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
Current Biobank: DNA Available Baseline. Banked at Coriell

Natural History Enrollment
August 2009 - Present
Current Biobank: DNA Available Baseline. Banked at Coriell

Dystonia Type:
- Focal Dystonia: 68%
- Segmental Dystonia: 21%
- Multifocal Dystonia: 7%
- Hemidystonia: 0%
- Generalized Dystonia: 4%
Current Biobank: DNA by site

[Graph showing DNA by site count for various institutions]

- Medical College of Wisconsin: 138
- Westmead Hospital (Australia): 66
- Sanford Health (Fargo): 44
- Booth Gardner Parkinson Care Center: 35
- Lahey Clinic: 32
- U New Mexico: 58
- Mayo Clinic: 41
- Parkinsons and Movement Disorders Institute: 142
- VCU: 83
- U Rochester: 184
- CHUM (University of Montreal): 30
- U Colorado-Denver: 44
- U Cincinnati: 150
- NIH: 66
- Beth Israel Deaconess Medical Center: 13
- Hospital de la Salpetriere: 54
- U Rome: 40
- Parkinsons and Movement Disorders Center of Maryland: 20
- Johns Hopkins: 74
- College of London: 116
- Veracyt Neuroscience: 121
- U Penn: 42
- Toronto Western Hospital: 42
- Houston Methodist: 271
- U Tennessee: 81
- U Maryland: 157
- U Iowa: 143
- U Florida: 40
- U Alabama: 40
- Luebeck: 40
- Baylor College of Medicine, Houston, TX: 381
- Washington University: 404
- Rush University: 404

[Logo: DYSTONIA COALITION]
Genetic Characterization of DC participants

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On behalf of the Dystonia Coalition Investigators,
Dystonia Genetic Consortium

Clinical and genetic features of cervical dystonia in a large multicenter cohort

OPEN
## Genetic Characterization of DC participants

<table>
<thead>
<tr>
<th>Gene</th>
<th>Participant (s)</th>
<th>cDNA</th>
<th>Protein</th>
<th>ACMG classification</th>
<th>dbSNP</th>
<th>EVS</th>
<th>1K</th>
<th>ExAC</th>
<th>Minor allele frequency</th>
<th>In silico pathogenicity/disease causation</th>
<th>Splicing (human splicing finder 3.0)</th>
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<tbody>
<tr>
<td>GNAL</td>
<td>DYS1579</td>
<td>e.40C&gt;T</td>
<td>p.Q116*</td>
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<td>rs73397885</td>
<td>0.01</td>
<td>0.008</td>
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<td>Polymorphisms</td>
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<td>0.348</td>
<td>0.298</td>
<td>0.087</td>
<td>Disease causing</td>
<td>2.55</td>
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<td>Benign</td>
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<td>Disease causing</td>
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<td>0.005</td>
<td>Tolerated</td>
<td>Disease causing</td>
</tr>
</tbody>
</table>

**Abbreviations:** 1K = 1000 Genomes Project; ACMG = American College of Medical Genetics and Genomics; CADD = Combined Annotation-Dependent Depletion; CD = cervical dystonia; cDNA = complimentary DNA; dbSNP = Single Nucleotide Polymorphism database; DC = Dystonia Coalition; ESE = exonic splicing enhancer; ESR = exonic splicing repressor; ESS = exonic splicing silencer; EVS = Exome Variant Server.
Genome-Wide Association studies

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

Yan V. Sun¹,², Chengchen Li¹, Qin Hui¹, Joel S. Perlmutter³, Samantha Ruehl⁴, Christine Klein⁵, Joseph Jankovic⁶, Richard L. Barbano⁷, Stephen G. Reich⁸, J. Douglas Bremner⁹,¹⁰, Viola Vaccarino¹, Arshed A. Quyyumi¹¹, H. A. Jinnah¹², on behalf of the Dystonia Coalition Investigators

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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$<5\times10^{-8}$) in 1 distinct 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 $1.23\times10^{-6}$).

- One low-frequency variant was associated with lower age-at-onset (16.4±2.9 years, $p$-value=$3.07\times10^{-8}$, 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
Goal: to Understand the Phenotypic Variability

- We need to go beyond just GWAS/WGS
- Molecularly Phenotype Clinical cohorts
- Generating multiple layers of omic data
Genetics is just the first layer
A metabolomic study of cervical dystonia

Chang Liu, Laura Scorr, Gamze Kilic-Berkmen, Adam Cotton, Stewart A. Factor, Alan Freeman, ViLinh Tran, Ken Liu, Karan Uppal, Dean Jones, H.A. Jinnah, and Yan V. Sun.
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

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
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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