SUPPLEMENTAL MATERIAL

3-tiered EGFr domain risk stratification for individualized NOTCH3-small vessel disease prediction

Remco J. Hack,[1] Gido Gravesteijn, [1,†] Minne N. Cerfontaine, [1,†] Mark A. Santcroos,[2] Laura Gatti,[3] Anna Kopczak,[4] Anna Bersano,[5] Marco Duering,[4,6] Julie W. Rutten[1,‡] and Saskia A.J. Lesnik Oberstein[1,‡]

Author affiliations:

1 Department of Clinical Genetics, Leiden University Medical Center, 2333 ZA Leiden, the Netherlands.

2 Department of Human Genetics, Leiden University Medical Center, 2333 ZA Leiden, the Netherlands.

3. Laboratory of Neurobiology, Fondazione IRCSS Istituto Neurologico Carlo Besta, Milan, Italy.

4 Institute for Stroke and Dementia Research, LMU University Hospital Munich, 81377 Munich, Germany.

5 Cerebrovascular Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy.

6 Medical Image Analysis Center (MIAC) and Department of Biomedical Engineering, University of Basel, 4051 Basel, Switzerland

Supplementary Figure 1

A

	Disease	No disease
Exposed	A	B
Unexposed	C	D

$$OR = \frac{\text{odds of exposure (disease)}}{\text{odds of exposure (no disease)}} = \frac{A / C}{B / D}$$

B

	CADASIL	Population
In EGFr X	20	1
Outside EGFr X	80	99

$$NVFOR = \frac{20 / 80}{1 / 99} = 25$$

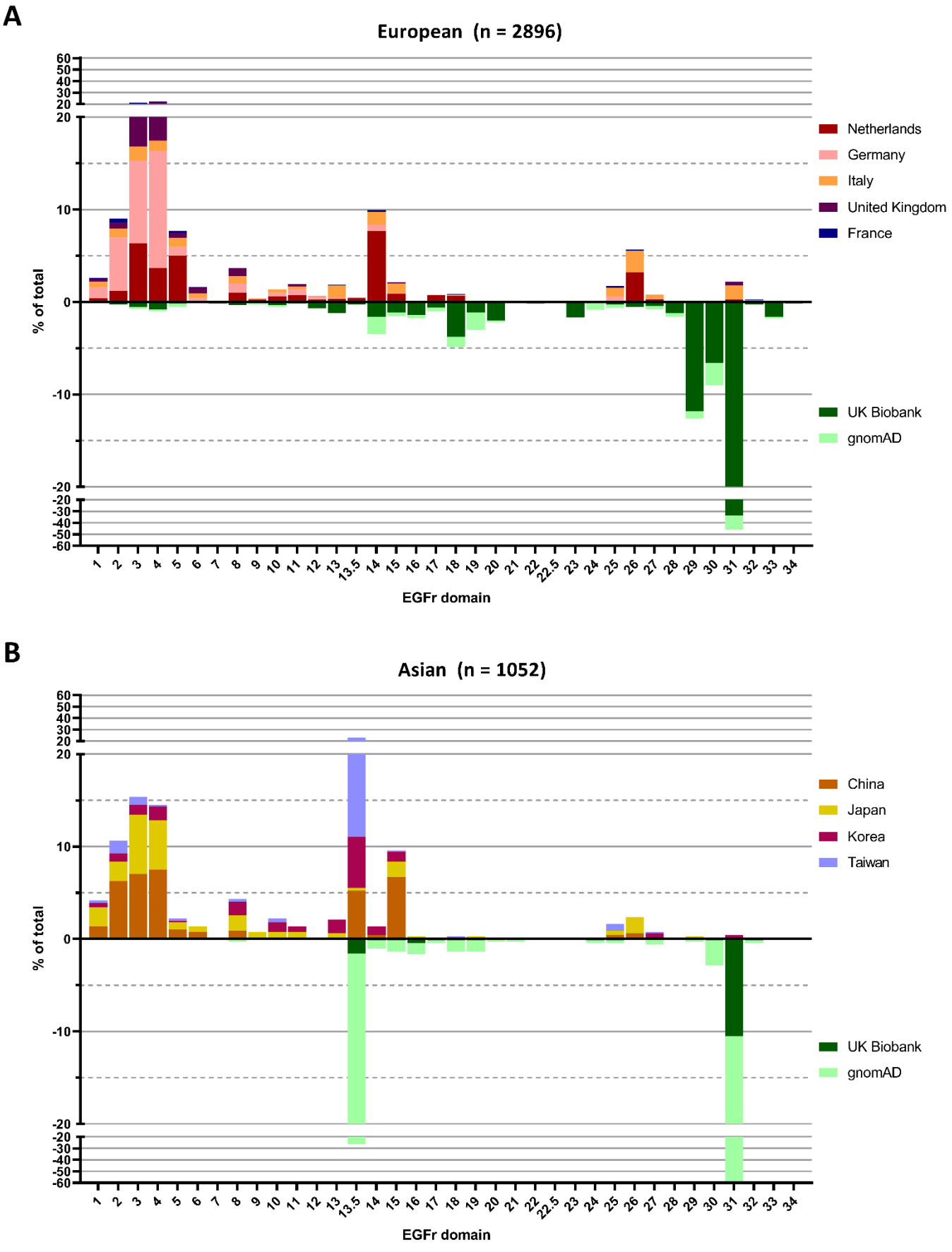
C

	CADASIL	Population
In EGFr Y	1	20
Outside EGFr Y	99	80

$$NVFOR = \frac{1 / 99}{20 / 80} = 0.04$$

Supplementary Figure 1. Hypothetical examples of the calculation of *NOTCH3*^{cys} Variant Frequency Odds Ratio. (A) In case-control studies the odds ratio is calculated by dividing "*the odds of exposure in the disease group*" by *"the odds of exposure in the group without disease*". **(B-C)** The calculation of the *NOTCH3*^{cys} Variant Frequency Odds Ratio (NFVOR) is performed in the same manner: "*the odds that a NOTCH3*^{cys} *variant is located in a certain EGFr domain in CADASIL patients* " is divided by *"the odds that a NOTCH3*^{cys} *variant is located in the same EGFr domain in individuals with a NOTCH3*^{cys} *variant from population databases*". In our examples, we have calculated the NVFOR for hypothetical EGFr domains "*X*" and "*Y*". Our hypothetical CADASIL cohort and population cohort both include 100 individuals with a *NOTCH3*^{cys} variant. (**B**) 20% of the CADASIL patients have a *NOTCH3*^{cys} variant located in EGFr domain X, whereas only 1% of the individuals from population databases have a NOTCH3^{cys} variant located in EGFr domain X, which corresponds to a high NVFOR of 25. (**C**) Only 1% of CADASIL patients have a *NOTCH3*^{cys} variant located in EGFr domain Y, whereas 20% of the individuals from population databases have a *NOTCH3*^{cys} variant located in EGFr domain Y, which corresponds to a low NVFOR of 0.04.

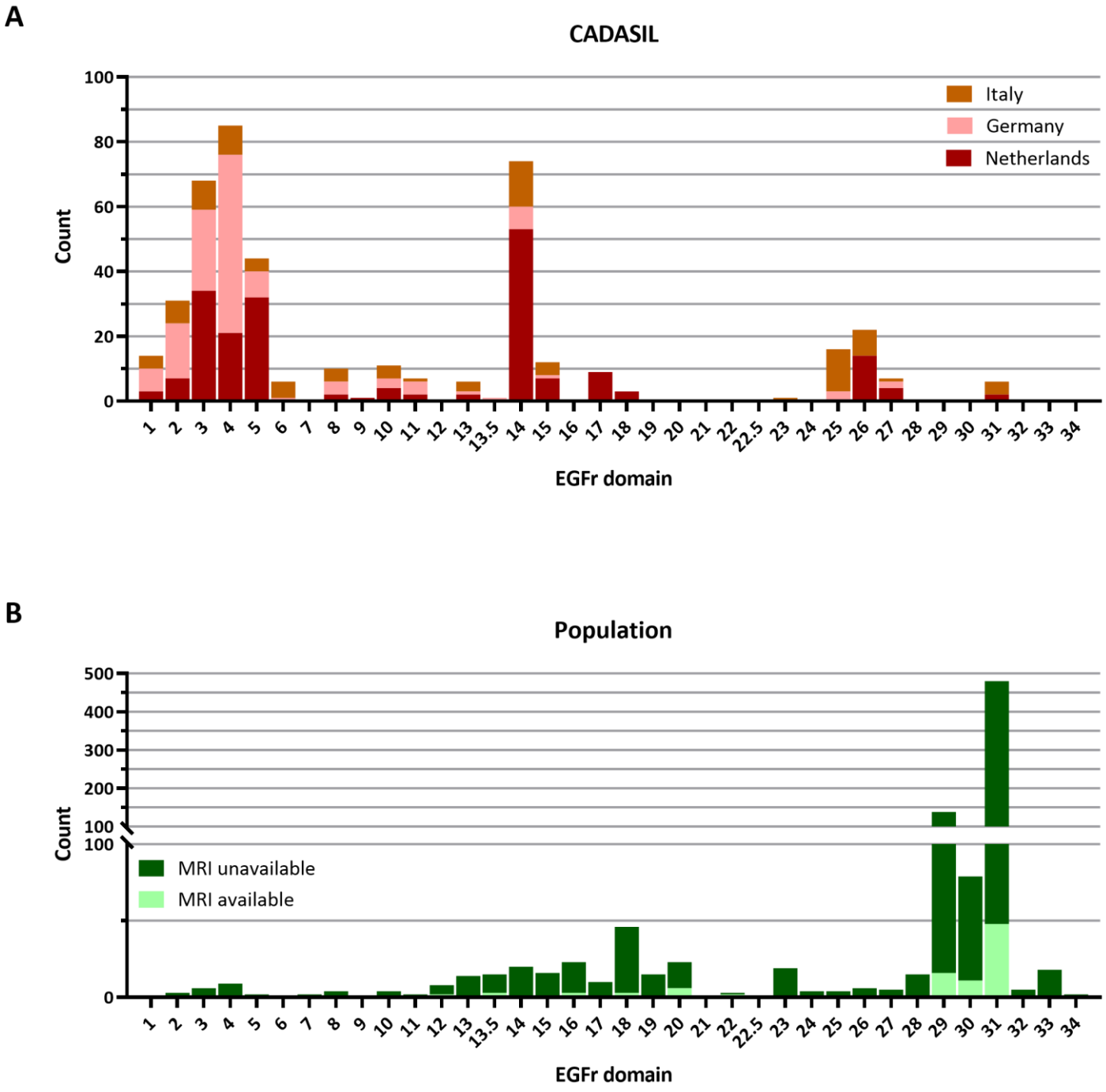
Supplementary Figure 2



Supplementary Figure 2. The distribution of *NOTCH3*^{cys} variants in CADASIL cohorts and in population database in individuals with a *NOTCH3*^{cys} variant from European and Asian descent.

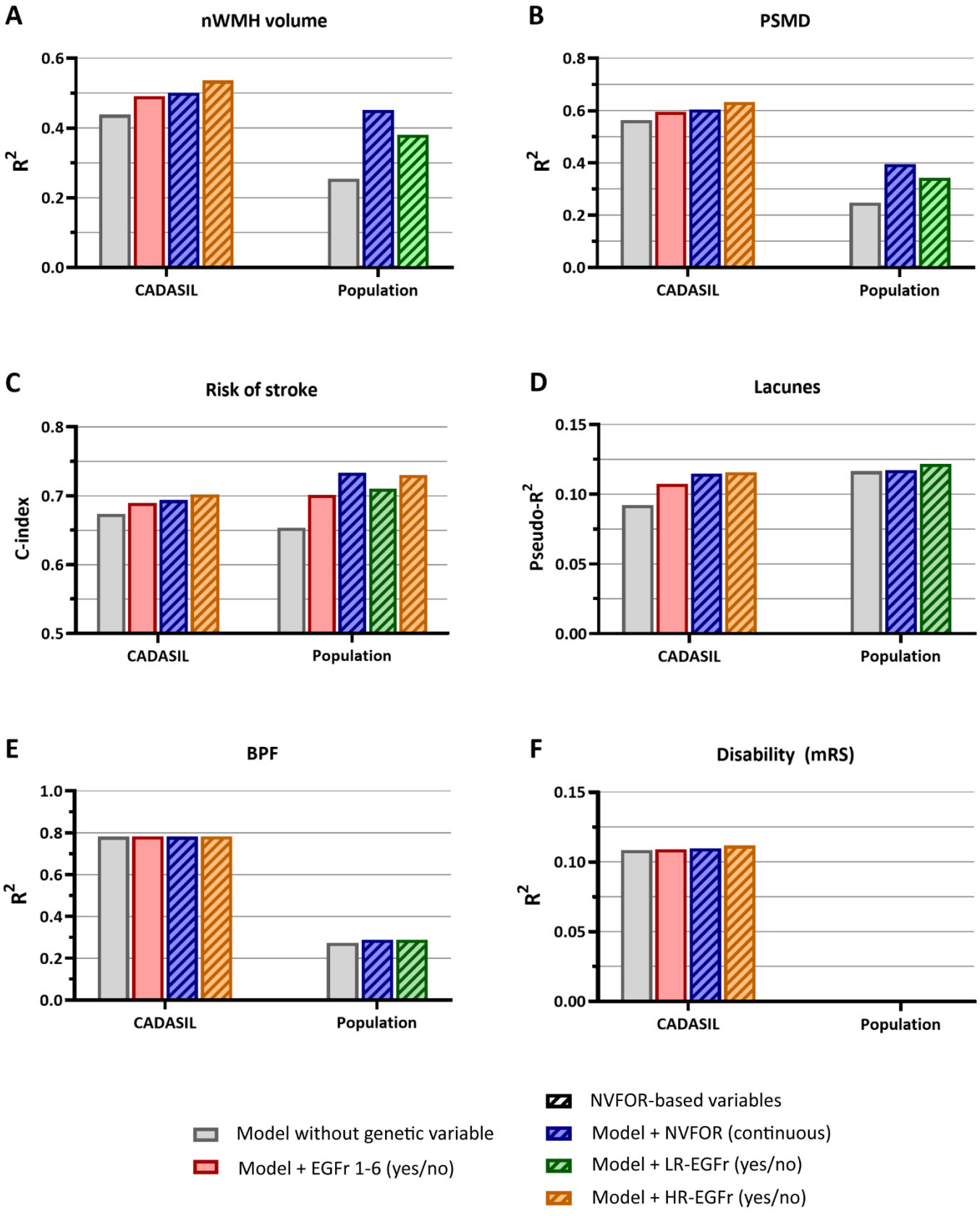
Distribution of *NOTCH3*^{cys} variants in CADASIL cohorts (top) and population databases (bottom) along the 34 EGFr domains in individuals from European (**A**) and Asian (**B**) descent. The European dataset consisted of 2896 individuals with a *NOTCH3*^{cys} variant, of which 1905 were CADASIL patients and 991 were community-dwelling individuals. The Asian dataset consisted of 1052 individuals with a *NOTCH3*^{cys} variant, of which 669 were CADASIL patients and 383 were community-dwelling individuals. The p.Arg544Cys located in EGFr domain 13,5 had a high frequency in Asian CADASIL patients (22.9 %) and Asian community-dwelling individuals (24.3 %), whereas this *NOTCH3*^{cys} variant was only rarely identified in European CADASIL patient (0.7 %) and community-dwelling individuals (0.3 %). In European CADASIL patients the p.Arg578Cys located in EGFr domain 14 had a relatively high frequency compared to Asian CADASIL patients (10.2 % versus 0.3 %), due to a high frequency of this variant in Dutch CADASIL patients (19.1 % of Dutch CADASIL patients). The p.Arg1231Cys variant had a higher frequency in Asian community-dwelling individuals (62.4 %) compared to European community-dwelling individuals (19.6 %). As DiscovEHR and BRAVO had no data regarding the ethnicity available, these datasets were excluded.

Supplementary Figure 3



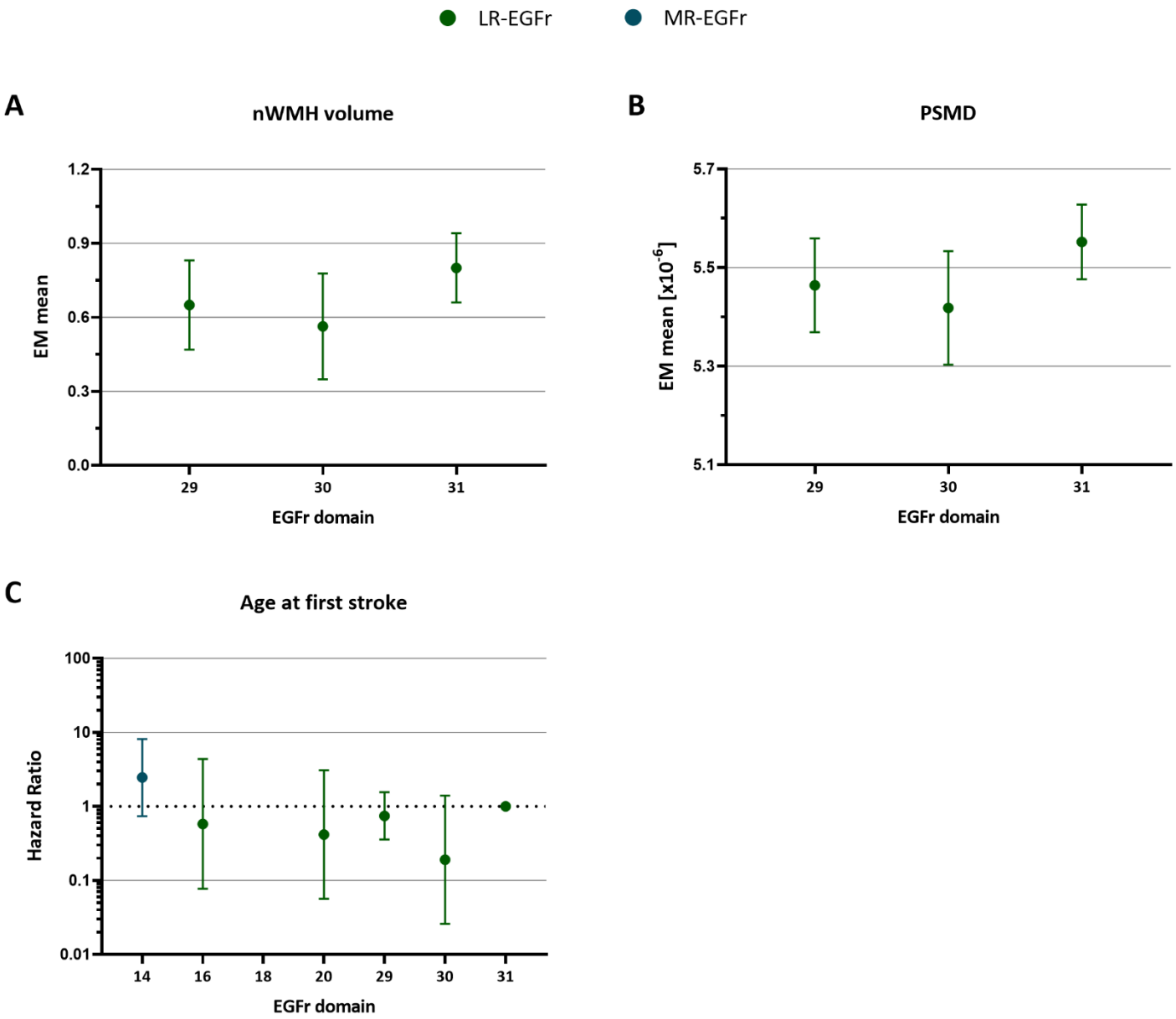
Supplementary Figure 3. Number of *NOTCH3*^{cys} variants per EGFr domain for genotype-phenotype analysis in the CADASIL and population datasets. *NOTCH3*^{cys} variant distribution in the CADASIL (**A**) and population (**B**) datasets.

Supplementary Figure 4



Supplementary Figure 4. Using NVFOR increases the explained variance of SVD imaging markers and clinical outcomes in the CADASIL and population datasets. Six grouped bar charts (**A-F**) showing the change in explained variance expressed as R^2, McFadden's pseudo R^2 and c-index of SVD imaging markers and clinical outcomes by adding the following genetic variables to multivariable models: "EGFr 1-6 (yes/no)", "NVFOR as a continuous variable", "LR-EGFr (yes/no)" and "HR-EGFr (yes/no)". All models included the following independent variables: age, sex and cardiovascular risk factors. "LR-EGFr (yes/no)" was not added as a variable to the models in the CADASIL dataset, because only 10 CADASIL patients harbored an LR-EGFr variant. As none of the individuals with a brain MRI in the population dataset harbored a *NOTCH3*^{cys} EGFr 1-6 variant and only two individuals harbored an HR-EGFr variant, the variables "EGFr 1-6 (yes/no)" and "HR-EGFr (yes/no)" were not added to the models with SVD imaging markers as outcomes in the population dataset. (**A-C**) In the CADASIL dataset, using NVFOR- increased the explained variance of nWMHv, PSMD and age at first stroke compared to using "EGFr 1-6 (yes/no)". In the population dataset, NVFOR increased the c-index of age at first stroke compared to using "EGFr 1-6 (yes/no)", and increased the explained variance of nWMHv and PSMD. (**D**) In the CADASIL dataset, using NVFOR increased the explained variance of lacune volume compared to using "EGFr 1-6 (yes/no)", but using NVFOR in the population dataset did not improve the explained variance of the presence of lacunes. (**E-F**) In the CADASIL and population dataset, using NVFOR did not increase the explained variance for BPF or disability. There was no data available regarding disability in the population dataset.

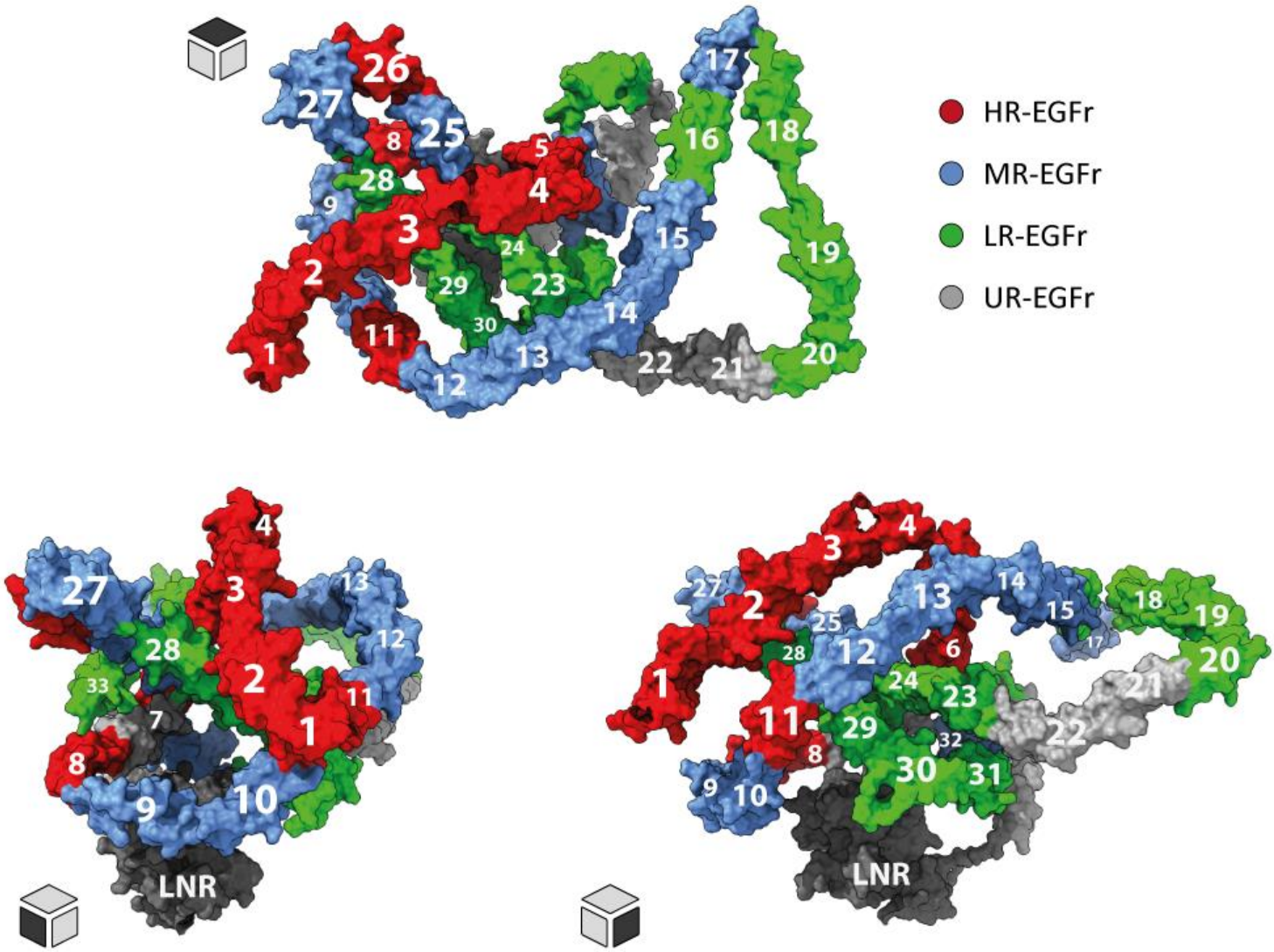
Supplementary Figure 5



Supplementary Figure 5. NOTCH3-SVD severity associated with EGFr domains most frequently harboring *NOTCH3*^{cys} variants in the population dataset. Three interval plots showing the estimated marginal means and hazard ratios of nWMHv, PSMD and risk of stroke for the EGFr domains most frequently harboring *NOTCH3*^{cys} variants in the population dataset. Only EGFr domains which had high *NOTCH3*^{cys} variant counts (≥ 10 individuals for nWMHv and PSMD, and ≥ 20 individuals for risk of stroke) were included in the analyses. Error bars indicate 95% confidence intervals of the group means. **(A-C)** Of all frequent LR-EGFr domains, EGFr domain 30 was associated with the lowest burden of nWMHv, PSMD and risk of stroke. EGFr domain 14 is the only MR-EGFr domain which has high variant counts in both CADASIL cohorts and in the population, and is associated with a higher risk of stroke than LR-EGFr domains frequently harboring *NOTCH3*^{cys} variants in the population. As none of the individuals with a variant in EGFr domain 18 had experienced a stroke, the stroke risk for this domain could not be calculated.

Further details including statistically significant differences in nWMHv, PSMD and risk of stroke between EGFr domains are shown in **Supplementary Table 5 & 6**.

Supplementary Figure 6



Supplementary Figure 6. AlphaFold prediction of the NOTCH3 protein 3D structure. The predicted 3D structure of the extracellular domain of the NOTCH3 protein by Alphafold is shown from three different angles. The predicted model with the highest confidence score is shown (pLDDT=68.2). HR-EGFr and MR-EGFr domains are located at the surface of one side of the NOTCH3 protein model, whereas LR-EGFr domains are located more internally or in a loop directed away from the HR-EGFr and MR-EGFr domains. The newly identified HR-EGFr domain 26 is predicted to be located in a loop at the surface, in close proximity to HR-EGFr domains 1-6. Taken together, this model suggests HR-EGFr domains may be located more externally at the surface at one side of the protein, but the model does not provide clear clues as to potential tertiary structural differences between HR-, MR- and LR-EGFr domains.

Supplementary Table 1. Acquisition parameters of brain MRIs

Sequence		DiViNAS	Munich Signa scanner	Munich Verio scanner	Munich Skyra scanner	UK Biobank
T1	TR [ms]	3.5	22	2500	2500	2000
	TE [ms]	7.9	6	4.37	4.37	2.01
	Slice [mm]	1.10	1.2	1	1	1
	In-plane [mm]	1.04 x 1.04	0.90 x 0.90	1 x 1	1 x 1	1 x 1
T2	TR [ms]	3000	3300	6500	NA	NA
	TE [ms]	80	95	117	NA	NA
	Slice [mm]	5	5	3.3	NA	NA
	In-plane [mm]	0.4 x 0.4	0.94 x 0.94	1 x 1	NA	NA
FLAIR	TR [ms]	4800	8402	5000	5000	5000
	TE [ms]	250	151	395	398	395
	TI [ms]	1650	2002	1800	1800	1800
	Slice [mm]	0.56	5	1	1	1.05
	In-plane [mm]	0.74 x 0.74	0.94 x 0.94	1 x 1	1 x 1	1 x 1
DWI	TR [ms]	6250	8300	12700	3800	3600
	TE [ms]	72	96	81	104.8	92
	Slice [mm]	2.1	5	2	2	2
	In-plane [mm]	2 x 2	0.94 x 0.94	2 x 2	2 x 2	2 x 2
	b-value [s/mm2]	1000	1000	1000	1000; 2000	1000; 2000
	Directions	30	41	30	30 (b=1000); 60 (b=2000)	50 (b=1000); 50 (b=2000)

Abbreviations: DWI = diffusion weighted imaging; FLAIR = fluid-attenuated inversion recovery; TE = echo time; TI = inversion time; TR = repetition time.

Supplementary Table 2. List of codes used in UK Biobank for data retrieval.

	Code type	Code	Date of last linkage
Stroke	**ICD-9**	431, 433, 434, 436	January 2021
	ICD-10	I61, I63, I64	June 2021
	Illness code	1081, 1583	July 2021
	UK biobank algorithmically defined	42006, 42008, 42010	March 2019
Hypertension	**ICD-9**	401	January 2021
	ICD-10	I10, I15	June 2021
	Illness code	1065, 1072	July 2021
Diabetes type I and II	**ICD-9**	250	January 2021
	ICD-10	E10, E11	June 2021
	Illness code	1220, 1222, 1223	July 2021
Hypercholesterolemia	**ICD-9**	272	January 2021
	ICD-10	E78	June 2021
	Illness code	1473	July 2021
Smoking	**UK Biobank variable**	20116, 20160	July 2021

Supplementary Table 3. *NOTCH3*^{cys} variants of CADASIL patients used for analysis of NOTCH3 aggregation in the skin vasculature.

EGFr risk category	#	Age	Sex	Nucleotide alteration	Protein alteration	Exon	EGFr domain
HR-EGFr 1-6	1	54	M	c.421C>T	p.Arg141Cys	4	3
	2	58	M	c.431G>T	p.Cys144Phe	4	3
	3	58	F	c.457C>T	p.Arg153Cys	4	3
	4	57	M	c.486C>G	p.Cys162Trp	4	4
	5	47	F	c.544C>T	p.Arg182Cys	4	4
	6	56	M	c.619C>T	p.Arg207Cys	4	5
HR-EGFr 26	7	48	M	c.3043 T>C	p.Cys1015Arg	19	26
	8	54	M	c.3043T>C	p.Cys1015Arg	19	26
	9	59	M	c.3043T>C	p.Cys1015Arg	19	26
	10	59	F	c.3043T>C	p.Cys1015Arg	19	26
	11	52	M	c.3091C>T	p.Arg1031Cys	19	26
	12	56	M	c.3091C>T	p.Arg1031Cys	19	26
MR-EGFr	13	54	M	c.1591T>G	p.Cys531Gly	10	13
	14	52	F	c.1672C>T	p.Arg558Cys	11	14
	15	54	M	c.1703G>A	p.Cys568Tyr	11	14
	16	50	M	c.1732C>T	p.Arg578Cys	11	14
	17	52	F	c.1759C>T	p.Arg587Cys	11	15
	18	55	M	c.1999G>T	p.Gly667Cys	13	17
LR-EGFr	19	48	F	c.2182C>T	p.Arg728Cys	14	18
	20	49	M	c.3691C>T	p.Arg1231Cys	22	31
	21	60	F	c.3691C>T	p.Arg1231Cys	22	31

Supplementary Table 4. Individuals with a *NOTCH3*^{cys} variant in CADASIL cohorts and population databases.

	Individuals with *NOTCH3*^{cys} variant	% of total	Weight in the calculation of NVFOR
CADASIL cohorts			
Netherlands	950	36.9	0.52
Germany	497	19.3	1
China	263	10.2	1
Italy	242	9.4	1
Japan	180	7.0	1
United Kingdom	171	6.6	1
Korea	114	4.4	1
Taiwan	112	4.4	1
France	45	1.7	1
Total	2574	100	
Population databases			
UK Biobank	1003	61.0	0.47
gnomAD	473	28.7	1
DiscovEHR	131	8.0	1
BRAVO	40	2.4	1
Total	1647	100	

Supplementary Table 5. Statistically significant differences in the burden of SVD imaging markers, risk of stroke and disability between EGFr domains with the highest frequency of *NOTCH3*^{cys} variants in the CADASIL and population datasets.

Dataset	Outcome	Comparison	*P*	P_{corr} *
CADASIL	nWMHv	EGFr 1 vs. 5	**0.006**	0.085
		EGFr 1 vs. 14	**<.0001**	**<.0001**
		EGFr 2 vs. 4	**0.001**	**0.019**
		EGFr 2 vs. 5	**<.0001**	**<.001**
		EGFr 2 vs. 14	**<.0001**	**<.0001**
		EGFr 3 vs. 4	**<.0001**	**<.001**
		EGFr 3 vs. 5	**<.0001**	**<.0001**
		EGFr 3 vs. 14	**<.0001**	**<.0001**
		EGFr 4 vs. 5	**0.031**	0.31
		EGFr 4 vs. 14	**<.0001**	**<.0001**
		EGFr 5 vs. 14	**<.001**	**0.014**
		EGFr 5 vs. 26	**0.024**	0.26
		EGFr 14 vs. 26	**<.0001**	**<.0001**
	PSMD	EGFr 2 vs. 5	**0.001**	**0.014**
		EGFr 2 vs. 14	**<.0001**	**<.0001**
		EGFr 3 vs. 4	**<.001**	**0.009**
		EGFr 3 vs. 5	**<.0001**	**<.001**
		EGFr 3 vs. 14	**<.0001**	**<.0001**
		EGFr 4 vs. 14	**<.0001**	**<.0001**
		EGFr 5 vs. 14	**<.001**	**0.003**
		EGFr 14 vs. 26	**<.0001**	**<.0001**
	nLV	EGFr 2 vs. 5	**<.001**	**<.0001**
		EGFr 2 vs. 14	**<.0001**	**0.006**
		EGFr 3 vs. 5	**<.0001**	**<.0001**
		EGFr 3 vs. 14	**<.0001**	**<.001**
		EGFr 4 vs. 5	**0.004**	0.057
		EGFr 4 vs. 14	**<.0001**	**<.0001**
		EGFr 14 vs. 26	**0.005**	0.070
	Age at first stroke	EGFr 2 vs. 14	**0.004**	0.055
		EGFr 3 vs. 5	**0.002**	**0.033**
		EGFr 3 vs. 14	**<.0001**	**<.0001**
		EGFr 4 vs. 5	**0.045**	0.68
		EGFr 4 vs. 14	**<.001**	**0.0051**
		EGFr 14 vs. 26	**0.006**	0.091
	Disability	EGFr 2 vs. 14	**0.029**	0.43
		EGFr 3 vs. 14	**0.021**	0.32
Population	nWMH volume	EGFr 30 vs. 31	**0.028**	0.070
	PSMD	EGFr 30 vs. 31	**0.021**	0.054
	Age at first stroke	EGFr 14 vs. 30	**0.028**	0.41

***** = P-value after correction for multiple testing

Supplementary Table 6. The burden of SVD imaging markers, risk of stroke and disability of the EGFr domains with the highest frequency of *NOTCH3*^{cys} variants in the CADASIL and population datasets.

Dataset	Comparison	nWMHv *	PSMD †	nLV ‡	Risk of stroke	Disability
		B [95% CI]	B [95% CI]	OR [95% CI]	HR [95% CI]	OR [95% CI]
CADASIL	EGFr 1	2.44 [2.01 – 2.87]	x	x	x	x
	EGFr 2	2.57 [2.25 – 2.88]	6.42 [6.28 – 6.56]	12.34 [4.45 – 35.17]	3.23 [1.46 – 7.14]	2.67 [1.10 – 6.51]
	EGFr 3	2.55 [2.30 – 2.79]	6.43 [6.32 – 6.54]	11.08 [4.86 – 26.15]	4.88 [2.57 – 9.29]	2.28 [1.12 – 4.72]
	EGFr 4	2.09 [1.87 – 2.32]	6.26 [6.16 – 6.36]	6.41 [2.84 – 14.94]	3.36 [1.73 – 6.51]	1.71 [0.83 – 3.59]
	EGFr 5	1.81 [1.55 – 2.07]	6.18 [6.06 – 6.29]	1.80 [0.78 – 4.17]	1.58 [0.72 – 3.48]	1.17 [0.54 – 2.49]
	EGFr 14	1.37 [1.13 – 1.62]	5.97 [5.86 – 6.08]	1 [reference]	1 [reference]	1 [reference]
	EGFr 26	2.25 [1.86 – 2.65]	6.39 [6.21 – 6.57]	5.10 [1.66 – 16.00]	3.30 [1.41 – 7.75]	1.80 [0.67 – 4.82]
Population	EGFr 14	-	-	-	2.46 [0.74 – 8.14]	-
	EGFr 16	-	-	-	0.58 [0.08 – 4.37]	-
	EGFr 18	-	-	-	NA	-
	EGFr 20	-	-	-	0.42 [0.06 – 3.08]	-
	EGFr 29	0.65 [0.47 – 0.83]	5.46 [5.37 – 5.56]	-	0.75 [0.36 – 1.56]	-
	EGFr 30	0.56 [0.35 – 0.78]	5.42 [5.30 – 5.53]	-	0.19 [0.03 – 1.40]	-
	EGFr 31	0.80 [0.66 – 0.94]	5.55 [5.48 – 5.63]	-	1 [reference]	-

Abbreviations: nWMHv = normalized white matter hyperintensity volume; PSMD = peak width of skeletonized mean diffusivity; nLV = normalized lacune volume.

* = nWMHv was square root transformed

† = PSMD was natural log transformed

‡ = normalized lacune volume was stratified in 5 quantiles

Supplementary Table 7. Frequency of *NOTCH3*^{cys} variants in CADASIL cohorts and population databases used for the calculation of the *NOTCH3*^{cys} Variant Frequency Odds Ratio.

Abbreviations: BRA = BRAVO; CHI = China; DIS = DiscovEHR; FRA = France; GER = Germany; GNO = GnomAD; ITA = Italy; JAP= Japan; KOR = Korea; NL = the Netherlands; TAI = Taiwan; UK = United Kingdom; UKB = UK Biobank.

Genetic information			CADASIL									Population			
p.mut	exon	EGFR	NL	GER	CHI	ITA	JAP	UK	KOR	TAI	FRA	UKB	GNO	DIS	BRA
p.Cys43Gly	2	1	0	3	0	0	0	0	0	0	0	0	0	0	0
p.Cys43Tyr	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys43Phe	2	1	1	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys43Arg	2	1	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Cys49Tyr	2	1	0	0	0	2	0	0	0	0	1	0	0	0	0
p.Cys49Phe	2	1	0	2	0	0	0	0	0	1	0	0	0	0	0
p.Cys49Arg	2	1	0	0	6	0	0	0	0	0	0	0	0	0	0
p.Gly53Cys	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Arg54Cys	2	1	6	0	0	3	3	3	2	1	0	1	0	0	0
p.Cys55Arg	2	1	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys55Gly	2	1	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys55Ser	2	1	0	0	0	0	0	0	1	0	0	0	0	0	0
p.Ser60Cys	2	1	1	3	0	0	0	0	0	0	0	0	0	0	0
p.Cys65Tyr	2	1	0	0	0	2	1	0	0	0	0	0	0	0	0
p.Cys65Ser	2	1	0	5	0	2	3	0	0	0	0	0	0	0	0
p.Cys67Ser	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Trp71Cys	3	1	0	0	1	0	1	0	0	0	1	0	0	0	0
p.Cys76Arg	3	1	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys76Tyr	3	1	3	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys76Trp	3	1	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Cys82Phe	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3
p.Gly85Cys	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys87Arg	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys87Tyr	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys87Phe	3	2	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Arg90Cys	3	2	5	48	26	6	3	7	2	2	4	1	0	0	0
p.Cys93Phe	3	2	0	6	0	0	0	0	0	0	0	0	0	0	0
p.Cys93Gly	3	2	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys93Tyr	3	2	0	1	0	0	2	0	0	0	0	0	0	0	0
p.Cys106Arg	3	2	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys106Trp	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys108Arg	3	2	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys108Gly	3	2	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys108Phe	3	2	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys108Tyr	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys108Ser	3	2	0	0	0	2	0	0	0	0	0	0	0	0	0
p.Arg110Cys	3	2	26	13	11	4	2	3	4	2	2	2	0	0	0
p.Cys117Arg	4	2	0	0	1	2	0	0	0	0	0	0	0	0	0
p.Cys117Tyr	4	2	2	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys117Phe	4	2	0	11	1	0	0	0	0	0	0	0	0	0	0
p.Cys117Thr	4	2	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys117Trp	4	2	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Ser118Cys	4	2	0	0	0	0	0	0	0	5	0	0	0	0	0
p.Cys123Phe	4	3	0	5	0	0	0	0	0	0	0	0	0	0	0
p.Cys123Thr	4	3	0	0	0	0	0	0	1	0	0	0	0	0	0
p.Ser126Cys	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys128Phe	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Arg133Cys	4	3	32	61	7	7	11	4	4	3	3	0	3	0	0
p.Cys134Tyr	4	3	0	0	1	1	0	0	0	0	0	0	0	0	0
p.Cys134Gly	4	3	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys134Trp	4	3	3	2	0	0	0	0	0	0	0	0	0	0	0
p.Arg141Cys	4	3	76	18	12	11	22	33	2	2	6	5	0	0	0

p.Phe142Cys	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys144Ser	4	3	0	1	1	0	0	0	0	0	0	0	0	0	0
p.Cys144Phe	4	3	6	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys144Tyr	4	3	0	4	7	0	0	0	0	0	0	0	0	0	0
p.Cys144Trp	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys144Thr	4	3	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Ser145Cys	4	3	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys146Arg	4	3	0	0	1	0	0	0	0	0	1	0	0	0	0
p.Cys146Trp	4	3	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys146Tyr	4	3	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Gly149Cys	4	3	0	9	0	0	0	0	0	0	0	0	0	0	0
p.Tyr150Cys	4	3	0	10	0	0	0	0	0	0	0	0	0	0	0
p.Arg153Cys	4	3	56	14	16	2	9	14	0	1	2	1	0	0	0
p.Ser154Cys	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys155Trp	4	3	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys155Ser	4	3	0	3	0	0	0	0	0	0	0	0	0	0	0
p.Cys155Tyr	4	3	2	1	0	0	0	0	0	0	0	0	0	0	0
p.Trp156Cys	4	3	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys162Ser	4	4	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys162Trp	4	4	20	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys162Tyr	4	4	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Gly165Cys	4	4	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Arg169Cys	4	4	10	43	25	6	6	30	3	1	5	2	0	0	0
p.His170Cys	4	4	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Gly171Cys	4	4	0	0	1	0	0	0	0	0	1	0	0	0	0
p.Cys174Arg	4	4	0	3	0	0	0	0	1	0	0	0	0	0	0
p.Cys174Tyr	4	4	0	21	0	1	0	0	0	0	0	0	0	0	0
p.Ser180Cys	4	4	0	0	0	0	9	0	0	0	0	0	0	0	0
p.Arg182Cys	4	4	58	94	15	6	15	24	2	0	3	7	1	0	0
p.Cys183Arg	4	4	0	3	0	0	0	3	0	0	0	0	0	0	0
p.Cys183Tyr	4	4	6	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys183Ser	4	4	0	2	0	1	0	0	0	0	0	0	0	0	0
p.Cys183Phe	4	4	0	4	0	0	0	0	0	0	0	0	0	0	0
p.Cys185Arg	4	4	1	12	0	0	0	0	0	0	1	0	0	0	0
p.Cys185Ser	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys185Tyr	4	4	0	0	1	0	5	0	0	0	0	0	0	0	0
p.Cys185Gly	4	4	0	0	0	2	0	0	0	0	0	0	0	0	0
p.Tyr189Cys	4	4	6	0	1	0	0	1	0	0	0	0	0	0	0
p.Cys194Arg	4	4	0	0	1	0	0	0	4	0	0	0	0	0	0
p.Cys194Ser	4	4	0	0	1	0	0	5	0	0	0	0	0	0	0
p.Cys194Tyr	4	4	0	0	3	0	1	0	0	0	0	0	0	0	0
p.Cys194Phe	4	4	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys201Arg	4	5	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys201Ser	4	5	0	0	1	0	0	0	0	0	0	0	0	1	0
p.Cys201Tyr	4	5	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Cys206Ser	4	5	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Arg207Cys	4	5	109	6	1	13	2	6	0	0	0	2	2	0	0
p.Cys212Arg	4	5	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys212Trp	4	5	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys212Ser	4	5	13	0	0	0	0	0	0	0	1	0	0	0	0
p.Cys212Tyr	4	5	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys222Gly	4	5	0	0	0	0	0	0	0	0	1	0	0	0	0
p.Cys222Arg	4	5	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys222Ser	4	5	0	0	2	0	0	0	0	1	0	0	0	0	0
p.Cys222Tyr	4	5	9	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys222Thr	4	5	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Cys222Phe	4	5	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys224Arg	4	5	0	0	0	0	0	0	0	1	0	0	0	0	0
p.Cys224Tyr	4	5	4	0	0	0	0	0	0	0	1	0	0	0	0
p.Phe228Cys	5	5	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys233Ser	5	5	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys233Arg	5	5	0	0	1	1	0	0	0	0	0	0	0	0	0
p.Cys233Tyr	5	5	1	1	0	0	0	0	1	0	0	0	0	0	0
p.Cys233Trp	5	5	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys240Tyr	5	6	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys240Ser	5	6	0	1	1	2	0	0	0	0	0	0	0	0	0

p.Cys245Arg	5	6	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys245Ser	5	6	0	0	0	0	0	2	0	0	0	0	0	0	0
p.Cys245Tyr	5	6	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys251Arg	5	6	0	0	1	2	0	5	0	0	0	0	0	0	0
p.Cys251Tyr	5	6	0	0	1	1	0	0	0	0	0	0	0	0	0
p.Cys251Ser	5	6	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Tyr258Cys	5	6	2	0	1	1	1	0	0	0	1	1	0	0	0
p.Cys260Arg	5	6	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys260Phe	5	6	0	0	1	0	2	0	0	0	0	0	0	0	0
p.Cys260Tyr	5	6	0	3	0	0	0	1	0	0	0	0	0	0	0
p.Cys262Arg	5	6	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys291Tyr	6	7	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys311Ser	6	7	0	0	0	0	0	1	0	0	0	2	0	0	0
p.Cys318Phe	6	8	9	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys323Ser	6	8	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys323Tyr	6	8	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys323Trp	6	8	0	0	0	0	2	0	0	0	0	0	0	0	0
p.Cys329Tyr	6	8	0	0	0	1	1	0	0	0	0	0	0	0	0
p.Arg332Cys	6	8	12	5	4	10	8	12	10	2	0	1	0	0	0
p.Ser335Cys	6	8	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Tyr337Cys	6	8	3	8	1	0	0	0	0	0	0	1	0	0	1
p.Cys338Arg	6	8	0	0	0	1	0	0	0	0	0	0	1	0	0
p.Cys338Ser	6	8	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys340Phe	6	8	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys349Ser	7	8	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys355Ser	7	9	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys360Tyr	7	9	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys377Gly	7	9	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys377Tyr	7	9	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys379Tyr	7	9	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys379Phe	7	9	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys379Ser	7	9	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Gly382Cys	7	9	3	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys388Arg	7	9	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys388Tyr	7	9	0	0	0	0	3	0	0	0	0	0	0	0	0
p.Cys395Arg	7	10	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Ser396Cys	7	10	4	0	0	3	1	0	0	0	0	0	0	0	0
p.Cys402Ser	8	10	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys408Arg	8	10	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys408Gly	8	10	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys408Tyr	8	10	0	0	0	0	0	0	0	1	0	0	0	0	0
p.Cys408Trp	8	10	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Ser414Cys	8	10	8	0	0	0	0	0	7	0	0	0	0	0	0
p.Cys417Arg	8	10	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys419Ser	8	10	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys419Arg	8	10	0	0	0	0	3	0	0	0	0	0	0	0	0
p.Cys419Trp	8	10	0	0	0	0	0	0	0	1	0	0	0	0	0
p.Gly420Cys	8	10	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Arg421Cys	8	10	2	1	1	0	0	0	0	0	0	2	0	0	0
p.Arg427Cys	8	10	2	1	0	1	0	0	0	1	0	0	0	0	0
p.Cys428Arg	8	10	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys428Tyr	8	10	0	3	0	0	0	0	0	0	0	0	0	0	0
p.Cys435Arg	8	11	1	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys435Tyr	8	11	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys435Thr	8	11	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys435Phe	8	11	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys440Gly	8	11	0	0	0	0	0	3	0	0	0	0	0	0	0
p.Cys440Arg	8	11	0	2	0	1	0	0	0	0	0	0	0	0	0
p.Cys446Ser	8	11	0	7	0	0	0	0	0	0	0	0	0	0	0
p.Cys446Gly	8	11	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys446Phe	8	11	4	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys446Tyr	8	11	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Arg449Cys	8	11	14	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys455Arg	8	11	0	0	0	0	1	0	1	0	0	0	0	0	0
p.Cys455Phe	8	11	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys455Tyr	8	11	0	0	0	0	0	0	0	0	0	1	0	0	0

p.Cys457Ser	8	11	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Tyr465Cys	9	11	1	0	0	0	1	0	3	0	0	1	0	0	0
p.Cys466Tyr	9	11	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Ser476Cys	9	12	0	0	0	0	0	0	0	0	0	3	0	0	0
p.Gly481Cys	9	12	0	0	0	0	1	0	0	0	0	2	0	0	1
p.Cys484Tyr	9	12	0	4	0	0	0	0	0	0	0	0	0	0	0
p.Cys484Arg	9	12	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Ser492Cys	9	12	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Cys493Ser	9	12	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys493Arg	9	12	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys495Tyr	9	12	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys495Gly	9	12	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly498Cys	10	12	7	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys504Arg	10	12	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys504Gly	10	12	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys511Arg	10	13	0	1	0	0	0	0	0	0	0	0	0	1	0
p.Cys511Tyr	10	13	0	0	0	4	0	0	0	0	0	0	0	0	0
p.Cys511Phe	10	13	0	0	0	1	0	0	0	0	0	1	0	0	0
p.Cys516Phe	10	13	0	0	0	0	0	0	0	0	0	7	0	0	0
p.Cys516Tyr	10	13	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys522Ser	10	13	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys522Trp	10	13	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Gly528Cys	10	13	0	0	0	13	0	0	0	0	0	0	0	0	0
p.Cys531Gly	10	13	7	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys531Tyr	10	13	1	0	0	0	0	0	0	0	0	0	0	0	0
p.Arg532Cys	10	13	0	0	0	1	0	0	0	0	0	4	1	0	0
p.Cys533Ser	10	13	1	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys542Arg	11	13	0	0	0	0	3	0	9	0	0	0	0	0	0
p.Cys542Tyr	11	13	0	0	0	0	1	0	1	0	1	0	0	0	0
p.Arg544Cys	11	13.5	12	1	35	0	2	0	37	79	0	15	83	1	0
p.Cys549Ser	11	14	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys549Tyr	11	14	0	4	0	0	0	0	0	0	0	0	0	0	0
p.Cys549Arg	11	14	2	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys551Arg	11	14	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys554Phe	11	14	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly557Cys	11	14	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Arg558Cys	11	14	21	5	1	3	0	0	4	0	2	4	9	0	0
p.Cys559Trp	11	14	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys568Tyr	11	14	9	0	0	0	0	0	0	0	0	0	0	0	0
p.Tyr574Cys	11	14	0	0	0	4	0	0	0	0	0	0	0	0	0
p.Arg578Cys	11	14	181	0	0	13	0	0	2	0	1	13	10	1	0
p.Cys579Tyr	11	14	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Arg587Cys	11	15	8	0	6	0	1	0	3	1	0	7	10	0	0
p.Arg592Cys	11	15	0	0	0	0	0	0	0	0	0	1	1	0	0
p.Gly595Cys	11	15	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys597Arg	11	15	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys597Ser	11	15	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys597Tyr	11	15	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Tyr604Cys	11	15	2	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys606Arg	11	15	0	0	0	0	0	0	2	0	0	0	0	0	0
p.Cys606Tyr	11	15	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Cys606Ser	11	15	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys606Phe	11	15	0	0	2	0	0	0	0	0	0	0	0	0	0
p.Arg607Cys	11	15	9	1	37	15	9	2	2	0	0	7	1	4	0
p.Cys608Tyr	11	15	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys608Trp	11	15	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys629Arg	12	16	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys634Gly	12	16	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Arg635Cys	12	16	0	0	0	0	0	0	0	0	0	0	2	4	0
p.Arg640Cys	12	16	3	0	1	0	1	0	0	0	0	20	9	0	0
p.Cys645Tyr	12	16	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys654Gly	13	16	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Cys654Tyr	13	16	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Ser664Cys	13	17	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Gly667Cys	13	17	21	0	0	0	0	0	0	0	0	2	1	1	0
p.Ser671Cys	13	17	0	0	0	0	0	0	0	0	0	4	0	0	0

p.Cys672Tyr	13	17	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg680Cys	13	17	0	0	1	0	0	0	0	0	0	3	0	0	1
p.Tyr710Cys	13	18	3	0	0	0	0	0	0	0	0	1	0	0	2
p.Arg717Cys	14	18	0	0	0	0	0	0	0	1	0	29	3	2	7
p.Cys720Tyr	14	18	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg728Cys	14	18	15	0	0	2	0	0	0	0	1	15	0	2	2
p.Cys729Gly	14	18	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Ser740Cys	14	19	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys743Tyr	14	19	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys749Tyr	14	19	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys758Tyr	14	19	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg767Cys	15	19	0	0	1	1	0	0	0	0	0	12	14	0	0
p.Cys769Tyr	15	19	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys775Arg	15	20	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Arg785Cys	15	20	0	0	0	0	0	0	0	0	0	12	1	0	0
p.Cys796Phe	15	20	0	0	0	0	0	0	0	0	0	1	0	0	1
p.Cys796Ser	15	20	0	0	0	0	0	0	0	0	0	1	0	0	1
p.Cys796Tyr	15	20	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys798Tyr	15	20	0	0	0	0	0	0	0	0	0	2	0	0	1
p.Trp802Cys	15	20	0	0	0	0	0	0	0	0	0	6	0	0	0
p.Phe833Cys	16	21	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Cys846Tyr	16	21	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys853Tyr	16	22	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys858Trp	17	22	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly861Cys	17	22	0	0	0	0	0	0	0	0	0	1	1	0	0
p.Cys873Arg	17	22	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg886Cys	17	22.5	0	0	1	0	0	0	0	0	0	0	0	0	1
p.Cys891Gly	17	23	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys910Tyr	17	23	0	0	0	0	0	0	0	0	0	5	0	1	2
p.Cys910Arg	17	23	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys912Ser	17	23	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Tyr916Cys	17	23	0	0	0	1	0	0	0	0	0	10	0	1	0
p.Cys928Tyr	17	24	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Ser932Cys	18	24	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys933Gly	18	24	0	0	0	0	0	0	0	0	0	0	2	0	0
p.Cys939Ser	18	24	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys939Trp	18	24	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Gly942Cys	18	24	0	0	0	0	0	0	0	0	0	0	2	0	0
p.Cys948Phe	18	24	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys950Gly	18	24	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Arg951Cys	18	24	0	0	0	1	0	0	0	0	0	1	2	0	0
p.Gly953Cys	18	24	0	0	0	0	0	1	0	0	0	0	0	0	0
p.Cys959Ser	18	24	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys971Tyr	18	25	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly975Cys	18	25	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys977Ser	18	25	0	0	1	0	0	0	0	5	0	0	0	0	0
p.Phe984Cys	18	25	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Arg985Cys	18	25	0	6	0	5	1	0	0	0	2	0	0	0	0
p.Cys986Arg	18	25	0	0	0	0	0	1	0	0	0	1	3	0	0
p.Cys986Gly	18	25	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys988Tyr	18	25	0	0	1	0	0	0	0	0	0	0	0	0	0
p.Cys988Arg	18	25	0	1	0	0	0	0	0	0	0	0	0	0	0
p.Cys988Phe	18	25	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Gly994Cys	18	25	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys997Gly	18	25	0	0	0	8	0	0	0	0	0	0	0	0	0
p.Cys997Ser	18	25	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Trp1003Cys	19	26	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys1004Tyr	19	26	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1004Gly	19	26	0	0	0	0	6	0	0	0	0	0	0	0	0
p.Arg1006Cys	19	26	1	0	1	29	0	0	0	0	1	1	0	1	0
p.Cys1009Phe	19	26	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys1015Arg	19	26	80	0	0	0	1	0	0	0	0	1	0	0	0
p.Cys1015Trp	19	26	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Tyr1021Cys	19	26	0	0	1	5	2	0	0	0	0	0	1	0	0
p.Cys1022Gly	19	26	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Arg1031Cys	19	26	8	0	2	0	0	0	0	0	1	3	0	0	0

p.Cys1055Tyr	20	27	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly1058Cys	20	27	0	0	0	0	0	0	3	0	0	0	0	0	0
p.Cys1061Arg	20	27	0	0	0	0	0	0	0	0	0	0	2	0	0
p.Cys1061Tyr	20	27	0	0	0	0	0	0	0	0	0	3	0	0	0
p.Gly1165Cys	20	27	0	0	0	0	0	0	0	0	0	3	0	0	0
p.Ser1067Cys	20	27	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Tyr1069Cys	20	27	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Cys1070Ser	20	27	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Cys1072Tyr	20	27	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Arg1072Cys	20	27	0	2	0	0	0	0	0	0	0	0	0	0	0
p.Arg1076Cys	20	27	8	0	0	5	0	0	0	1	0	1	1	0	0
p.Cys1099Phe	20	28	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Arg1100Cys	20	28	0	0	0	0	0	0	0	0	0	3	0	1	0
p.Cys1108Arg	20	28	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys1110Arg	21	28	0	0	0	0	0	0	0	0	0	4	0	0	0
p.Cys1110Ser	21	28	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys1119Tyr	21	28	0	0	0	0	0	0	0	0	0	6	1	0	1
p.Cys1131Trp	21	29	0	0	1	1	0	0	0	0	0	0	0	0	0
p.Cys1137Arg	21	29	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1143Cys	21	29	0	0	0	0	1	0	0	0	0	133	5	6	0
p.Tyr1144Cys	21	29	0	0	0	0	0	0	0	0	0	2	0	2	0
p.Cys1148Phe	21	29	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1157Arg	22	29	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1176Tyr	22	30	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1182Trp	22	30	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1190Cys	22	30	0	0	0	0	0	0	0	0	0	21	15	7	0
p.Cys1191Ser	22	30	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys1193Tyr	22	30	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1201Cys	22	30	0	0	0	0	0	0	0	0	0	52	10	4	0
p.Cys1202Ser	22	30	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Arg1210Cys	22	31	1	0	0	0	0	0	0	0	0	3	2	0	0
p.Cys1222Gly	22	31	0	0	0	0	0	2	0	0	0	212	29	0	0
p.Cys1222Ser	22	31	0	0	0	3	0	0	0	0	0	0	0	0	0
p.Cys1222Arg	22	31	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1231Cys	22	31	6	0	0	19	0	3	3	0	1	255	225	84	0
p.Cys1232Trp	22	31	0	0	0	0	0	0	0	0	0	0	0	1	0
p.Arg1242Cys	23	31	0	0	0	0	0	0	0	0	0	9	2	0	0
p.Cys1250Arg	23	32	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1250Gly	23	32	0	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys1261Arg	23	32	0	0	0	0	0	0	0	0	1	0	0	0	0
p.Cys1261Tyr	23	32	0	1	0	0	0	0	0	0	0	0	0	0	1
p.Cys1261Trp	23	32	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1262Cys	23	32	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Gly1266Cys	23	32	3	0	0	0	0	0	0	0	0	0	0	0	0
p.Cys1275Ser	23	32	0	0	0	0	0	0	0	0	0	1	0	0	1
p.Cys1277Tyr	23	32	0	0	0	0	0	0	0	0	0	0	1	0	0
p.Gly1283Cys	24	32	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Arg1291Cys	24	33	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys1293Phe	24	33	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1293Trp	24	33	0	0	0	0	1	0	0	0	0	0	0	0	0
p.Cys1298Phe	24	33	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys1313Gly	24	33	0	0	0	0	0	0	0	0	0	0	0	0	1
p.Cys1313Ser	24	33	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1315Phe	24	33	0	0	0	0	0	0	0	0	0	10	0	0	0
p.Cys1315Trp	24	33	0	0	0	0	0	0	0	0	0	1	0	0	1
p.Cys1315Tyr	24	33	0	0	0	1	0	0	0	0	0	0	0	0	0
p.Cys1324Ser	24	33	0	0	0	0	0	0	0	0	0	2	0	0	0
p.Cys1324Tyr	24	33	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1350Gly	24	34	0	0	0	0	0	0	0	0	0	0	0	0	2
p.Arg1360Cys	24	34	0	0	0	0	0	0	0	0	0	1	0	0	0
p.Cys1372Trp	24	34	0	0	0	0	0	0	0	0	0	1	0	0	0
Total			**950**	**497**	**263**	**242**	**180**	**171**	**114**	**112**	**45**	**1003**	**473**	**131**	**40**
			2574									**1647**			

Supplementary Table 8. Frequency of *NOTCH3*^{cys} variants in the CADASIL cohorts and population genotype-phenotype datasets.

Abbreviations: GER = Germany; ITA = Italy; NL = the Netherlands; UKB = UK Biobank.

Genetic information			CADASIL			Population
p.mut	exon	EGFR	NL	GER	ITA	UKB
p.Cys43Gly	2	1	0	3	0	0
p.Arg54Cys	2	1	3	0	2	1
p.Cys65Ser	2	1	0	3	2	0
p.Cys76Trp	3	1	0	1	0	0
p.Arg90Cys	3	2	0	10	3	1
p.Cys93Phe	3	2	0	2	0	0
p.Cys93Tyr	3	2	0	1	0	0
p.Arg110Cys	3	2	5	3	2	2
p.Cys117Arg	4	2	0	0	2	0
p.Cys117Tyr	4	2	2	0	0	0
p.Cys117Thr	4	2	0	1	0	0
p.Arg133Cys	4	3	3	9	5	0
p.Arg141Cys	4	3	16	1	4	5
p.Cys144Phe	4	3	4	0	0	0
p.Cys144Tyr	4	3	0	1	0	0
p.Cys144Thr	4	3	0	1	0	0
p.Gly149Cys	4	3	0	4	0	0
p.Tyr150Cys	4	3	0	4	0	0
p.Arg153Cys	4	3	11	2	0	1
p.Cys155Ser	4	3	0	2	0	0
p.Cys155Tyr	4	3	0	1	0	0
p.Cys162Trp	4	4	3	0	0	0
p.Gly165Cys	4	4	0	1	0	0
p.Arg169Cys	4	4	3	11	3	2
p.Cys174Arg	4	4	0	1	0	0
p.Cys174Tyr	4	4	0	1	0	0
p.Arg182Cys	4	4	13	34	6	7
p.Cys183Arg	4	4	0	2	0	0
p.Cys183Tyr	4	4	2	0	0	0
p.Cys183Phe	4	4	0	1	0	0
p.Cys185Arg	4	4	0	4	0	0
p.Cys201Tyr	4	5	0	1	0	0
p.Cys206Ser	4	5	0	1	0	0
p.Arg207Cys	4	5	28	2	4	2
p.Cys212Ser	4	5	1	0	0	0
p.Cys212Tyr	4	5	0	1	0	0
p.Cys222Tyr	4	5	1	1	0	0
p.Cys222Thr	4	5	0	2	0	0
p.Cys224Tyr	4	5	1	0	0	0
p.Cys233Tyr	5	5	1	0	0	0
p.Cys240Ser	5	6	0	0	2	0
p.Cys251Arg	5	6	0	0	2	0
p.Cys251Tyr	5	6	0	0	1	0
p.Tyr258Cys	5	6	0	0	0	1
p.Cys260Tyr	5	6	0	1	0	0
p.Cys311Ser	6	7	0	0	0	2
p.Cys318Phe	6	8	2	0	0	2
p.Arg332Cys	6	8	0	1	4	1
p.Tyr337Cys	6	8	0	3	0	1
p.Cys360Tyr	7	9	0	0	0	1
p.Cys377Tyr	7	9	1	0	0	0
p.Ser396Cys	7	10	2	0	3	0
p.Cys408Arg	8	10	0	0	0	1
p.Cys419Ser	8	10	0	0	0	1

p.Arg421Cys	8	10	1	0	0	2
p.Arg427Cys	8	10	1	1	1	0
p.Cys428Tyr	8	10	0	2	0	0
p.Cys435Thr	8	11	0	1	0	0
p.Cys440Arg	8	11	0	1	0	0
p.Cys446Ser	8	11	0	2	0	0
p.Cys446Tyr	8	11	0	0	1	0
p.Arg449Cys	8	11	2	0	0	0
p.Cys455Tyr	8	11	0	0	0	1
p.Tyr465Cys	9	11	0	0	0	1
p.Ser476Cys	9	12	0	0	0	3
p.Gly481Cys	9	12	0	0	0	2
p.Cys484Arg	9	12	0	0	0	1
p.Cys495Gly	9	12	0	0	0	1
p.Cys504Arg	10	12	0	0	0	1
p.Cys511Phe	10	13	0	0	1	1
p.Cys516Phe	10	13	0	0	0	7
p.Cys516Tyr	10	13	0	0	0	1
p.Cys522Ser	10	13	0	0	0	1
p.Gly528Cys	10	13	0	0	2	0
p.Cys531Gly	10	13	2	0	0	0
p.Arg532Cys	10	13	0	0	0	4
p.Cys533Ser	10	13	0	1	0	0
p.Arg544Cys	11	13.5	2	1	0	15
p.Cys549Tyr	11	14	0	3	0	0
p.Cys551Arg	11	14	0	1	0	0
p.Cys554Phe	11	14	0	0	0	1
p.Arg558Cys	11	14	1	3	0	4
p.Cys568Tyr	11	14	5	0	0	0
p.Tyr574Cys	11	14	0	0	4	0
p.Arg578Cys	11	14	45	0	10	13
p.Cys579Tyr	11	14	0	0	0	2
p.Arg587Cys	11	15	2	0	0	7
p.Arg592Cys	11	15	0	0	0	1
p.Gly595Cys	11	15	2	0	0	0
p.Arg607Cys	11	15	3	1	4	7
p.Cys608Trp	11	15	0	0	0	1
p.Cys629Arg	12	16	0	0	0	1
p.Arg640Cys	12	16	0	0	0	20
p.Cys645Tyr	12	16	0	0	0	1
p.Cys654Tyr	13	16	0	0	0	1
p.Gly667Cys	13	17	9	0	0	2
p.Ser671Cys	13	17	0	0	0	4
p.Cys672Tyr	13	17	0	0	0	1
p.Arg680Cys	13	17	0	0	0	3
p.Tyr710Cys	13	18	0	0	0	1
p.Arg717Cys	14	18	0	0	0	29
p.Cys720Tyr	14	18	0	0	0	1
p.Arg728Cys	14	18	3	0	0	15
p.Ser740Cys	14	19	0	0	0	1
p.Cys758Tyr	14	19	0	0	0	1
p.Arg767Cys	15	19	0	0	0	12
p.Cys769Tyr	15	19	0	0	0	1
p.Arg785Cys	15	20	0	0	0	12
p.Cys796Phe	15	20	0	0	0	1
p.Cys796Ser	15	20	0	0	0	1
p.Cys796Tyr	15	20	0	0	0	1
p.Cys798Tyr	15	20	0	0	0	2
p.Trp802Cys	15	20	0	0	0	6
p.Cys858Trp	17	22	0	0	0	1
p.Gly861Cys	17	22	0	0	0	1
p.Cys873Arg	17	22	0	0	0	1
p.Cys910Tyr	17	23	0	0	0	5
p.Cys910Arg	17	23	0	0	0	2
p.Cys912Ser	17	23	0	0	0	2
p.Tyr916Cys	17	23	0	0	1	10

p.Cys939Ser	18	24	0	0	0	2
p.Cys948Phe	18	24	0	0	0	1
p.Arg951Cys	18	24	0	0	0	1
p.Cys971Tyr	18	25	0	0	0	1
p.Arg985Cys	18	25	0	0	5	0
p.Cys986Arg	18	25	0	0	0	1
p.Cys986Gly	18	25	0	0	0	1
p.Cys988Arg	18	25	0	1	0	0
p.Gly994Cys	18	25	0	0	0	1
p.Cys997Gly	18	25	0	0	8	0
p.Cys997Ser	18	25	0	2	0	0
p.Cys1004Tyr	19	26	0	0	0	1
p.Arg1006Cys	19	26	0	0	5	1
p.Cys1015Arg	19	26	12	0	0	1
p.Tyr1021Cys	19	26	0	0	3	0
p.Arg1031Cys	19	26	2	0	0	3
p.Cys1055Tyr	20	27	0	0	0	1
p.Cys1061Tyr	20	27	0	0	0	3
p.Gly1165Cys	20	27	0	0	0	3
p.Arg1072Cys	20	27	0	2	0	0
p.Arg1076Cys	20	27	4	0	1	1
p.Arg1100Cys	20	28	0	0	0	3
p.Cys1108Arg	20	28	0	0	0	2
p.Cys1110Arg	21	28	0	0	0	4
p.Cys1119Tyr	21	28	0	0	0	6
p.Cys1137Arg	21	29	0	0	0	1
p.Arg1143Cys	21	29	0	0	0	133
p.Tyr1144Cys	21	29	0	0	0	2
p.Cys1148Phe	21	29	0	0	0	1
p.Cys1157Arg	22	29	0	0	0	1
p.Cys1176Tyr	22	30	0	0	0	1
p.Cys1182Trp	22	30	0	0	0	1
p.Arg1190Cys	22	30	0	0	0	21
p.Cys1193Tyr	22	30	0	0	0	1
p.Arg1201Cys	22	30	0	0	0	52
p.Arg1210Cys	22	31	0	0	0	3
p.Cys1222Gly	22	31	0	0	0	212
p.Cys1222Ser	22	31	0	0	3	0
p.Cys1222Arg	22	31	0	0	0	1
p.Arg1231Cys	22	31	2	0	1	255
p.Arg1242Cys	23	31	0	0	0	9
p.Cys1250Arg	23	32	0	0	0	1
p.Cys1261Trp	23	32	0	0	0	1
p.Arg1262Cys	23	32	0	0	0	1
p.Cys1275Ser	23	32	0	0	0	1
p.Gly1283Cys	24	32	0	0	0	1
p.Arg1291Cys	24	33	0	0	0	2
p.Cys1293Phe	24	33	0	0	0	1
p.Cys1313Ser	24	33	0	0	0	1
p.Cys1315Phe	24	33	0	0	0	10
p.Cys1315Trp	24	33	0	0	0	1
p.Cys1324Ser	24	33	0	0	0	2
p.Cys1324Tyr	24	33	0	0	0	1
p.Arg1360Cys	24	34	0	0	0	1
p.Cys1372Trp	24	34	0	0	0	1
Total			**200**	**139**	**95**	**1003**
			434			**1003**