Biobank Project:
Progress & Plans

Carlos Cruchaga. PhD

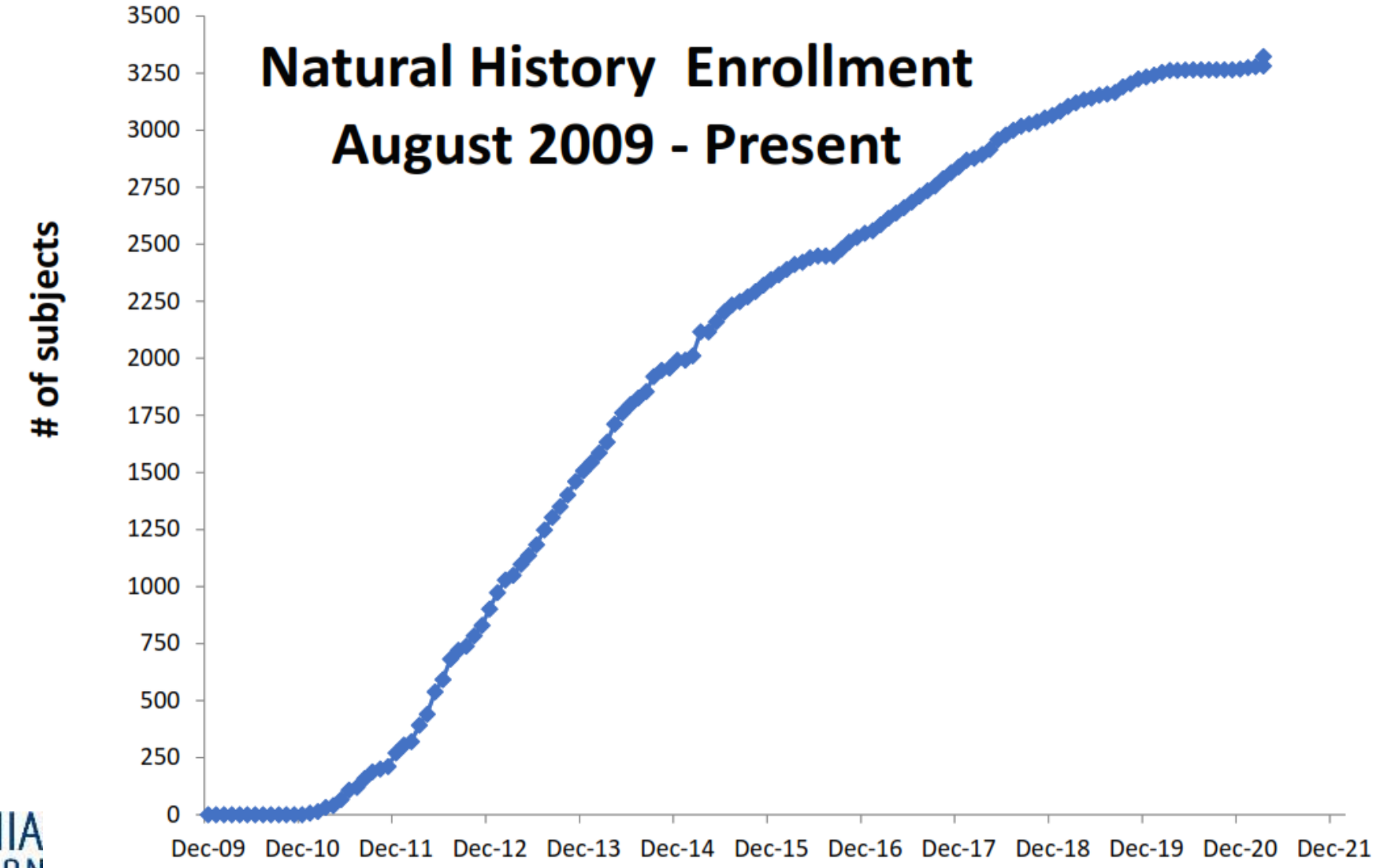
Current Biobank

- Obtain baseline blood for DNA-> Coriell
- DNA for more than >3,200 Dystonia Coalition participants.
  - Around 50% are from cervical dystonia (CD)
- DNA has been instrumental to identify new genes for dystonia

DYSTONIA COALITION

Current Biobank: DNA Available

Baseline. Banked at Coriell



DYSTONIA COALITION

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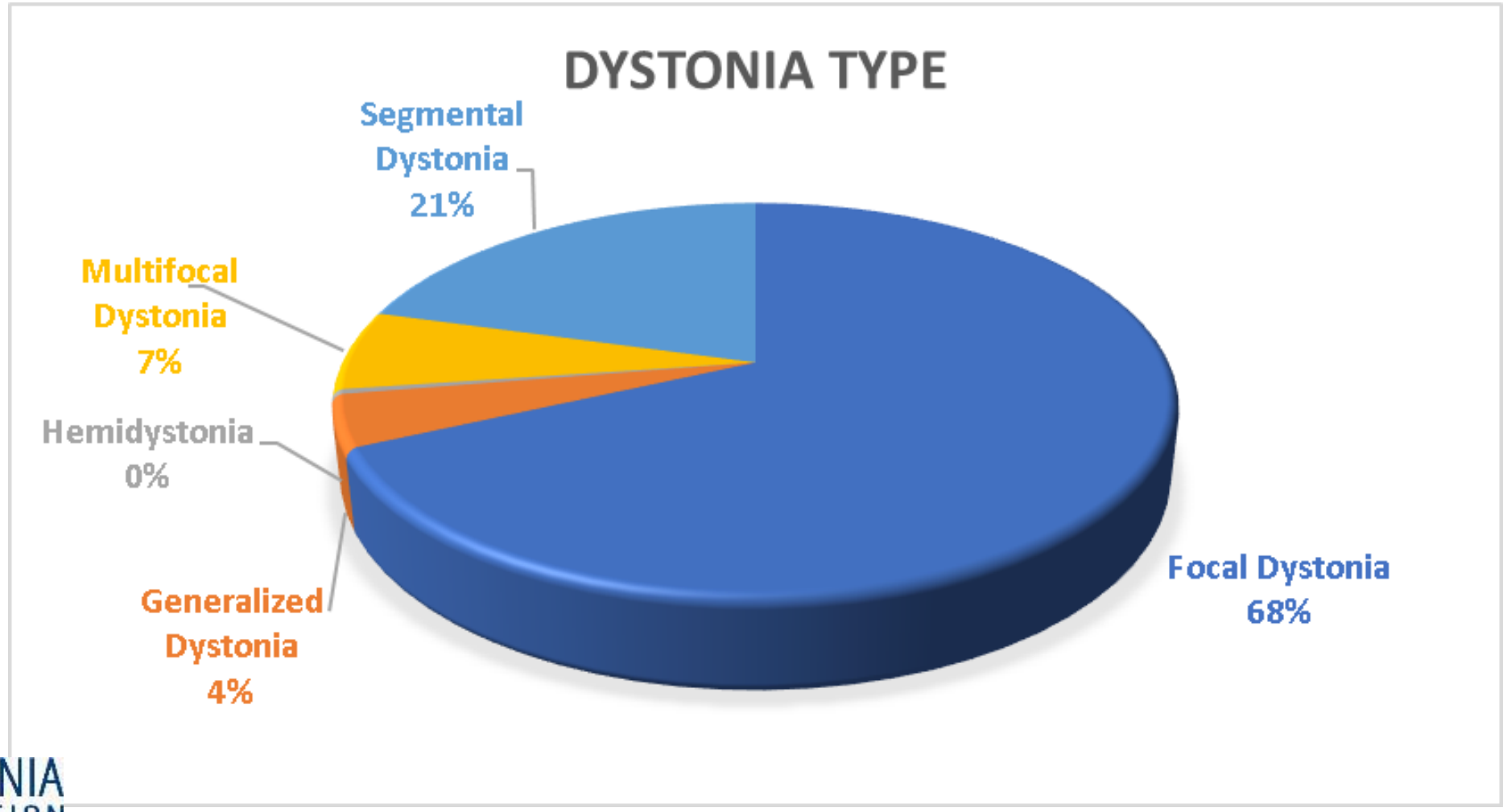
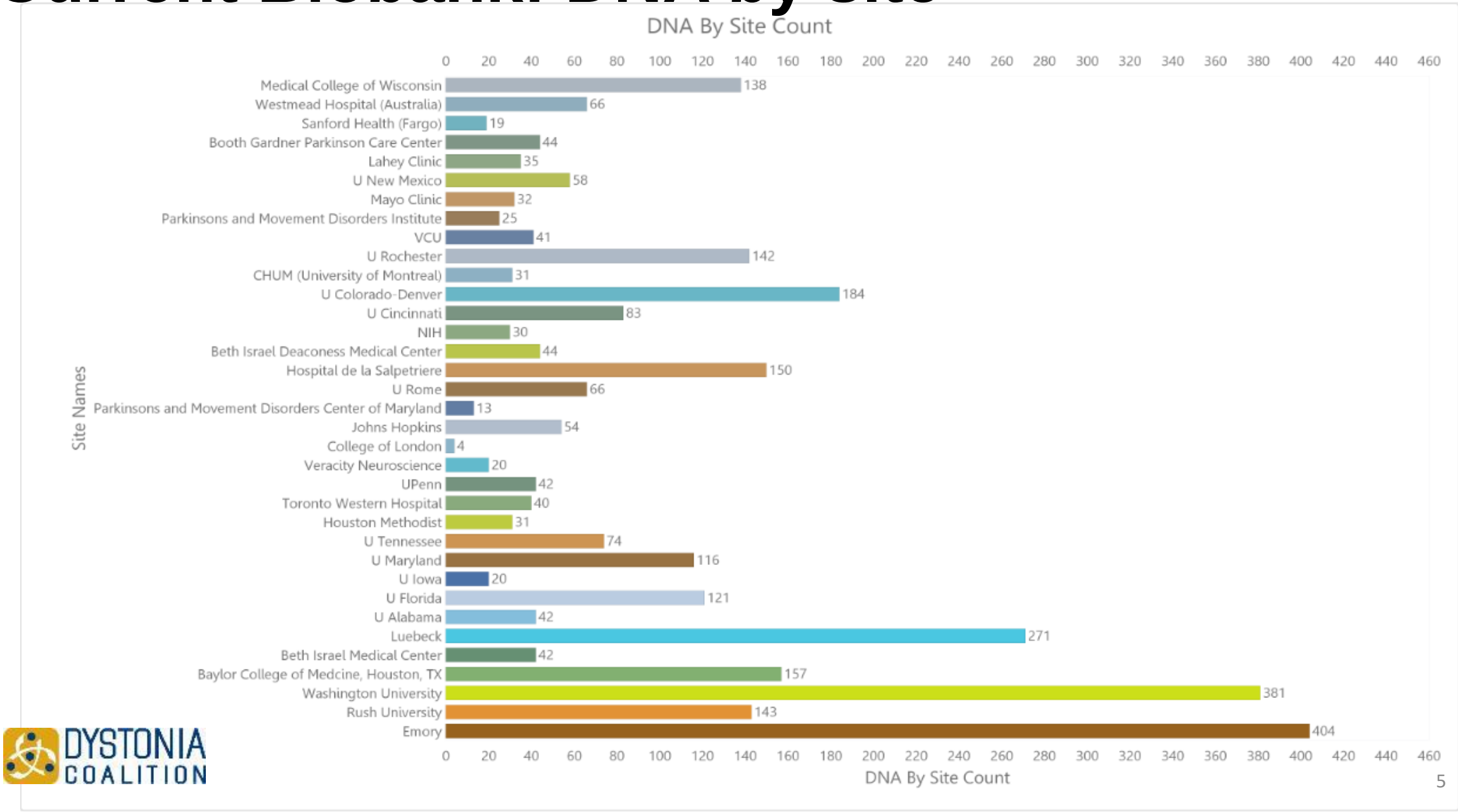


DYSTONIA COALITION

Current Biobank: DNA by site



DYSTONIA COALITION

Genetic Characterization of DC participants

Mark S. LeDoux, MD, PhD
Satya R. Vemula, PhD
Jianfeng Xiao, MD, PhD
Misty M. Thompson, PhD
Joel S. Perlmutter, MD
Laura J. Wright, MA
H.A. Jinnah, MD, PhD
Ami R. Rosen, MS
Peter Hedera, MD, PhD
Cynthia L. Comella, MD
Anne Weissbach, MD
Johanna Junker, MD
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Natividad P. Stover, MD
On behalf of the Dystonia Coalition Investigators, Dystonia Genetic Consortium

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Neurology: Genetics

Table 3 Bioinformatic analysis of SVs identified in participants with CD

						Minor allele frequency				In silico pathogenicity/deleteriousness					Splicing (human splice finder 3.0)			
Gene	Participant (s)	cDNA	Protein	ACMG classification	dbSNP	EVS	1KG	ExAC	DC	SIFT	MutationTaster	PolyPhen-2	CADD raw	CADD Phred	Splice site distance	HSF matrices	ESE finder	ESR sequences
GNAL	DYS1579	c.40C>T	p.Q14*	Pathogenic					0.0005	NA	Disease causing	NA	2.72	22.5	142	None	None	ESE site broken
GNAL	n = 5	c.66C>T	p.R22R	Uncertain significance	rs73397885	0.01	0.008	0.00562	0.0025	Tolerated	Polymorphism	NA	2.43	22.1	79	New donor site	ESE site broken	None
GNAL	DYS497	c.139C>A	p.L47I	Likely pathogenic					0.0005	Damaging	Disease causing	Benign	2.55	22.3	6	None	ESE site broken	ESE site broken
GNAL	DYS734	c.214C>G	p.P72A	Likely pathogenic					0.0005	Tolerated	Disease causing	Benign	1.49	15.9	4	None	None	New ESS site
GNAL	n = 135	c.218+19C>A	NA	Likely benign	rs1895689	0.000307	0.348	0.2968	0.078	NA	NA	NA	1.16	14.1	19	None	None	None
GNAL	n = 74	c.932-7T>G	NA	Benign	rs3892113	0.06	0.044	0.0628	0.041	NA	NA	NA	0.05	4.1	7	None	None	None
GNAL	n = 33	c.1014C>T	p.A338A	Uncertain significance	rs41289504	0.01	0.0034	0.008831	0.016	Tolerated	Disease causing	NA	2.01	19.2	15	None	ESE site broken	New ESS site
GNAL	DYS41	c.1018G>A	p.G340S	Likely pathogenic	rs142792291	0.0001538		0.0000249	0.0005	Tolerated	Disease causing	Probably damaging	2.13	20.3	19	New acceptor site	None	New ESS site
GNAL	DYS87	c.1060G>A	p.V354M	Pathogenic					0.0005	Damaging	Disease causing	Probably damaging	2.57	22.4	61	None	ESE site broken	New ESS site
THAP1	DYS1729	c.57C>T	p.P19P	Uncertain significance	rs146087734	0.00023		0.000099	0.0005	Tolerated	Disease causing	NA	1.93	18.6	14	None	None	None
THAP1	DYS1706	c.71+9C>A	NA	Likely pathogenic	rs200209986	0.001999		0.001291	0.0005	NA	NA	NA	0.93	12.6	9	None	None	None
THAP1	DYS88	c.153C>G	p.S51R	Pathogenic					0.0005	Damaging	Disease causing	Probably damaging	5.06	27.1	81	None	None	None
THAP1	DYS1068	c.427A>G	p.M143V	Uncertain significance	rs374512193	0.00007		0.00007413	0.0005	Tolerated	Polymorphism	Benign	0.85	12.1	159	New acceptor site	None	None
TOR1A Exon 5	DYS266	c.823A>G	p.K275E	Uncertain significance	rs148036363	0.0002307		0.0003789	0.0005	Tolerated	Disease causing	Probably damaging	2.27	21.4	74	None	ESE site broken	None
TOR1A Exon 5	DYS1754	c.907_909 delGAG	p.E303del	Pathogenic	rs724159981				0.0005	NA	Disease causing	NA	2.73	22.5	158	None	ESE site broken	New ESS site
TOR1A Exon 5	DYS1565	c.962C>T	p.T321M	Uncertain significance				0.00001647	0.0005	Damaging	Disease causing	Probably damaging	2.06	19.6	213	None	None	New ESS site

cDNA/protein (*GNAL*-NM_001142339.2/NP_001135811.1, *THAP1*- NM_018105.2/NP_060575.1, *TOR1A*-NM_000113.2/NP_000104.1).
Abbreviations: 1KG = 1000 Genomes Project; ACMG = American College of Medical Genetics and Genomics; CADD = Combined Annotation-Dependent Depletion; CD = cervical dystonia; cDNA = complementary DNA; dbSNP = Single Nucleotide Polymorphism database; DC = Dystonia Coalition; ESE = exonic splicing enhancer; ESR = exonic splicing regulator; ESS = exonic splicing silencer; EVS = Exome Variant Server;

Genome-Wide Association studies

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH

Genome-wide Association Study Identifies Common Genetic Variants Associated with Cervical Dystonia

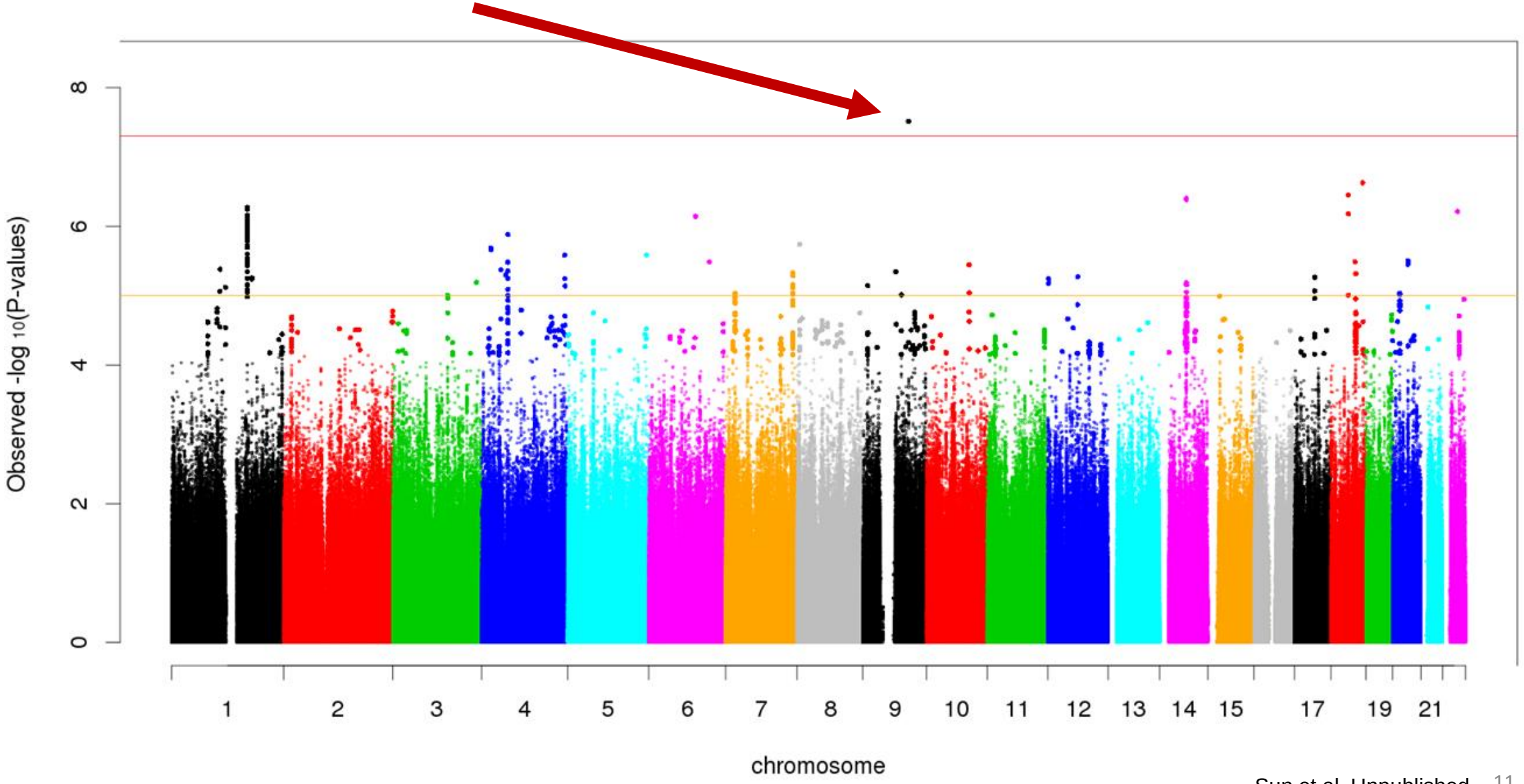
Yan V. Sun[1,2], Chengchen Li[1], Qin Hui[1], Joel S. Perlmutter[3], Samantha Ruehl[4], Christine Klein[5], Joseph Jankovic[6], Richard L. Barbano[7], Stephen G. Reich[8], J. Douglas Bremner[9,10], Viola Vaccarino[1], Arshed A. Quyyumi[11], H. A. Jinnah[12], on behalf of the Dystonia Coalition Investigators

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA; [2]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, Georgia, USA; [3]Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA; [4]Department of Neurological Sciences, Rush Medical College, Chicago, IL, USA; [5]The Institute of Neurogenetics, University of Luebeck, Luebeck, Germany; [6]Department of Neurology, Baylor College of Medicine, Houston, TX, USA; [7]Department of Neurology, University of Rochester Medical center, Rochester, NY, USA; [8]Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA; [9]Atlanta VA Medical Center, Decatur, Georgia, USA; [10]Departmnt of Radiology, Emory University School of Medicine, Atlanta, Georgia, USA; [11]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA; [12]Department of Neurology and Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA

EMORY UNIVERSITY SCHOOL OF MEDICINE

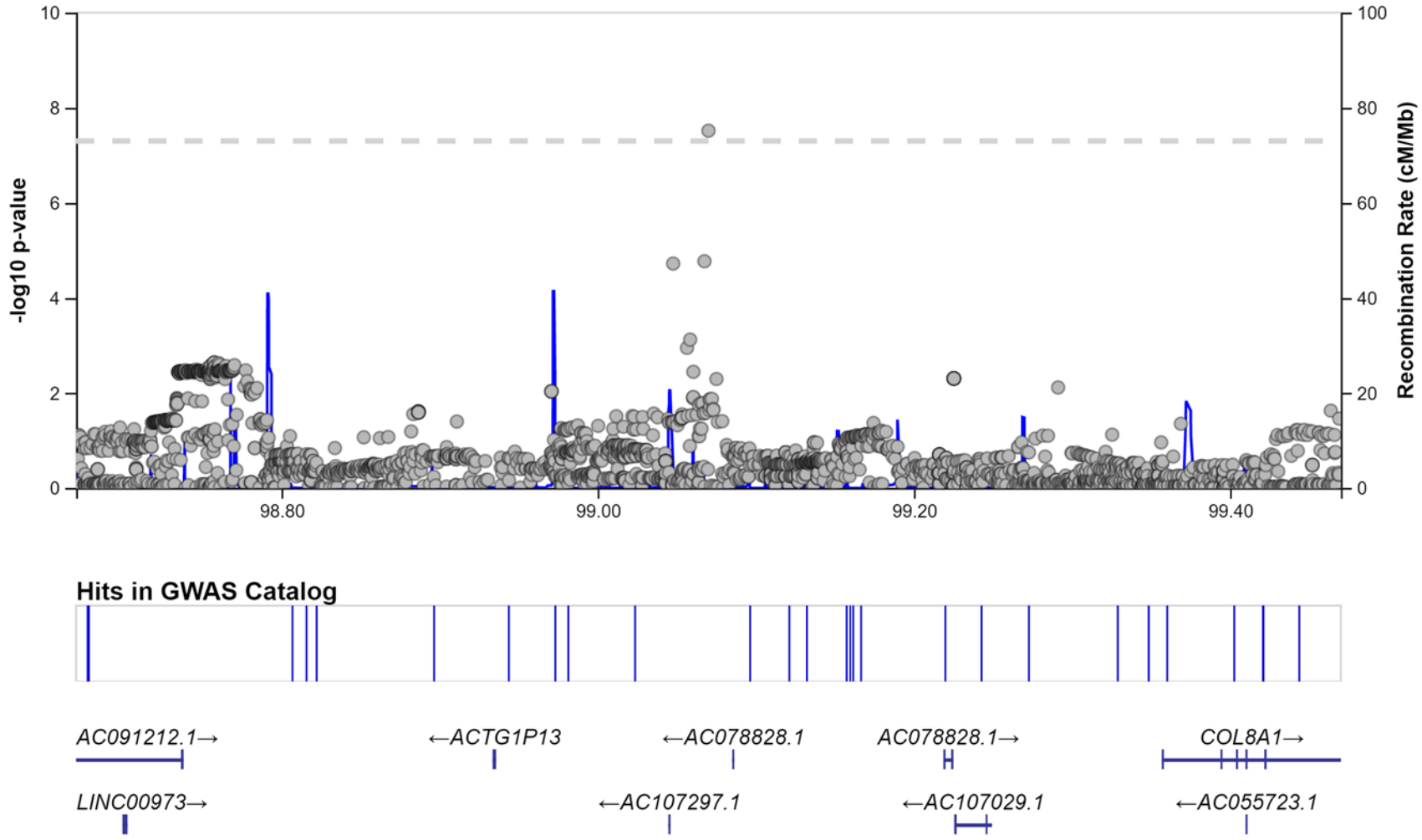
919 cases and 1,491 controls

Genome-Wide Association studies



Sun et al, Unpublished

Genome-Wide Association studies



Sun et al, Unpublished

Genome-Wide Association studies

- largest GWAS for any type of dystonia to date
- 1 common genome-wide significant variants (*p*-value<5×10^{-8}) in 1distinct loci
- Chromosome 3 signal is close upstream of *COL8A1*
  - Defects in *COL8A1* are associated with corneal dystrophy and age-related macular degeneration.
- Gene-based analysis identified *DENND1A* to be significantly associated with cervical dystonia (p-value 1.23×10^{-6}).
- One low-frequency variant was associated with lower age-at-onset (16.4±2.9 years, p-value=3.07×10^{-8}, MAF=0.01), located within the *GABBR2* gene on chromosome 9 (rs147331823

Sun et al, Unpublished

Genetics of dystonia

- Dystonia Coalition with GWAS data: 2,257
  - Collaboration with Drs. Klein and Lohmann

- Identification of variants and genes associated with risk and onset

- **Goal**: have GWAS data for all dystonia DNA
    - This will allow to identify genes, but also prediction models (PRS)

  - Generating WES (Drs. Klein and Lohmann) to look a rare coding variants

Goals for the Biobank

- To extend the current DNA repository by targeting BSP, LD and limb dystonia subjects as well as multiplex families.
    - Sporadic and familial presentations
    - Longitudinal (each visit)

- To develop a centralized repository of other blood-based materials
    - DNA
    - RNA
    - Plasma

- To identify novel genetic and proteomic factors for dystonia risk

- To identify genetic and proteomic factors that influence spread of dystonia

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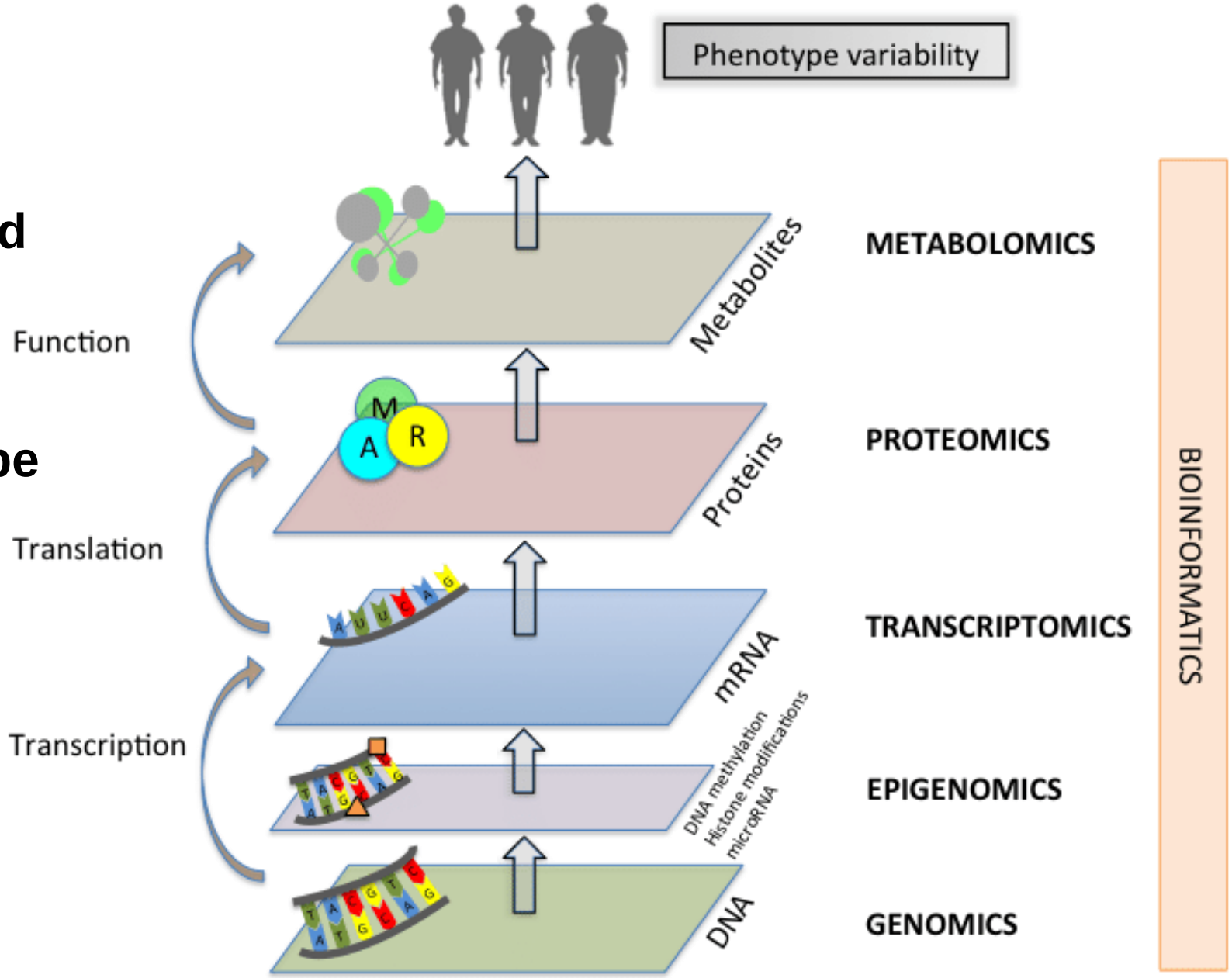
Goal: to Understand the Phenotypic Variability

- **We need to go beyond just GWAS/WGS**
- **Molecularly Phenotype Clinical cohorts**
- **Generating multiple layers of omic data**



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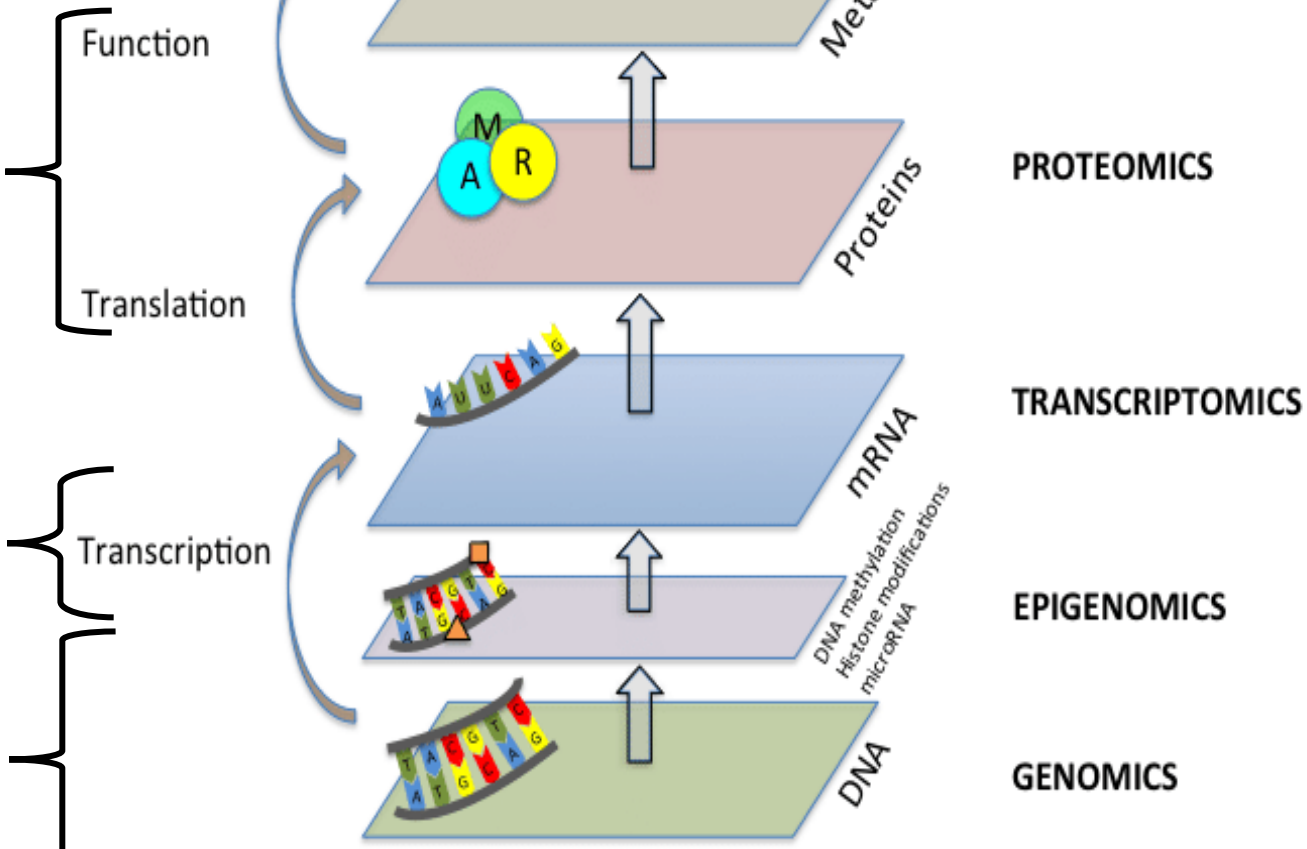
Genetics is just the first layer

Plasma

Blood-RNA

Blood-DNA



DYSTONIA COALITION

A Metabolomic Study of Cervical Dystonia

Parkinsonism and Related Disorders 82 (2021) 98–103

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

A metabolomic study of cervical dystonia

Chang Liu [a], Laura Scorr [b], Gamze Kilic-Berkmen [b], Adam Cotton [b], Stewart A. Factor [b], Alan Freeman [b], ViLinh Tran [c], Ken Liu [c], Karan Uppal [d], Dean Jones [d], H.A. Jinnah [b,e], Yan V. Sun [a,f,*]

[a] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA
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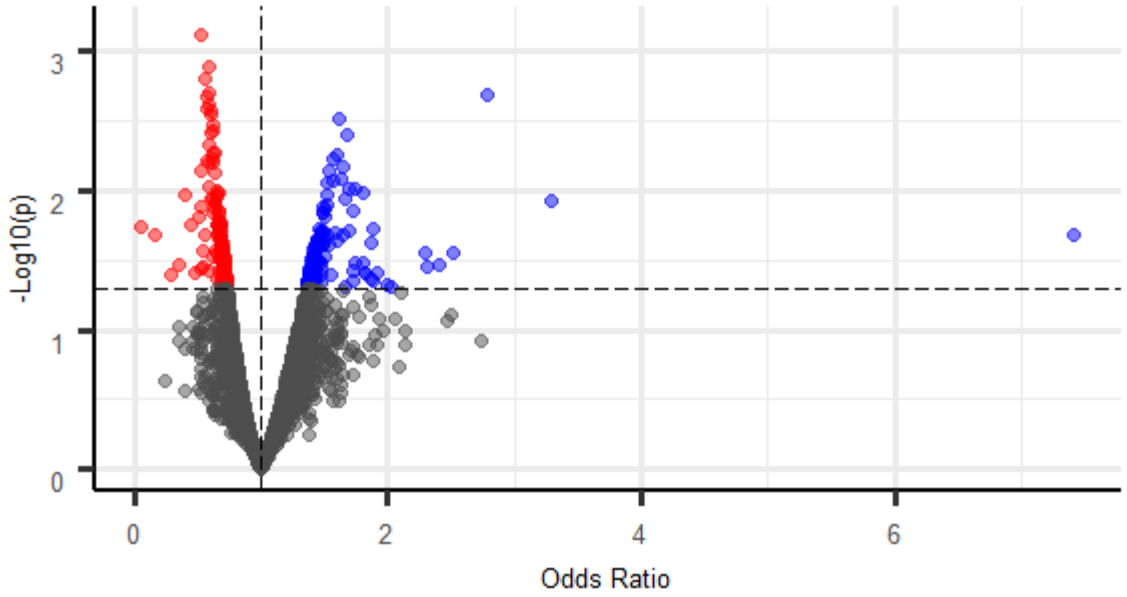
[f] Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA

DYSTONIA COALITION

Liu et al, 2021

A Metabolomic Study of Cervical Dystonia

- Plasma samples from 100 cases with idiopathic cervical dystonia and 100 controls
- 7,346 metabolic features remained after quality control
- 289 significantly associated with case-control status



DYSTONIA COALITION

Liu et al, 2021

A Metabolomic Study of Cervical Dystonia

- Plasma samples from 100 cases with idiopathic cervical dystonia and 100 controls
- 7,346 metabolic features remained after quality control
- 289 significantly associated with case-control status
- 9 biological processes to be significantly associated at $p<0.05$,
  - 5 carbohydrate metabolism pathways
  - 3 lipid metabolism pathways

DYSTONIA COALITION

Liu et al, Unpublished

Summary

- **The goals is to molecularly characterized the DC cohort**
  - Genetic (GWAS, WGS), epigenomics (longitudinal), transcriptomics (longitudinal), proteomic (longitudinal), metabolomic and lipidomics

- **Deep molecular phenotyping of well clinically characterized cohorts will lead to the identification of:**
  - Novel genes and pathways implicated on the diseases
  - A deeper understanding pathologic events
  - Novel molecular phenotypes
  - Novel therapeutic targets

- **The multi-omic data (genetic, epigenetic, transcriptomic, proteomic, metabolomic, between others) will allow to a more personalize prediction of disease risk and treatment**

Q & A

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Washington University in St. Louis
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Study Coordinator: JoAnne Norton nortonj@wustl.edu