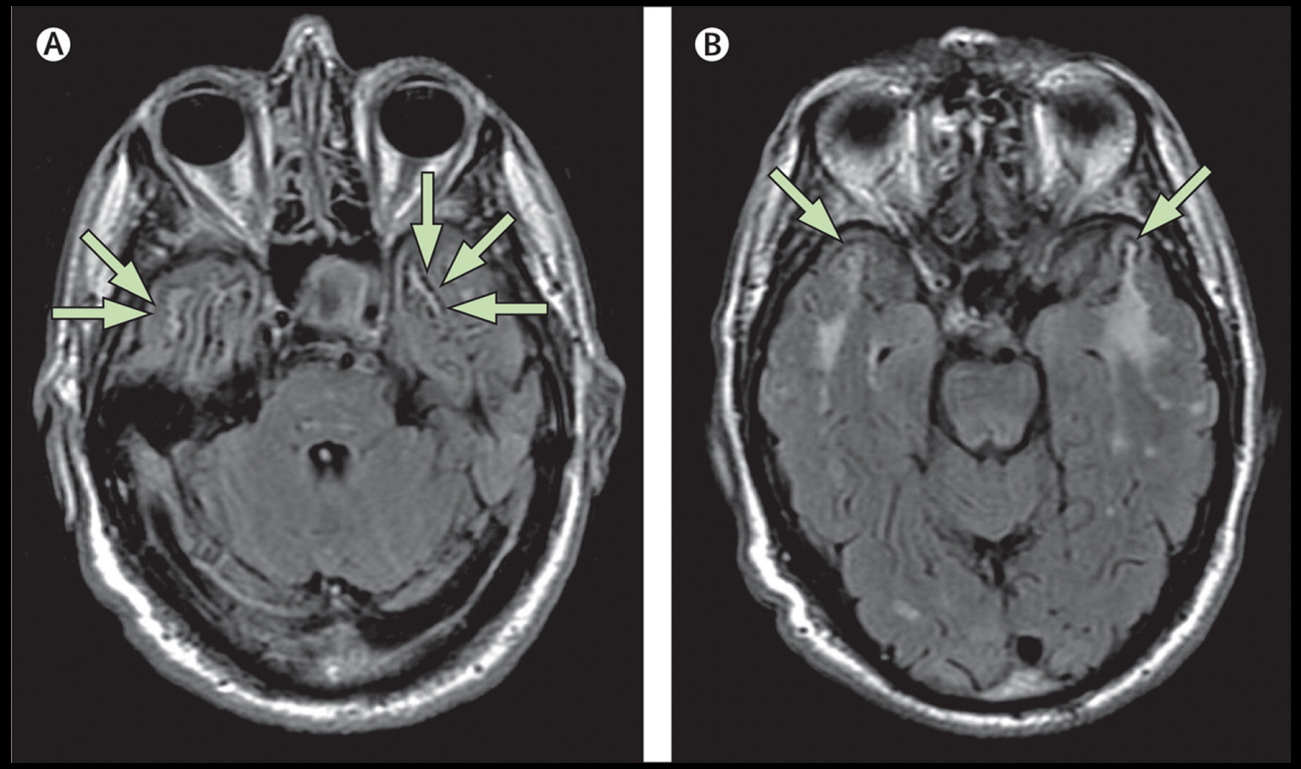
GENOTYPE AND PHENOTYPE DIFFERENCES IN CADASIL AN ASIAN PERSPECTIVE

Jordan Clemsen

CADASIL

- Constituent of Dementia
- Progressive ministrokes
- Comorbidities
- Symptoms
- Tests
- NOTCH3



QUESTIONS ABOUT CADASIL?

True or false; CADASIL may cause manic episodes.

NOTCH3

- 19p13.12
- Exon 2-23
- Exon 25-33
- EGFr contains six cysteine residues that form three pairs of disulfide bonds to maintain the normal NOTCH3 protein's tertiary structure

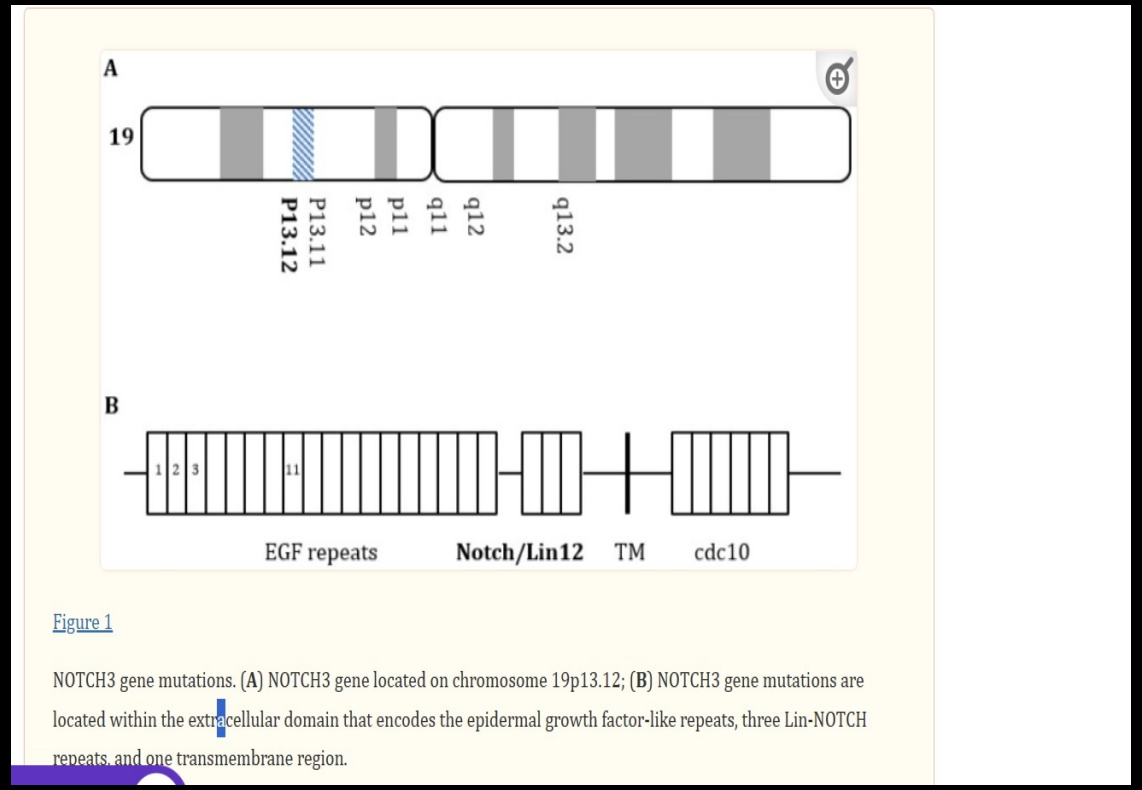


Figure 1

NOTCH3 gene mutations. (**A**) NOTCH3 gene located on chromosome 19p13.12; (**B**) NOTCH3 gene mutations are located within the extracellular domain that encodes the epidermal growth factor-like repeats, three Lin-NOTCH repeats, and one transmembrane region.

SPECTRUM OF MUTATIONS IN BIOPSY-PROVEN CADASIL IMPLICATIONS FOR DIAGNOSTIC STRATEGIES

- 125 German patients
- Skin biopsy
- Central dogma
- 54 distinct mutations
- 96% missense, with some frameshift
- EGF protein 4 = 32.5%

Table. *NOTCH3* Mutations in 120 Biopsy-Proven CADASIL Cases

Exon	Nucleotide Exchange	AA Exchange	EGF Repeat	Frequency of Mutation	Mutations per Exon, No. (%)*
2	205T>G	C43G	1	2	6 (5.0)
	224G>T	C49F	1	1	
	257C>G	S60C	1	1	
	272G>C	C65S	1	2	
3	306T>G	C76W	1	1	13 (10.8)
	317_331del	D80_S84del	2	1	
	337T>C	C87R	2	1	
	346C>T	R90C	2	6	
	356G>T	C93F	2	1	
	401G>A	C108Y	2	1	
	406C>T	R110C	2	2	
4	428G>T	C117F	2	1	70 (58.3)
	446G>T	C123F	3	2	
	475C>T	R133C	3	11	
	480C>G	C134W	3	1	
	499C>T	R141C	3	4	
	509G>C	C144S	3	1	
	509G>A	C144Y	3	1	
	523G>T	G149C	3	1	
	527A>G	Y150C	3	1	
	535C>T	R153C	3	6	
	537_545del	R153_C155del	3	1	
	583C>T	R169C	4	11	
	598T>C	C174R	4	2	
	599G>A	C174Y	4	2	
	622C>T	R182C	4	20	
	625T>A	C183S	4	1	
	626G>T	C183F	4	1	
	631T>C	C185R	4	1	
	659G>T	C194F	4	1	
	697C>T	R207C	5	1	
5	776G>A	C233Y	5	1	5 (4.2)
	797G>C	C240S	6	1	
	811T>C	C245R	6	1	
	857G>A	C260Y	6	1	
	792_836del	D239_D253del	6	1	
6	1033_1034GC>TG	A319C	8	1	9 (7.5)
	1072C>T	R332C	8	3	
	1082C>G	S335C	8	2	
	1088A>G	Y337C	8	3	
7	1214G>C	C379S	9	1	2 (1.7)
	1261T>C	C395R	10	1	
8	1339C>T	R421C	10	1	4 (3.3)
	1361G>A	C428Y	10	2	
	1396T>C	C440R	11	1	
9	1529G>T	C484F	12	1	2 (1.7)
	1562G>A	C495Y	12	1	
10	1609T>C	C511R	13	1	1 (0.8)
11	1724G>A	C549Y	14	1	2 (1.7)
	1750C>T	R558C	14	1	
14	2260C>T	R728C	18	1	1 (0.8)
15	2402G>C	C775S	20	1	1 (0.8)
18	3031C>T	R985C	25	3	3 (2.5)
23	3860G>A	C1261Y	32	1	1 (0.8)

Abbreviations: AA, amino acid; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EGF, epidermal growth factor.
*Percentages do not total 100 because of rounding.

CLINICAL FEATURES AND SPECTRUM OF NOTCH3 VARIANTS IN FINNISH PATIENTS WITH CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

- 294 patients
- Clinical recordings and gene testing from 1996 to 2019
- p.Arg133Cys (68%)
- Different alleles within Finland
- Different clinical symptoms

TABLE 2 Comparison of clinical features between Finnish CADASIL patients carrying the *NOTCH3* variants p.Arg133Cys and p.Tyr1069Cys and other *NOTCH3* variants

	p.Arg133Cys (*n* = 200)	p.Tyr1069Cys (*n* = 52)	Other (*n* = 42)	*p*-value (p.Arg133Cys vs. other)	*p*-value (p.Tyr1069Cys vs. other)
Sex (F/M)	104/96	28/24	23/19		
Family history	118 (59%)	29 (56%)	26 (62%)		
Predictive cases	16 (8%)	7 (13%)	3 (7%)		
Age at the time of predictive testing, mean ± SD	33 ± 10.8	43 ± 10.8	41 ± 18.0		
Clinical features					
Clinical information available	142 (71%)	35 (67%)	40 (95%)		
Age at onset, mean ± SD	46 ± 12.5 (*n* = 68)	53 ± 5.7 (*n* = 8)	49 ± 9.2 (*n* = 27)	.208	.235
Risk factors[a]	32/142 (23%)	6/35 (17%)	13/40 (33%)	.216	.184
Migraine/headache	48/142 (34%)	8/35 (23%)	21/40 (52%)	**.042**	**.010**
Ischemic stroke/TIA	59/142 (42%)	8/35 (23%)	23/40 (58%)	.105	**.004**
ICH	1/142 (1%)	2/35 (6%)	5/40 (13%)	**.002**	.438
Epilepsy	6/142 (4%)	1/35 (3%)	5/40 (13%)	.066	.206
Psychiatric symptom	15/142 (11%)	3/35 (9%)	7/40 (18%)	.272	.321
Cognitive impairment	44/142 (31%)	11/35 (31%)	15/40 (38%)	.449	.633
GOM detected in skin biopsy[b]	11/142 (8%)	1/35 (3%)	7/40 (18%)	.078	.061

Abbreviations: F, female; GOM, granular osmiophilic material; ICH, intracerebral hemorrhage; M, male; SD, standard deviation; TIA, transient ischemic attack.

[a]Risk factors include hypertension, smoking, diabetes, and hyperlipidemia.

[b]GOM was detected in all patients with skin biopsy result available.

POPULATION-SPECIFIC SPECTRUM OF NOTCH3 MUTATIONS, MRI FEATURES AND FOUNDER EFFECT OF CADASIL IN CHINESE

- 21 patients
- qPCR
- 9 different heterozygous point mutations
- Haplotypes with other studies

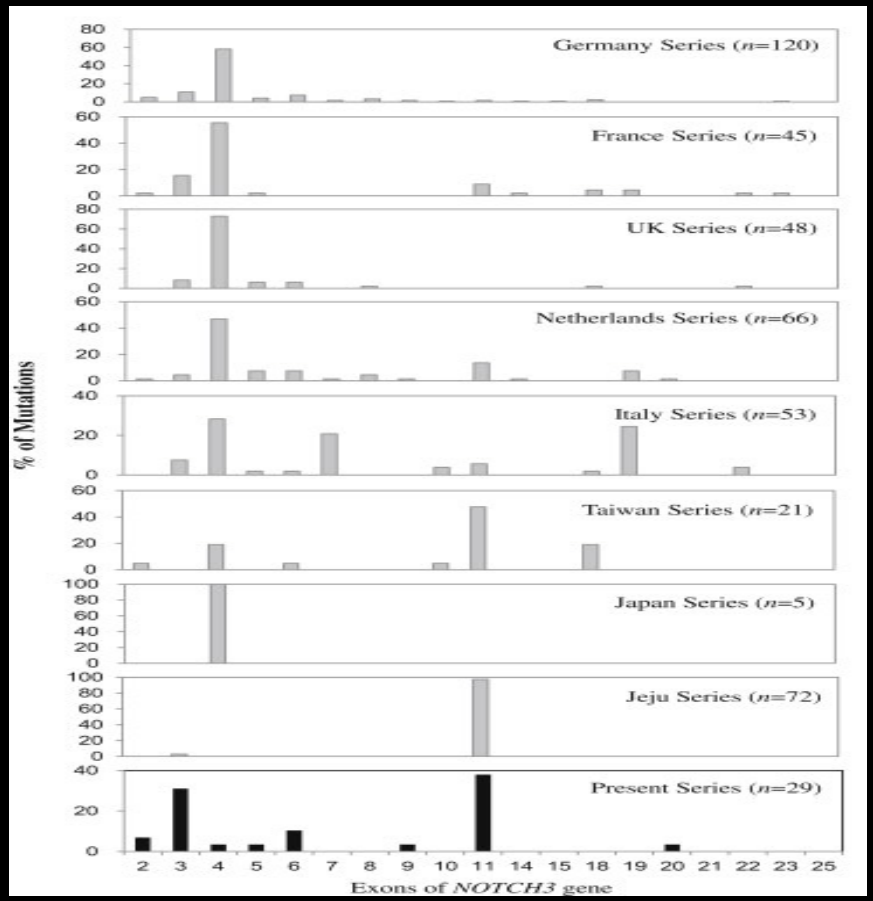
Table 3 Comparison of the mutational spectrum of NOTCH3, MRI features, and initial manifestations of CADASIL

Study	Number of patients (male/female)	Age of onset (± SD)	Mutational spectrum of *NOTCH3*	T2 weighted MRI features of diffuse WMA	Initial clinical manifestations				
					Ischemic events	Cognitive impairment	Psychiatric syndrome	Headaches	Seizures
This study	21 (16/5)	48.6 ± 13.8 (range 20–77)	Exon 2–6: 28.6 % Exon 10: 4.8 % Exon 11 (R544C): 47.6 % Exon 18 (C977S): 19 %	Anterior temporal: 42 % External capsule: 95.2 % ICH: 23.8 %	52.4 %	4.8 %	9.5 %	4.8 %	4.8 %
Markus et al., 2002 [11]	48 (25/23)	35.9 ± 14.6 (range 5–66)	Exon 2–6: 93.8 % Exon 8, Exon 18, Exon 22: 2.1 % each	Anterior temporal: 89 % External capsule: 93 % ICH: not specified	29.2 %	2.1 %	8.3 %	54.2 %	4.2 %
Desmond et al., 1999 [23]	105 (55/50)	36.7 ± 12.9 (range 10–59)	Not specified	Not specified	42.9 %	5.7 %	8.6 %	40 %	2.9 %
Choi et al., 2007 [7]	20 (9/11)	57.2 ± 10.2 (range 43–85)	Exon 2–6: 10 % (R75P) Exon 11: 85 % (R544C: 75 %)	Anterior temporal: 20 % External capsule: 90 % ICH: 25 %	55 %	15 %	0	10 %	0

SD standard deviation; *WMA* white matter abnormalities; *ICH* intracerebral hemorrhage

SPECTRUM OF *NOTCH3* MUTATIONS IN KOREAN PATIENTS WITH CLINICALLY SUSPICIOUS CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

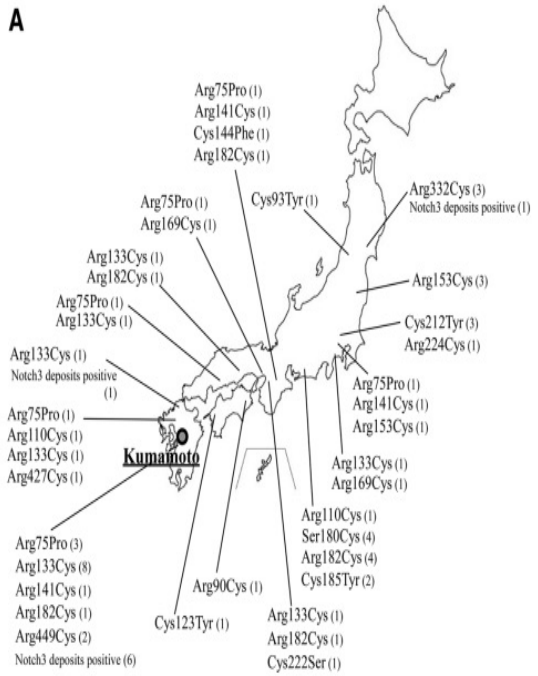
- 156 patients clinically suspicious
- p.R544C most prevalent (8)
- p.R75P (7)
- Jeju Island



GENOTYPIC AND PHENOTYPIC SPECTRUM OF CADASIL IN JAPAN: THE EXPERIENCE AT A REFERRAL CENTER IN KUMAMOTO UNIVERSITY FROM 1997 TO 2014

- 215 patients skin biopsy
- Allele by region
- Different features in MRI
- Different features in immunostaining
- Arg133Cys more WMH

A



B

NOTCH3 mutations		Number of cases
Exon 3 Frequency: 21%	Arg75Pro	8
	Arg90Cys	1
	Cys93Tyr	1
	Arg110Cys	2
	Cys123Tyr	1
Exon 4 Frequency: 69%	Arg133Cys	14
	Arg141Cys	3
	Cys144Phe	1
	Arg153Cys	4
	Arg169Cys	2
	Ser180Cys	4
	Arg182Cys	8
	Cys185Tyr	2
	Cys212Tyr	3
	Cys222Ser	1
	Arg224Cys	1
Exon 6 Frequency: 5%	Arg332Cys	3
Exon 8 Frequency: 5%	Arg427Cys	1
	Arg449Cys	2

Fig. 1 **a** Geographic distribution of CADASIL cases according to *NOTCH3* mutations in Japan. **b** The spectrum of *NOTCH3* mutations found in Japanese CADASIL patients. *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

QUESTIONS ABOUT THE GENETIC SECTION?

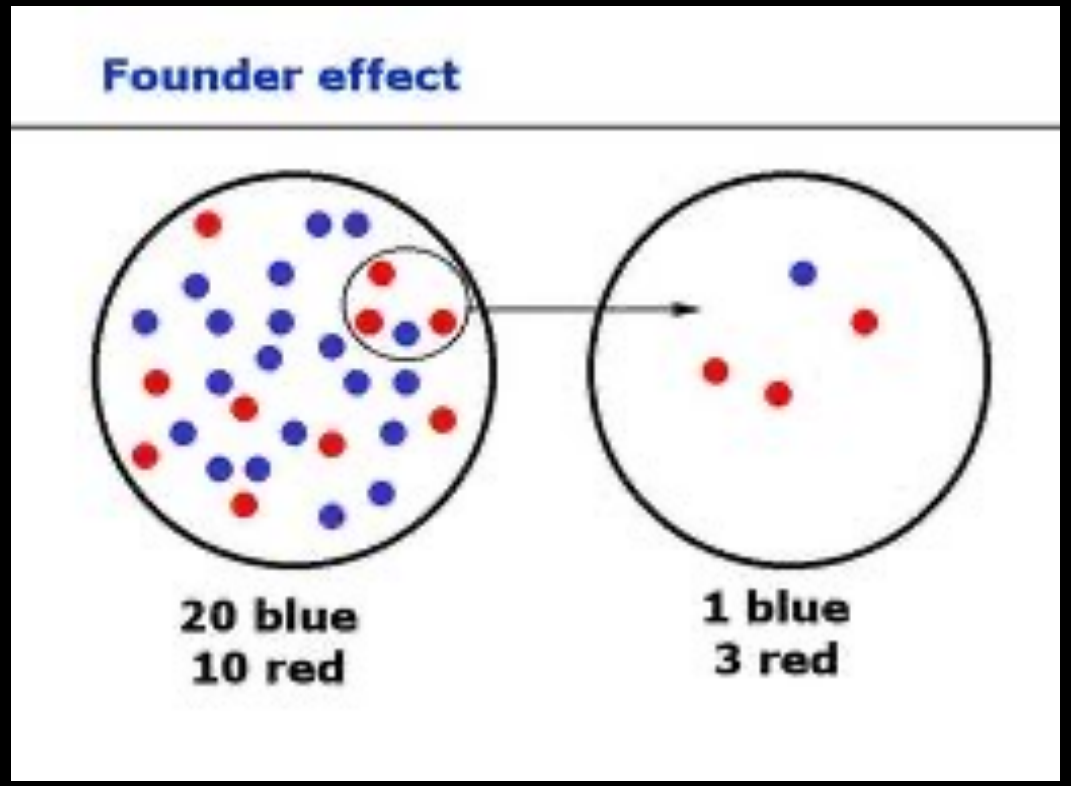
What does EGFr stand for?

DIFFERENCES BY REGION

- Exons 2-6 Europe 60-80%
- Exon 4 = Germany, United Kingdom and France
- Exon 4 = Italy 20%
- Exon 11 = 40-85%
- Exon 11 mutation rare in Japan
- 70 CADSIL, 0 EXON 11 mutations
- Japan variant produces greater disease severity.

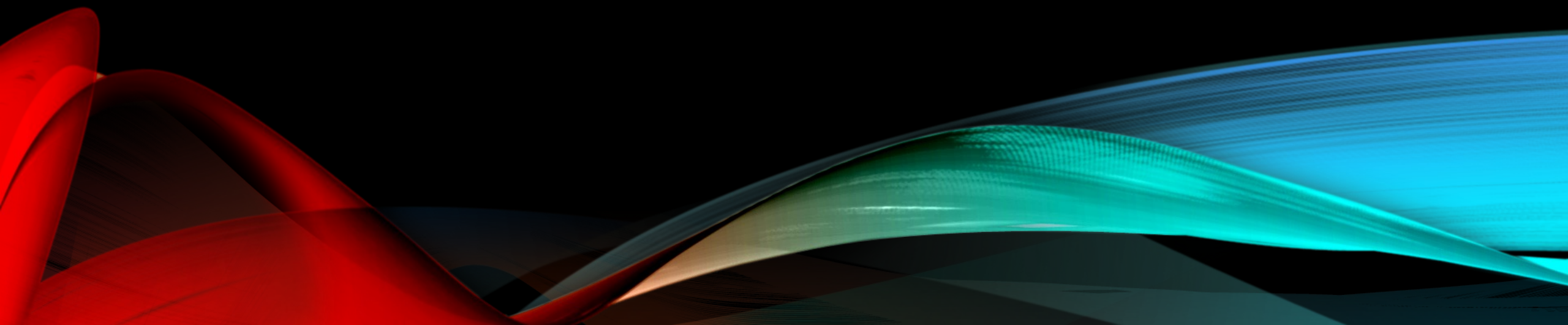
FOUNDER EFFECT

- Genetic variability decreases heterogeneous disorder increases
- California Condor
- California Cougar
- Isolated islands in Asia



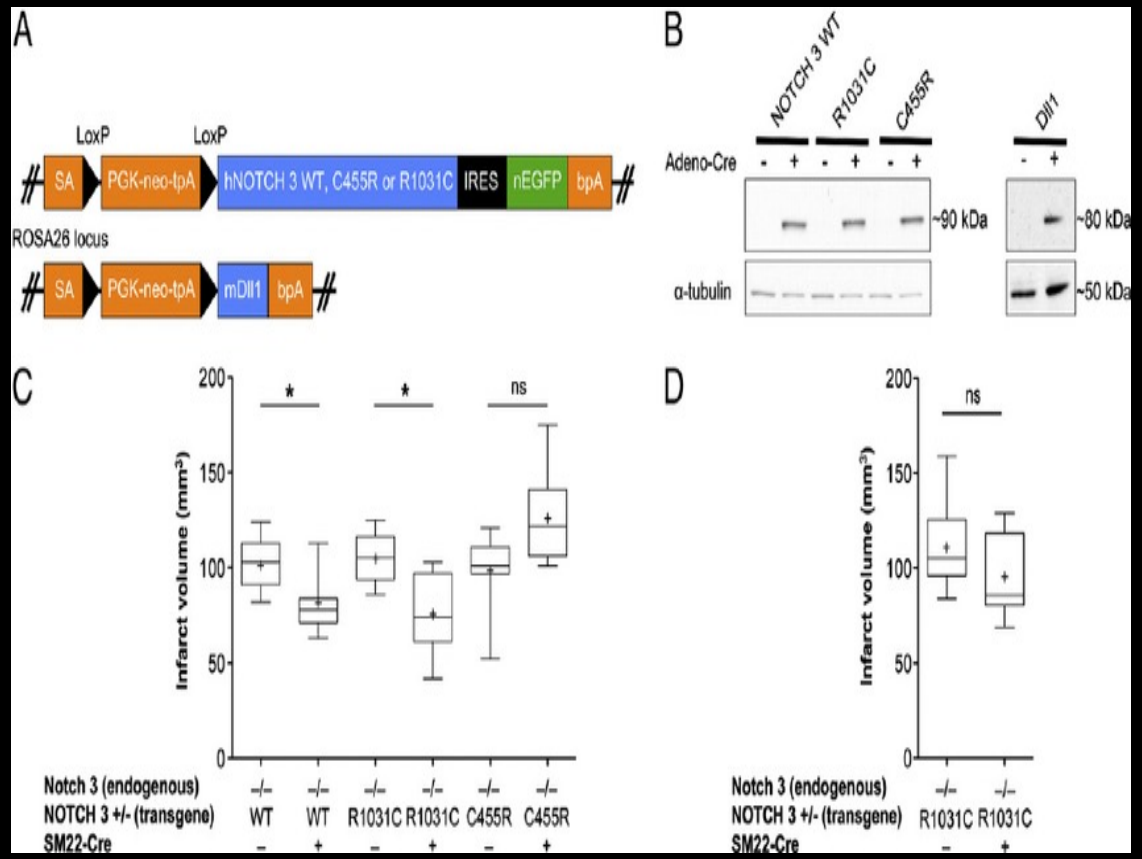
QUESTIONS ABOUT POPULATION ECOLOGY SECTION?

Jordan catches Metagross that are shiny, is this an example of the founder effect why or why not?



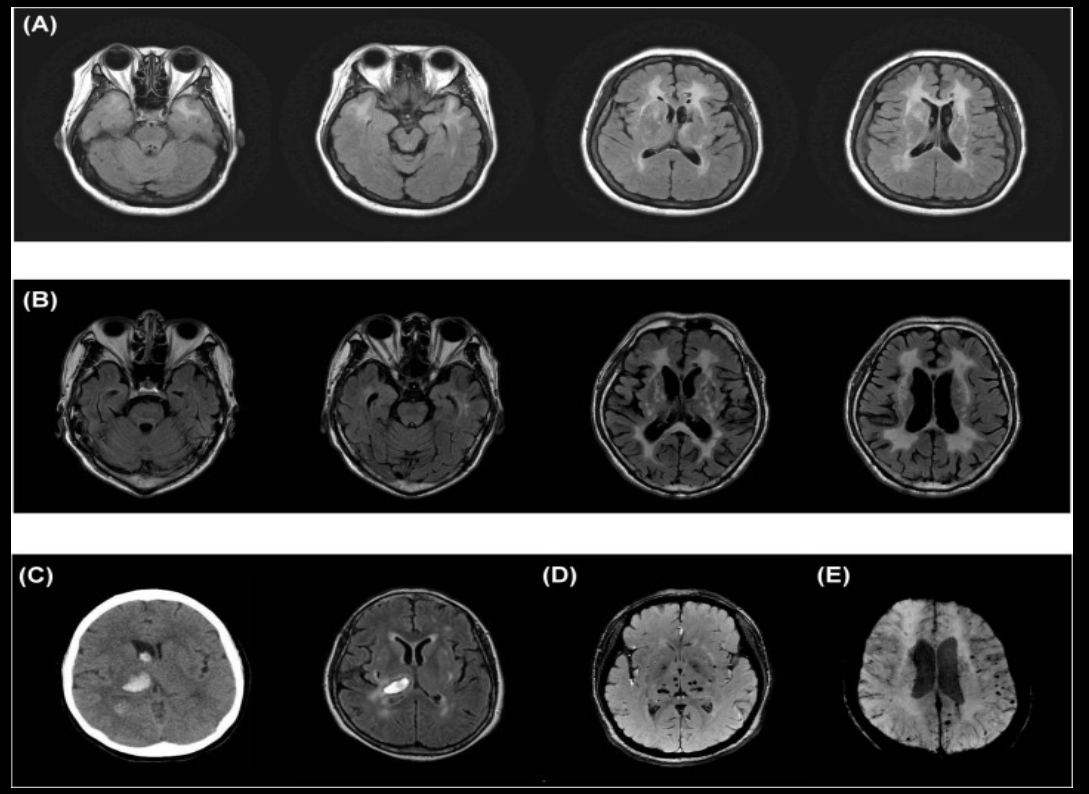
CLINICAL AND GENETIC ASPECTS OF CADASIL

- 34 EGFrs
- Missense mutations typical
- Excess "NOTCH" protein
- Nonsense mutations differ
- frameshift mutations since 2007
- Third cleavage S3 cleavage: γ-secretase–dependent intra-membrane proteolysis



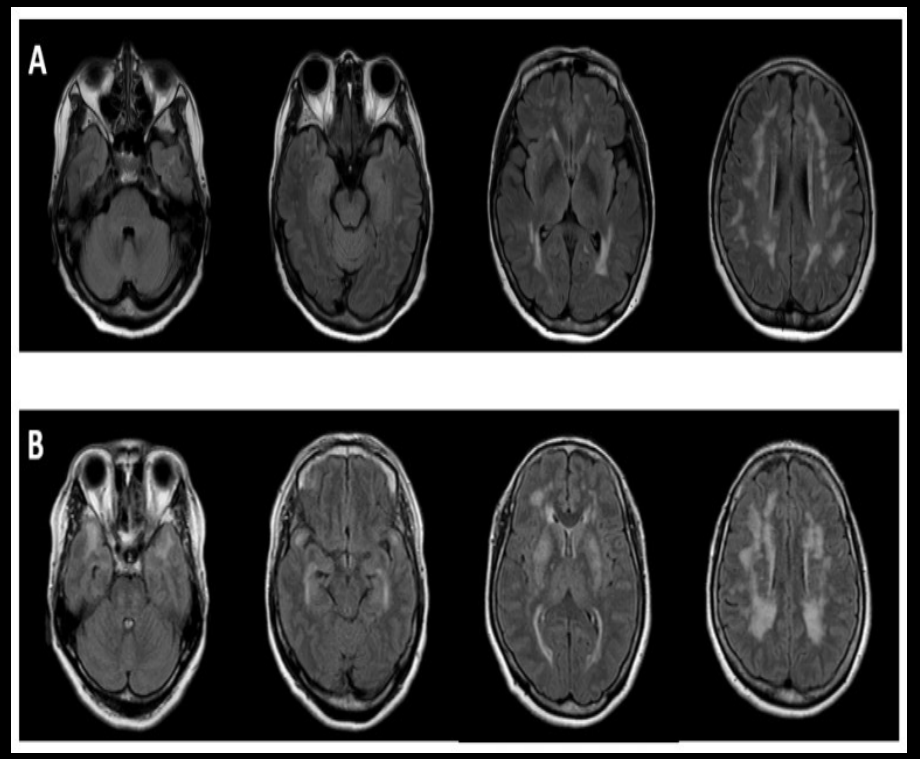
CHARACTERIZATION OF CADASIL AMONG THE HAN CHINESE IN TAIWAN: DISTINCT GENOTYPIC AND PHENOTYPIC PROFILES

- 112 patients
- Exons 2 to 24
- R544C mutation is associated with lower frequency of anterior temporal involvement, later age at onset and higher frequency of cognitive dysfunction.
- CMBs were detected in 87.5% of patients, which were most frequently observed in thalami (62.5%), followed by infra-tentorium regions (46.9%) and basal ganglia (43.8%), and least frequently in corona radiata (31.3%)



IMAGING DIFFERENCES

- Asian lower ATP and EC with WMH
- 89% and 93% Europe and Korea 45%
- Suggested area of mutation and WMH



QUESTIONS ABOUT MRI SECTION?

What CADASIL MRI biomarkers are different between Germany to Japan?