THE GENETIC ARCHITECTURE OF AMYGDALA NUCLEI

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MY PHD
2019-2021

NORMENT
Norwegian Centre for
Mental Disorders Research

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The Genetic Architecture of Amygdala Nuclei

Mary S Mufford [1], Dennis van der Meer [2], Tobias Kaufmann [3], Oleksandr Frei [4], Raj Ramesar [5], Paul M Thompson [6], Neda Jahanshad [6], Rajendra A Morey [7], Ole A Andreassen [8], Dan J Stein [9], Shareefa Dalvie [5]

Affiliations + expand

PMID: 37391117 DOI: 10.1016/j.biopsych.2023.06.022

MEGAN CAMPBELL
2021-2024

> Acta Neuropsychiatr. 2023 Aug 24:1-8. doi: 10.1017/neu.2023.32. Online ahead of print.

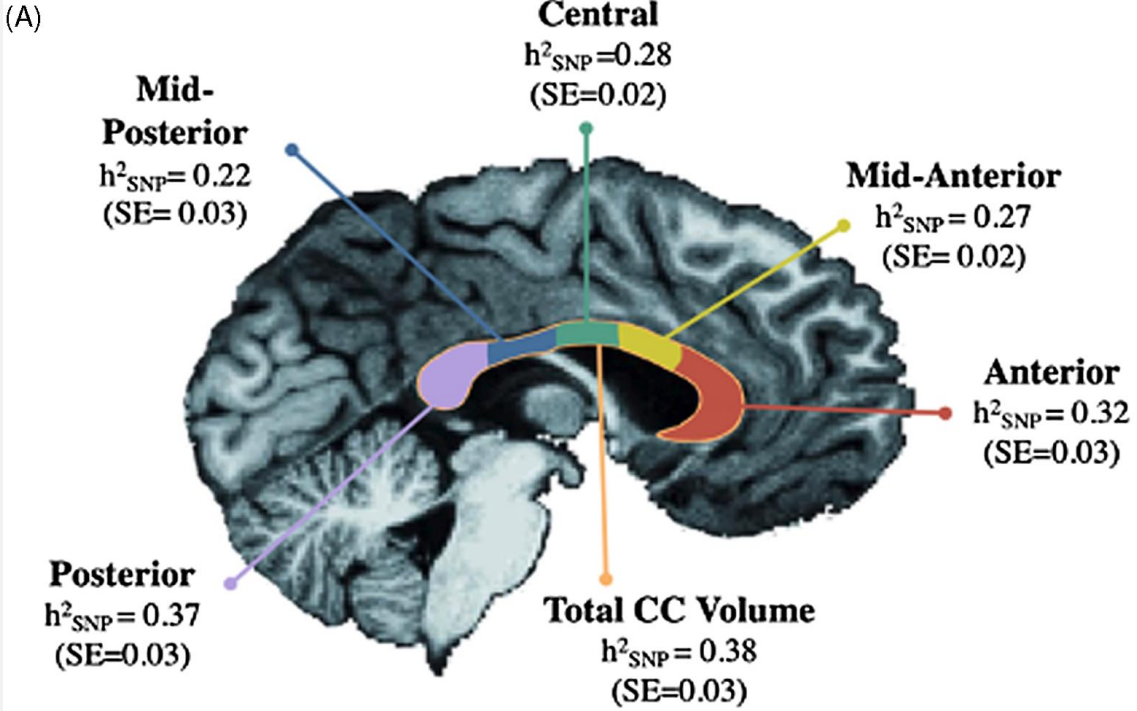
Distributed genetic effects of the corpus callosum subregions suggest links to neuropsychiatric disorders and related traits

Megan L Campbell [1 2], Shareefa Dalvie [3], Alexey Shadrin [4], Dennis van der Meer [4 5], Kevin O'Connell [4], Oleksander Frei [4], Ole A Andreassen [4], Dan J Stein [1], Jaroslav Rokicki [4 6]

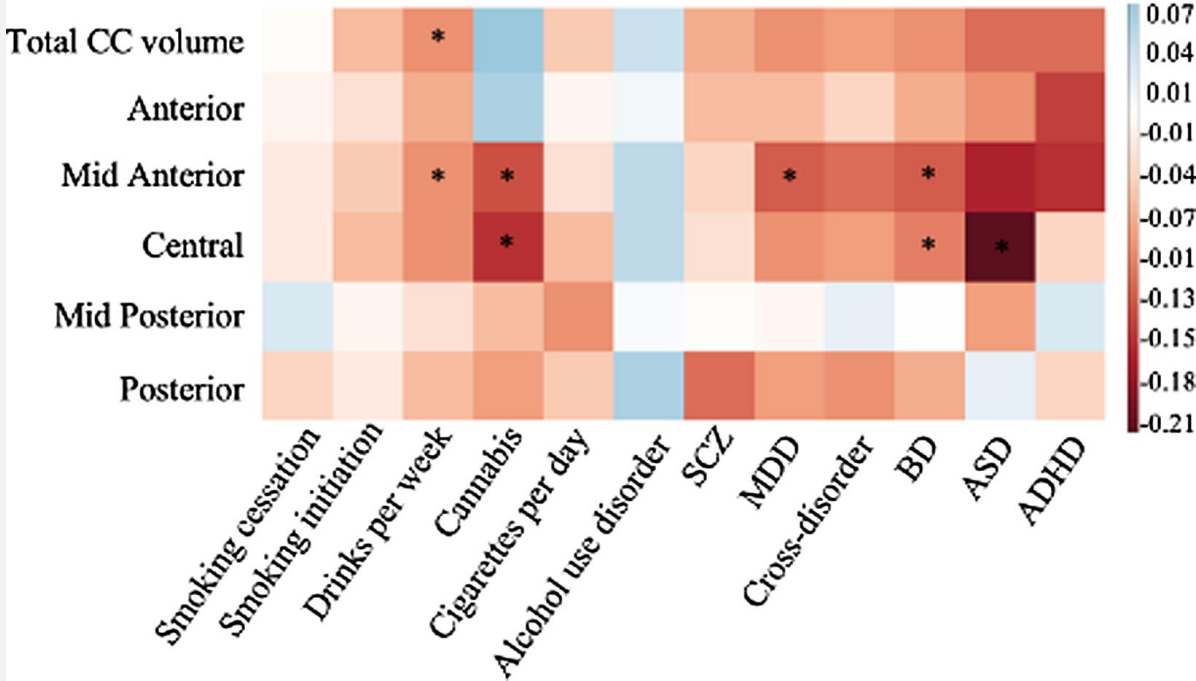
Affiliations + expand

PMID: 37612147 PMCID: PMC10891296 (available on 2025-02-24) DOI: 10.1017/neu.2023.32

(A)



(B)



OLIVIA WOOTTON
2021-2024

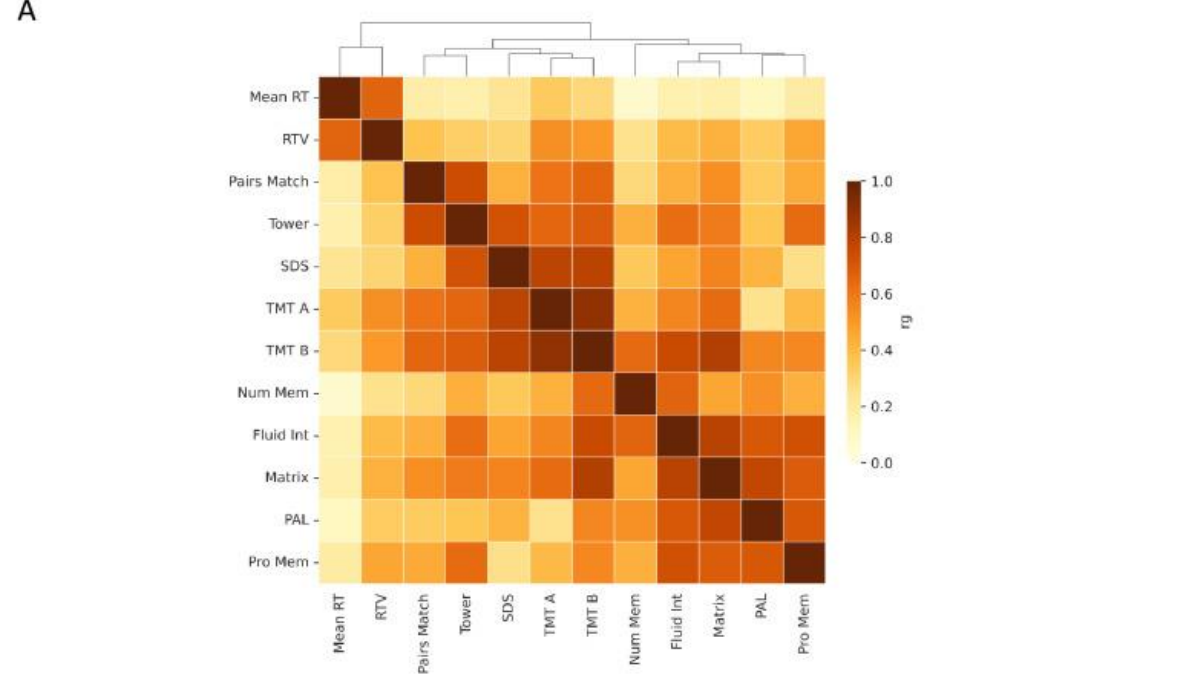
› Sci Rep. 2024 Jul 4;14(1):15356. doi: 10.1038/s41598-024-66085-y.

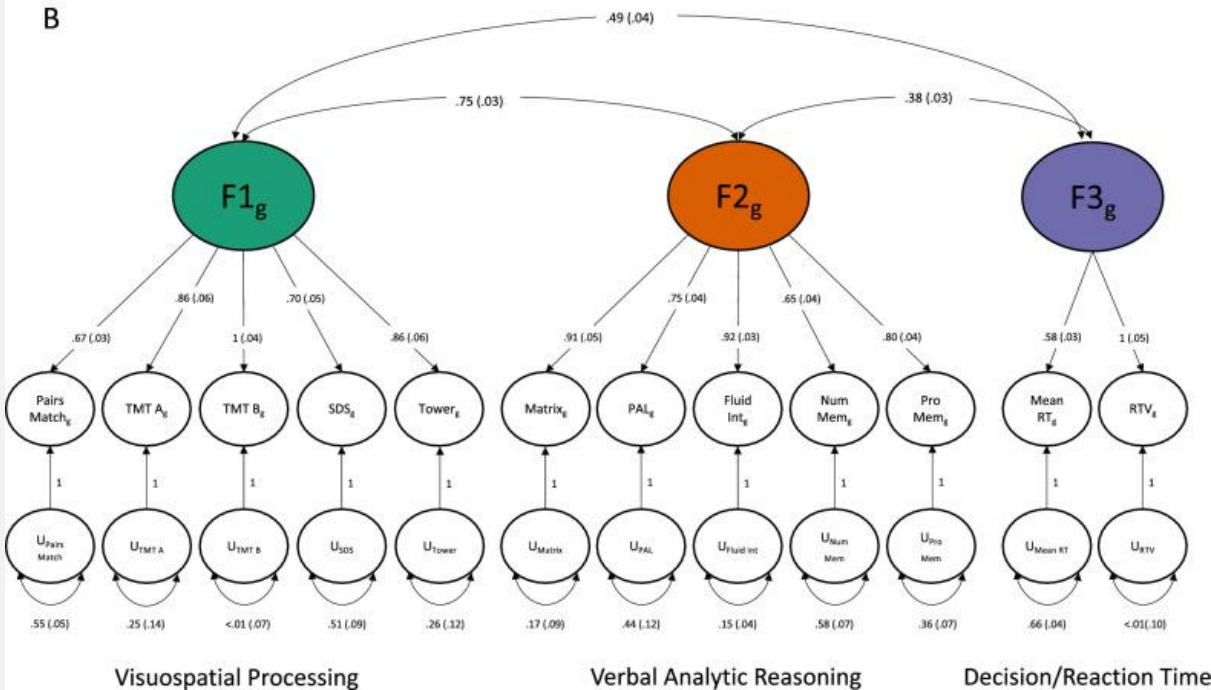
Genomic insights into the shared and distinct genetic architecture of cognitive function and schizophrenia

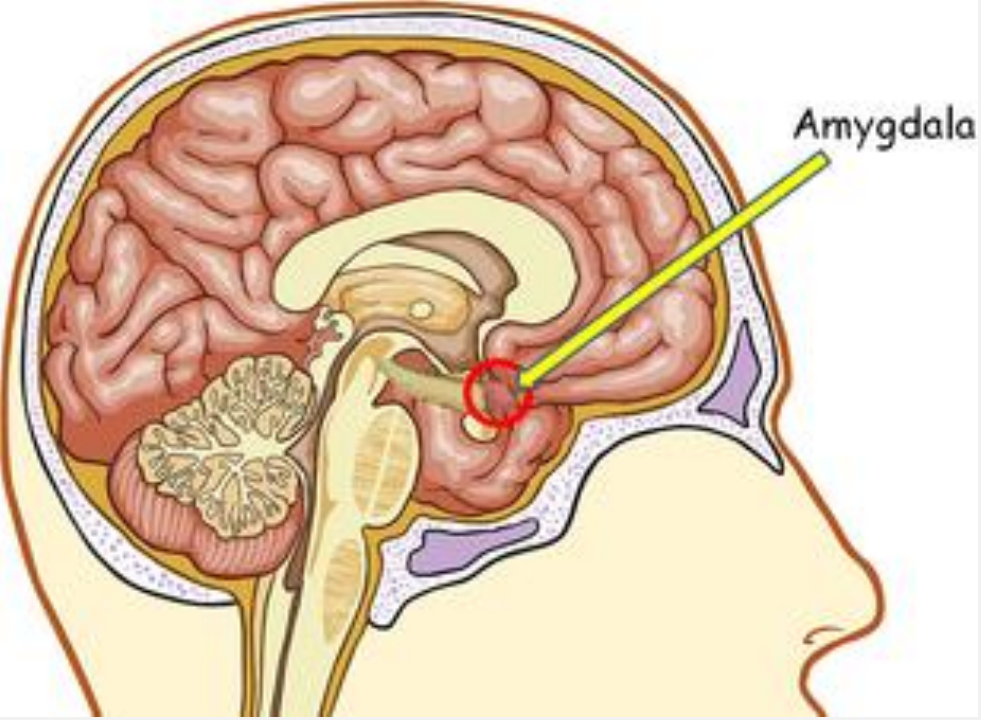
Olivia Wootton [1], Alexey A Shadrin [2], Thomas Bjella [2], Olav B Smeland [2], Dennis van der Meer [2 3], Oleksandr Frei [2 4], Kevin S O'Connell [2], Torill Ueland [2 5], Ole A Andreassen [2], Dan J Stein [6 7], Shareefa Dalvie [8]

Affiliations + expand

PMID: 38961113 PMCID: PMC11222449 DOI: 10.1038/s41598-024-66085-y







THE AMYGDALA

Subcortical brain region involved in emotion

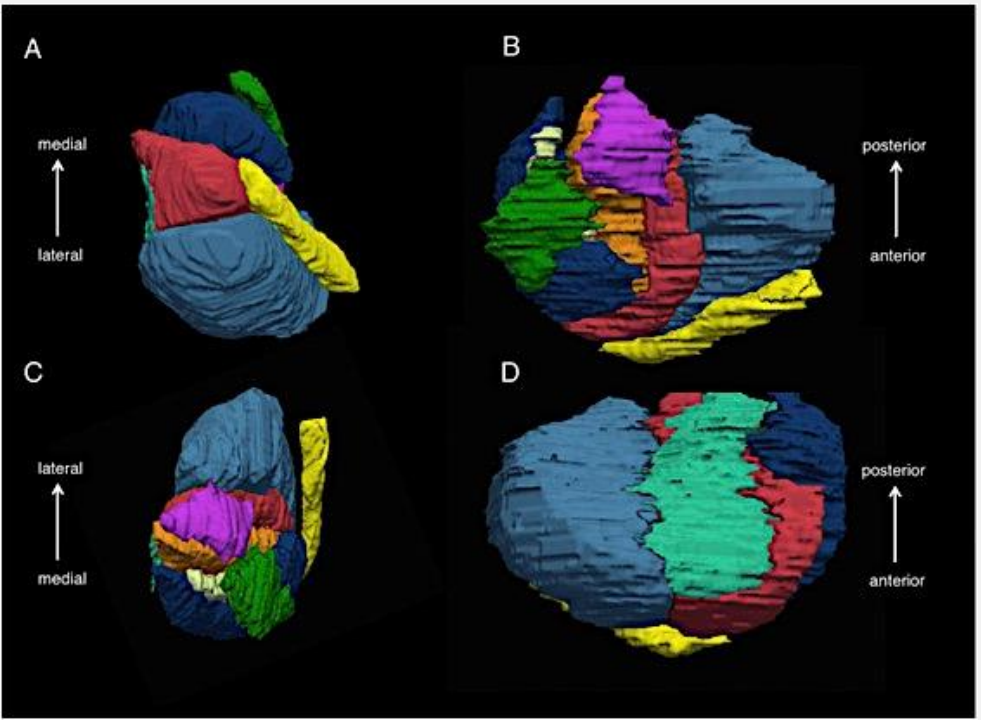
Family based heritability=34–59%

SNP based h^2~9-17%

Few genetic variants associated

Distinct nuclei

- Cytoarchitecture
- Neurotransmitters
- Connectivity
- Function



Satizabal *et al.*, 2019, Saygin *et al.*, 2017

AIMS

Whether increased phenotypic specificity through segmentation of the amygdala into its nuclei aids:

- Genetic discoverability
- Shared genetic architecture
- Informative biological pathways

Segmented the amygdala into nine nuclei (**FreeSurfer v6.1**)

Genome-wide association analyses **(PLINK v2)**

SNP-based heritability **(GCTA)**

Estimates of polygenicity, discoverability and power **(MiXeR)**

Genetic correlations **(LDSC)** and polygenic overlap **(MiXeR)** across nuclei

Shared loci **(cFDR)** between psychiatric disorders

Functional annotation **(FUMA)**

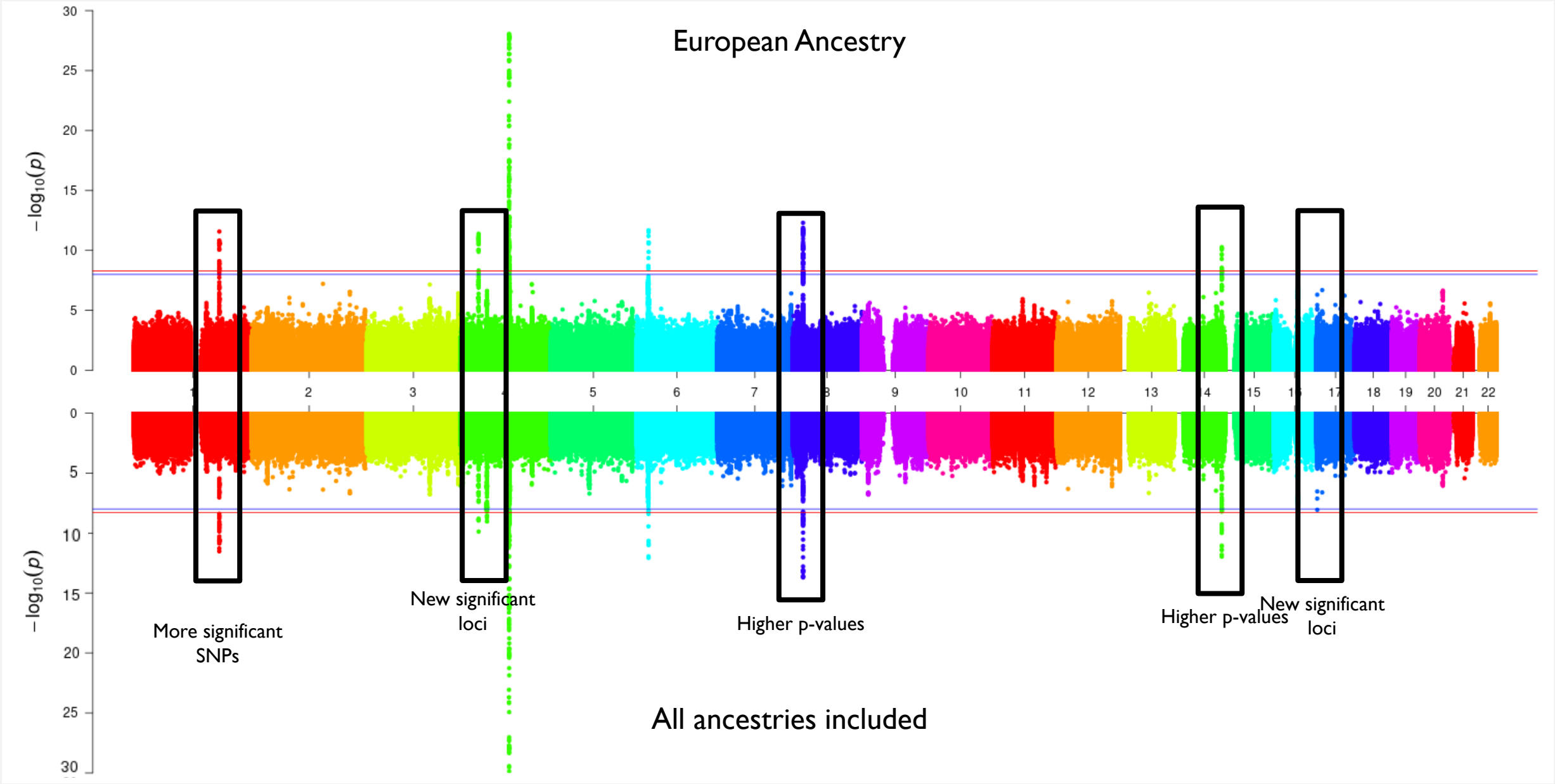
Mufford, Mary S., *et al*. "The Genetic Architecture of Amygdala Nuclei." *Biological Psychiatry* (2023)

OBJECTIVES

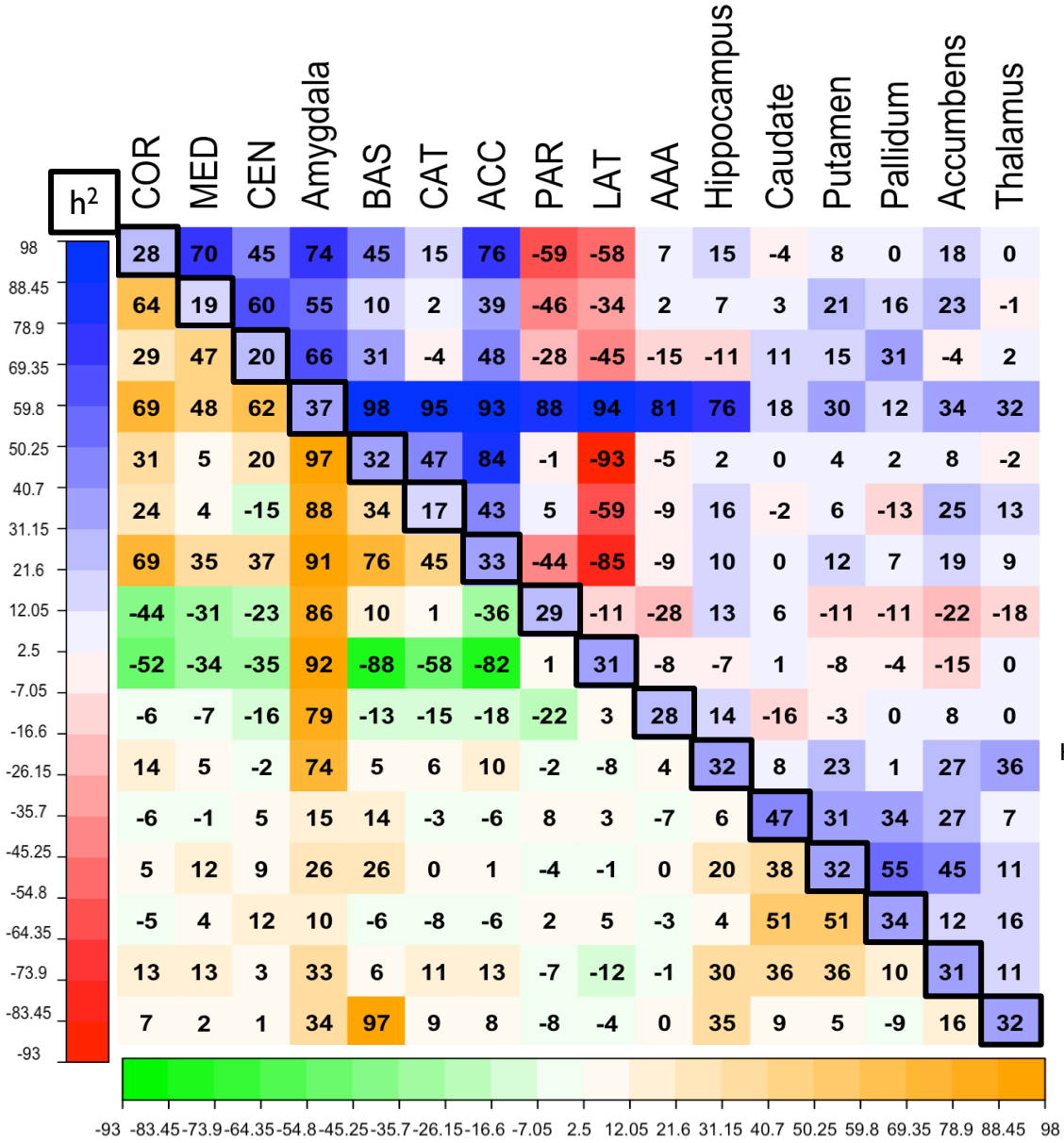
biobank uk

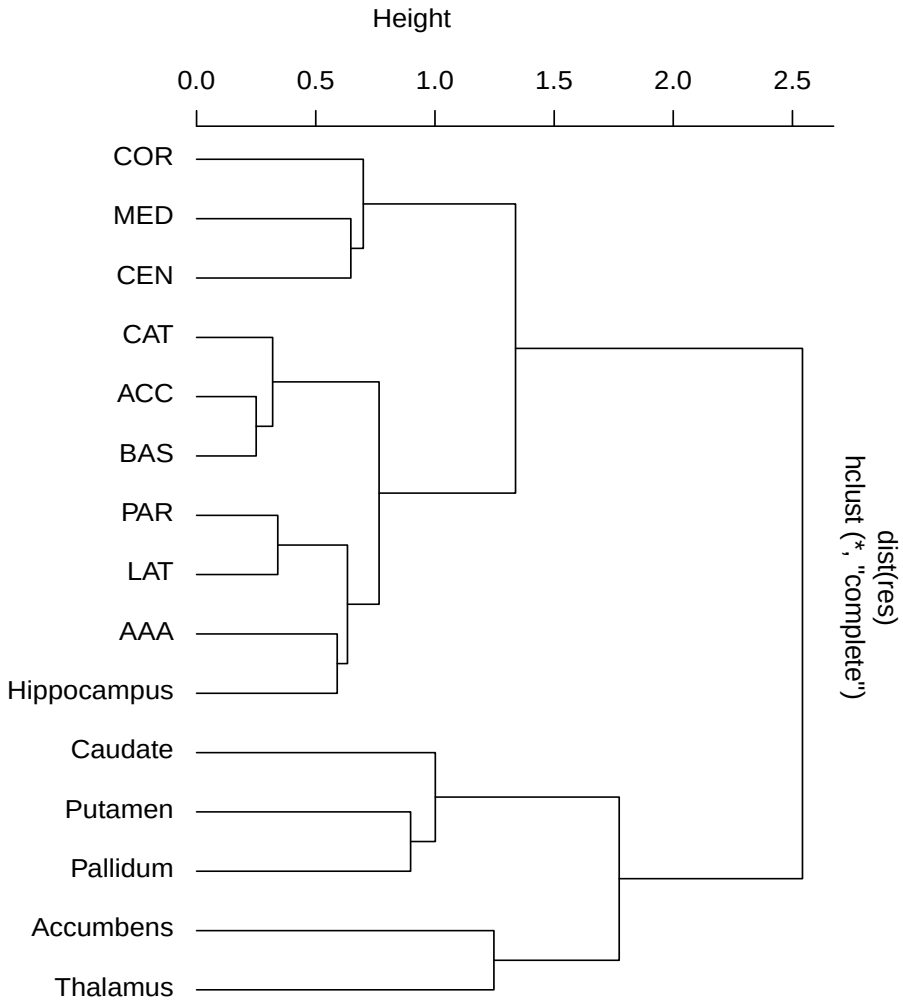
- 42k participants
- MRI data
- Genotyping data
- 96% European ancestry
- Mean age of 64.26 years
- 52% female

CENTRAL NUCLEUS



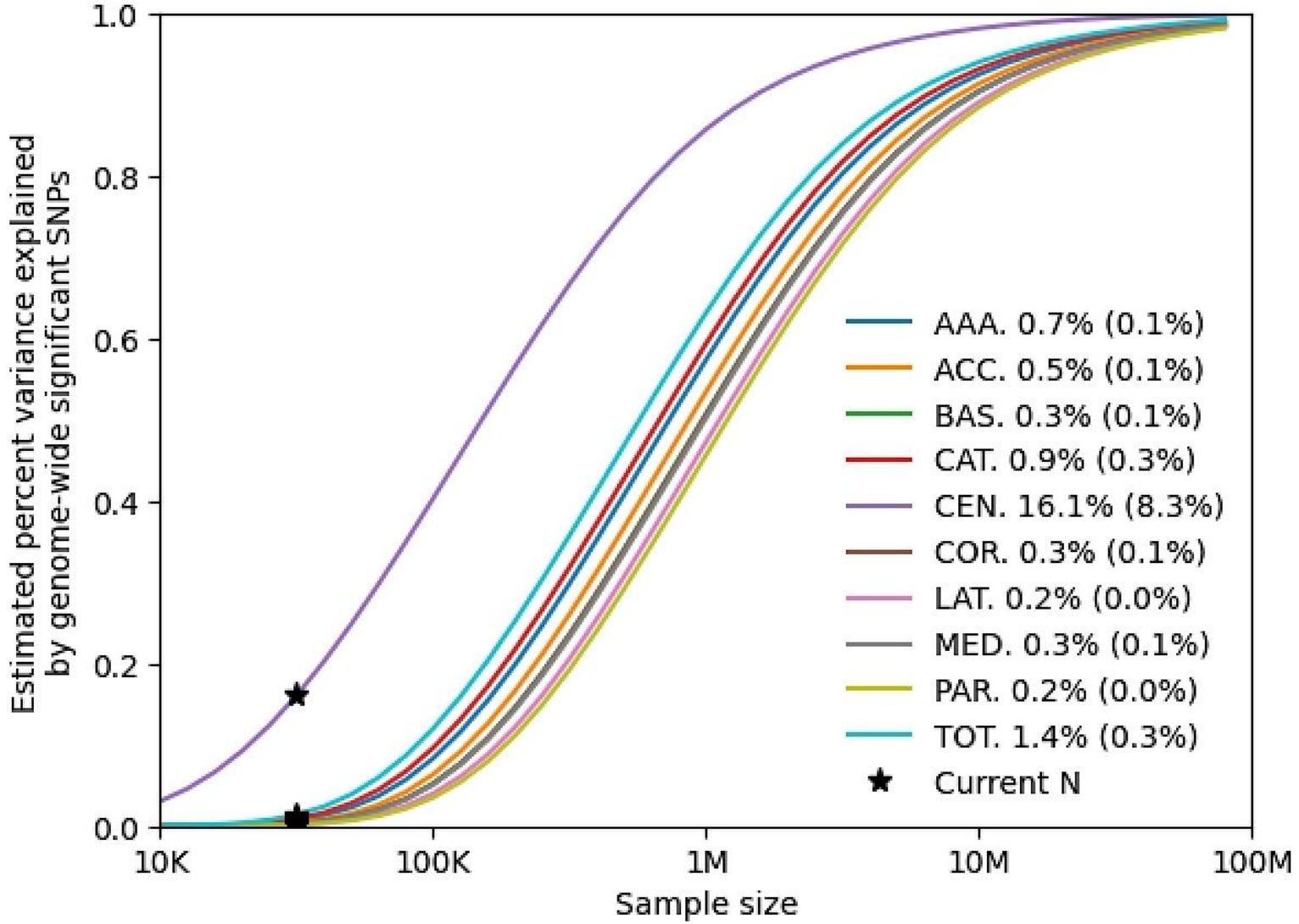
SNP-BASED HERITABILITY & GENETIC CORRELATION



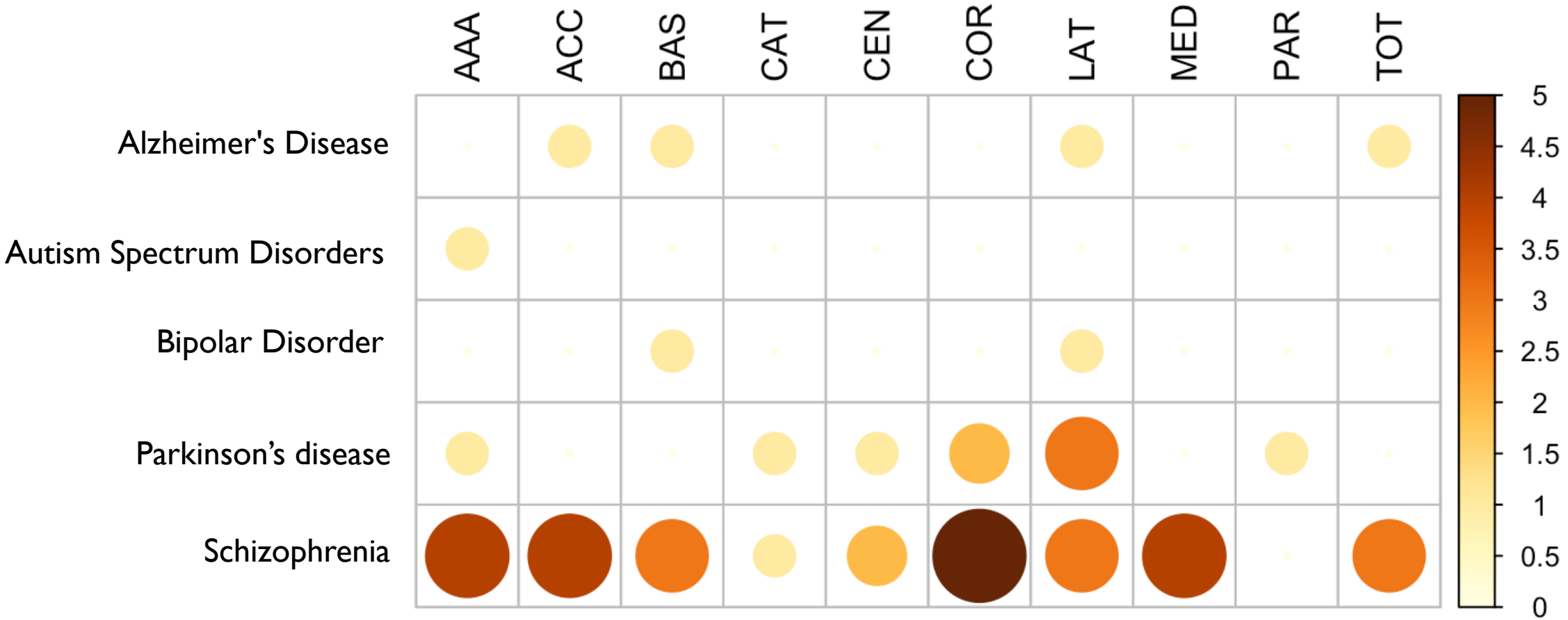


MIXER

POWER, DISCOVERABILITY & POLYGENICITY



SHARED GENETICS (FDR)



SUMMARY

Nuclei segmentation aids genetic discoverability

Divergent cytoarchitectures of the amygdala nuclei are driven by both overlapping and unique genetic influence

Justification for studying these nuclei separately in future;

- Heritability
- Power for discovery
- Unique genetic contributions

Highlights the importance of trans-ancestry research

NEW UKB INITIATIVES

- E.g. UK Biobank Research Analysis Platform

- Provides access to computational power not available locally
- Financial support in a resource-constricted environment
- The community forum can provide guidance

- Allows African researchers to navigate the UKB resource independently
- Allow us to address research questions that are highly relevant to the continent

ACKNOWLEDGEMENTS

- University of Cape Town
  - Dr Shareefa Dalvie
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  - Prof Raj Ramesar
- NORMENT
  - Dr Dennis van der Meer
  - Prof Ole' Andreasen
  - Oleksandr Frei
- ENIGMA-PTSD
  - Prof Rajendra Morey
  - Lexi Baird

THANK YOU!

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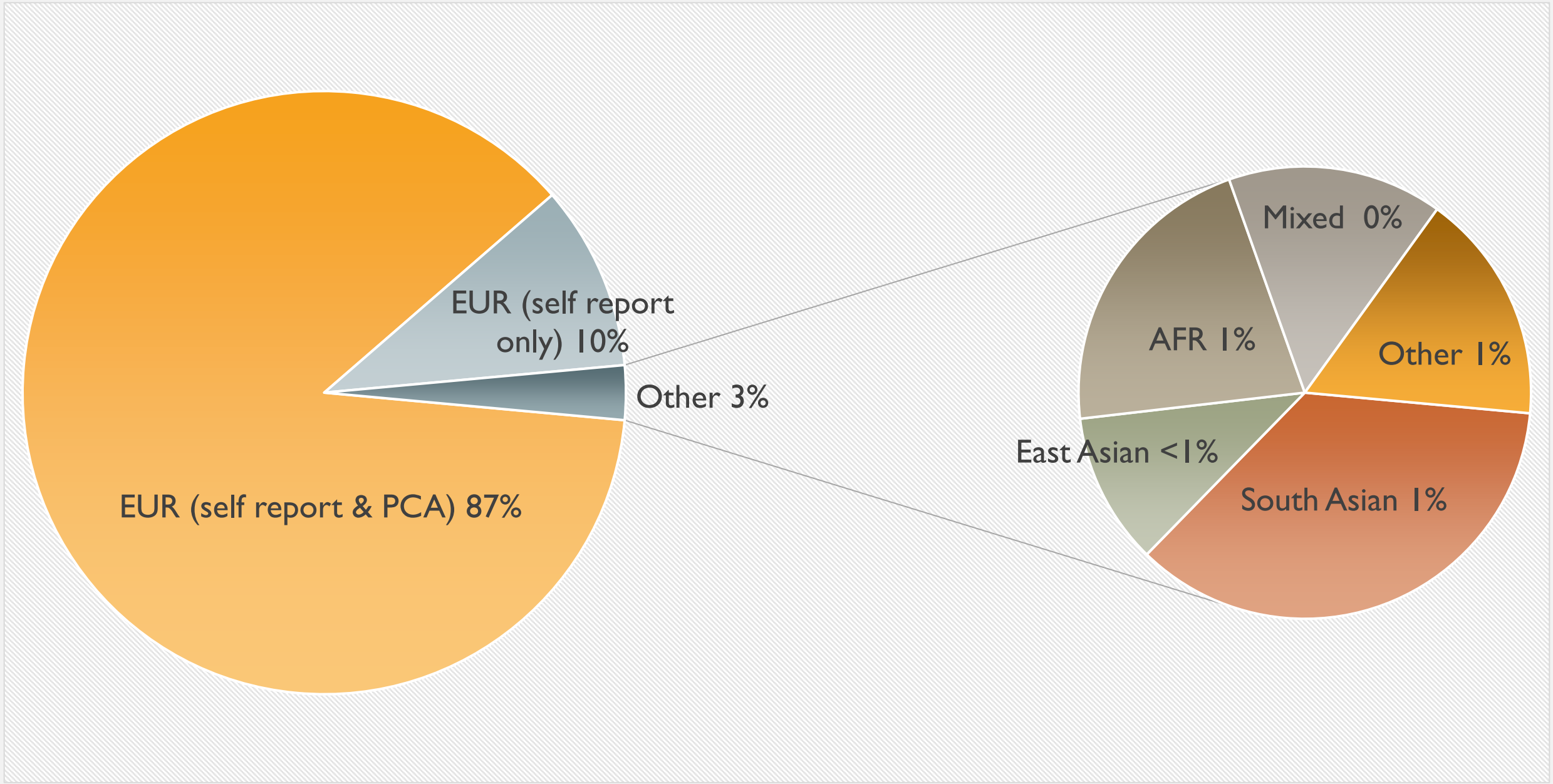

EUR (self report only) 10%
Other 3%
EUR (self report & PCA) 87%
Mixed 0%
AFR 1%
Other 1%
East Asian <1%
South Asian 1%

NUCLEI

TOT, whole amygdala;

LAT, Lateral nucleus;

CAT, Corticoamygdaloid transition area;

BAS, Basal nucleus;

AAA, Anterior Amygdaloid Area;

CEN, Central nucleus;

ACC, Accessory basal nucleus;

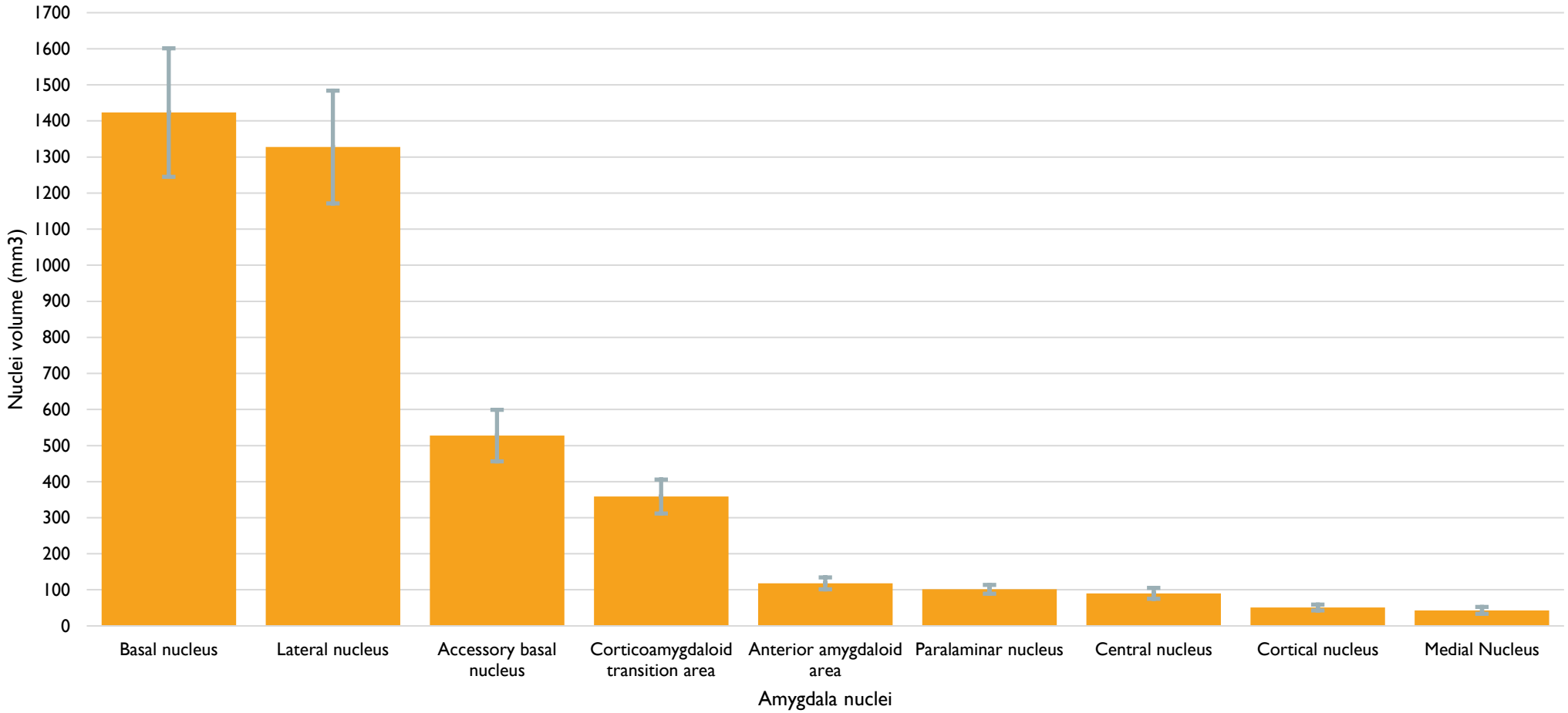
PAR, Paralaminar nucleus;

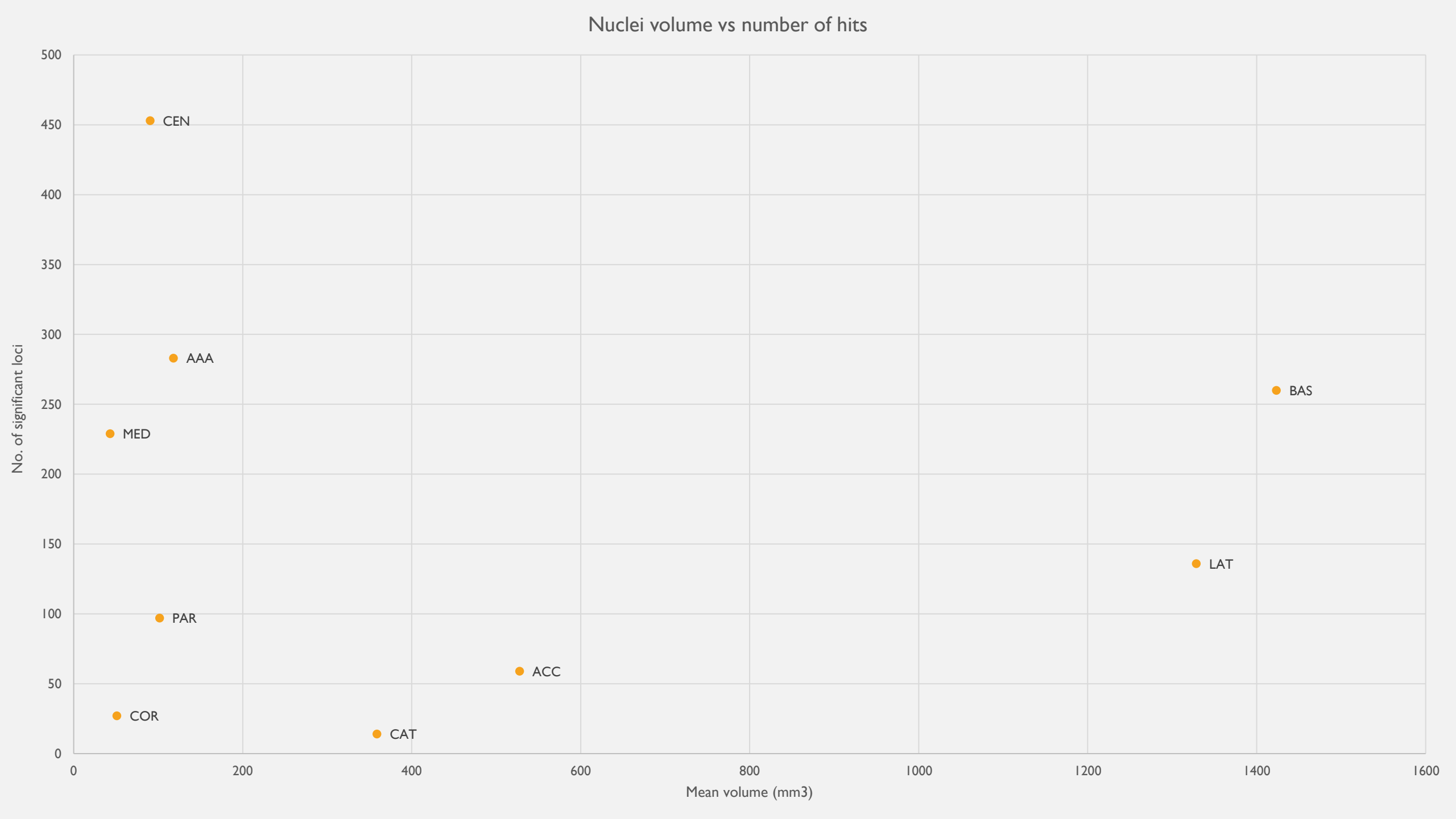
MED, Medial nucleus;

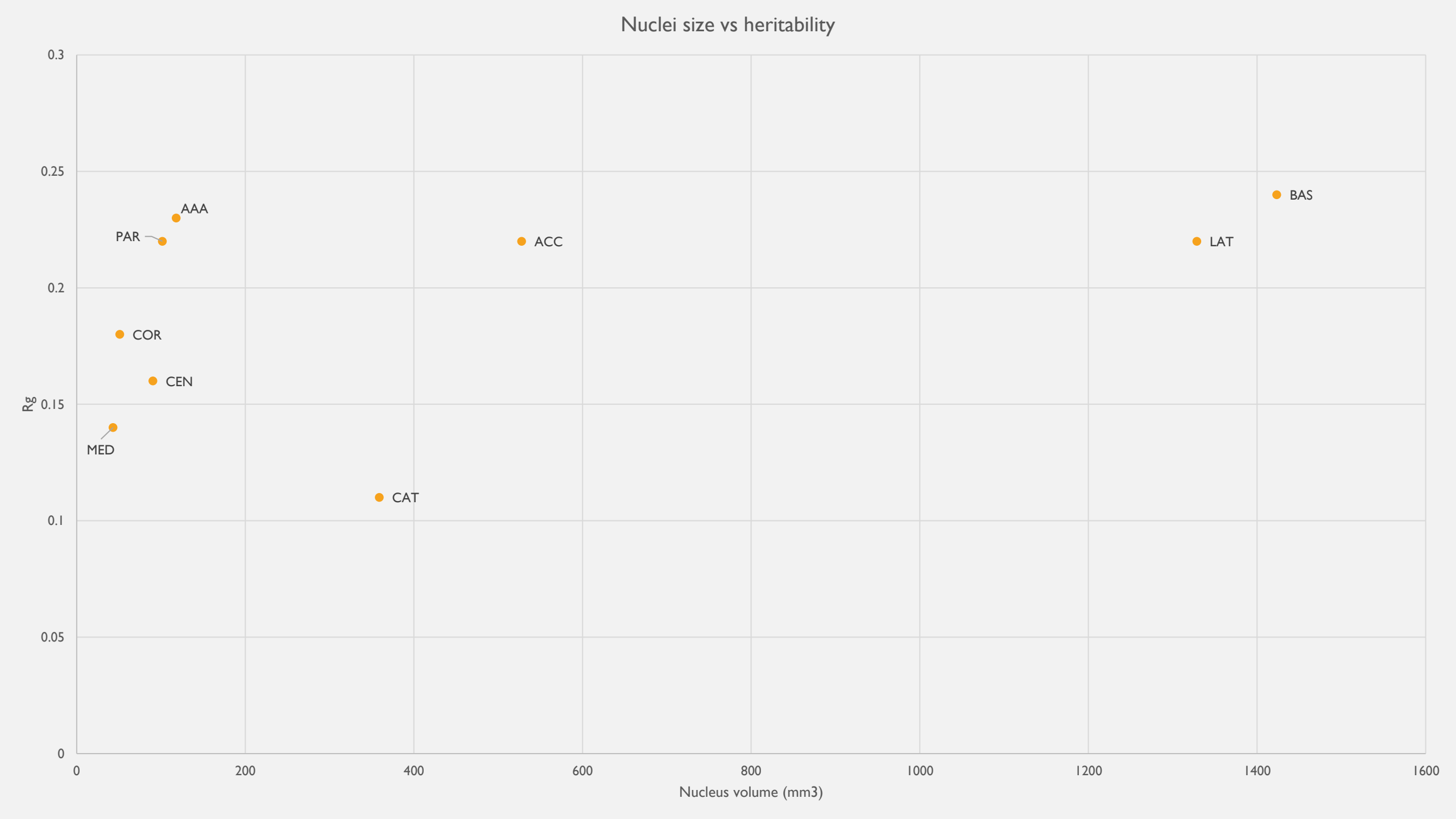
COR, Cortical nucleus

UKBB QC

	European	
Filtering steps	# Subjects	#SNPs
START: Version 3 imputed bgen files provided by UKBB**	487,411	89,387,505
Remove participants without MRI data	42,067	89,387,505
Remove participants with missing covariates	41,035	89,387,505
Remove duplicate participants	41,035	89,387,505
Remove unused factor levels	41,035	89,387,505
Keep validated Europeans only	35,660	89,387,505
Genotyping filters: SNPs only, poorly imputed SNPs (r2<0.5), low minor allele frequency (<0.1%), genotyping rate (<0.1), Hardy-Weinberg Equilibrium (p<1x10-9), duplicate markers	35,660	12,245,112
Remove participants with missing Euler numbers	35,657	12,245,112
Remove participants with Euler number outliers (4SD)	35,186	12,245,112
Remove participants with a disorder affecting the brain	32,215	12,245,112
Remove participants for which the amygdala nuclei segmentation failed	31,971	12,245,112
Remove participants with amygdala nuclei volume outliers for each hemisphere (4SD)	31,714	12,245,112
Remove participants with ICV outliers (4SD)	31,690	12,245,112
Remove participants without ancestry information	N/A	N/A
Total	31,690	12,245,112


1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Nuclei volume (mm3)
Basal nucleus
Lateral nucleus
Accessory basal nucleus
Corticoamygdaloid transition area
Anterior amygdaloid area
Paralaminar nucleus
Central nucleus
Cortical nucleus
Medial Nucleus
Amygdala nuclei


Nuclei volume vs number of hits
No. of significant loci
Mean volume (mm3)
0
50
100
150
200
250
300
350
400
450
500
0
200
400
600
800
1000
1200
1400
1600
CEN
AAA
MED
PAR
COR
CAT
ACC
BAS
LAT


Nuclei size vs heritability
0.3
0.25
0.2
0.15
0.1
0.05
0
Rg
AAA
PAR
ACC
BAS
LAT
COR
CEN
MED
CAT
0
200
400
600
800
1000
1200
1400
1600
Nucleus volume (mm3)

JUSTIFICATION FOR COMBINING HEMISPHERES

Genetic correlation

- rg between, all 0.56-0,91 $p < 5.27e\text{-}11$

Volumetric correlation

- Raw Pearson's rg between 0.54-0.86, all $p < 2.2x10^{-16}$

Heritability

- h^2 is higher when hemispheres are combined
  - AAA - $h^2_{combined}= 0.23$, $h^2_{right}=0.15$, $h^2_{left}=0.21$
  - ACC - $h^2_{combined}= 0.22$, $h^2_{right}=0.2$, $h^2_{left}=0.14$
  - BAS - $h^2_{combined}= 0.24$, $h^2_{right}=0.13$, $h^2_{left}=0.12$
  - CAT - $h^2_{combined}= 0.11$, $h^2_{right}=0.1$, $h^2_{left}=0.09$
  - CEN - $h^2_{combined}= 0.16$, $h^2_{right}=0.11$, $h^2_{left}=0.1$
  - COR - $h^2_{combined}= 0.18$, $h^2_{right}=0.15$, $h^2_{left}=0.11$
  - LAT - $h^2_{combined}= 0.22$, $h^2_{right}=0.2$, $h^2_{left}=0.14$
  - MED - $h^2_{combined}= 0.14$, $h^2_{right}=0.11$, $h^2_{left}=0.1$
  - PAR - $h^2_{combined}= 0.22$, h^2_{right} 0.16=, $h^2_{left}=0.18$
  - TOT - $h^2_{combined}= 0.27$, $h^2_{right}=0.25$, $h^2_{left}=0.24$