"Arquivo Brasileiro Online de Mutações" (ABraOM) can contribute to the neuromuscular genetics field?

Human **G**enome and Stem **Cell** Research Center

Prof. Dr. Michel S. Naslavsky

Conflicts of interest

Nothing to declare

HUG-CELL

Since 1960s, enrolling families affected by genetic disorders (mainly neuromuscular and neurodegenerative)

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	

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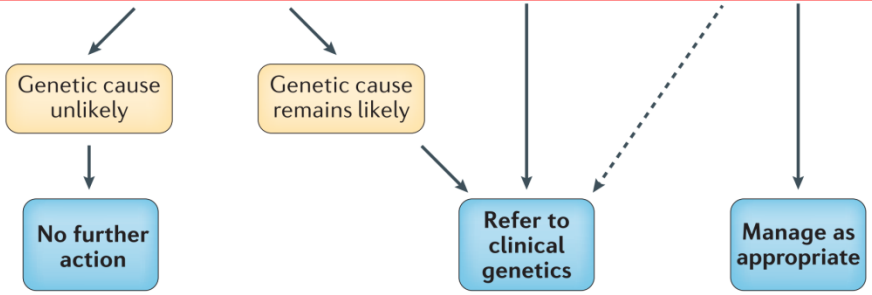
SPECIAL ARTICLE

WILEY

Updated recommendation for the benign stand-alone ACMG/AMP criterion

Rajarshi Ghosh[1,2] | Steven M. Harrison[3,4] | Heidi L. Rehm[4,5,6] | Sharon E. Plon[1,2] | Leslie G. Biesecker[7] | on behalf of ClinGen Sequence Variant Interpretation Working Group*



Wright et al, Nature Reviews Genetics 2018

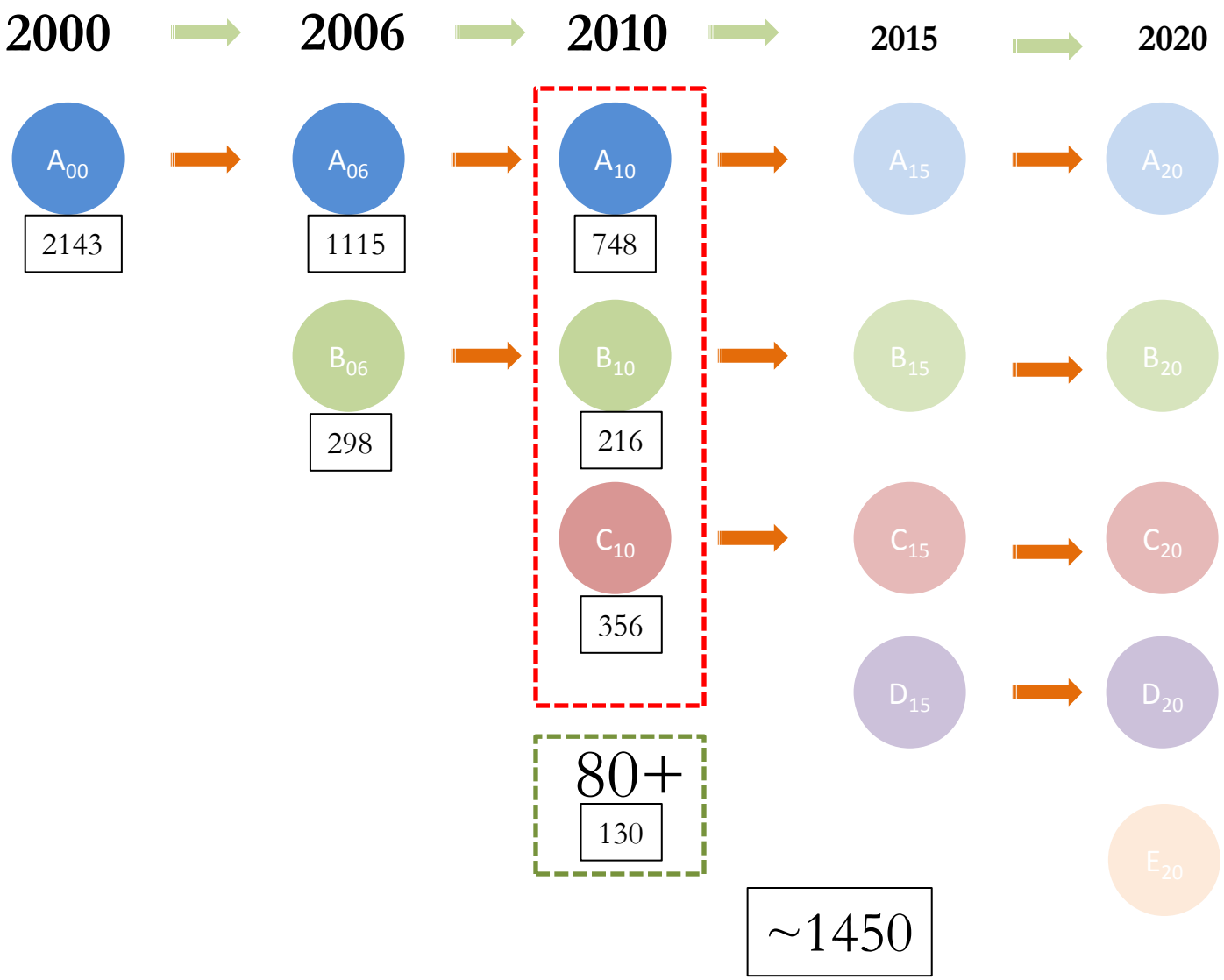
Goals

Database of reference controls with ancestry matching

Tool for interpretation of variant pathogenicity

Collaboration for studies in healthy aging

SABE & 80+


2000
2006
2010
2015
2020
A00
2143
A06
1115
A10
748
A15
A20
B06
298
B10
216
B15
B20
C10
356
C15
C20
D15
D20
80+
130
E20
~1450

Dr. Mayana Zatz
USP

Survey
(150 pages)

Dr. Maria Lucia Lebrão & Dr. Yeda Duarte
USP

Genomics

Blood analyses

SABE

Dr. Edson Amaro
USP/HIAE

Brain MRI

Biometry & Functional tests

Databases

Exomic variants of an elderly cohort of Brazilians in the ABraOM database

Michel Satya Naslavsky, Guilherme Lopes Yamamoto, Tatiana Ferreira de Almeida, Suzana A. M. Ezquina, Daniele Yumi Sunaga, Nam Pho, Daniel Bozoklian, Tatiana Orli Milkewitz Sandberg, Luciano Abreu Brito, Monize Lazar, Danilo Vicensotto Bernardo, Edson Amaro Jr, Yeda A. O. Duarte, Maria Lúcia Lebrão, Maria Rita Passos-Bueno and Mayana Zatz

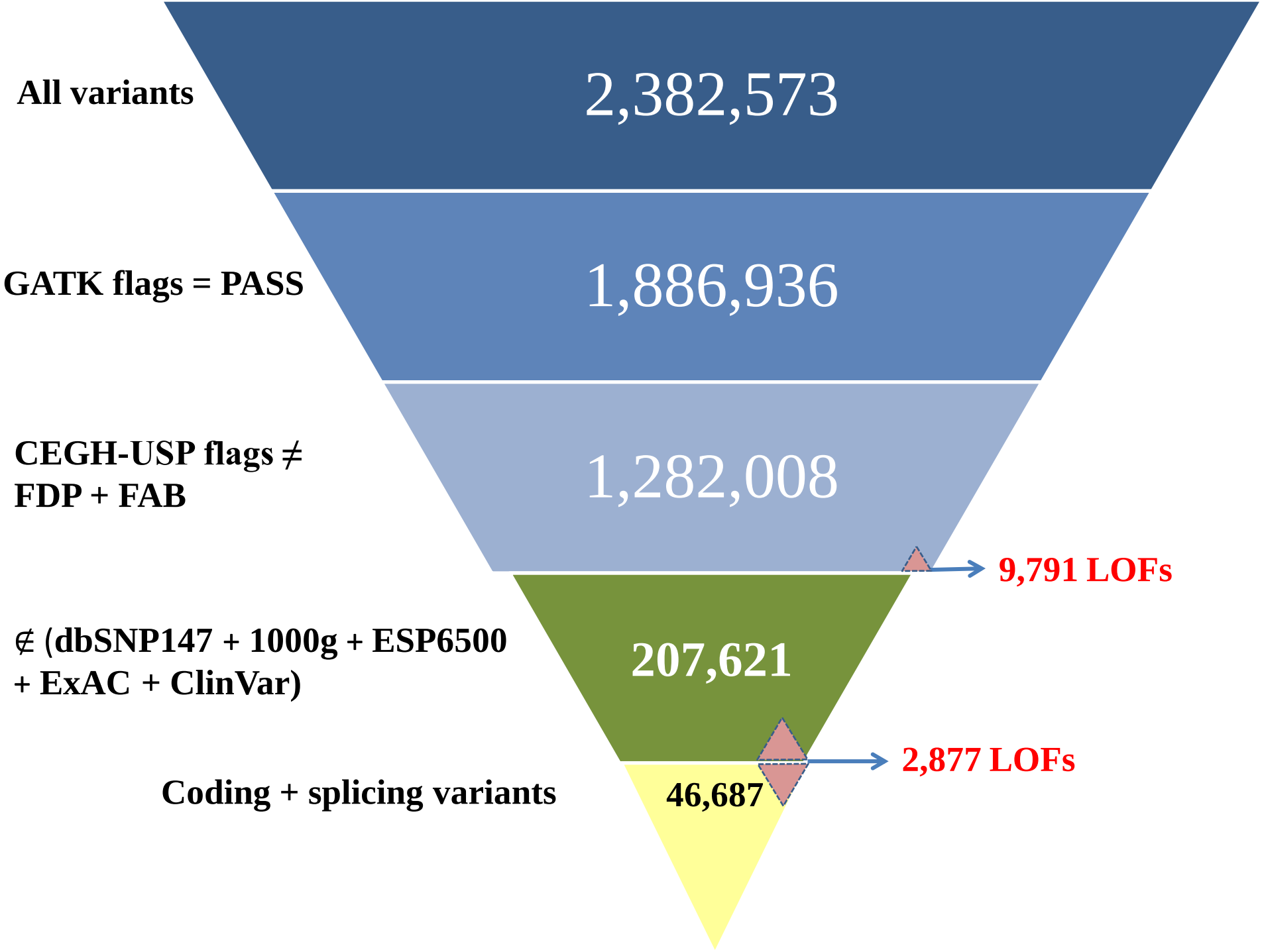
Accepted manuscript online: 23 MAR 2017 03:50AM EST | DOI: 10.1002/humu.23220

Abstract | **Article** | **PDF(769K)**

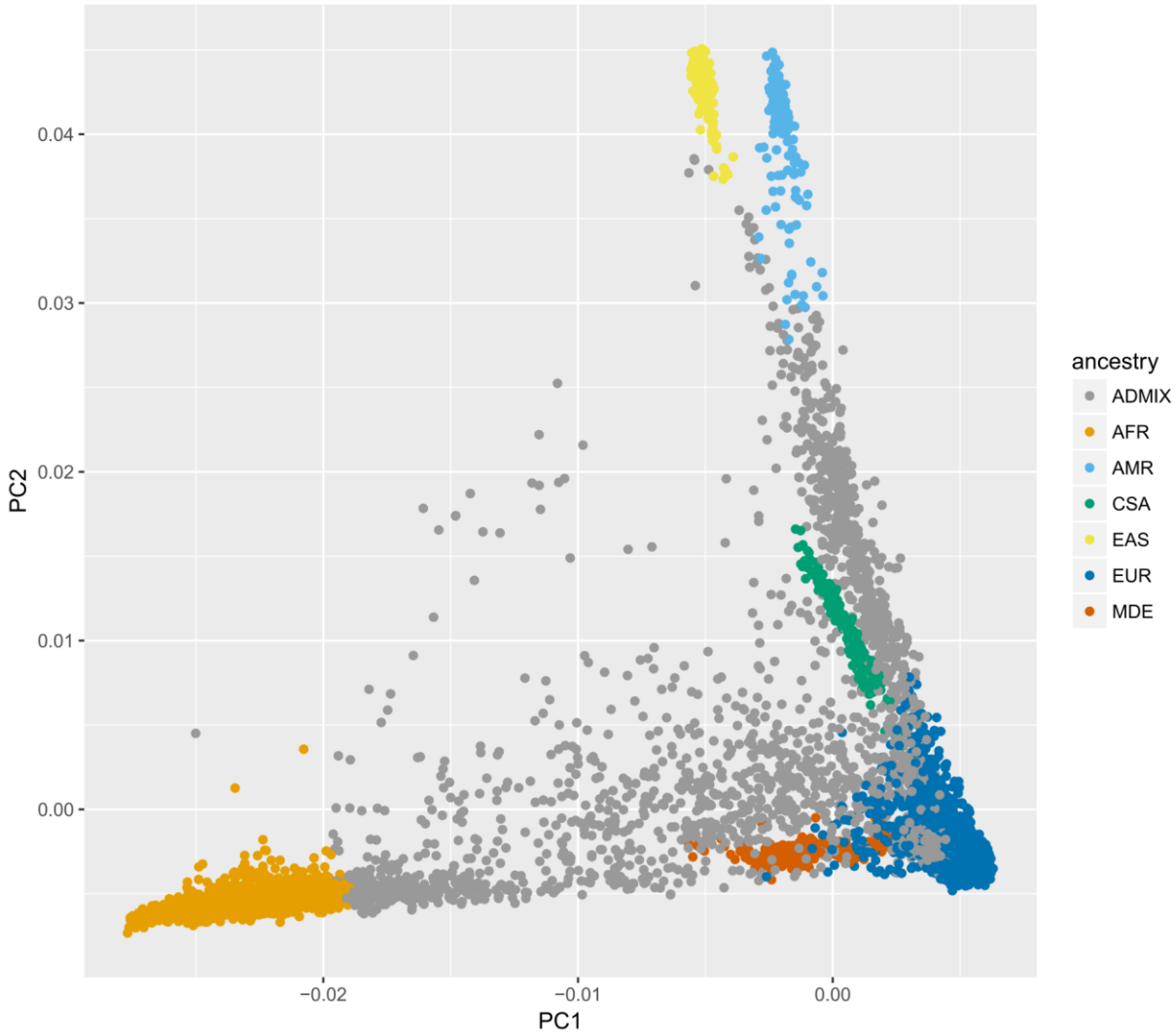
Human Mutation
Variation, Informatics, and Disease

OFFICIAL JOURNAL HGV HUMAN GENOME VARIATION SOCIETY

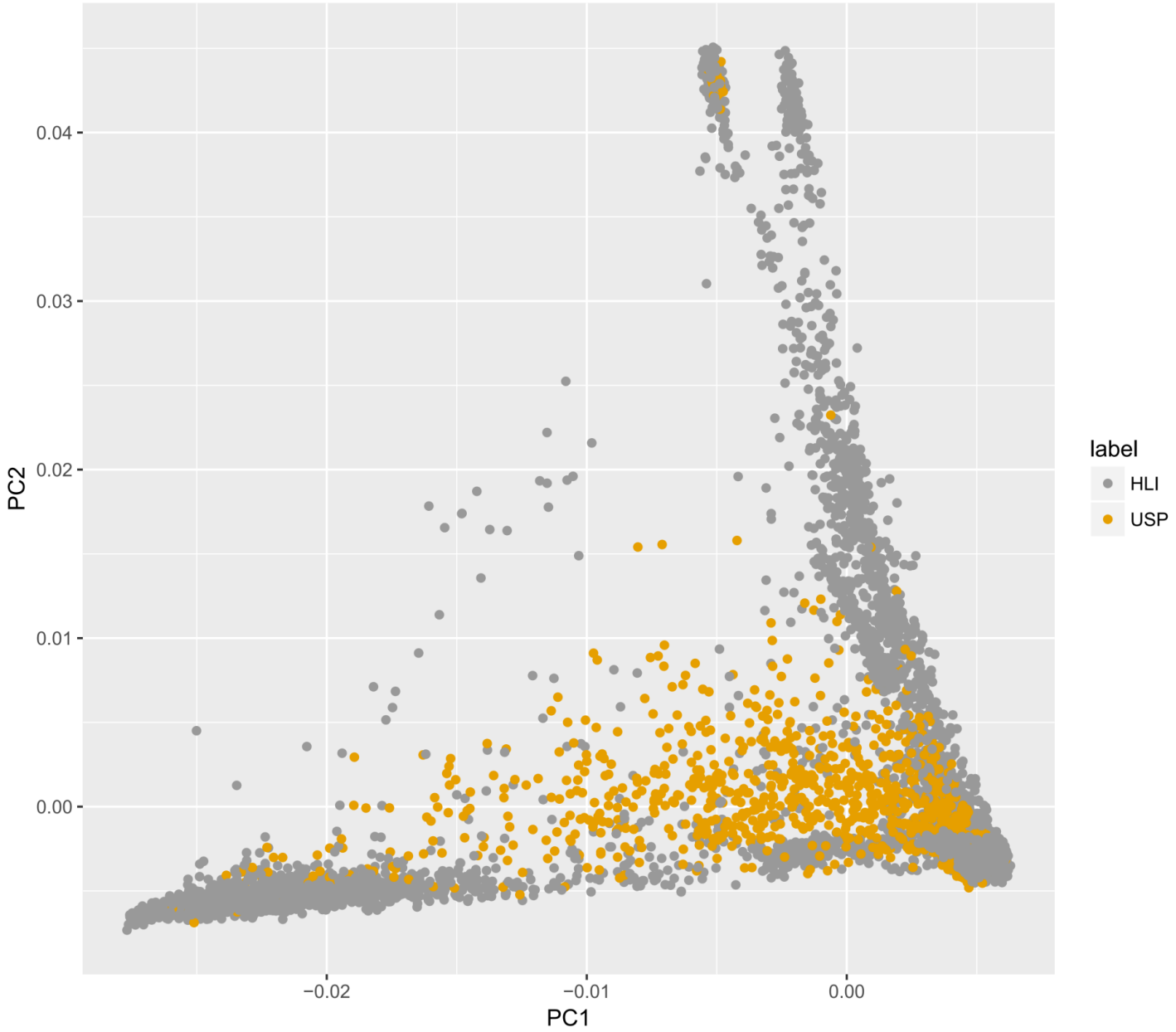
ABraOM v1: 609 WES (SNVs+INDELs)


All variants
2,382,573
GATK flags = PASS
1,886,936
CEGH-USP flags ≠
FDP + FAB
1,282,008
9,791 LOFs
∉ (dbSNP147 + 1000g + ESP6500
+ ExAC + ClinVar)
207,621
2,877 LOFs
Coding + splicing variants
46,687

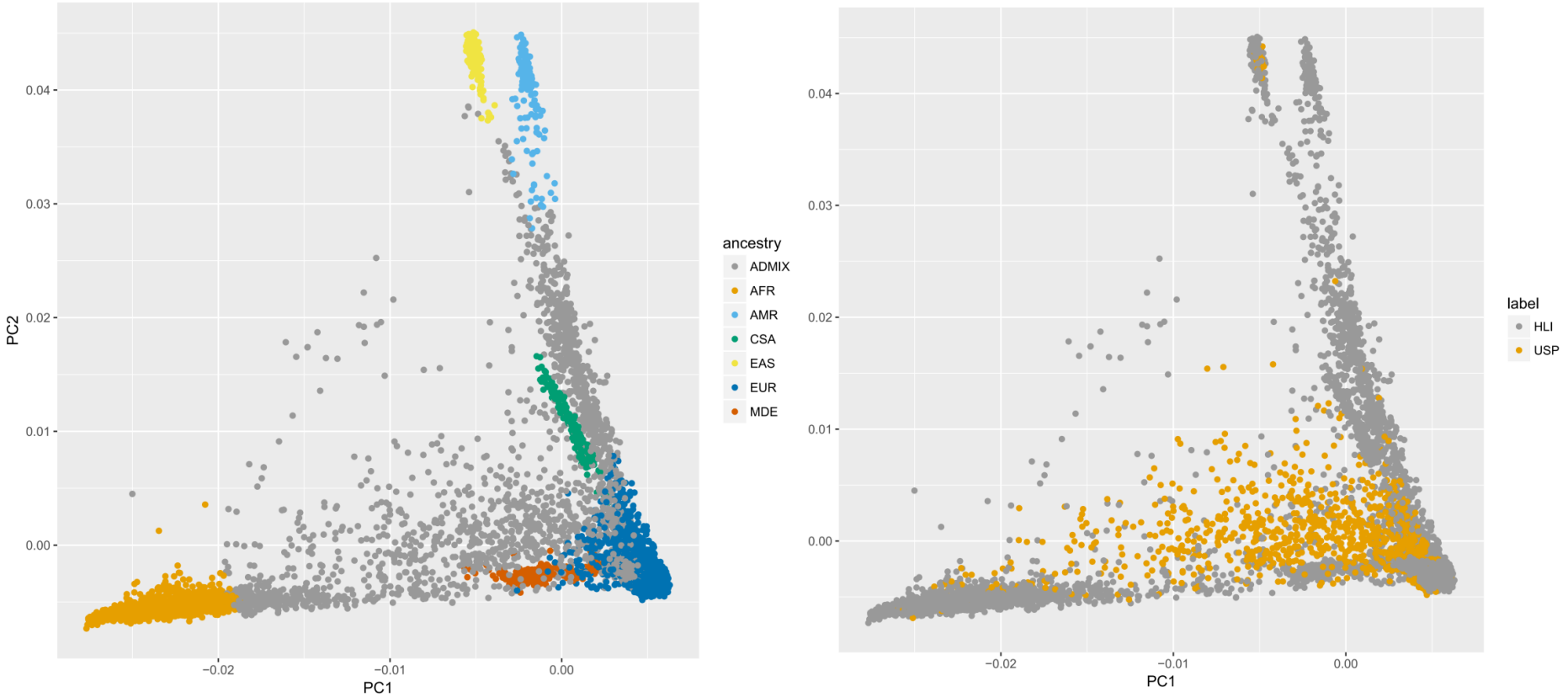
~15k WGS (HLI DB)

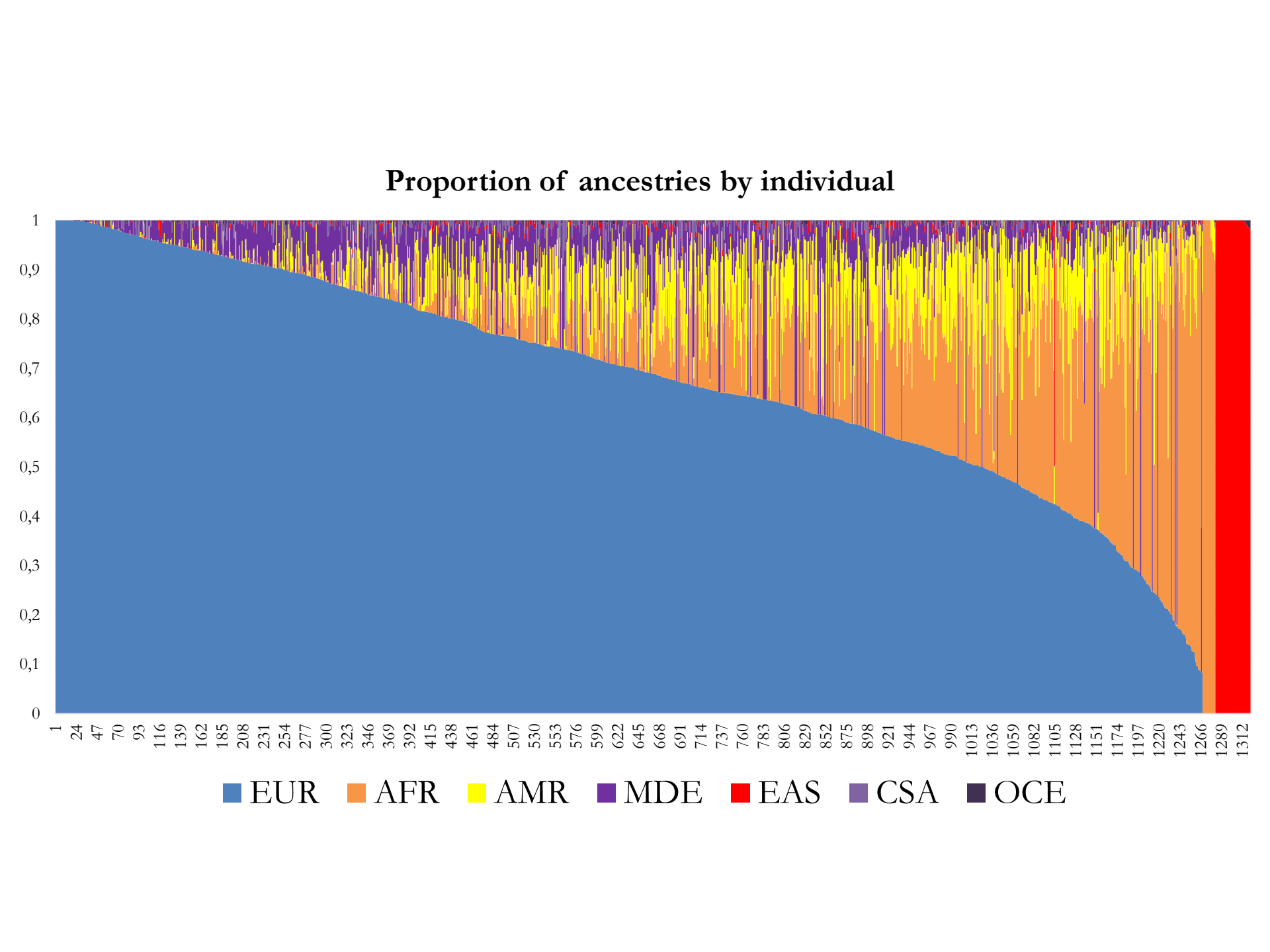


Criteria for attributing ancestry: >70% of one ancestry, or else assigned as ADMIX

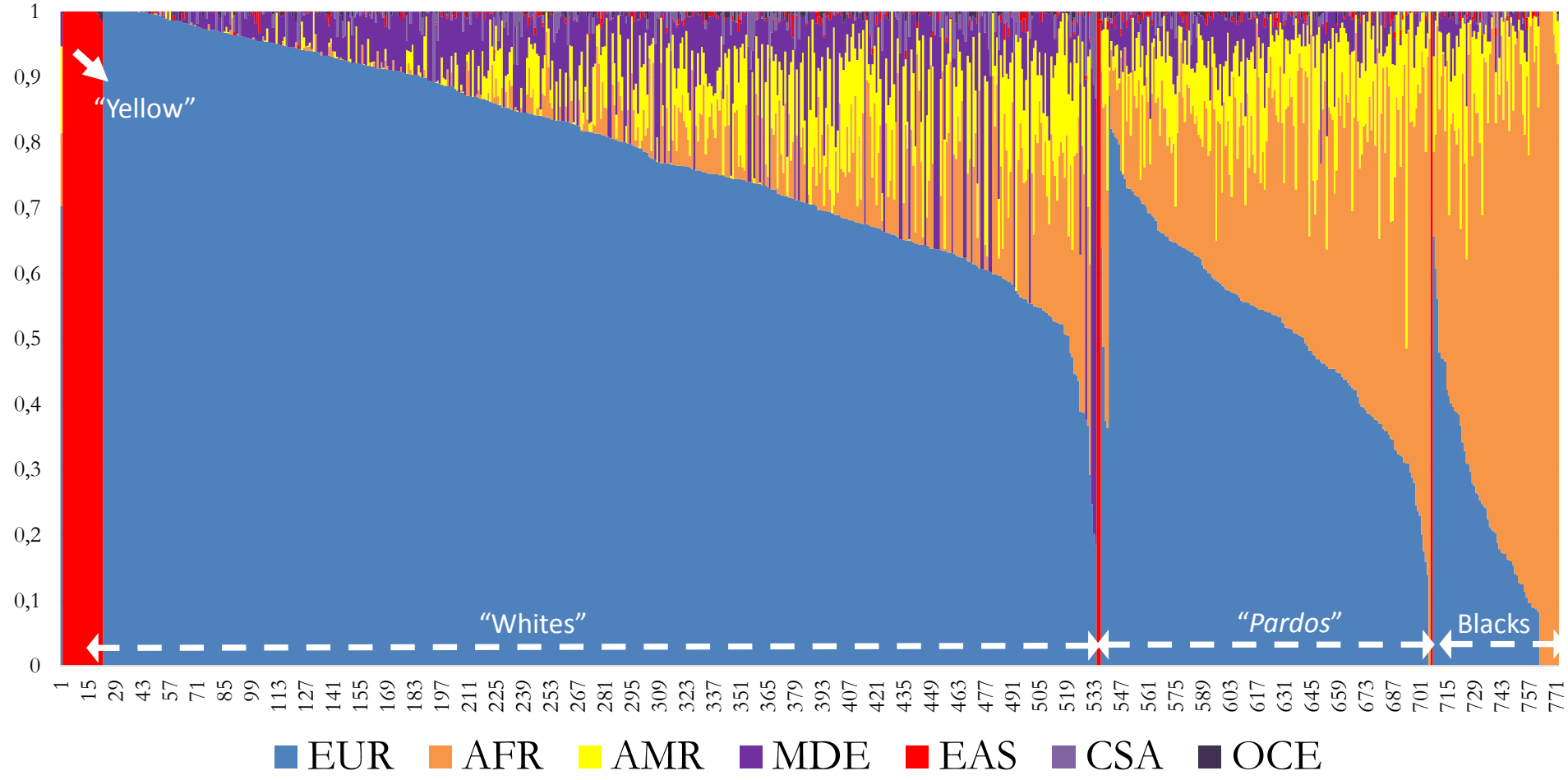


1324 Brazilians from SP


0.04
0.03
0.02
0.01
0.00
PC2
−0.02
−0.01
0.00
PC1
ancestry
ADMIX
AFR
AMR
CSA
EAS
EUR
MDE
label
HLI
USP


Proportion of ancestries by individual
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
1
24
47
70
93
116
139
162
185
208
231
254
277
300
323
346
369
392
415
438
461
484
507
530
553
576
599
622
645
668
691
714
737
760
783
806
829
852
875
898
921
944
967
990
1013
1036
1059
1082
1105
1128
1151
1174
1197
1220
1243
1266
1289
1312
EUR
AFR
AMR
MDE
EAS
CSA
OCE

Proportion by individual separated by self-described skin color



Results – Database application

Integration of allele frequencies to the clinical genomics diagnostic service and research projects of HUG-CELL:

Filtering over 3000 molecular diagnosis panels of disease-related genes and 1500 whole exomes – clinical and research patients

Collaboration in several studies:

14 articles published between 2014 and 2017 cited over 300 times
Flagship paper published in mid 2017 and >30 citations

ABraOM

Arquivo **Bra**sileiro **O**nline de **M**utações

Online Archive of Brazilian Mutations

ABraOM: Brazilian genomic variants

Home About

Search for Gene Name, Region, Position or Variant ID

Gene Name (ex: CFTR), Region (ex: 7:117120162-117122162 or chr7:117120162-117122162), Position (ex: 7:117120162 or chr7:117120162) or Variant ID (ex: rs193922501)

ABraOM

Arquivo **Bra**sileiro **O**nline de **M**utações

Online Archive of Brazilian Mutations

This variant repository contains genomic variants of Brazilians. Our goal is to provide the community with on genetic variability found in Brazil.

The initial deposited cohort 'SABE609' comprise exomic variants of 609 elderly individuals from a census-based sample from São Paulo.

A total of **2,382,573** variants were called before filtering and are available at our browser.

Please refer to the about page for more information on the cohort, flags, counts and summary statistics

http://abraom.ib.usp.br

WGS

1324 WGS (34x median) of the combined sample (2017)

In partnership with Human Longevity (San Diego)

Several technical steps ongoing:

Calling genotypes (in groups)

Strict quality control

Global ancestry

Phasing → Haplotyping → Local ancestry inference

→ Imputation panel

CNVs and structural calls

Setting a dynamic platform for search and integration

ABraOM v1: 609 WES (SNVs+INDELs) - 2016

ABraOM v2.1: 1172 WGS (SNVs+INDELs) – 2019

ABraOM v2.2: 1172 WGS (Haplotypes – imputation panel) - 2020

ABraOM v2.3: 1172 WGS (CNVs + SVs) - 2020

Strict pathogenic assertion for 6 cancer genes:

- Breast cancer: *BRCA1*, *BRCA2*
- Lynch syndrome (Mismatch repair genes):

MLH1, *MSH2*, *MSH6* and *PMS2*

In 1324 WGS:

> 12000 variants

577 coding or splicing consequences

35 potential LoF

9 ClinVar curated variants in 10 individuals

Among these 10 subjects:

2 reported cancer:

(*MSH6* ~ Digestive tract + *BRCA2* ~ Lung)

6 reported no history of cancer

2 lacked clinical information, but one of them was recontacted so far (*BRCA1* : exon9 : c.C1546T: p.Q516X)

She was enrolled at age 88 and had not manifested cancer until today (age 93), nor did her offspring

Reporting back? Essential to gather co-segregation data!

Neuromuscular-related pathogenic variants

In 106 genes, 30 variants across 47 individuals

Genes with biallelic mode of inheritance (AR)

Gene	Protein	AR disorder	Variants/individuals	Carriers per thousand
CAPN2	Calpain 3	LGMD2A	5/8	6,8
LAMA2	A2-laminin	CMD1A	3/3	2,6
NEB	Nebulin	Nemaline	3/6	5,1
POMT1	POMT1	Congenital	2/2	1,7
GSG	g-sarcoglican	LGMD2C	1/1	0,8
TCAP	Teletonina	LGMD2G	1/3	2,6
TTN	Titin	Several	2/2	1,7
		Total	17/25	21,3/1000 (~1/50)

What is pathogenicity after all?

- **Effect size of one (or a few) variants on the phenotype**

+

- **Interaction among Mendelian effect variants, "genetic background" and environment**

(for instance, genetic interaction with common and rare variants from non-European ancestries)

7 out of 10 carriers of cancer-related variants have less than 70% of European ancestry

Contextual Pathogenicity

TABLE 1 Variants that should be excluded from BA1 rule

Gene	Variant	Classification	ACMG/AMP criteria applied (not including BA1 or BS1)	ClinVar ID	ClinGen allele registry ID	Chr	Position	Ref	Alt	ExAC source pop	ExAC source pop minor allele frequency (MAF)	ClinVar disease entry
ACAD9	NM_014049.4: c.---44_---41dupTAAG	VUS	PS3_Supporting; BS2	1018	CA114709	3	128,598,490	C	CTAAG	AFR	0.1261	Deficiency of Acyl---CoA dehydrogenase family, member 9
GJB2	NM_004004.5: c.109G>A (p.Val37Ile)	Pathogenic	PS4; PP1_Strong; PM3_VeryStrong; PS3_Moderate	17023	CA172210	13	20,763,612	C	T	EAS	0.07242	Deafness, autosomal recessive
HFE	NM_000410.3: c.187C>G (p.His63Asp)	Pathogenic[a]	PS4	10	CA113797	6	26,091,179	C	G	NFE	0.1368	Hereditary hemochromatosis
HFE	NM_000410.3: c.845G>A (p.Cys282Tyr)	Pathogenic[a]	PS4; PP3	9	CA113795	6	26,093,141	G	A	NFE	0.05135	Hereditary hemochromatosis
MEFV	NM_000243.2: c.1105C>T (p.Pro369Ser)	VUS	PM3; PM5	2551	CA280114	16	3,299,586	G	A	EAS	0.07156	Familial Mediterranean fever
MEFV	NM_000243.2: c.1223G > A (p.Arg408Gln)	VUS	PM3; PM5	2552	CA280116	16	3,299,468	C	T	EAS	0.05407	Familial Mediterranean fever
PIBF1	NM_006346.2: c.1214G>A (p.Arg405Gln)	VUS	PM3; BS2	217689	CA210261	13	73,409,497	G	A	AMR	0.09858	Joubert syndrome
ACADS	NM_000017.3: c.511C>T (p.Arg171Trp)	VUS	PS3_Moderate; PM3; PP3	3830	CA312214	12	121,175,678	C	T	FIN[b]	0.06589	Deficiency of butyryl---CoA dehydrogenase
BTD	NM_000060.4: c.1330G>C (p.Asp444His)	Pathogenic	PS3; PM3_Strong; PP3; PP4	1900	CA090886	3	15,686,693	G	C	FIN[b]	0.05398	Biotidinase deficiency

VUS: variant of uncertain significance; AFR: African/African American; AMR: Latino; EAS: East Asian; ExAC: Exome Aggregation Consortium; FIN: Finnish; NFE: non-Finnish European.

[a]The American College of Medical Genetics and Genomics and the Association of Molecular Pathologists (ACMG/AMP) criteria selected does not match the classification as these variants are common low-penetrant variants and the ACMG/AMP guidelines are not designed for this variant type.

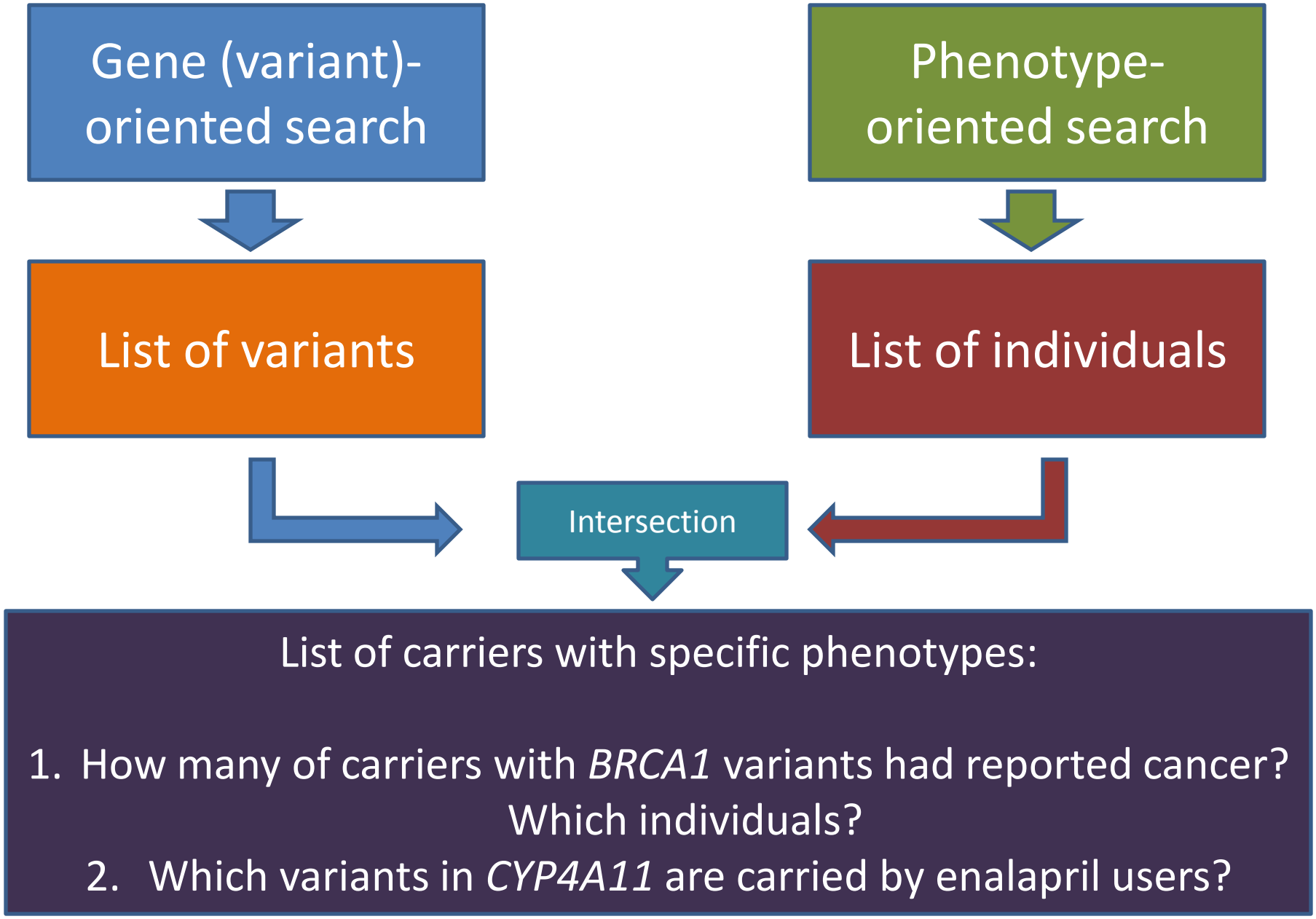
[b]Detected at >5% MAF only in Finnish population (see text). Genomic coordinates on build GRCh37.

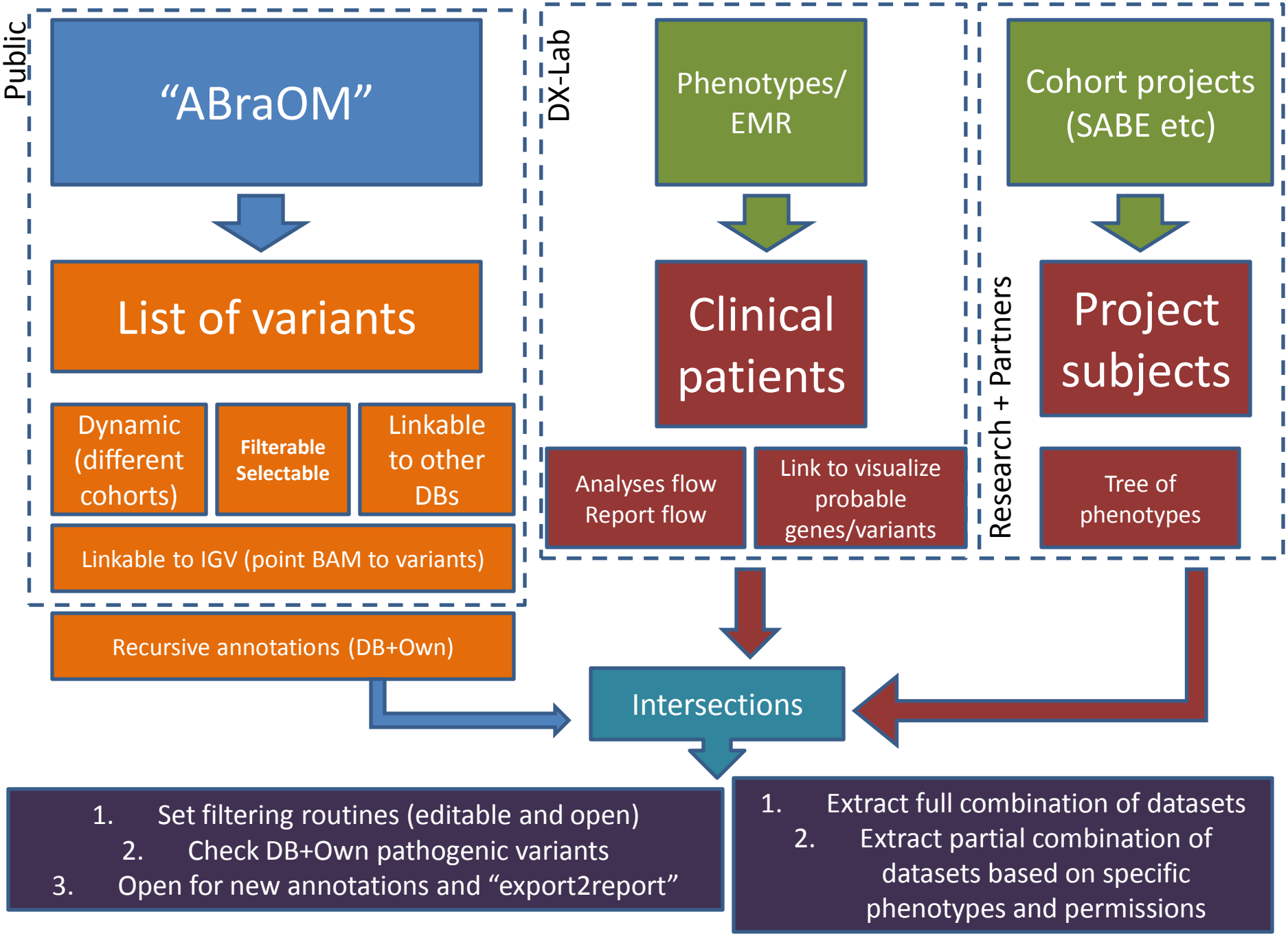
Next steps

- **Integrate the public allele frequencies to ABraOM, deposit in dbSNP, Annovar and international alliances;**

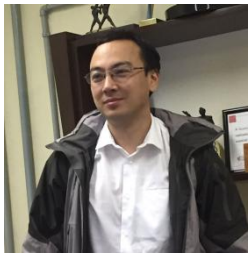
- **Create a dynamic database for adding new cohorts and recursively annotate;**

- **Create rings of access permissions to individual-level data to researchers, data-owners and collaborative partners.**


Gene (variant)-oriented search
Phenotype-oriented search
List of variants
List of individuals
Intersection
List of carriers with specific phenotypes:
1. How many of carriers with *BRCA1* variants had reported cancer? Which individuals?
2. Which variants in *CYP4A11* are carried by enalapril users?


Public
"ABraOM"
List of variants
Dynamic (different cohorts)
Filterable Selectable
Linkable to other DBs
Linkable to IGV (point BAM to variants)
DX-Lab
Phenotypes/ EMR
Clinical patients
Analyses flow Report flow
Link to visualize probable genes/variants
Research + Partners
Cohort projects (SABE etc)
Project subjects
Tree of phenotypes
Recursive annotations (DB+Own)
Intersections
1. Set filtering routines (editable and open)
2. Check DB+Own pathogenic variants
3. Open for new annotations and "export2report"
1. Extract full combination of datasets
2. Extract partial combination of datasets based on specific phenotypes and permissions

Acknowledgments



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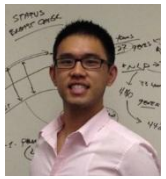

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