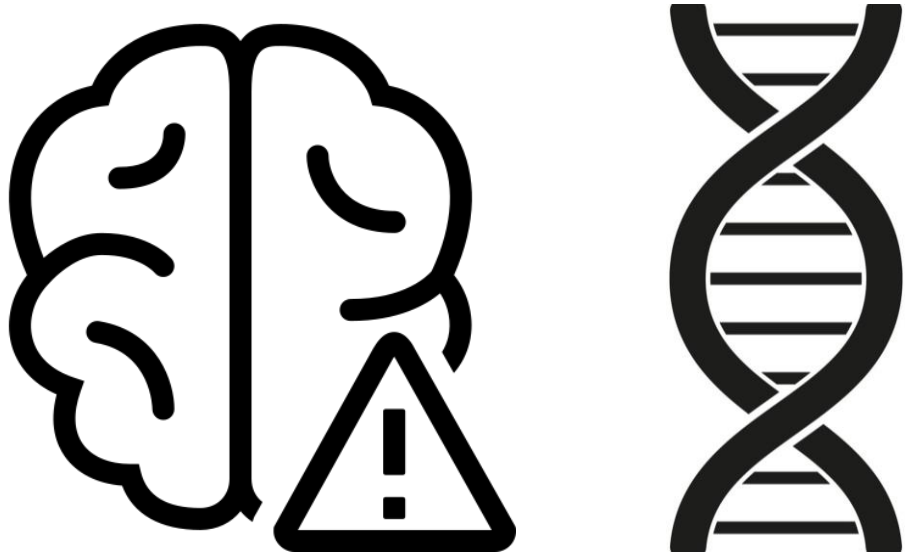
Genetica en beroerte:
Update over de laatste ontwikkelingen



Ynte Ruigrok

neuroloog

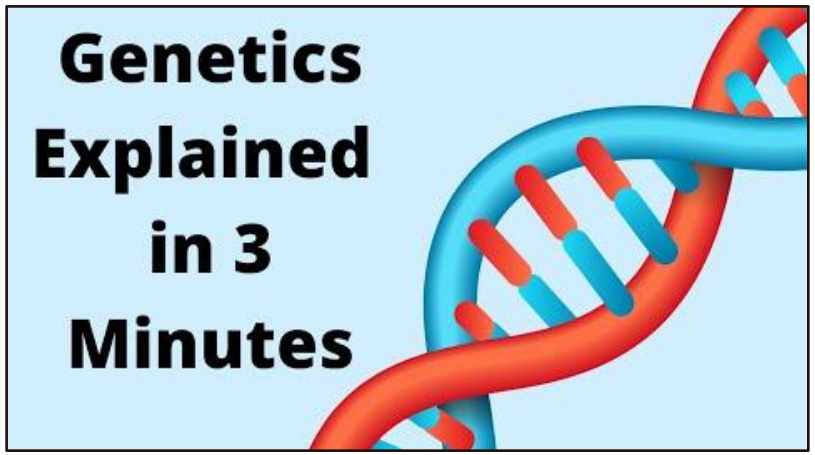
UMC Utrecht

vragen

- ✓ Wat is een genoom wijde associatie studie (GWAS)?
- ✓ Welke interessante ontwikkelingen zijn er op dat gebied?
- ✓ Hoe zit het met genetica van lacunaire infarcten/witte stof afwijkingen?
  - Wanneer moet je aan genetische oorzaak denken?
  - Wat vraag je aan?
  - Wat doe je als je DNA screening negatief terug komt?
  - Rol van whole exome sequencing (WES) daarbij?

disclaimers

1



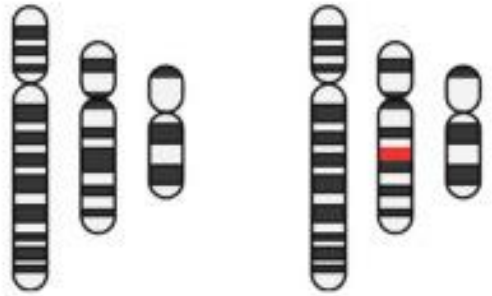
2

3

UMC Utrecht

inleiding

monogenetische ziekte

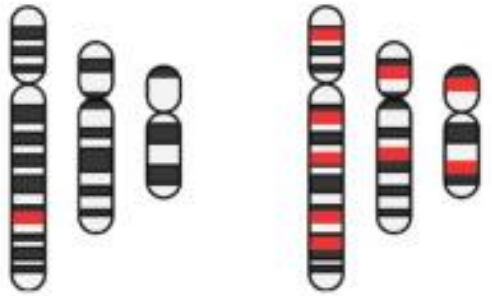


risico gen

loopt geen risico

loopt wel risico

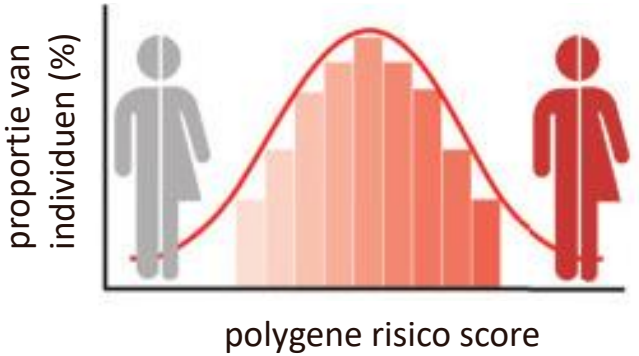
complexe / polygenetische ziekte



risico gen

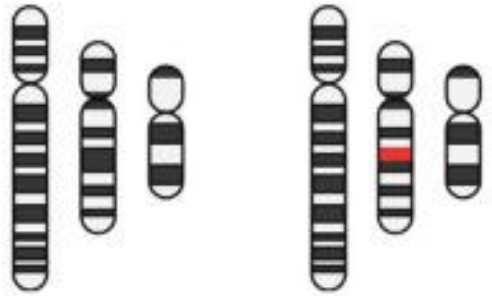
laag risico

hoog risico



UMC Utrecht

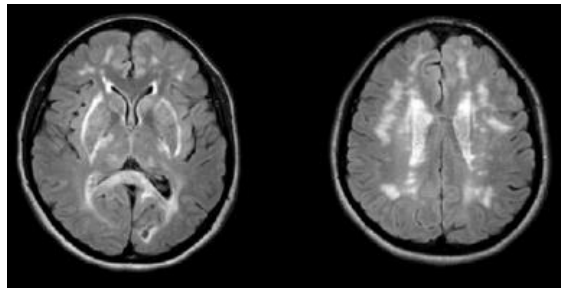
monogenetische ziekte



risico gen

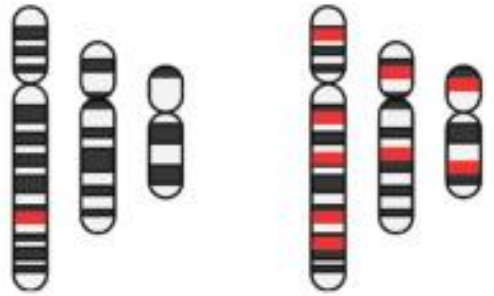
loopt geen risico

loopt wel risico



CADASIL

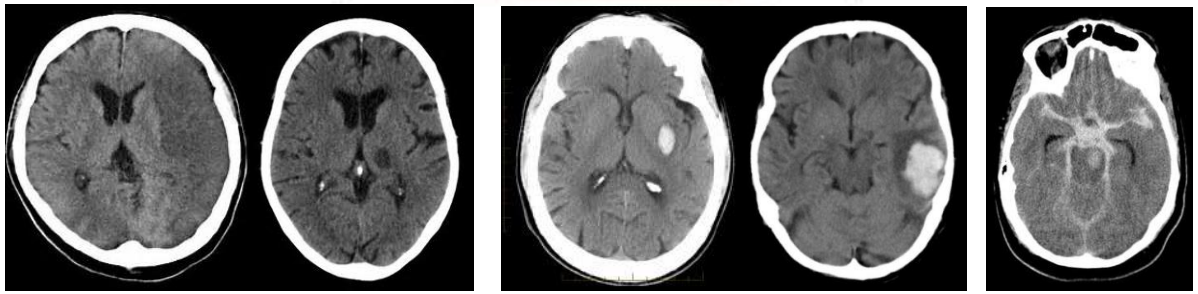
complexe / polygenetische ziekte



risico gen

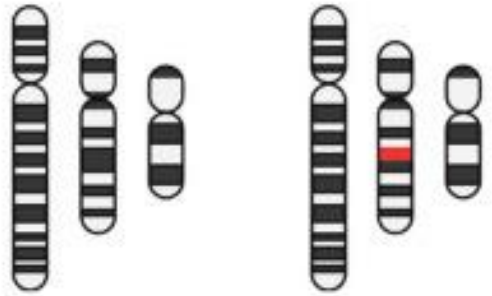
laag risico

hoog risico



UMC Utrecht

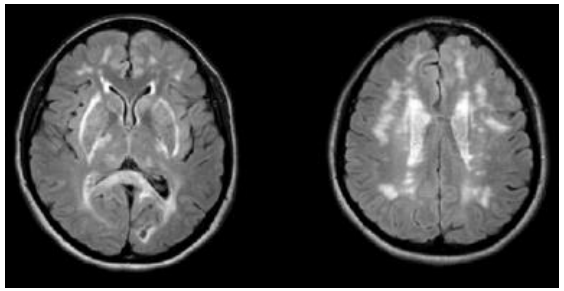
monogenetische ziekte



risico gen

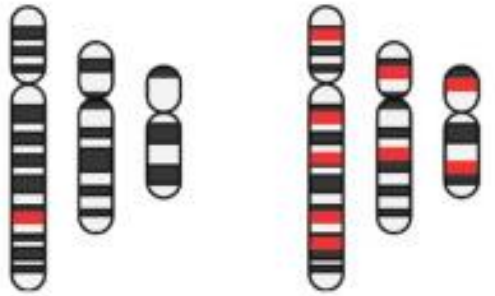
loopt geen risico

loopt wel risico



CADASIL

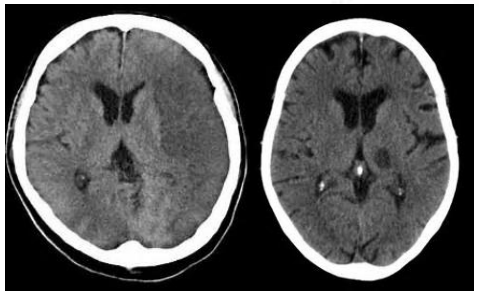
complexe / polygenetische ziekte



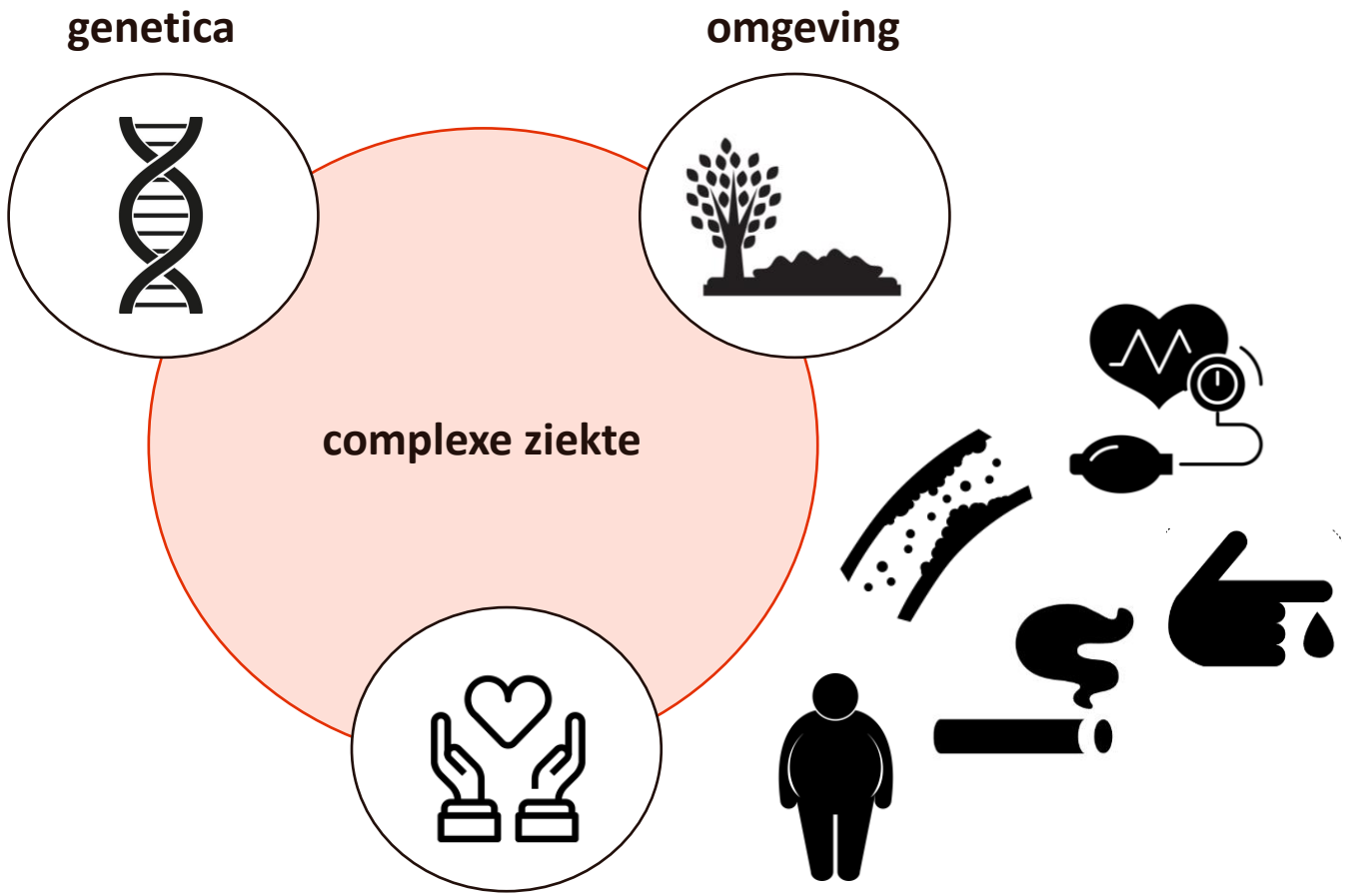
risico gen

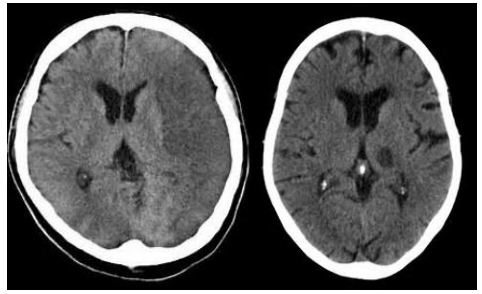
laag risico

hoog risico



UMC Utrecht



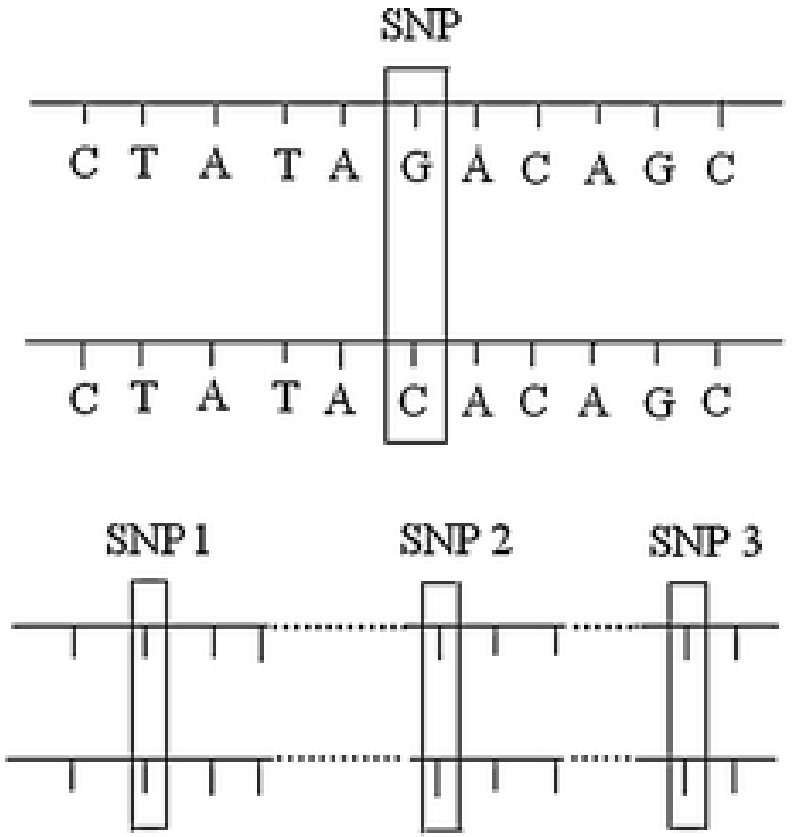


UMC Utrecht

single nucleotide polymorphism (SNP)

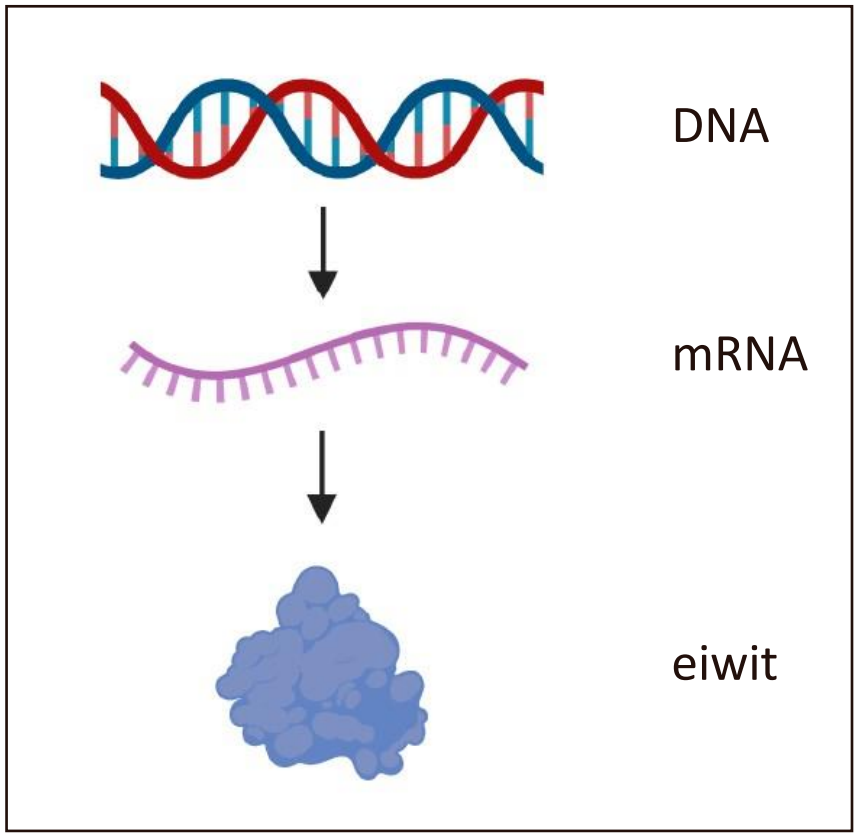
individu A

individu B



meest voorkomende genetische variatie tussen individuen

4-5 miljoen per individu

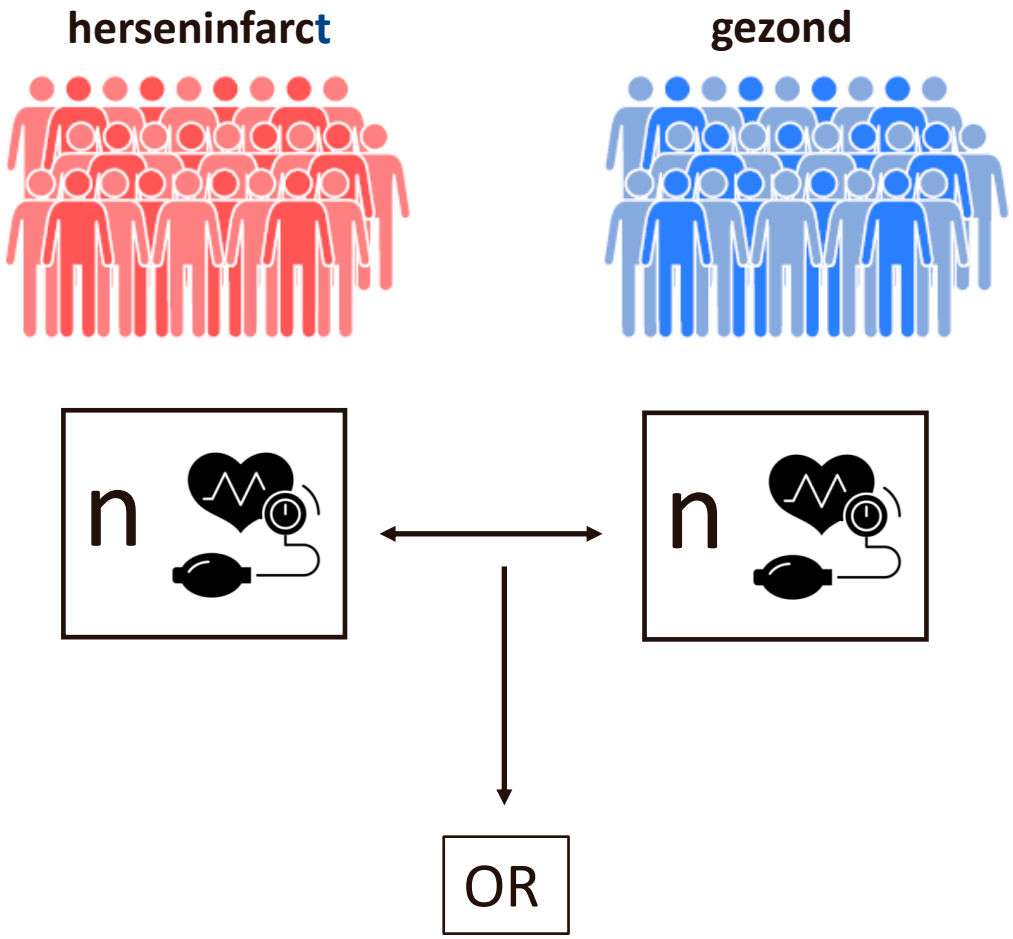


monogenetische ziekte

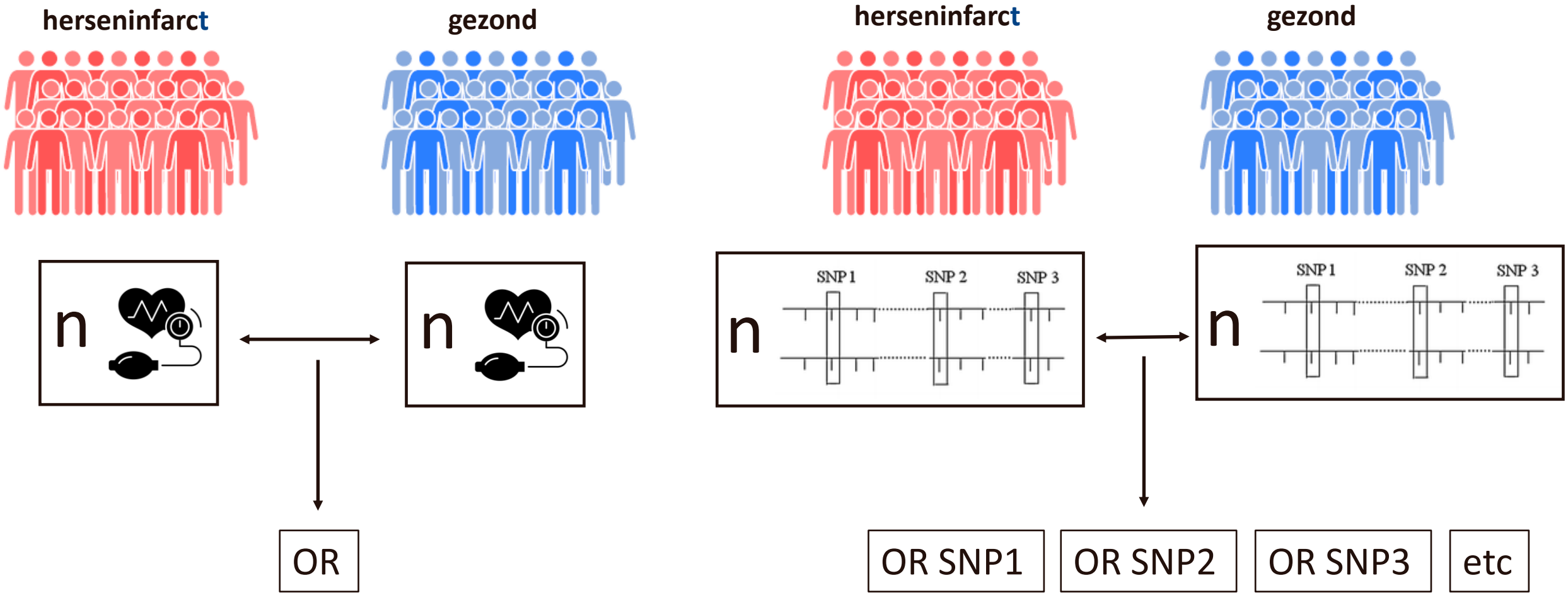
vs

complexe ziekte

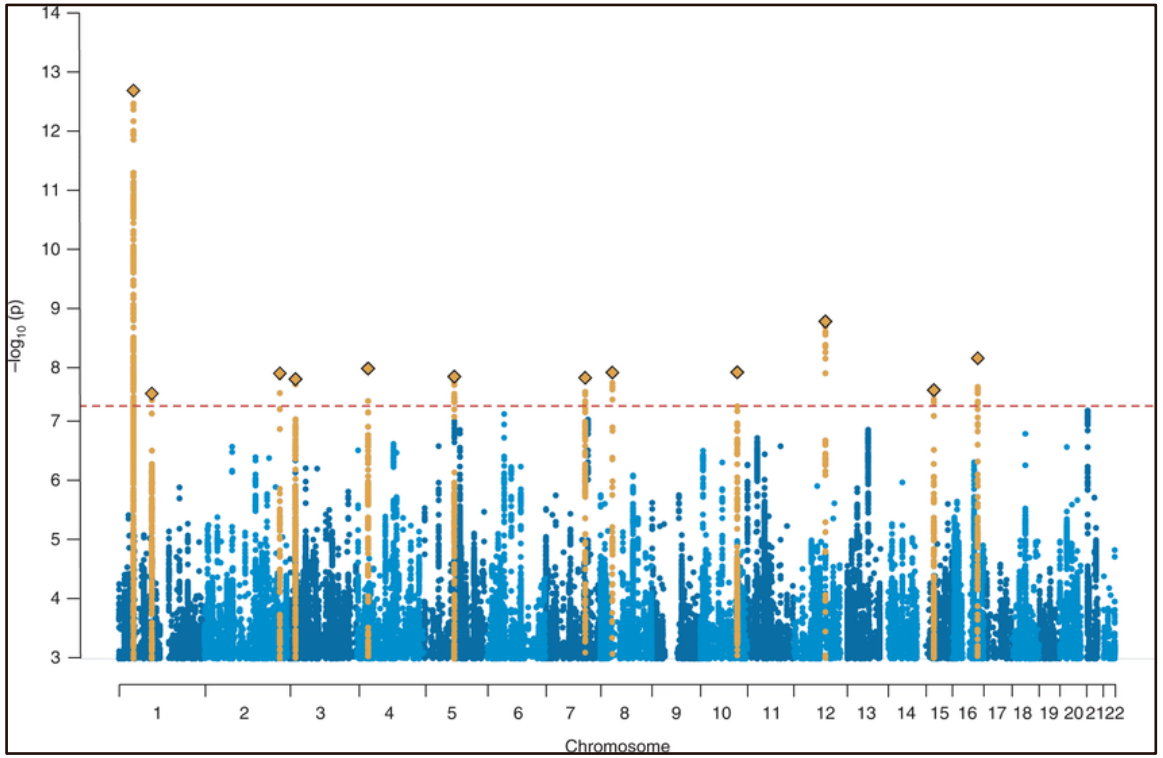
GWAS



GWAS


herseninfarct
gezond
n
n
OR
herseninfarct
gezond
n
SNP 1
SNP 2
SNP 3
n
SNP 1
SNP 2
SNP 3
OR SNP1
OR SNP2
OR SNP3
etc

manhattan plot



UMC Utrecht

nature

Stroke genetics informs drug discovery and risk prediction across ancestries

https://doi.org/10.1038/s41586-022-05165-3

Received: 15 December 2021

Accepted: 29 July 2022

Published online: 30 September 2022

Open access

Previous genome-wide association studies (GWASs) of stroke – the second leading cause of death worldwide – were conducted predominantly in populations of European ancestry[1,2]. Here, in cross-ancestry GWAS meta-analyses of 110,182 patients who have had a stroke (five ancestries, 33% non-European) and 1,503,898 control individuals, we identify association signals for stroke and its subtypes at 89 (61 new) independent loci: 60 in primary inverse-variance-weighted analyses and 29 in secondary meta-regression and multitrait analyses. On the basis of internal cross-ancestry validation and an independent follow-up in 89,084 additional cases of stroke (30% non-European) and 1,013,843 control individuals, 87% of the primary stroke risk loci and 60% of the secondary stroke risk loci were replicated ($P < 0.05$). Effect sizes were highly correlated across ancestries. Cross-ancestry fine-mapping, in silico mutagenesis analysis[3], and transcriptome-wide and proteome-wide association analyses revealed putative causal genes (such as *SH3PXD2A* and *FURIN*) and variants (such as at *GRK5* and *NOS3*). Using a three-pronged approach[4], we provide genetic evidence for putative drug effects, highlighting F11, KLKB1, PROC, GP1BA, LAMC2 and VCAM1 as possible targets, with drugs already under investigation for stroke for F11 and PROC. A polygenic score integrating cross-ancestry and ancestry-specific stroke GWASs with vascular-risk factor GWASs (integrative polygenic scores) strongly predicted ischaemic stroke in populations of European, East Asian and African ancestry[5]. Stroke genetic risk scores were predictive of ischaemic stroke independent of clinical risk factors in 52,600 clinical-trial participants with cardiometabolic disease. Our results provide insights to inform biology, reveal potential drug targets and derive genetic risk prediction tools across ancestries.

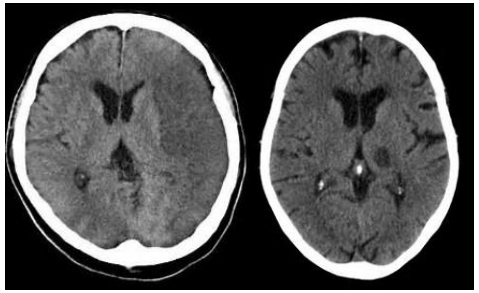
grote GWAS?

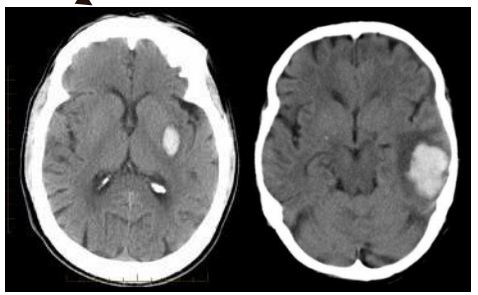
110.182 stroke cases	vs	300.000 insomnia cases

UMC Utrecht

Nat Genet 2019;51:394–403

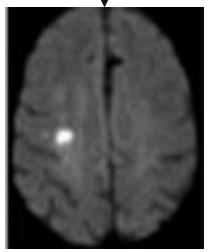
110.182 stroke cases

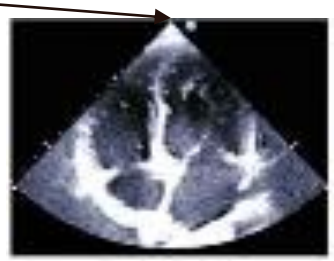




n=86.668

n=23.514

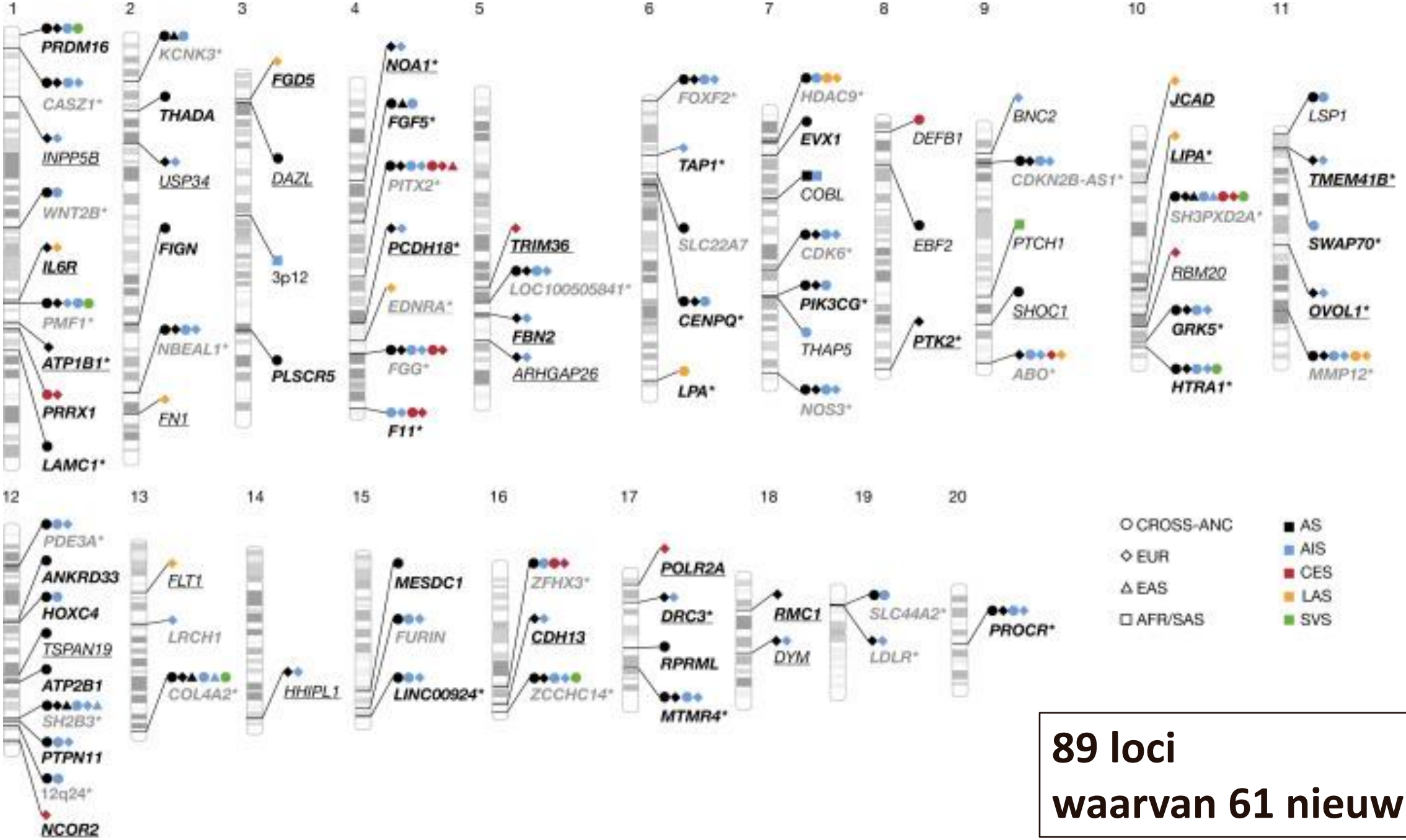




LAA
n=9.219

SVD
n=13.620

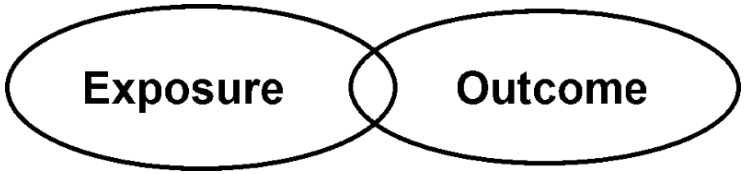
CES
n=12.790



89 loci
waarvan 61 nieuw

GWAS: wat kunnen we er mee?

GWAS: wat kunnen we er mee?



mendelian randomisation

genomics driven drug discovery

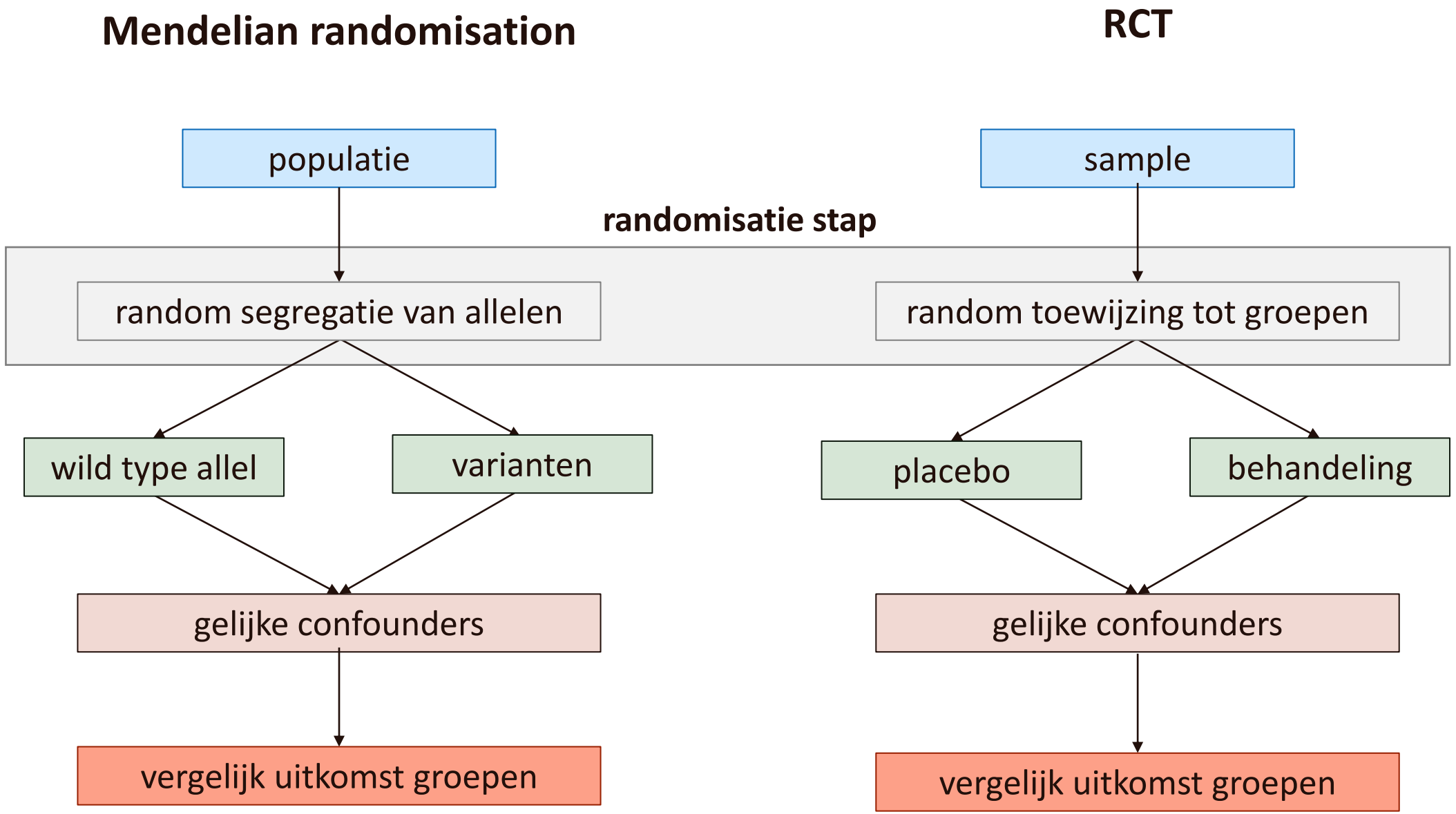
risico predictie

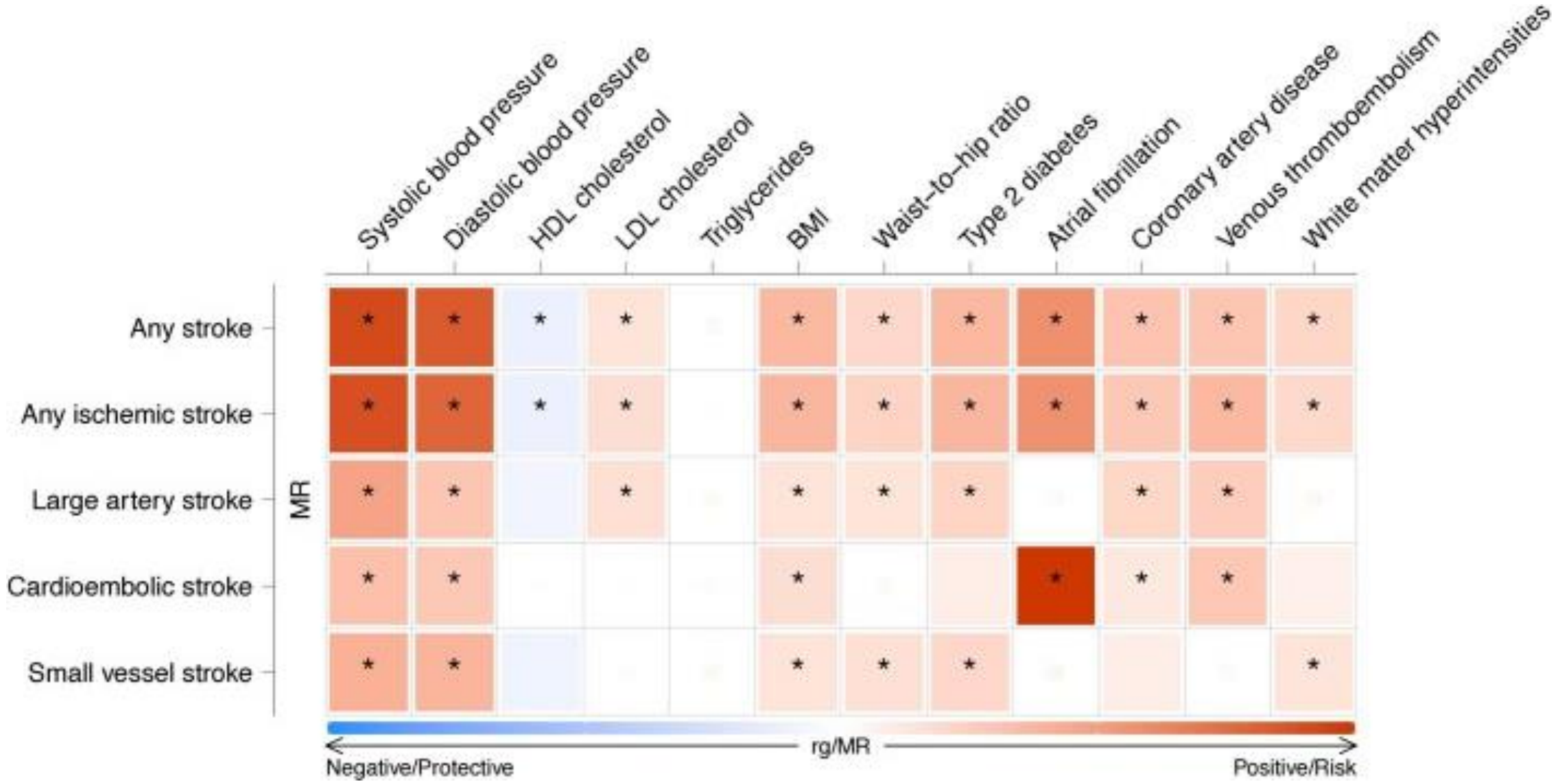
mendelian randomisation

m.b.v. genetische varianten invloed van exposure (bv risicofactor) op een outcome (bv ziekte) vaststellen

voordeel: geen confounding

genetisch instrument


Mendelian randomisation
RCT
populatie
sample
randomisatie stap
random segregatie van allelen
random toewijzing tot groepen
wild type allel
varianten
placebo
behandeling
gelijke confounders
gelijke confounders
vergelijk uitkomst groepen
vergelijk uitkomst groepen


Systolic blood pressure
Diastolic blood pressure
HDL cholesterol
LDL cholesterol
Triglycerides
BMI
Waist–to–hip ratio
Type 2 diabetes
Atrial fibrillation
Coronary artery disease
Venous thromboembolism
White matter hyperintensities
Any stroke
Any ischemic stroke
Large artery stroke
Cardioembolic stroke
Small vessel stroke
MR
rg/MR
Negative/Protective
Positive/Risk

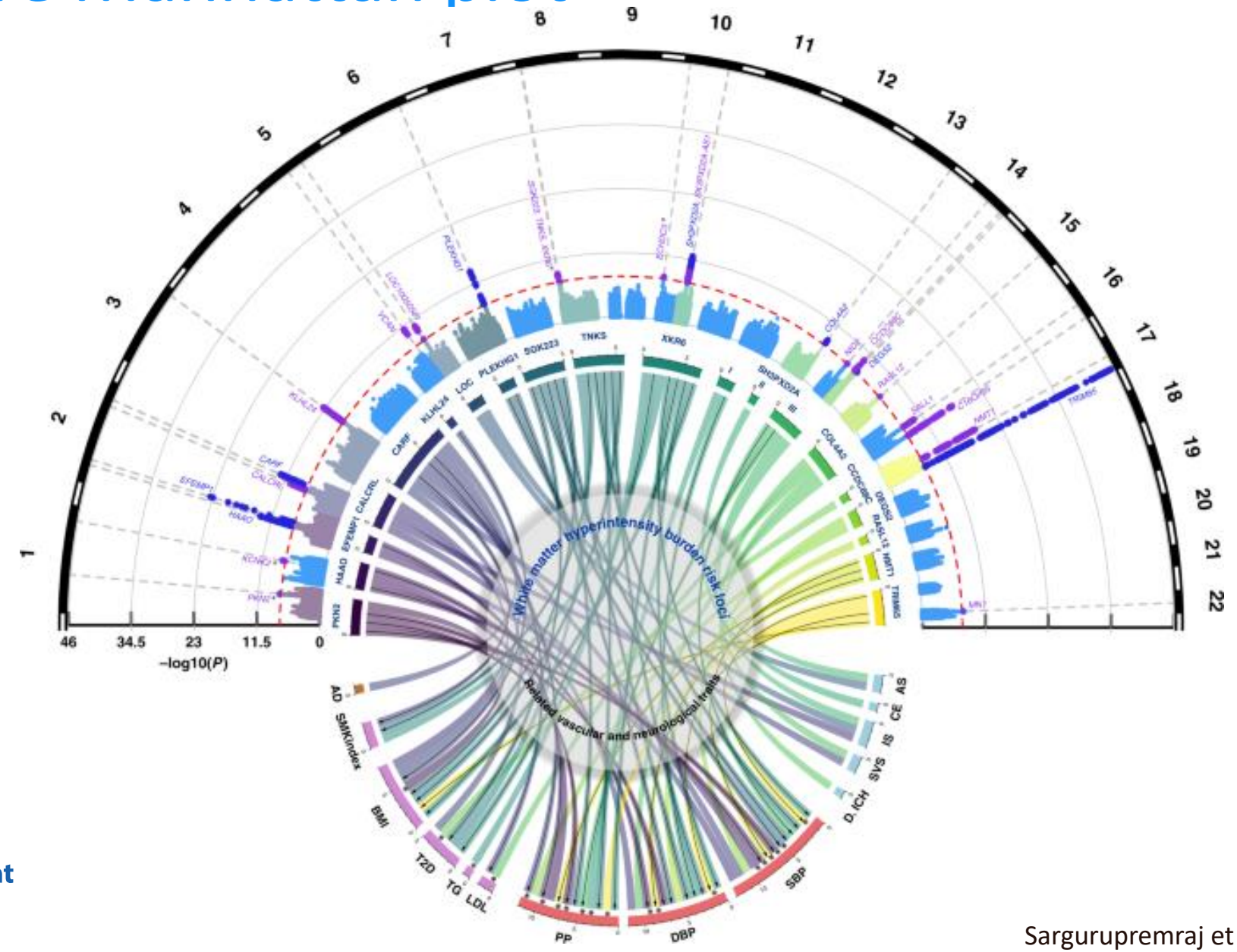
GWAS white matter hyperintensities (WMH)

- ✓ 50,970 oudere individuen, gem 66.0 ± 7.5 jaar
- ✓ 27 loci
- ✓ mendelian randomisation: causale relatie van ↑ WMH-volume met:
  - infarct+bloeding, infarct, infarct SVD
  - ↓cognitieve functie
  - dementie alzheimer-type

UMC Utrecht

Sargurupremraj et al. Nat Commun 2020;11:6285

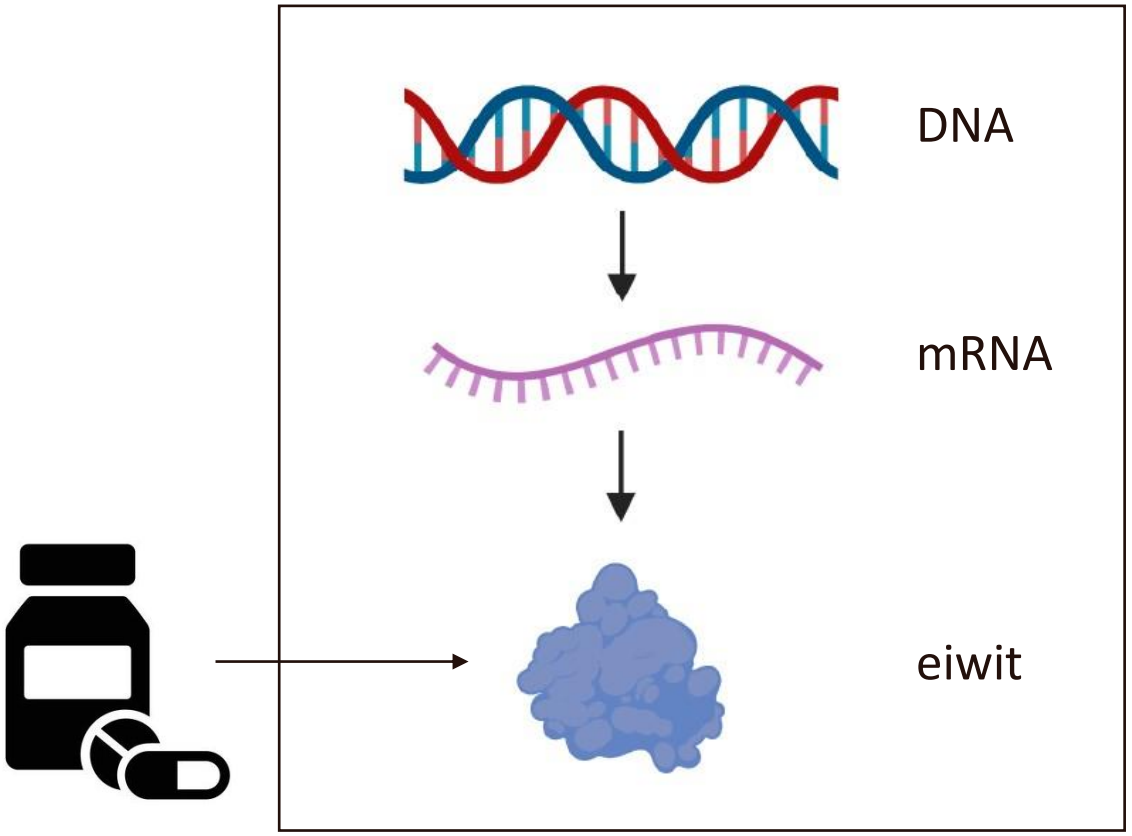
circulaire Manhattan plot



UMC Utrecht

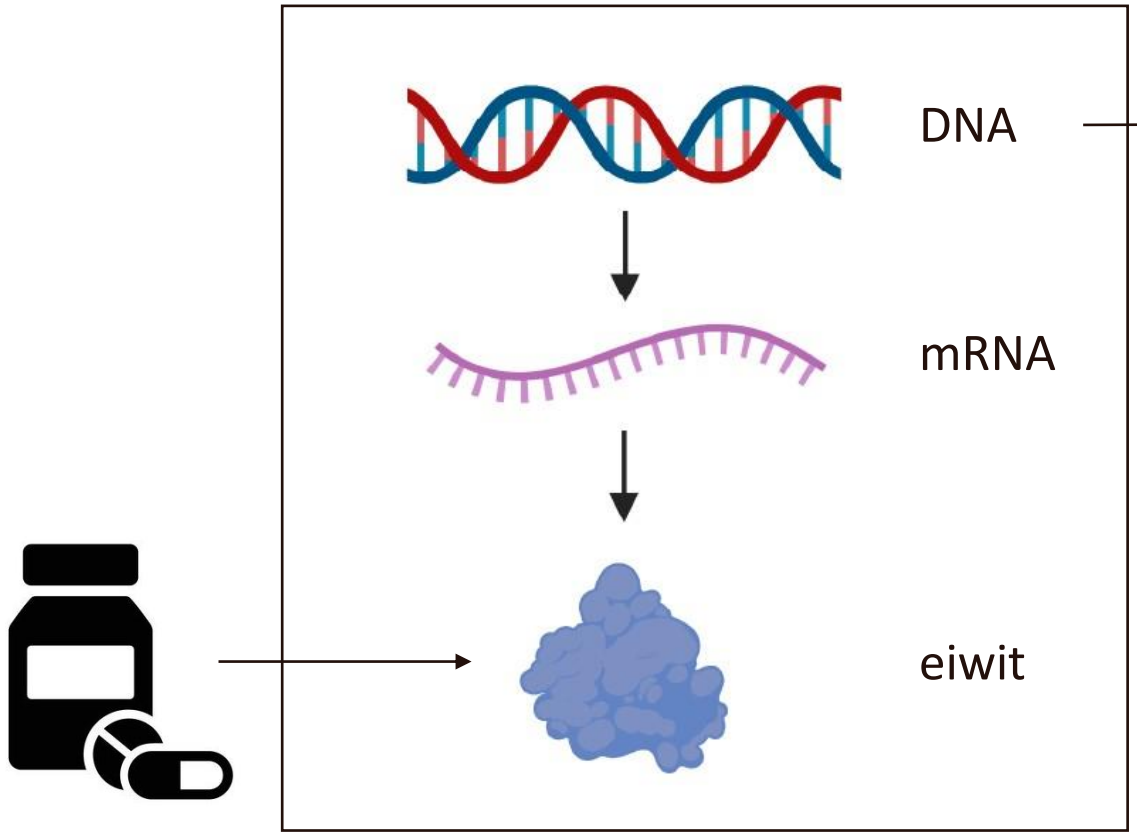
Sargurupremraj et al. Nat Commun 2020;11:6285

genomics driven drug discovery



drug target

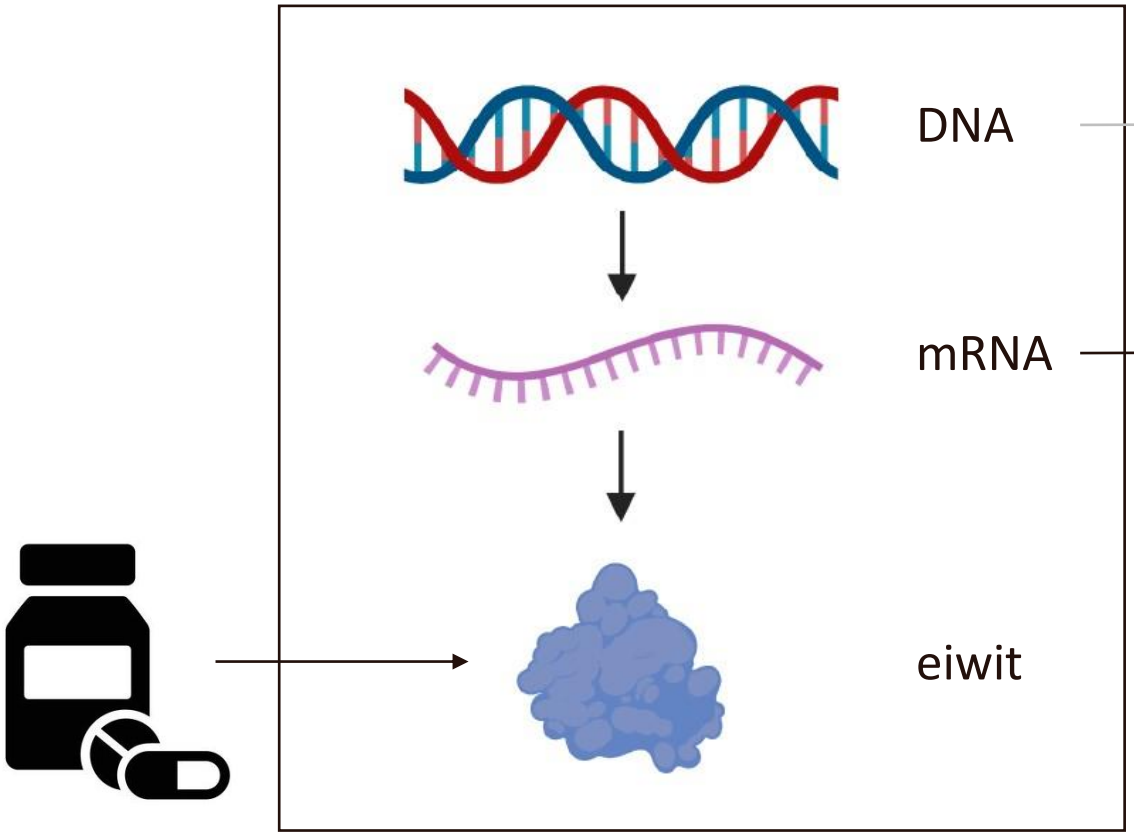
genomics driven drug discovery



1

overlap van genen coderend voor drug-targets in risico loci

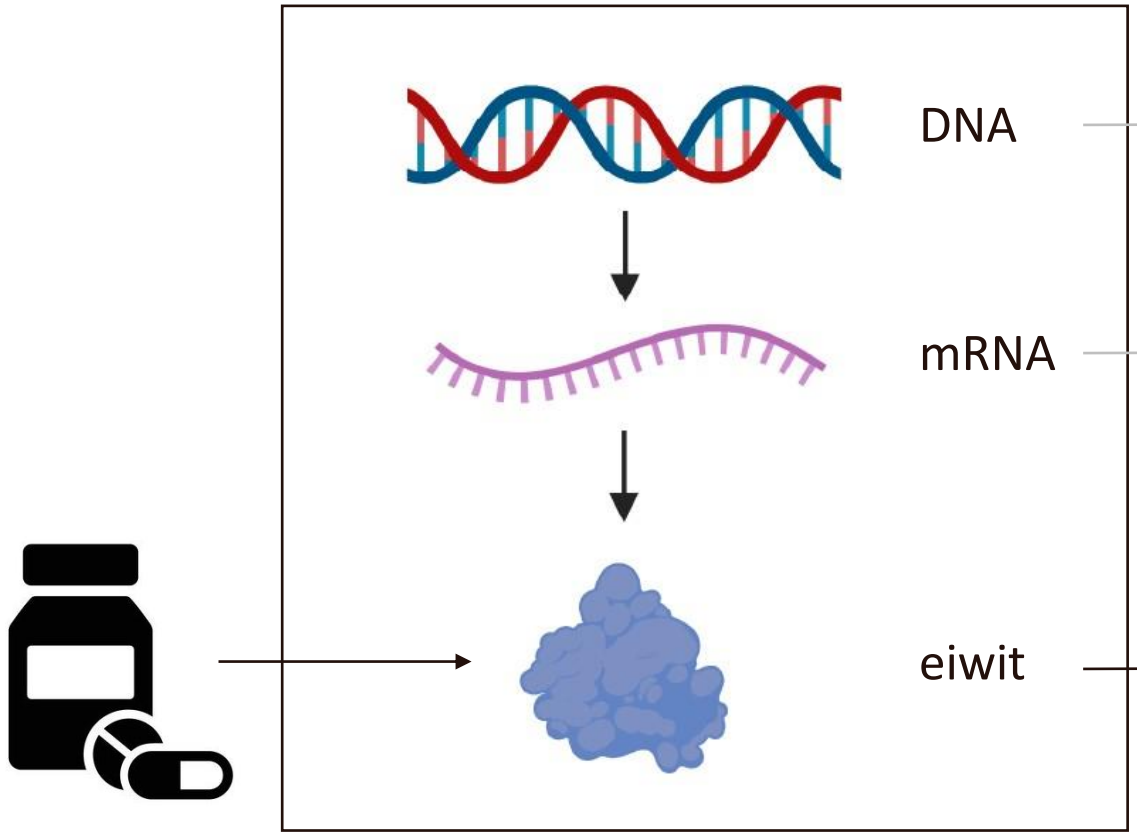
genomics driven drug discovery



1 → overlap van genen coderend voor drug-targets in risico loci

2 →
- genetisch bepaalde gen expressie profiel bij ziekte
- drug compounds met tegengesteld effect op genexpressie

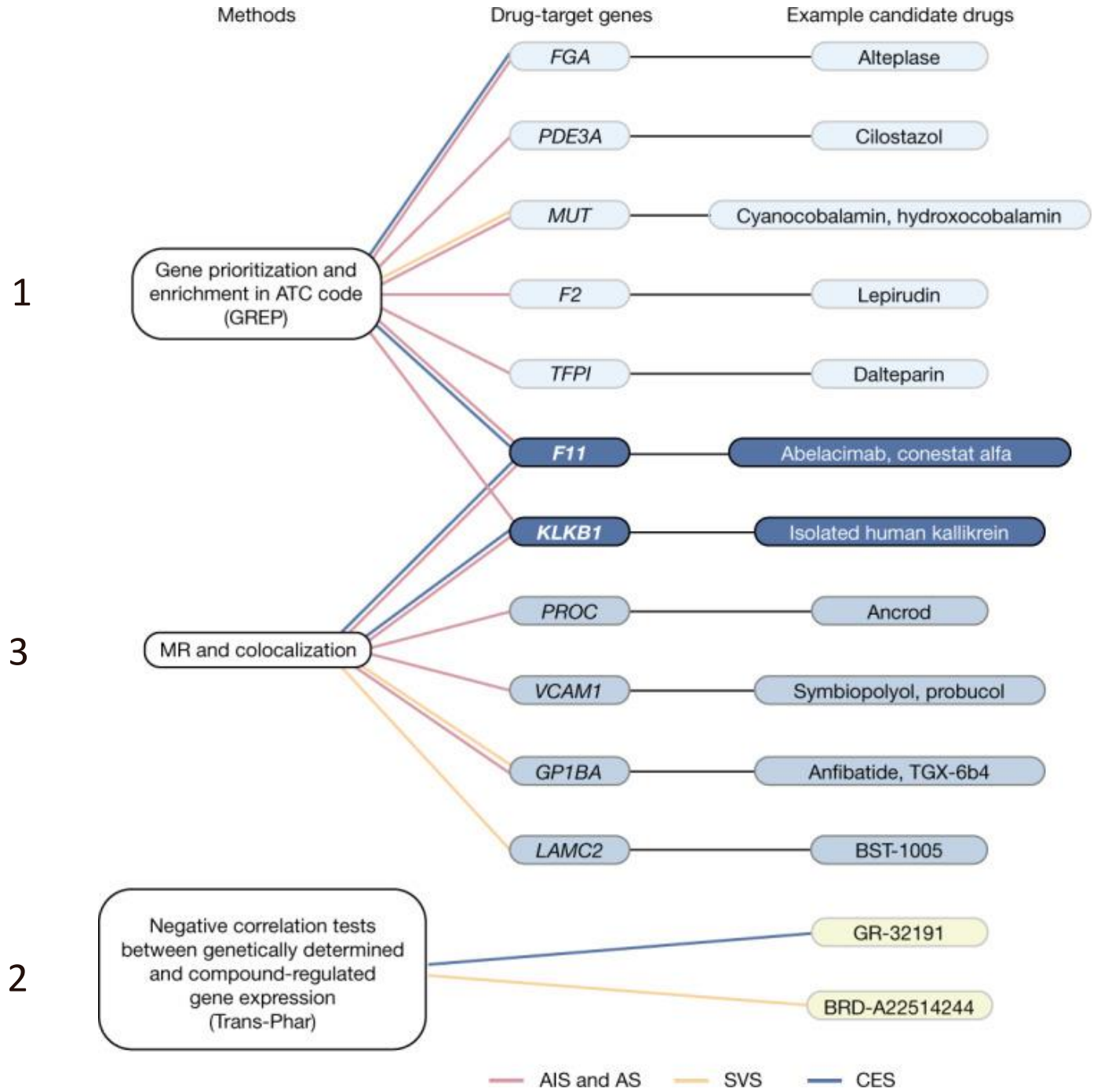
genomics driven drug discovery

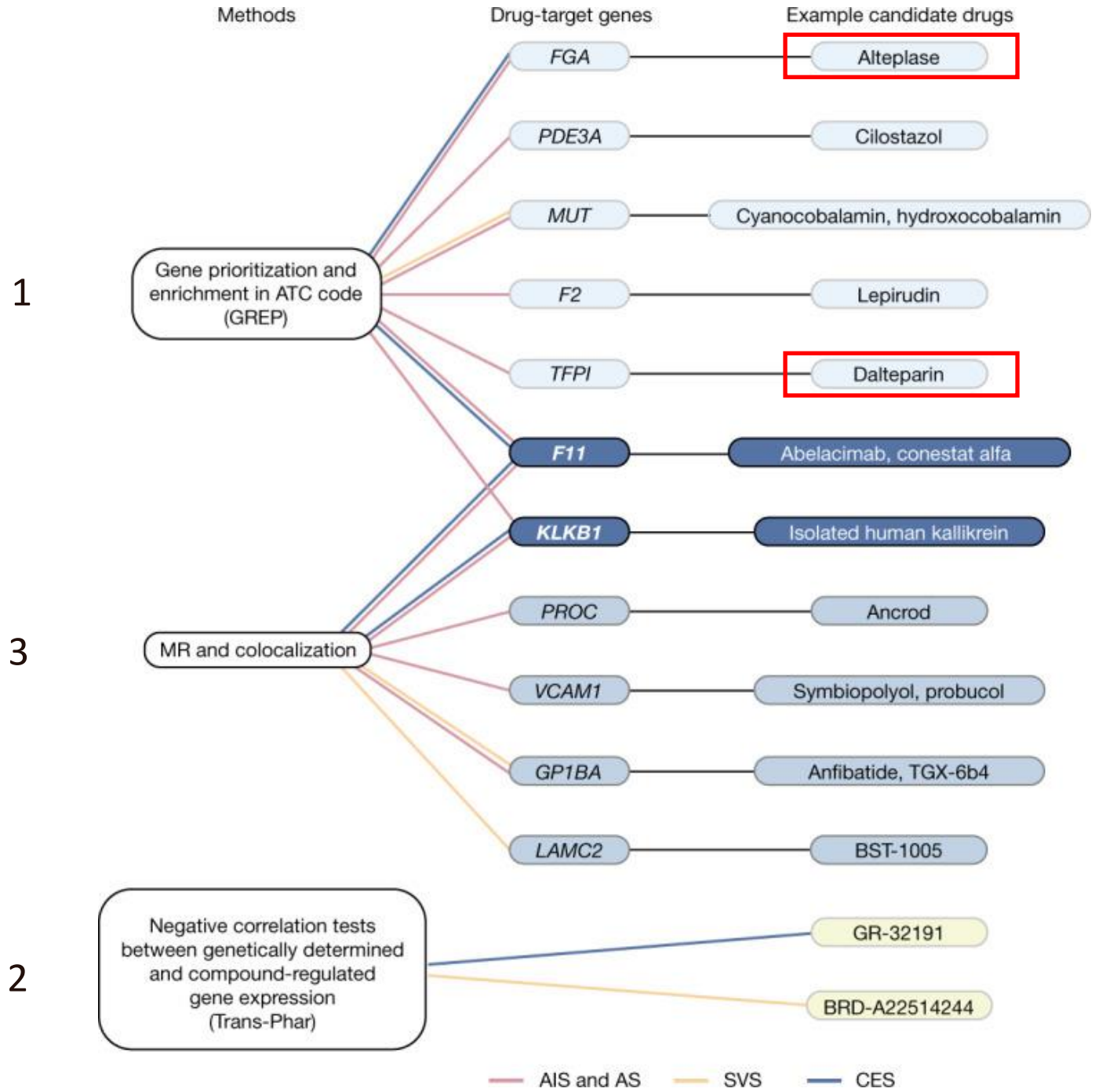


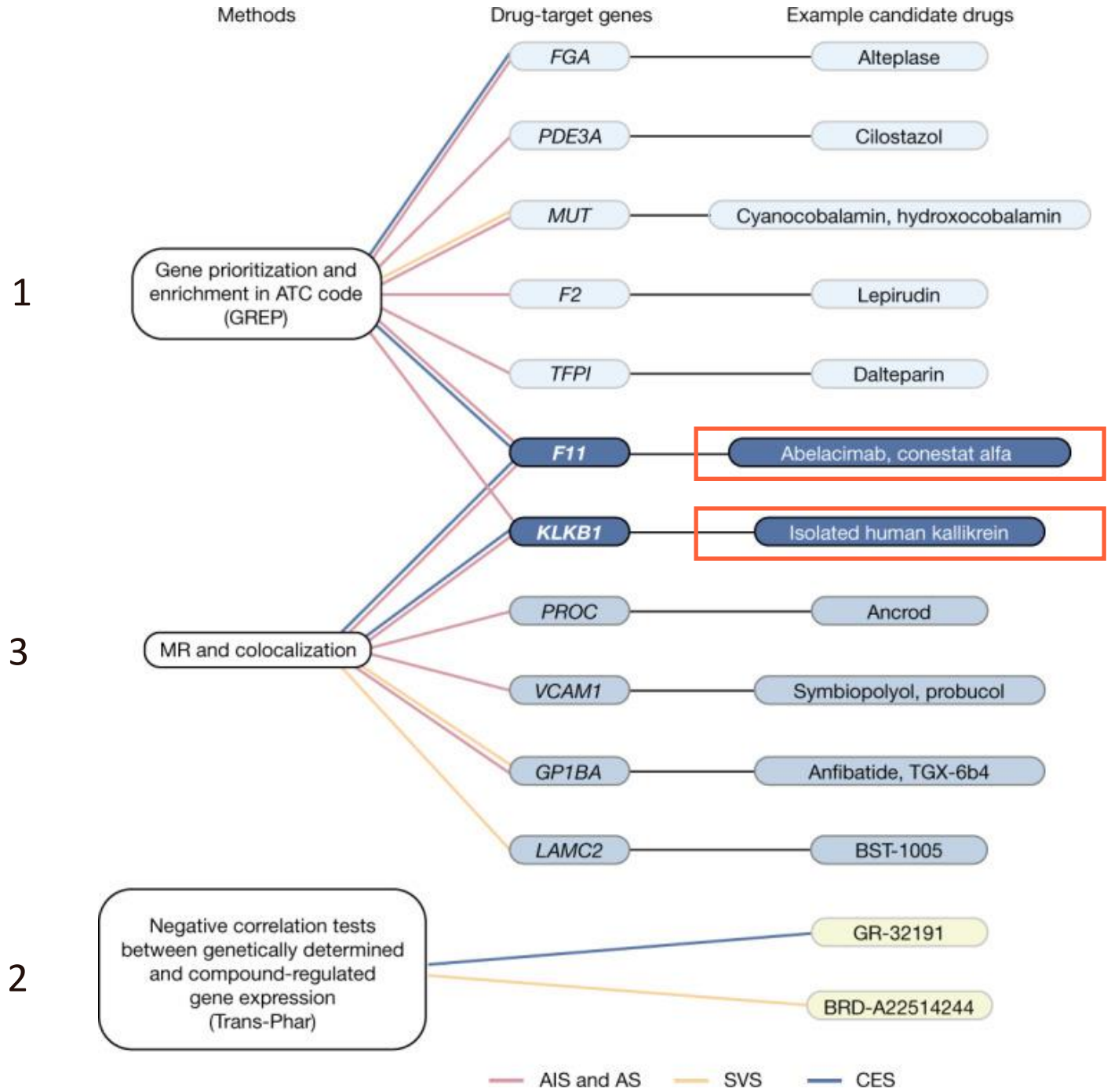
1 → overlap van genen coderend voor drug-targets in risico loci

2 →
- genetisch bepaalde gen expressie profiel bij ziekte
- drug compounds met tegengesteld effect op genexpressie

3 →
- genetisch bepaalde eiwit expressie in bloed
- drug compounds met tegengesteld effect op die expressie

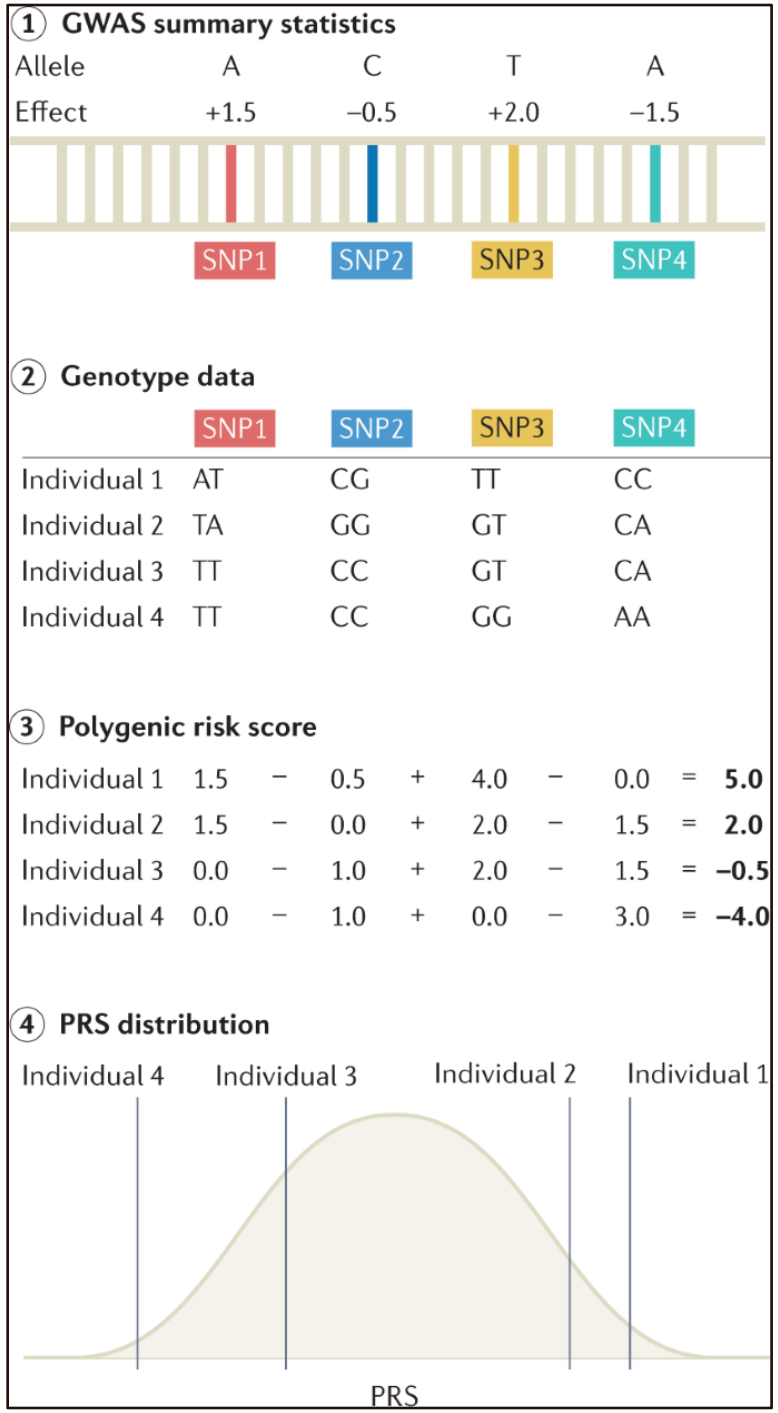

Methods
Drug-target genes
Example candidate drugs
1
Gene prioritization and enrichment in ATC code (GREP)
FGA
Alteplase
PDE3A
Cilostazol
MUT
Cyanocobalamin, hydroxocobalamin
F2
Lepirudin
TFPI
Dalteparin
3
MR and colocalization
F11
Abelacimab, conestat alfa
KLKB1
Isolated human kallikrein
PROC
Ancrod
VCAM1
Symbiopolyol, probucol
GP1BA
Anfibatide, TGX-6b4
LAMC2
BST-1005
2
Negative correlation tests between genetically determined and compound-regulated gene expression (Trans-Phar)
GR-32191
BRD-A22514244
AIS and AS
SVS
CES


Methods
Drug-target genes
Example candidate drugs
1
Gene prioritization and enrichment in ATC code (GREP)
FGA
Alteplase
PDE3A
Cilostazol
MUT
Cyanocobalamin, hydroxocobalamin
F2
Lepirudin
TFPI
Dalteparin
3
MR and colocalization
F11
Abelacimab, conestat alfa
KLKB1
Isolated human kallikrein
PROC
Ancrod
VCAM1
Symbiopolyol, probucol
GP1BA
Anfibatide, TGX-6b4
LAMC2
BST-1005
2
Negative correlation tests between genetically determined and compound-regulated gene expression (Trans-Phar)
GR-32191
BRD-A22514244
AIS and AS
SVS
CES

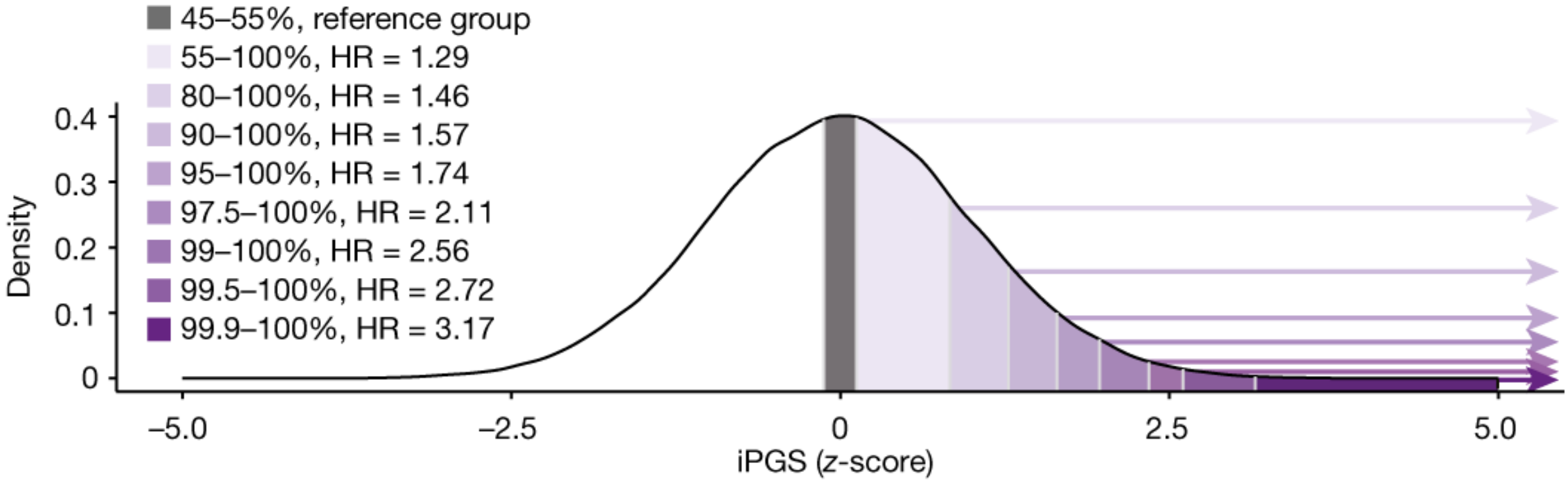


FXI and FXIa inhibitors: onderzocht in fase 2 trials voor primaire en secundaire stroke preventie

risico predictie



UMC Utrecht

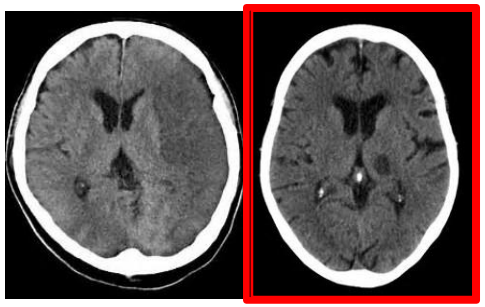

45–55%, reference group
55–100%, HR = 1.29
80–100%, HR = 1.46
90–100%, HR = 1.57
95–100%, HR = 1.74
97.5–100%, HR = 2.11
99–100%, HR = 2.56
99.5–100%, HR = 2.72
99.9–100%, HR = 3.17
Density
0.4
0.3
0.2
0.1
0
–5.0
–2.5
0
2.5
5.0
iPGS (z-score)

monogenetische ziekte:

- ✓ wanneer er aan denken
- ✓ wat vraag je aan?

UMC Utrecht

wanneer denken aan monogenetische ziekte?

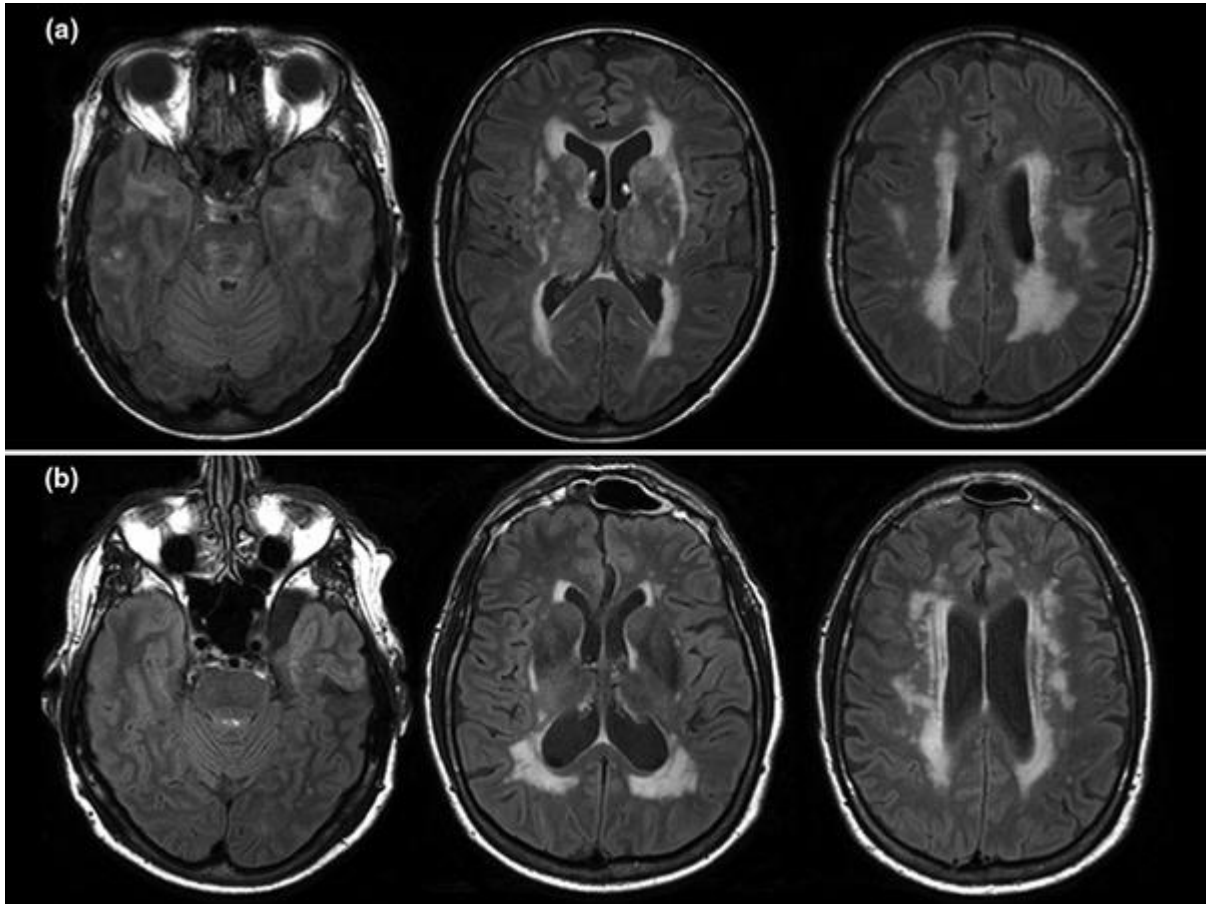


- jonge leeftijd (<50-55 jaar)
- positieve familie anamnese
- voorgeschiedenis / anamnese met andere aandoeningen
- additionele afwijkingen bij lichamelijk onderzoek
- uitgebreide afwijkingen op beeldvorming cerebrum

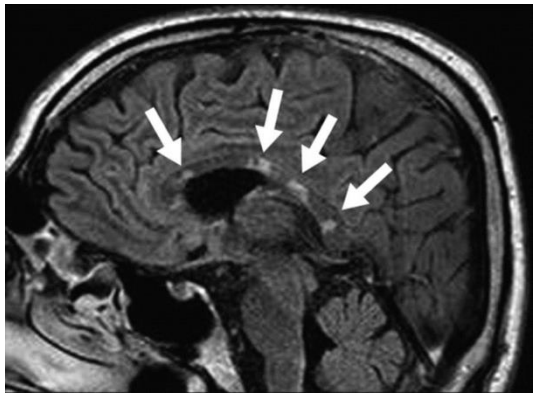
	Mode of inheritance	Underlying gene(s)	Stroke mechanism	Comment and selected key references*
Mendelian conditions mostly manifesting with ischaemic stroke				
CADASIL	Autosomal dominant	*NOTCH3*	Small vessel disease	Most common hereditary stroke syndrome[15]
CARASIL	Autosomal recessive	*HTRA1*	Small vessel disease	Heterozygous mutations in *HTRA1* might cause late-onset small vessel disease[5]
CARASAL	Autosomal dominant	*CTSA*	Small vessel disease	Can manifest with both ischaemic and haemorrhagic stroke, and hypertension[12]
Fabry's disease	X-linked	*GLA*	Small vessel disease, large artery disease, cardioembolism	Multi-organ disease; enzyme-replacement therapy available
PADMAL	Autosomal dominant	*COL4A1*	Small vessel disease	Ischaemic lacunar infarctions in the pons as a common presentation[4]
RVCL-S	Autosomal dominant	*TREX1*	Small vessel disease	Retinopathy and rim-enhancing mass lesions on brain MRI[16]
Sickle-cell disease	Autosomal recessive	*HBB*	Prothrombotic state, large artery disease	Most common cause of stroke in children; haemorrhagic strokes in adult patients[17]
FOXC1 deletion-related angiopathy	Autosomal dominant	*FOXC1*	Small vessel disease	Common manifestations are white matter hyperintensities on brain MRI[18]
DADA2	Autosomal recessive	*ADA2* (*CECR1*)	Small vessel vasculitis	Typically manifests in early childhood (before age 6 years); fever, skin changes, polyarteritis nodosa[19]
Pseudoxanthoma elasticum	Autosomal recessive	*ABCC6*	Large artery disease, small vessel disease	Common manifestations are skin and retinal changes; calcified elastic fibres[20]
Homocystinuria	Autosomal recessive	*CBS* and others (eg, *MTHFR*)	Large artery disease, cardioembolism, small vessel disease, arterial dissection	Common manifestations are thromboembolism, premature atherosclerosis, mental retardation, Marfan-like skeletal abnormalities

Dichgans et al. Lancet Neurol 2019;18:587–99

CADASIL



temporaal kwab
capsula externa
corpus callosum



UMC Utrecht

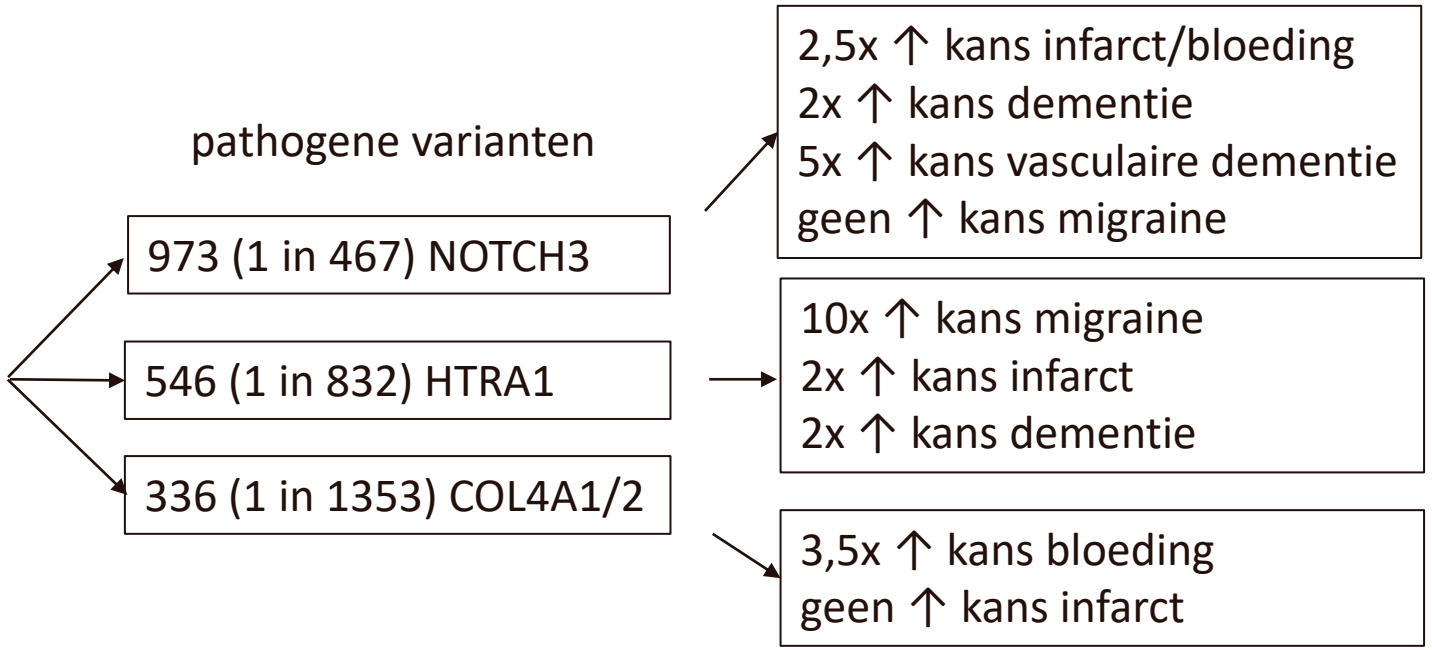
Hoe vaak komen deze ziekten/mutaties voor?

prevalentie CADASIL: 4 per 100 000

Hoe vaak komen deze ziekten/mutaties voor?

biobank uk

454 756 deelnemers



UMC Utrecht

Cho et al. JAMA Neurol 2022 Oct 27 : e223832

Hoe vaak komen deze ziekten/mutaties voor?

454 756 deelnemers

pathogene varianten

973 (1 in 467) NOTCH3

546 (1 in 832) HTRA1

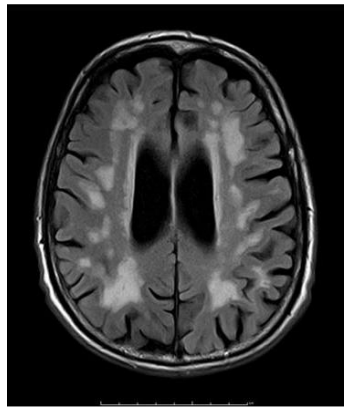
2,5x ↑ kans infarct/bloeding
2x ↑ kans dementie
5x ↑ kans vasculaire dementie
geen ↑ kans migraine

10x ↑ kans migraine
2x ↑ kans infarct
2x ↑ kans dementie

↑ kans infarct bij:
↑ cardiovasculaire RF (Framingham cardiovasculaire risico score)

UMC Utrecht

Cho et al. JAMA Neurol 2022 Oct 27 : e223832



witte stof afwijkingen

Associatie met varianten in:
NOTCH3
HTRA1

UMC Utrecht

Malik et al. Brain 2021;144:2670–82
Mishra et al. Brain 2019;142:1009–23

wat vraag je aan?

- ✓ indien geen mutatie in familie bekend dan CHA genpanel:

  cerebrale angiopathieën/adult-onset leukoencephalopathieën

- ✓ dnadiagnostiek.nl:

AFDELING KLINISCHE GENETICA
LABORATORIUM VOOR DIAGNOSTISCHE GENOOMANALYSE – LDGA
AANVRAAGFORMULIER VOOR MOLECULAIR GENETISCH ONDERZOEK

Het LDGA is NEN-EN-ISO 15189:2012 geaccrediteerd door de Raad voor Accreditatie. De scope van accreditatienummer M007 is in te zien op www.rva.nl.

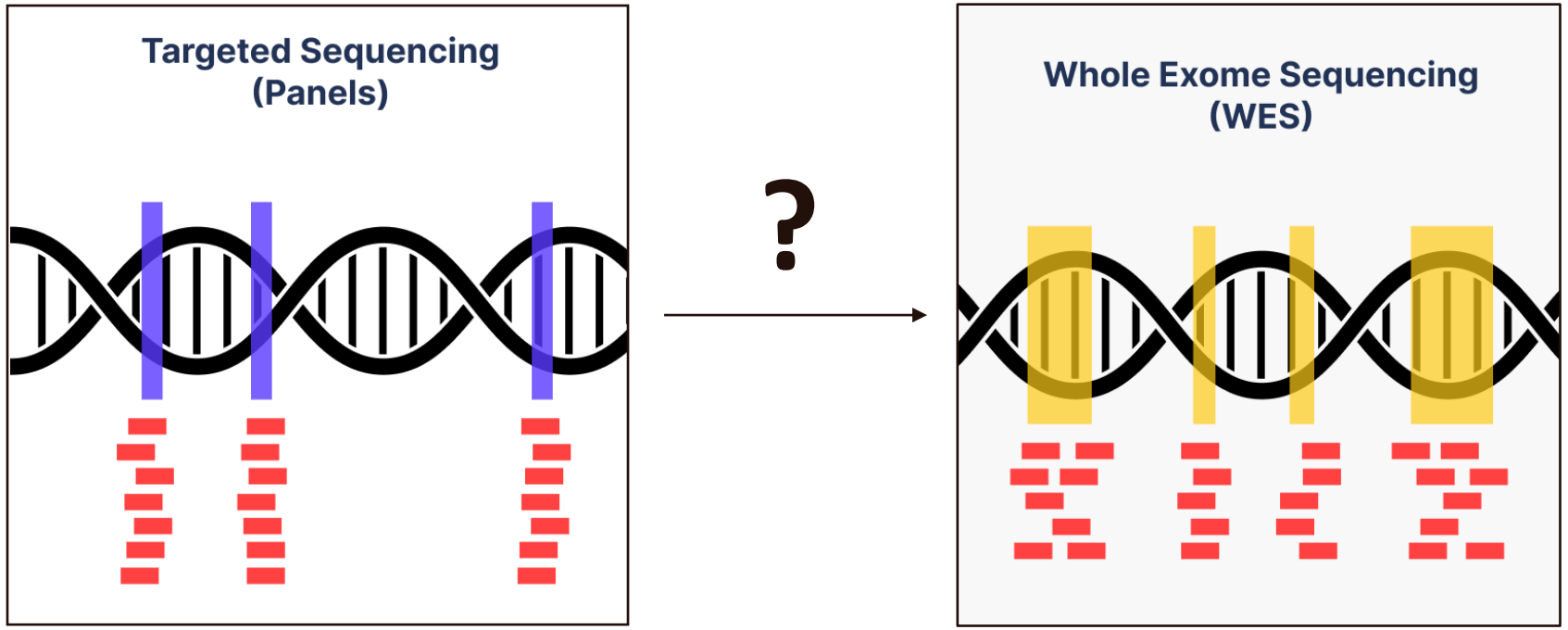
TESTEN RvA M007

Genpanels*	Alias
Zie volgende pagina's voor het aanvragen van individuele genen	
○ Borst- en ovariumkanker	HBOC-panel
○ Cerebrale angiopathieën/adult-onset leukoencephalopathieën	CHA-panel
○ Coffin-Siris / Nicolaides-Baraitser syndroom	CSS-panel
○ Colorectaal carcinoom**	CRC-panel
○ FAMMM (Familial Atypical Multiple Mole-Melanoma)**	Melanoompanel
○ Groeistoornissen ***	Groeipanel
○ LYNCH syndroom**	Lynchpanel
○ MODY (Maturity Onset Diabetes of the Young)	Diabetespanel MODYScan
○ Paragangliomen en/of feochromocytomen	PGL-panel
○ Polyposis coli, adenomateus**	Polieppanel
○ Spierdystrofieën / Myopathieën***	Spierpanel MuscleScan

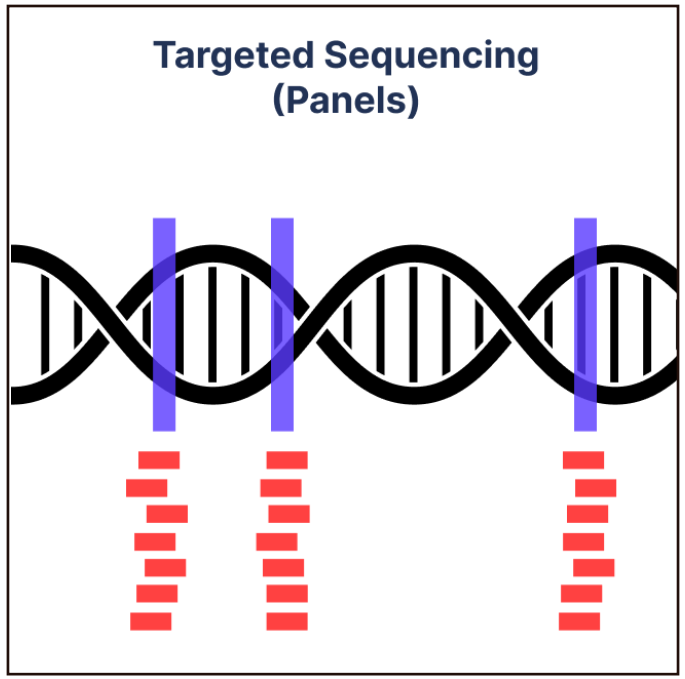
Gene panel CHA* version 1, 18-2-2018

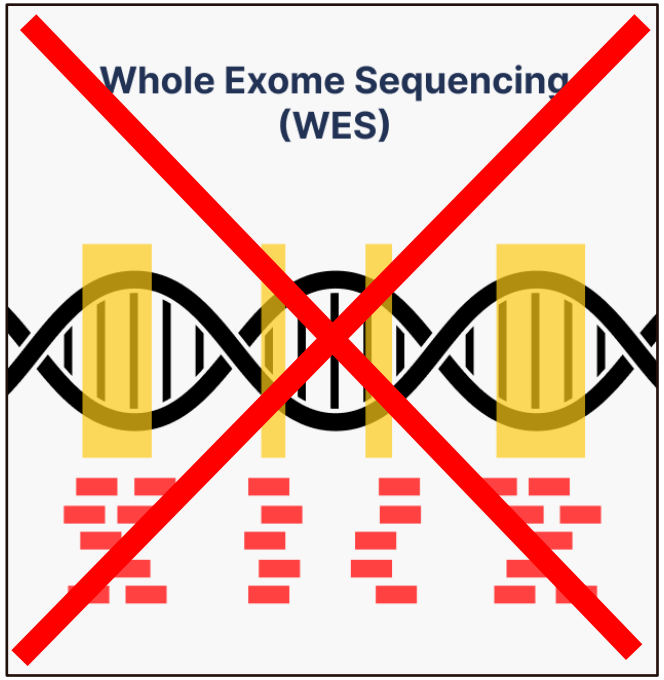
HGNC approved gene symbol
ABCD1
*APP***
AUH
CBS
CLCN2
COL4A1
COL4A2
CSF1R
CST3
CTSA
CYP27A1
DARS2
GBE1
GFAP
GLA
GSN
HTRA1
ITM2B
LMNB1
MMACHC
*NOTCH3***
TREM2
*TREX1***
TTR
TYMP
TYROBP

genpanel negatief: wat dan?

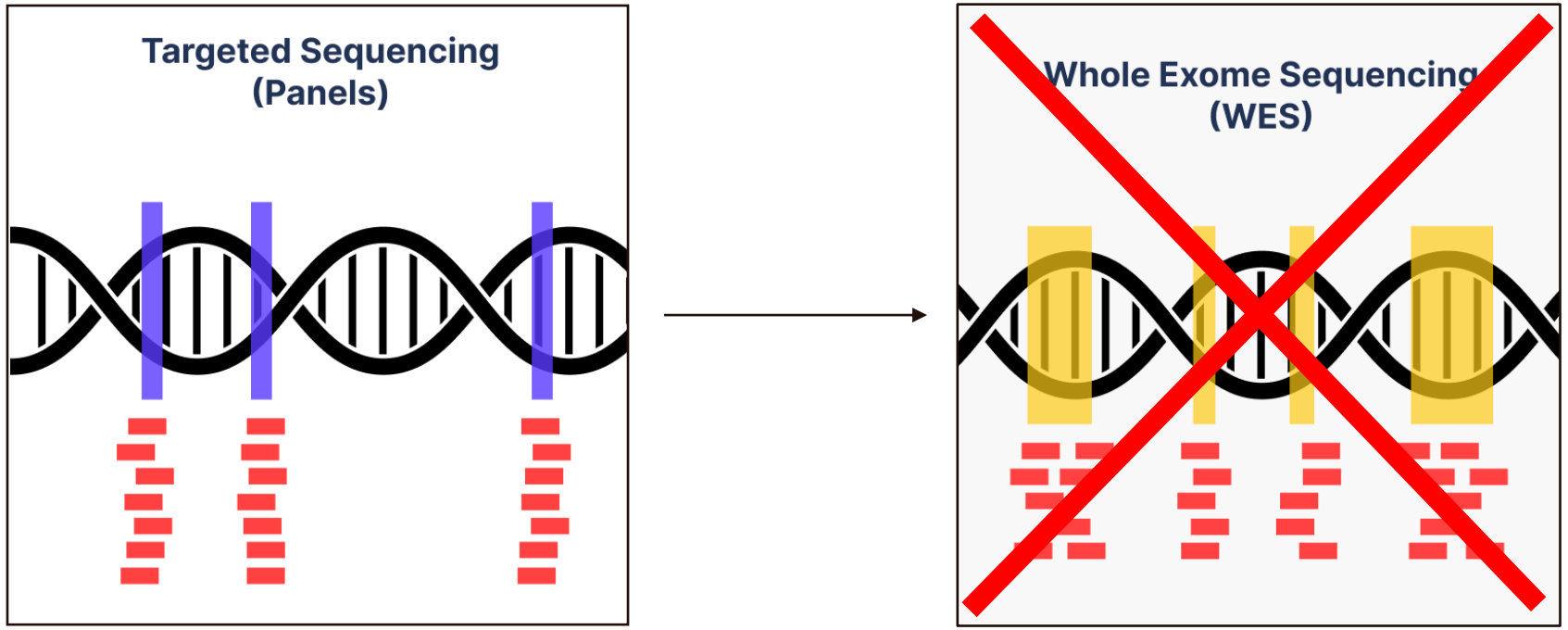


genpanel negatief: wat dan?





genpanel negatief: wat dan?



uitzonderingen (en dan bij voorkeur trio-analyse met ouders):

- op opvallend jonge leeftijd ernstige afwijkingen met negatieve familieanamnese
- bij kinderwens

UMC Utrecht

take home messages: complexe ziekte

GWAS:

- diverse loci voor beroerte en wittestof afwijkingen
- overlap

wat kunnen we met GWAS?

- mendelian randomisation: invloed van exposure op outcome
- genomics drug discovery
- risico predictie

take home messages: beroerte als monogenetische ziekte

vooral bij small vessel disease:

- komt vaker voor dan gedacht, niet altijd symptomatisch
- DNA diagnostiek m.b.v. CHA gen panel
- geen WES indien panel negatief

Dank voor de aandacht

email:
ij.m.ruigrok@umcutrecht.nl

UMC Utrecht