Update on ICH Genetics

Jonathan Rosand and Daniel Woo

ISGC Workshop
Salt Lake City, Utah
April 4, 2014

Funders

- GERFHS (R01NS036695)
- GOCHA (R01NS059727)
- ERICH (U01NS069763)
- NIH SPOTRIAS (P50NS061343)
- U Michigan GCRC (M01 RR000042)
- Registro BASICMAR (PI051737)
- GWALA Project (PI10/02064)
- FEDER/EDRF (RD12/0042)
- Polish Ministry of Education (N402 083934)
- Swedish Research Council (K2010-61X-20378-04-3)
- Wellcome Trust
- Philanthropy

Recent Publications

- **Novel Insights into the Genetics of Intracerebral Hemorrhage.** *Stroke.* 2013 Jun; 44(6 Suppl 1):S137.
- **Apolipoprotein e, Statins, and Risk of Intracerebral Hemorrhage.** *Stroke*. 2013 Nov; Epub ahead of print.
- **The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study Protocol.** *Stroke*. 2013 Oct; Epub 2013 Sep 10.
- **Accuracy of imputation to infer unobserved APOE epsilon alleles in genome-wide genotyping data.** *Eur J Hum Genet.* 2014 Jan 22.
- **Meta-analysis of Genome-Wide Association Studies Identifies 1q22 as a Susceptibility Locus for ICH.** *Am J Hum Genet.* 2014 Mar 18.
- **Current concepts and clinical applications of stroke genetics.** *Lancet Neurol*. 2014 Apr.

Outline

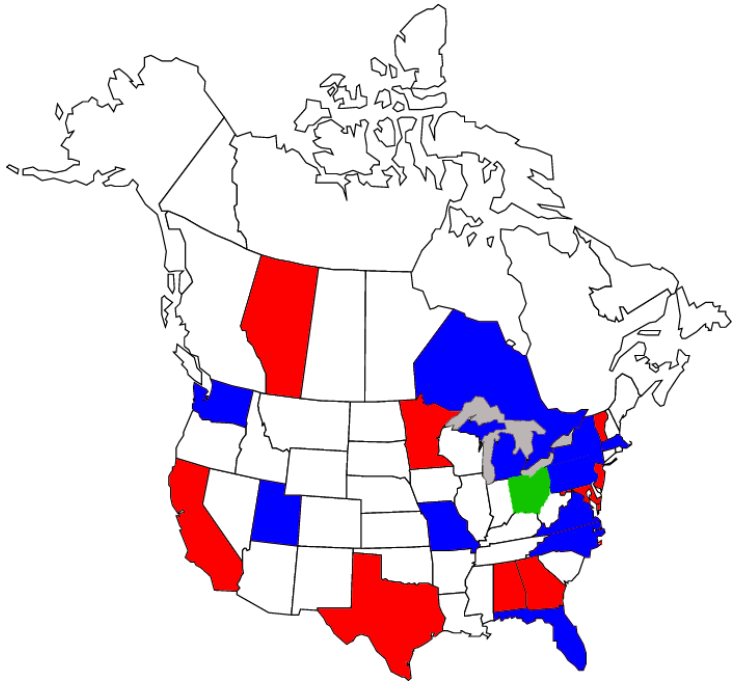
- Update on ISGC study samples, imaging
- ERICH update
- Exome array
- GWAS results
- NIH funding update
- Ongoing recruitment and phenotyping efforts

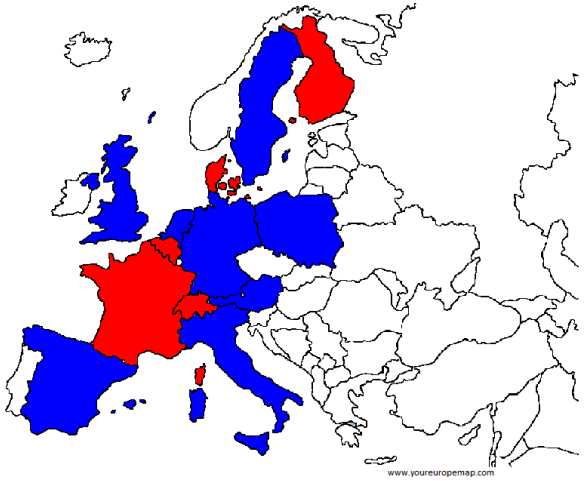
ISGC Study Sample

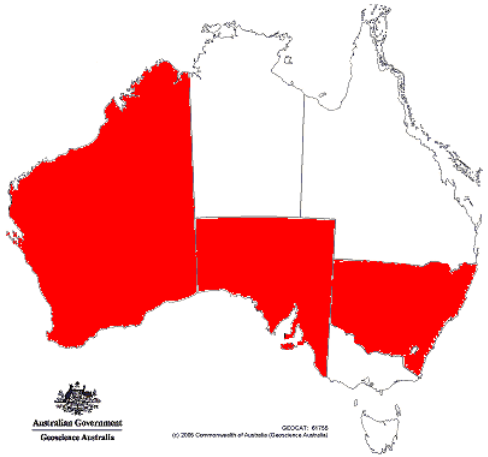
Imaging Update

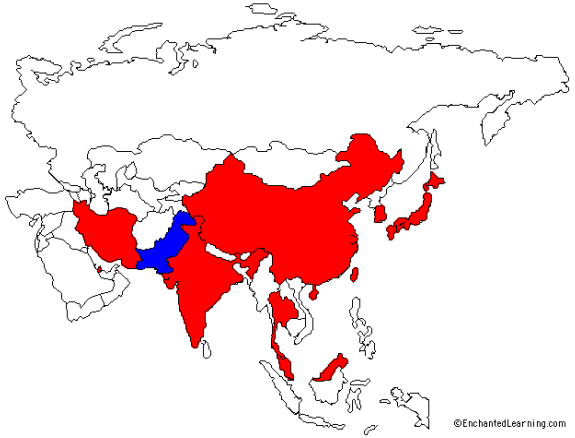
ERICH Update

Current ISGC ICH Samples/Data









ISGC US ICH Samples

Site	Cases	Controls	Cases		Controls	
			Genotyped	Available	Genotyped	Available
MGH (GOCHA)	938	975	740	198	960	113
Cincinnati (ERICH/GERFHS)	2409	1337	1182	1114	879	458
U Penn (RACE)	1446	4035	1446	0	4035	0
Georgetown	143	131	0	143	0	131
Cornell	11	20	8	3	10	10
Duke	126	0	0	126	0	0
U Virginia	119	98	99	20	80	18
Mayo Jacksonville	52	99	50	2	77	22
U Michigan	63	104	58	5	74	30
U Florida	34	49	34	0	29	20
BIDMC	26	45	19	7	27	18
U Washington	18	4	15	3	0	4
U Utah	8	9	3	5	0	9
Wash. U St. Louis	106	109	0	106	0	109

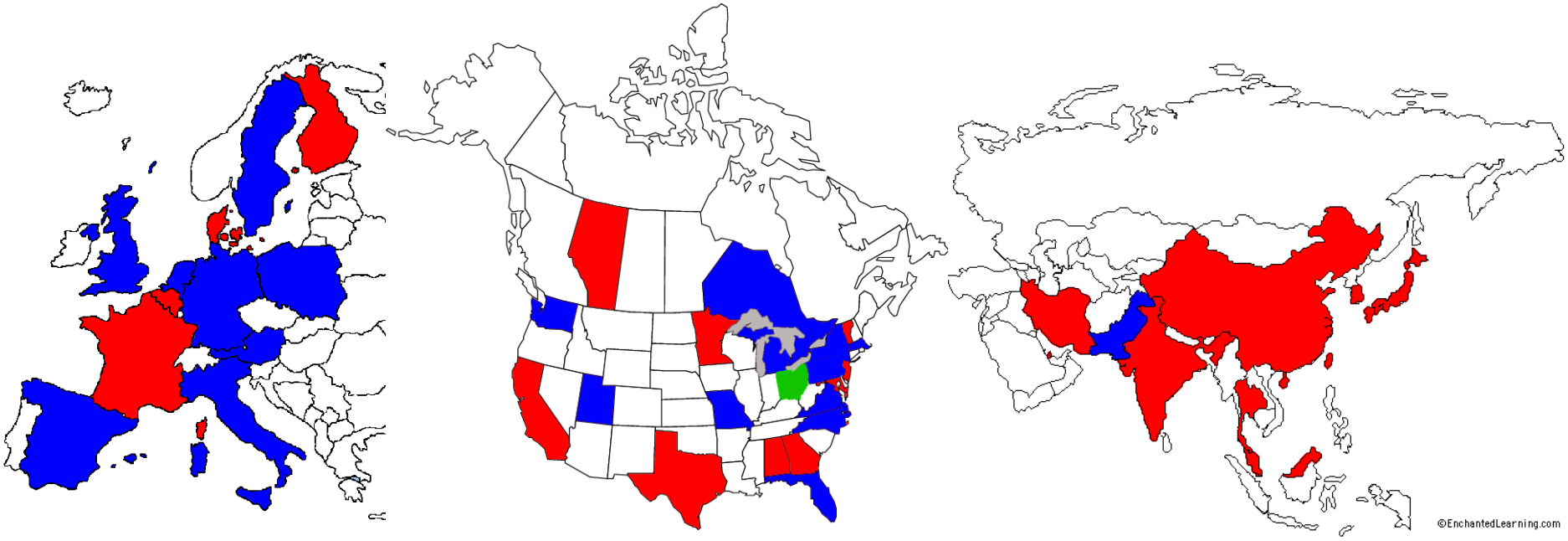
ISGC European ICH Samples

Site	Cases	Controls	Cases		Controls	
			Genotyped	Available	Genotyped	Available
Medical University Graz	62	920	45	17	920	0
Vall d'Hebron Hospital	168	169	124	44	145	24
Lund University	153	167	139	14	155	12
IMIM - Hospital del Mar	161	165	141	20	155	10
LMU Munich	125	KORA	0	125	-	KORA
Radcliffe Hospital, Oxford	62	WTCCC	49	13	-	WTCCC
Imperial College London	24	0	0	24	0	0
University College London	671	696	0	671	0	696
U Edinburgh	111	111*	0	111	111*	0
University of Brescia	201	186	0	201	0	186
UMC Utrecht	160	161	0	160	0	161

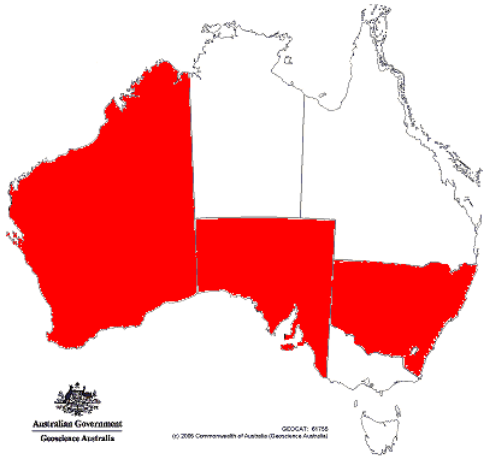
ISGC ICH *in silico* data

Site	Cases	Controls	Type
University of Newcastle	23	1200	Data
CHARGE	277	42840	Summary Stats
Malmo University Hospital	122	122	Data
McMaster University	781	2968	Summary Stats
TOTAL	**1203**	**47130**	

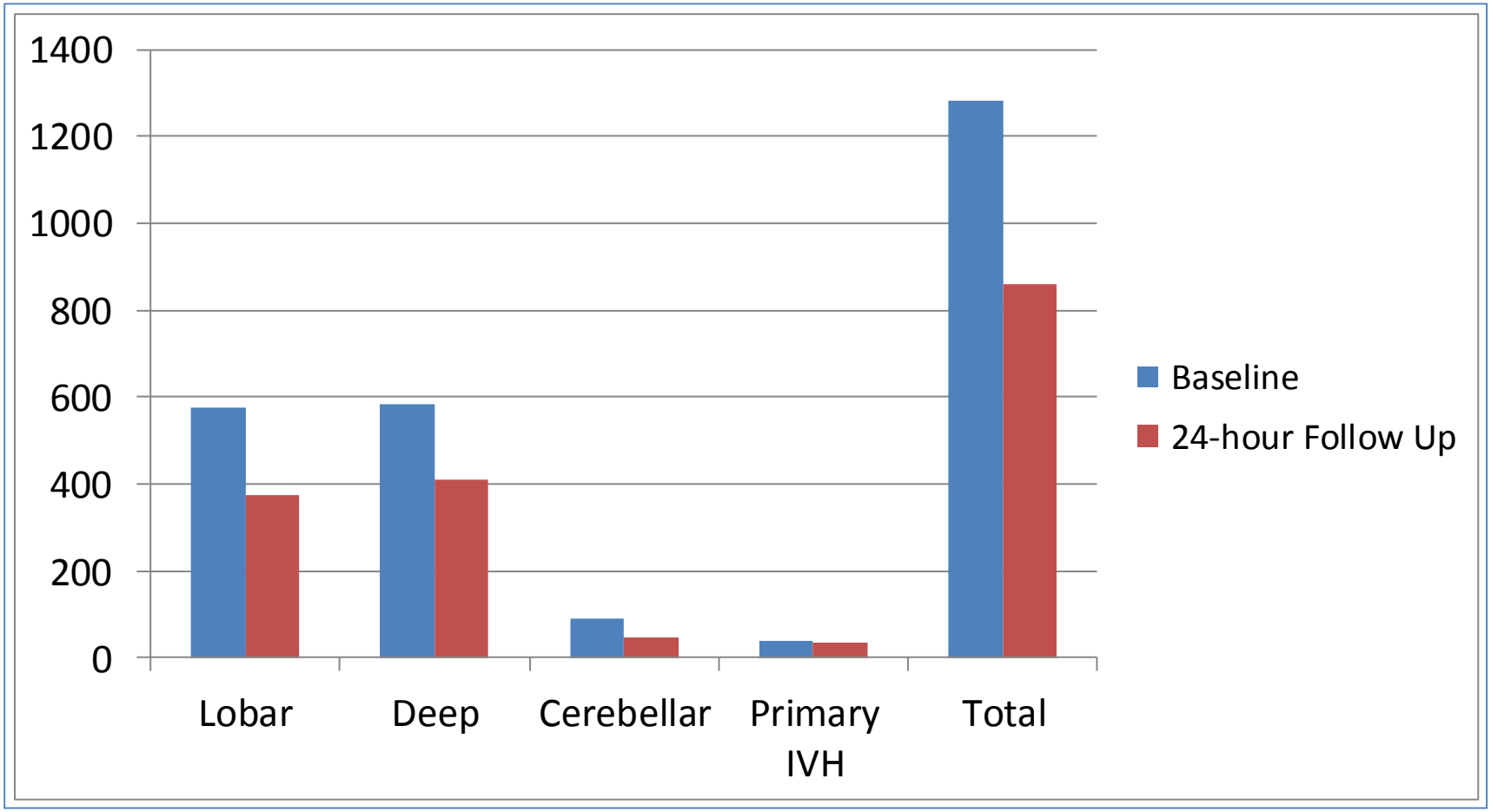
ISGC ICH Samples and Data



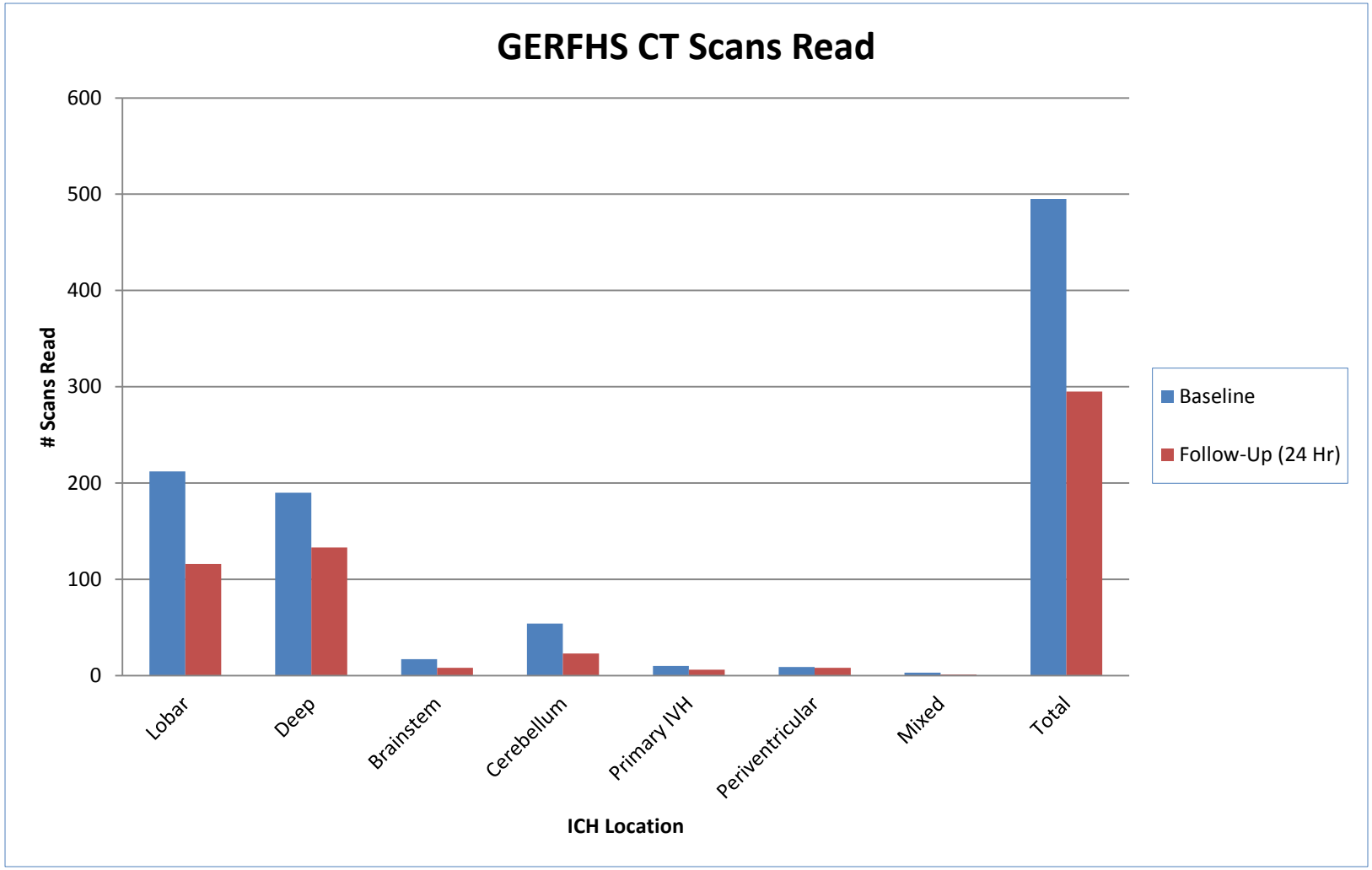
	Cases	Controls	Cases		Controls	
			Genotyped	Available	Genotyped	Available
Samples	7284	9688	4152	3132	7657	2031
Data	1203	5675	1203	-	5675	-
Total	**8487**	**15363**	**5355**	**3132**	**13332**	**2031**



ISGC CT Scans



GERFHS CT scans



- As of 3/21/14
- 2,570 cases enrolled; 108.8% of target for this date
  - 864 (35.3%) black
  - 767 (31.4%) white
  - 813 (33.3%) Hispanic
- 1662 controls enrolled; 83.2% of target
- Overall 4232/4361 expected = 97% of target
- Last 4 weeks, 64 cases, 131 controls; 195 subjects (goal of 120 per month)

Projections

- Cases
  - Black: 2/1/15
  - Hispanic: 12/1/14
  - White: 2/10/15
- Controls
  - Black: 5/9/15
  - Hispanic: 7/28/15
  - White: 10/25/14

ERICH Imaging

- Of 2205 subjects with CT sent, 2,845 scans read; over 80% have a 24 hour follow-up CT scan for hematoma expansion
- 1010 MRIs received, 780 with GRE, DWI, FLAIR although some post-op scans

ERICH Summary

- Have recruited 85.6% of total cases and ahead of schedule
- Have recruited 55.4% of total controls and a little behind schedule but picking up pace
- Most cases have a follow-up CT scan
- About a third have MRI with GRE, DWI and FLAIR
- All have blood sample with DNA extracted and many have plasma stored

ICH Exome Array Studies

Discoveries using Exome Chip

ARTICLES

nature genetics

Systematic evaluation of coding variation identifies a candidate causal variant in *TM6SF2* influencing total cholesterol and myocardial infarction risk

ARTICLE

Association of Low-Frequency and Rare Coding-Sequence Variants with Blood Lipids and Coronary Heart Disease in 56,000 Whites and Blacks

Cohort Characteristics: GOCHA & GERFHS

Variables	GOCHA		GERFHS	
	Cases (n = 442)	Controls (n = 480)	Case (n=372)	Control (n=340)
Age, mean (SD)	74 (10)	73 (8)	69 (15)	67 (12)
Female, n (%)	235 (50)	233 (49)	183 (48)	143 (42)
Deep ICH	---	---	232 (62)	---
Lobar ICH	442 (100)	---	140 (37)	---
Definite/probable CAA, n (%)	222 (50)	---	---	---

ICH Exome – Next Steps

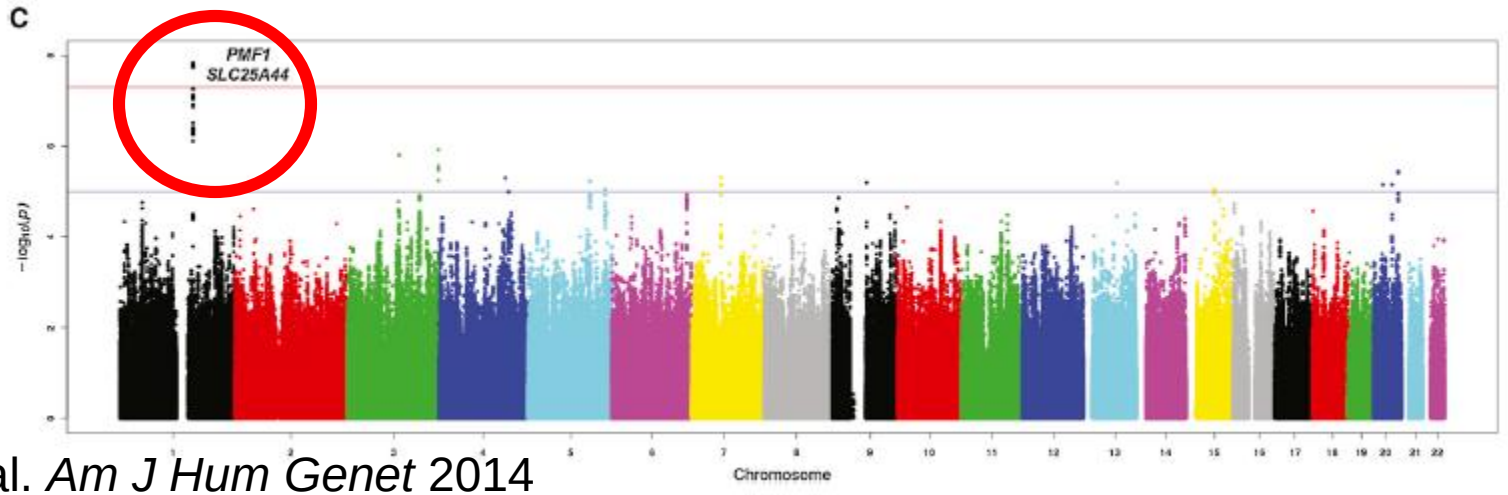
- Assemble existing genotype data
  - Malmo
  - McMaster University

- Further exome genotyping?

ICH GWAS Meta-analysis Report

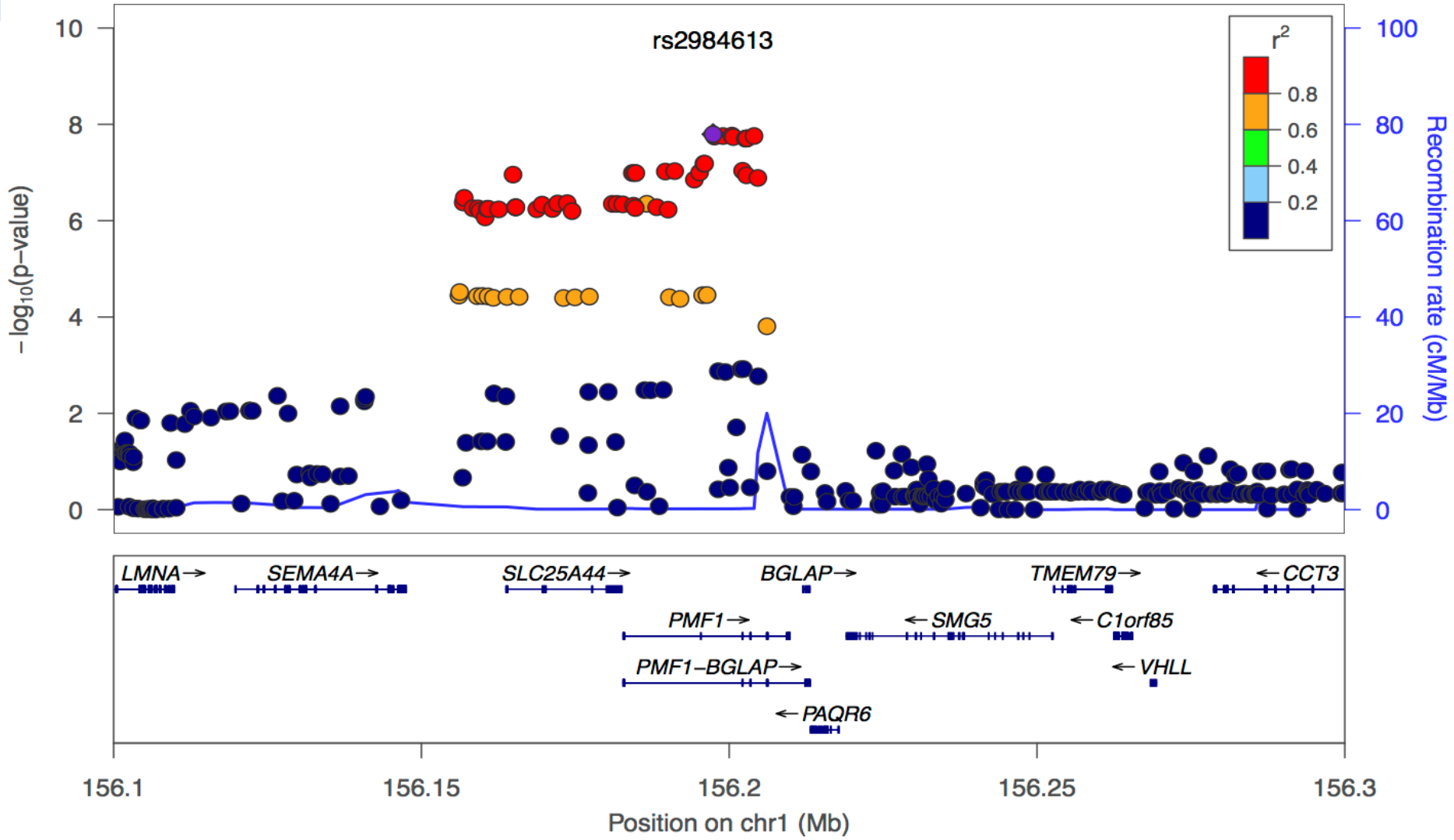
Meta-Analysis of Genome-Wide Association Studies Identifies 1q22 as a Susceptibility Locus for Intracerebral Hemorrhage

Daniel Woo,[1,34,*] Guido J. Falcone,[2,3,4,5,6,34] William J. Devan,[2,3,4,5] W. Mark Brown,[7] Alessandro Biffi,[2,3,4,5] Timothy D. Howard,[7] Christopher D. Anderson,[2,3,4,5] H. Bart Brouwers,[2,3,4,5] Valerie Valant,[2,3,4,5] Thomas W.K. Battey,[2,3,4,5] Farid Radmanesh,[2,3,4,5] Miriam R. Raffeld,[2,3,4,5] Sylvia Baedorf-Kassis,[2,3,4,5] Ranjan Deka,[8] Jessica G. Woo,[9] Lisa J. Martin,[10] Mary Haverbusch,[1] Charles J. Moomaw,[1] Guangyun Sun,[8] Joseph P. Broderick,[1] Matthew L. Flaherty,[1] Sharyl R. Martini,[1] Dawn O. Kleindorfer,[1] Brett Kissela,[1] Mary E. Comeau,[7] Jeremiasz M. Jagiella,[11] Helena Schmidt,[12] Paul Freudenberger,[12] Alexander Pichler,[13] Christian Enzinger,[13,14] Björn M. Hansen,[15,16] Bo Norrving,[15,16] Jordi Jimenez-Conde,[17,18] Eva Giralt-Steinhauer,[17,18] Roberto Elosua,[17,18] Elisa Cuadrado-Godia,[17,18] Carolina Soriano,[17,18] Jaume Roquer,[17,18] Peter Kraft,[6] Alison M. Ayres,[4] Kristin Schwab,[4] Jacob L. McCauley,[19] Joanna Pera,[11] Andrzej Urbanik,[20] Natalia S. Rost,[2,3,4,5] Joshua N. Goldstein,[21] Anand Viswanathan,[4] Eva-Maria Stögerer,[13] David L. Tirschwell,[22] Magdy Selim,[23] Devin L. Brown,[24] Scott L. Silliman,[25] Bradford B. Worrall,[26] James F. Meschia,[27] Chelsea S. Kidwell,[28] Joan Montaner,[29] Israel Fernandez-Cadenas,[29,30] Pilar Delgado,[29] Rainer Malik,[31,32] Martin Dichgans,[31,32] Steven M. Greenberg,[4] Peter M. Rothwell,[33] Arne Lindgren,[15,16] Agnieszka Slowik,[11] Reinhold Schmidt,[13] Carl D. Langefeld,[7,35] and Jonathan Rosand[2,3,4,5,35,*] on behalf of the International Stroke Genetics Consortium



Woo et al. *Am J Hum Genet* 2014

Non-Lobar ICH



PMF1: polyamine-modulated factor 1

Function: is required for normal chromosome alignmer and segregation during mitosis.

SLC25A44

solute carrier family 25, member 44

mitochondrial carrier proteins

Overlap with WMH

Genome-wide association results for SNPs associated with WMH burden at $P<1\times10^{-5}$.

SNP ID	Chr	Position (build 36.3)	Risk allele	Allele freq.	SNP function	Nearest gene/transcript	Distance from gene (kb)	Direction of association in each cohort*	P	Number of additional SNPs associated at $P<10^{-5}$	Number of additional SNPs associated at $P<10^{-4}$
rs3744028	17	71400267	C	0.18	Intronic	TRIM65	0	+++++++	4.0×10^{-9}	8	8
rs1055129	17	71384543	G	0.30	Intronic	TRIM47	0	+++++−+	4.1×10^{-8}	13	18
rs7894407	10	105166169	T	0.63	Intronic	PDCD11	0	++−++++	6.1×10^{-7}	4	13
rs1892525	1	68128202	G	0.69	Within transcribed sequence	RP11-518D3.1	0	+++++++	7.2×10^{-7}	10	29
rs10814323	9	36021610	A	0.21	Intergenic	RECK	−5.3	+++++++	1.7×10^{-6}	0	17
rs6992136	8	15786858	G	0.85	Intergenic	RPL32P19	−58.1	+−+++++	3.2×10^{-6}	8	9
rs11731436	4	66437855	C	0.64	Intergenic	AC097110.1	−82.1	+++++++	3.3×10^{-6}	0	22
rs1052053	1	154468797	A	0.62	Missense	PMF1	0	+++++−−	5.0×10^{-6}	2	12
rs2167089	3	29009407	G	0.73	Intronic	AC098970.2	0	+++++++	6.0×10^{-6}	0	0
rs10012573	4	110168035	A	0.94	Intronic	COL25A1	0	++++++−	6.0×10^{-6}	0	0
rs11625623	14	51829096	G	0.23	Intergenic	PTGDR	15.9	+++++++	7.7×10^{-6}	0	4
rs16901064	5	31422754	C	0.84	Intergenic	RNASEN	13.6	+++++++	7.8×10^{-6}	2	2
rs6945846	7	114190152	C	0.20	Intergenic	FOXP2	71.8	+++++++	7.9×10^{-6}	0	31
rs11629135	14	63982864	G	0.93	Intronic	MTHFD1	0	+++++++	8.6×10^{-6}	0	10
rs9410016	9	137360523	G	0.41	Intergenic	C9orf62	−14.4	+++++++	9.7×10^{-6}	0	5

*in alphabetical order: AGES-Reykjavik, ARIC, ASPS, CHS, FHS, RS-I, and RS-II

Fornage et al. Ann. Neurol. 2011;69:928–939.

ICH: A large role for genetics

	Cases	Controls	Heritability Estimate (%)	p
All ICH	789	876	**29**	0.001
Non-lobar ICH	366	876	**30**	0.023
Lobar ICH	338	876	**48**	0.002

But only 1 genome-wide significant locus discovered so far

Devan et al. 2013

GWAS Meta-Analysis Phase II

- Lobar and Non-lobar
  - ISGC
  - GERFHS
  - RACE
  - CROMIS
  - ERICH (replication)

Status Report: NIH Funding Applications

Rosand and Woo

- Not funded
  - GoAHEAD I
  - GoAHEAD II
  - US-Chinese Collaboration
- Under review
  - GERFHS IV
- In preparation
  - ERICH recovery
  - ERICH gene

ISGC Recruitment and Phenotyping Efforts

Objectives

- To collect, generate, and share phenotype and genotype data on cases and controls

- Requirement for any NIH grant application
  - Share genetic and limited phenotype data w/ dbGAP

- The MGH Ethics Committee requests:
  - English translation of applicable informed consent
  - Letter signed on behalf of local Ethics Board verifying to the Partners IRB the requirements necessary to share data.

How to participate

- Enroll cases and controls
- Characterize according to ISGC standards
- Return regulatory paperwork
- ISGC Phenotypes
  - basic demographics
  - medical history
  - warfarin related lab values
  - hemorrhage locations & volumes
  - outcome data
  - APOE genotypes

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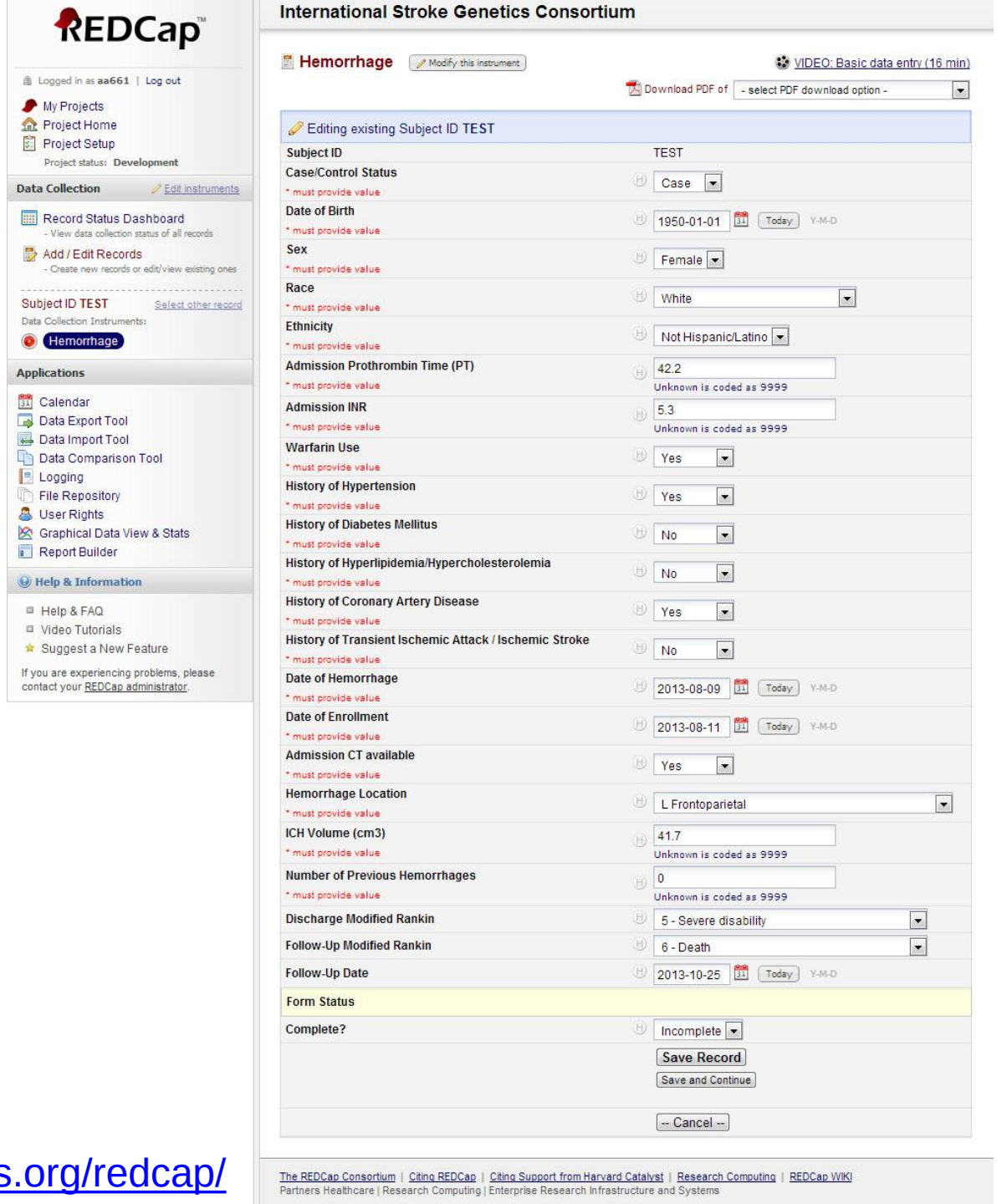

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