痛發作間期
EM_{ic} 陣發性偏頭痛發作期
CM 慢性偏頭痛

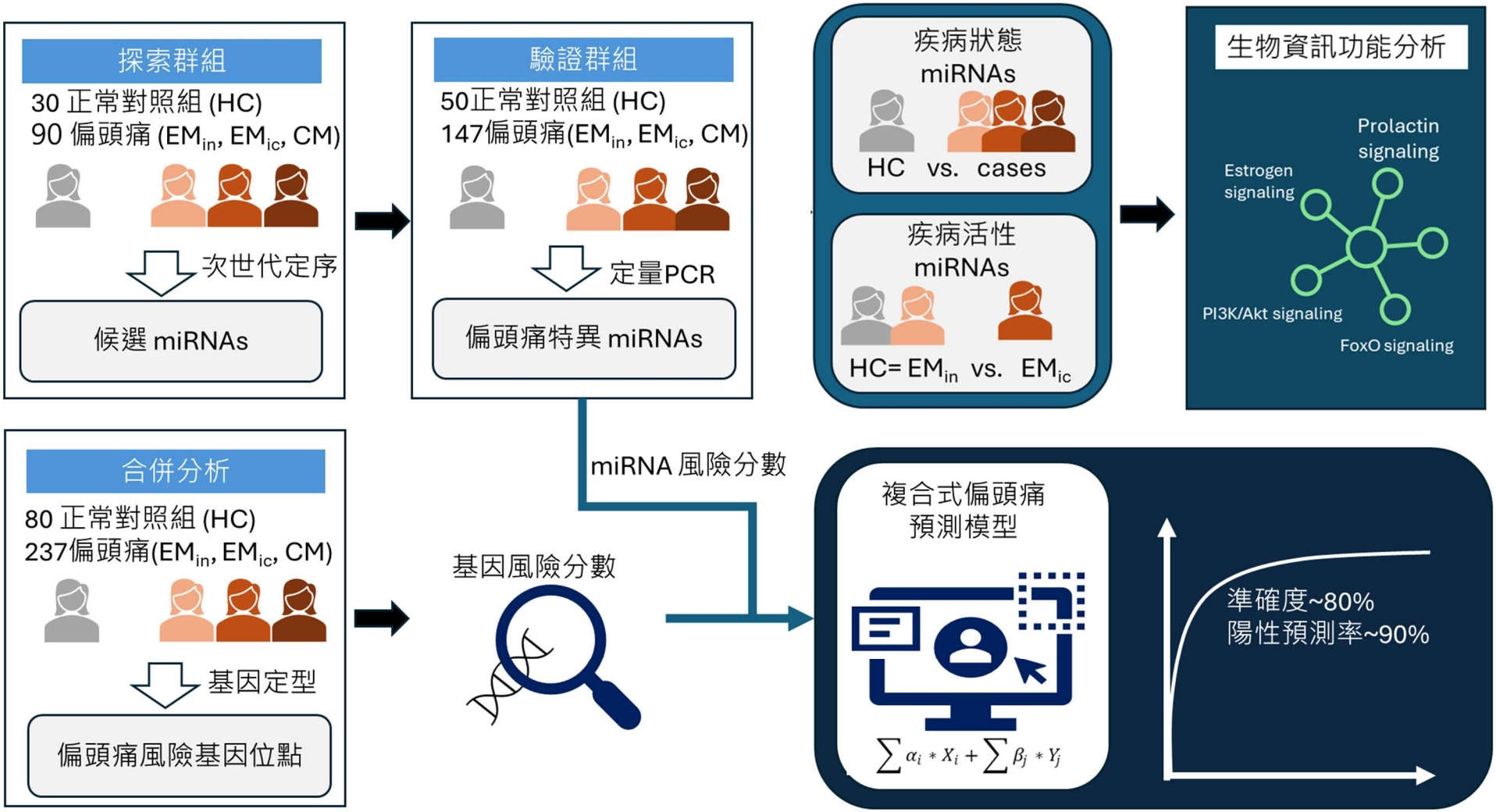

Discovery cohort
Validation cohort
GRS
miRNA risk score
Composite score
p-value=0.0194
p-value< 0.001
p-value=0.0170
p-value< 0.001
p-value< 0.001
Ctrl
Interictal EM
Ictal EM
CM
*: p-value<0.05 ; **: p-value <0.01; ***: p-value <0.001

Discovery Cohort

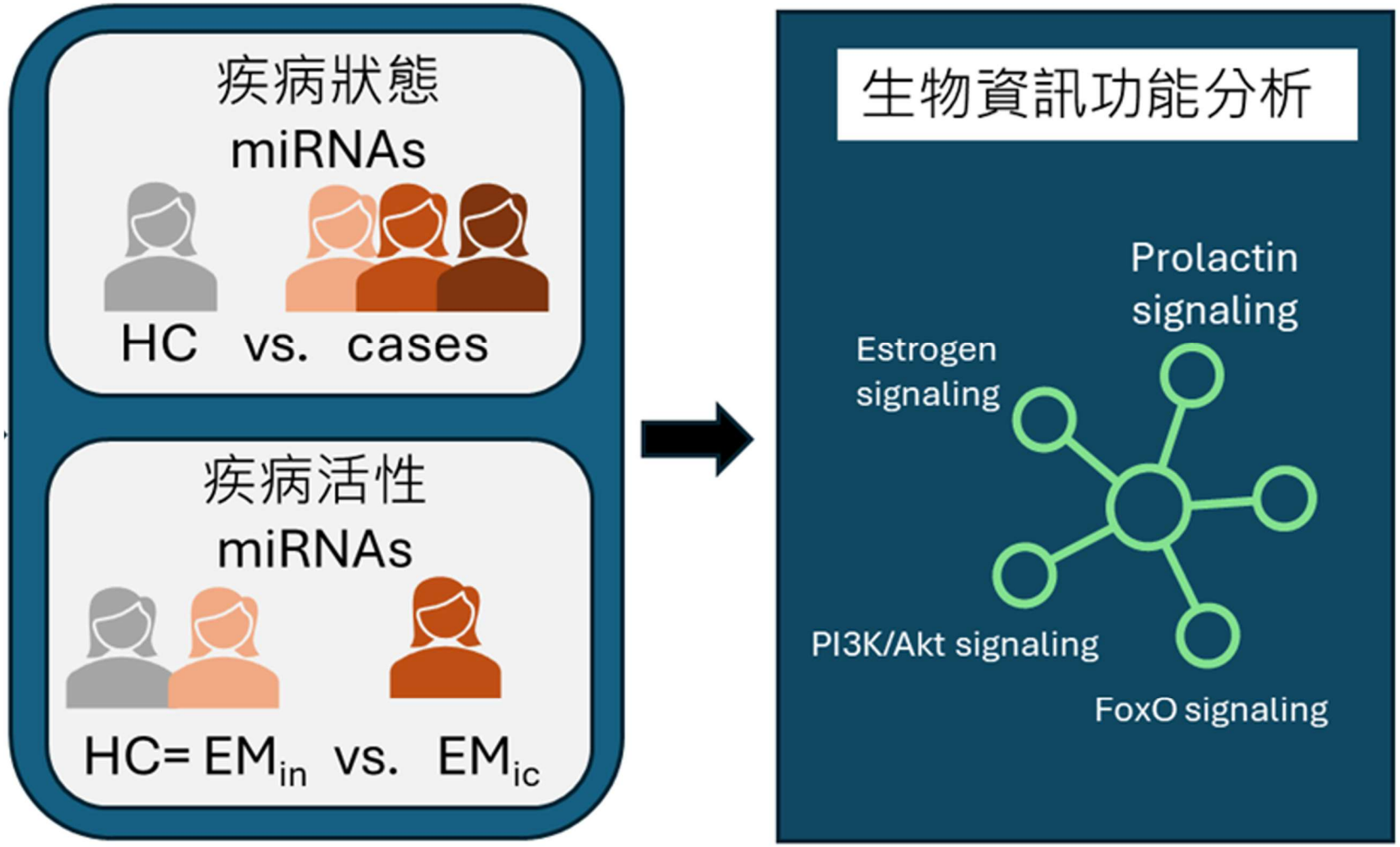


Validation Cohort

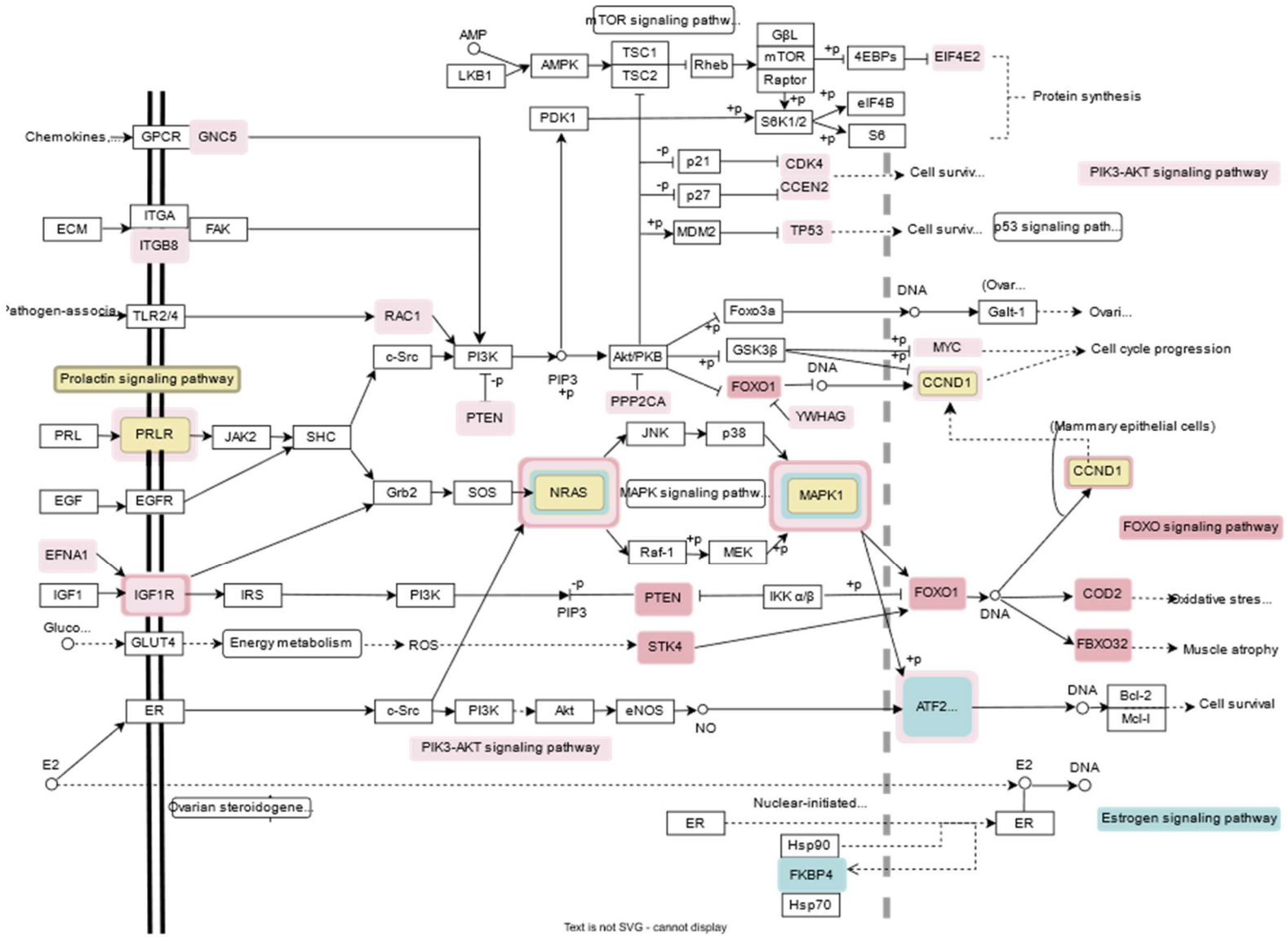




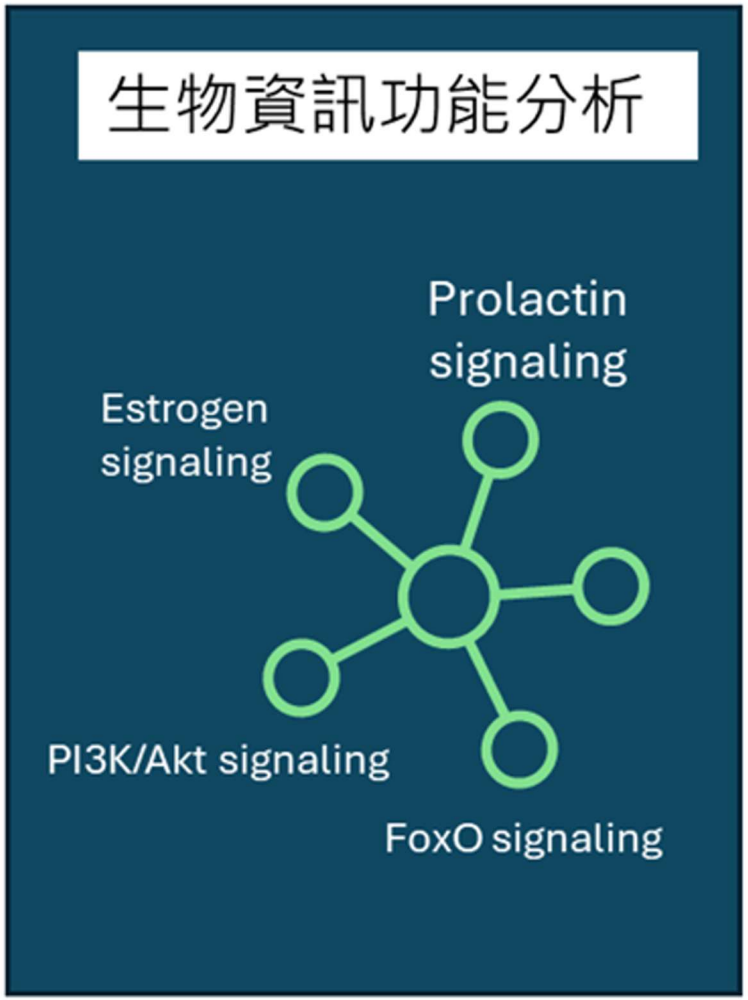
EM_{in} 陣發性偏頭痛發作間期
EM_{ic} 陣發性偏頭痛發作期
CM 慢性偏頭痛

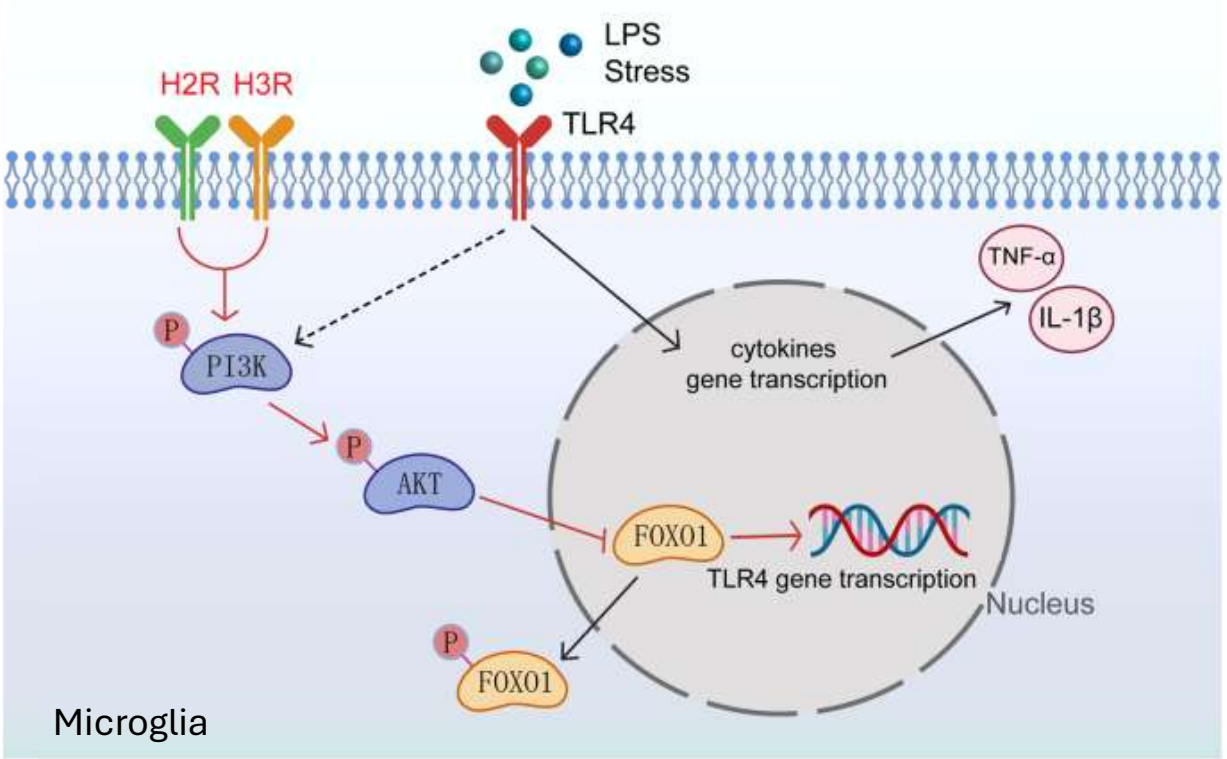


EM_{in} 陣發性偏頭痛發作間期
EM_{ic} 陣發性偏頭痛發作期
CM 慢性偏頭痛


mTOR signaling pathw...
AMP
LKB1
AMPK
TSC1
TSC2
Rheb
GβL
mTOR
Raptor
4EBPs
EIF4E2
Protein synthesis
eIF4B
S6K1/2
S6
PDK1
Chemokines
GPCR
GNC5
p21
CDK4
p27
CCEN2
Cell surviv...
PIK3-AKT signaling pathway
ECM
ITGA
ITGB8
FAK
MDM2
TP53
Cell surviv...
p53 signaling path...
DNA
(Ovar...
Foxo3a
Galt-1
Ovari...
TLR2/4
RAC1
GSK3β
MYC
Cell cycle progression
Prolactin signaling pathway
c-Src
PI3K
PIP3
Akt/PKB
PPP2CA
PTEN
FOXO1
CCND1
YWHAG
(Mammary epithelial cells)
PRL
PRLR
JAK2
SHC
JNK
p38
CCND1
EGF
EGFR
Grb2
SOS
NRAS
MAPK signaling pathw...
MAPK1
FOXO signaling pathway
EFNA1
IGF1
IGF1R
IRS
PI3K
Raf-1
MEK
PTEN
IKK α/β
FOXO1
COD2
Oxidative stres...
Gluco...
GLUT4
Energy metabolism
ROS
STK4
FBXO32
Muscle atrophy
ATF2...
Bcl-2
Mcl-l
Cell survival
ER
c-Src
PI3K
Akt
eNOS
NO
PIK3-AKT signaling pathway
E2
Ovarian steroidogene...
Nuclear-initiated...
Hsp90
FKBP4
Hsp70
Estrogen signaling pathway
Text is not SVG - cannot display

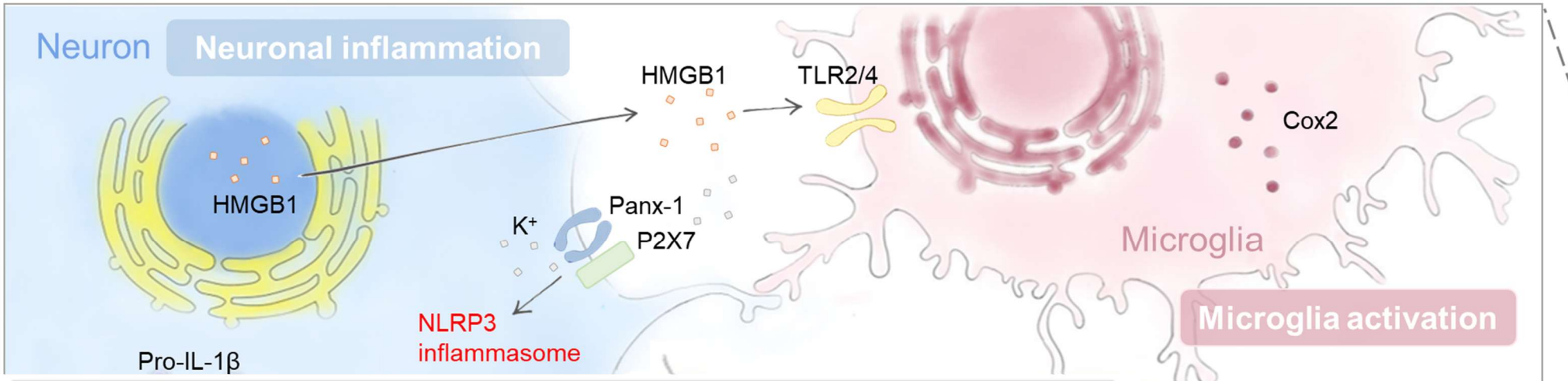
生物資訊功能分析

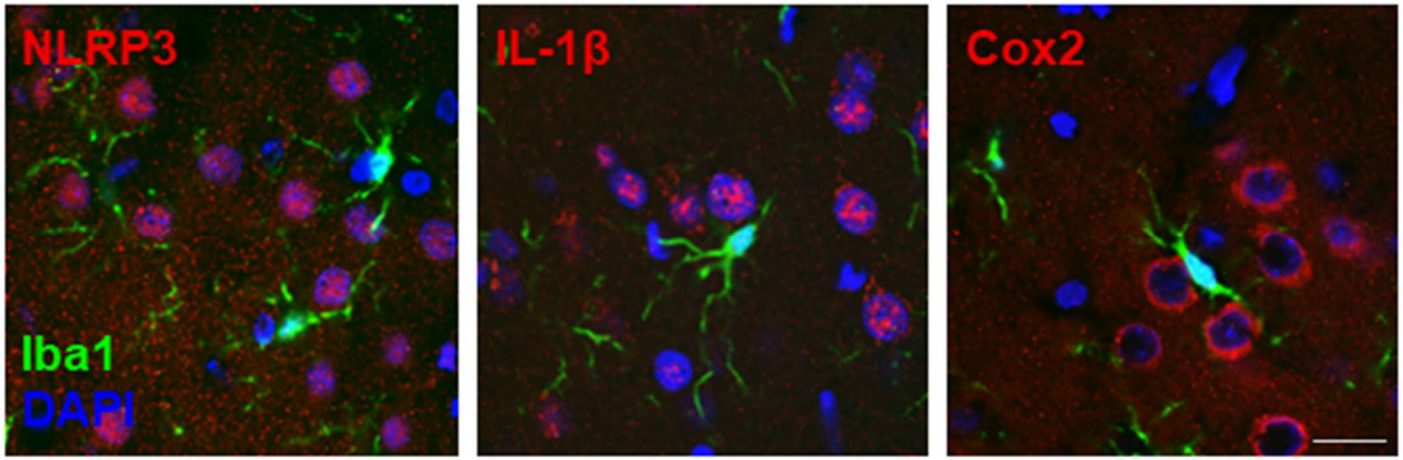


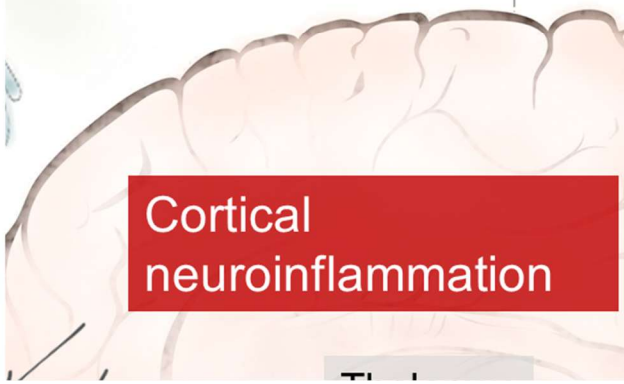


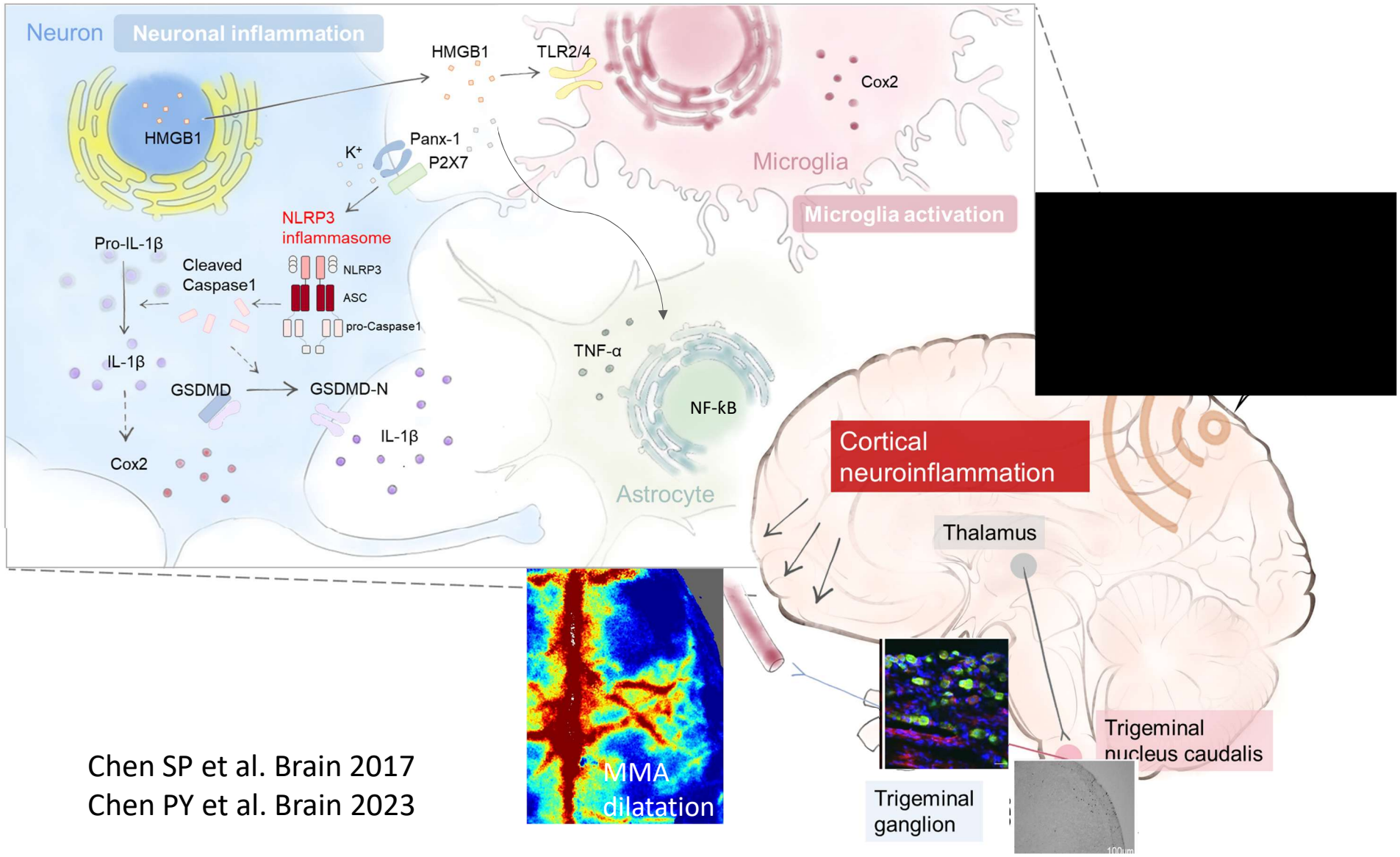
Chen et al. Journal of Neuroinflammation 2020

Activation of microglia via HMGB1-TLR2/4 pathway









Chen SP et al. Brain 2017
Chen PY et al. Brain 2023



偏頭痛不再是看不見的病

表現最佳的血液預測模型

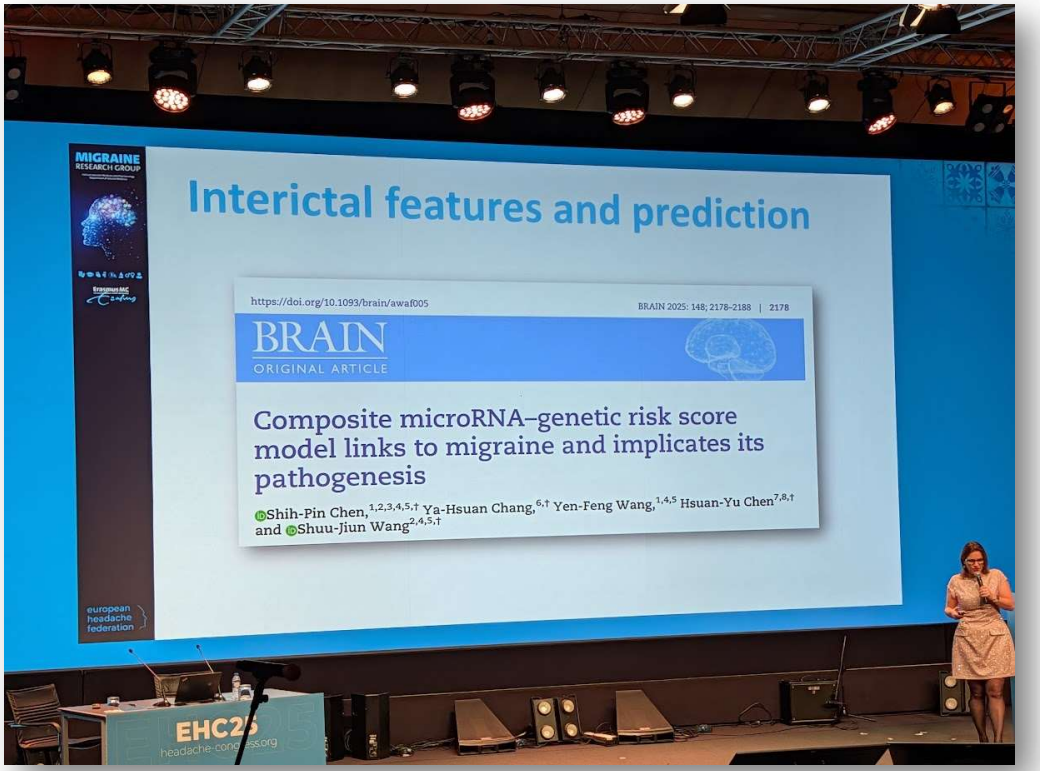
促進瞭解疾病病生理機轉

邁向精準醫療及液態切片

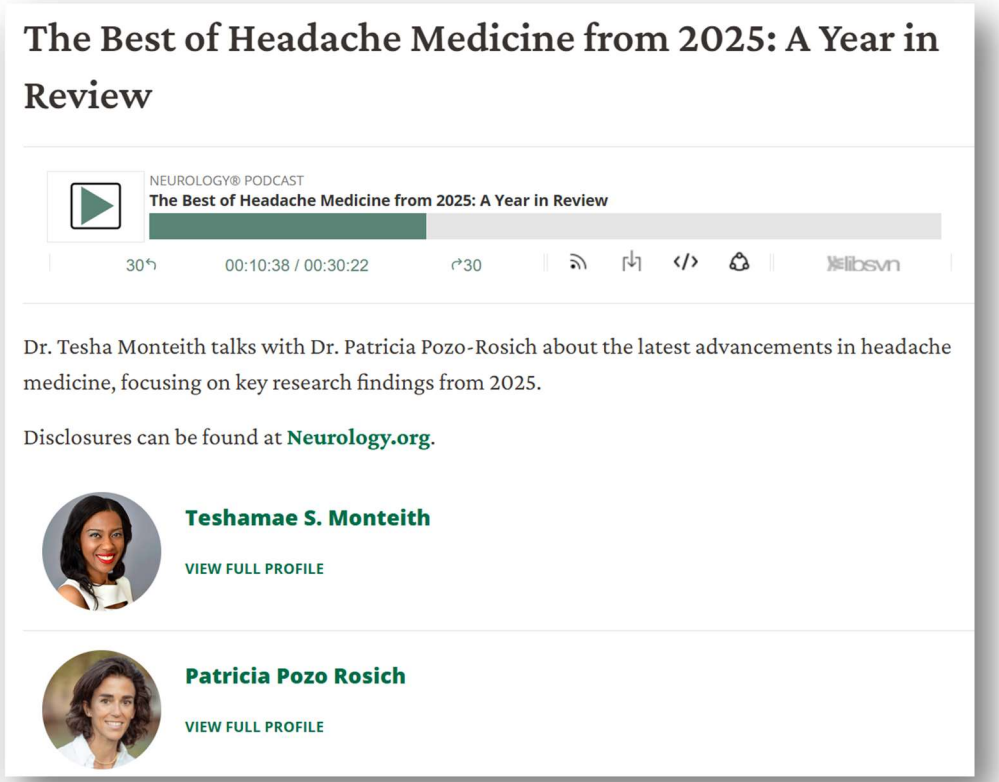


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- 偏頭痛診斷難題　北榮跨團隊研究用抽血驗體質 _ 生活 _ 中央社 CNA

歐洲頭痛聯盟理事長於2025歐洲頭痛年會Highlight當年頭痛領域最重要10大論文



國際頭痛學會準理事長於Neurology Podcast指出此研究為2025頭痛領域最重要研究



致謝

臺北榮民總醫院
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