# Biobank Project:
## Progress & Plans

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# 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

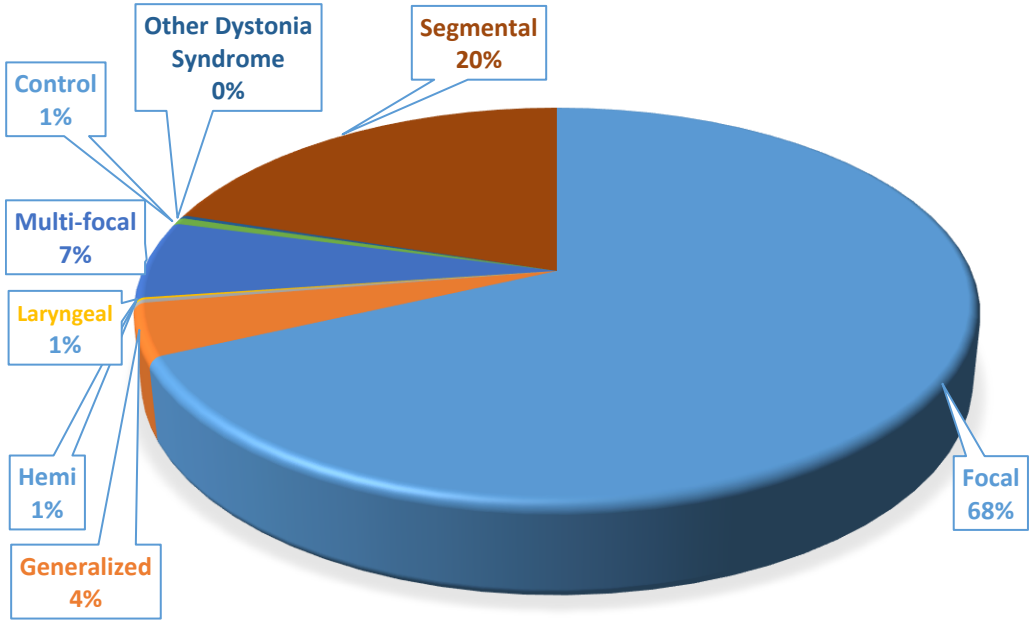
- To identify novel genetic and proteomic factors for dystonia risk

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

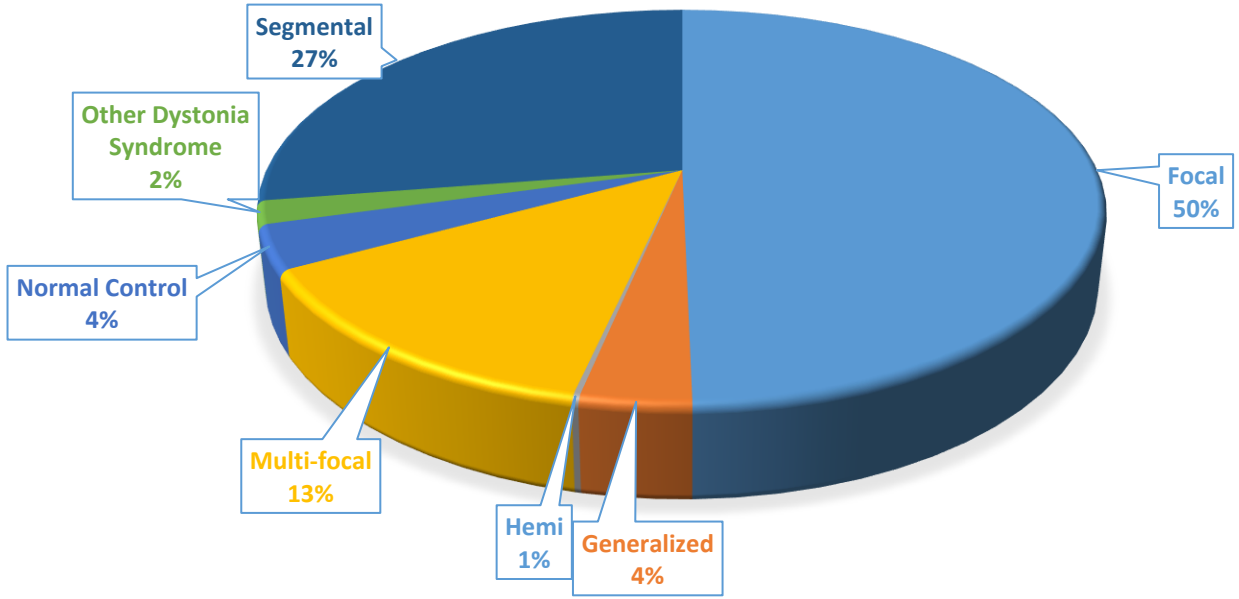
DYSTONIA COALITION

# Current Biobank: DNA Available

**Older and New sample visits**




**New sample only**

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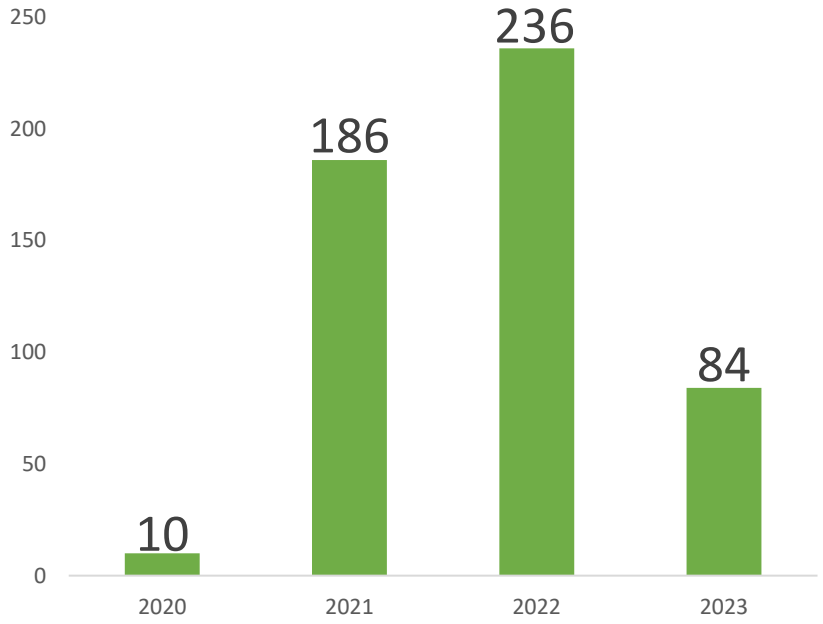
Data by Jen Gentsch

# Biobank: 2020-2022

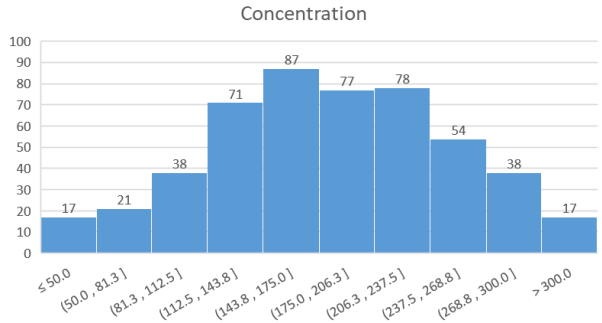
## # Samples Received per year




Samples include: DNA, RNA and plasma

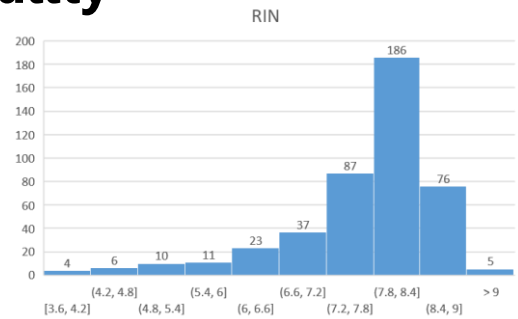
## DNA quality

| | Concentration | 260/280 | 260/230 |
|---|---|---|---|
| MIN | 42.97 | 1.73 | 0.7 |
| MAX | 370.90 | 1.92 | 2.64 |
| AVERAGE | 181.34 | 1.84 | 2.02 |




## RNA quality

| | Concentration | RIN |
|---|---|---|
| MIN | 5.48 | 3.60 |
| MAX | 713.00 | 9.90 |
| AVERAGE | 69.66 | 7.74 |

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Data by Pat Kohlfeld

# Genetic Characterization of DC participants

**RAW**
- Illumina's Multi-Ethnic Genotyping Array
  - - 919 samples, 1,359,498 SNPs
- Illumina Global Screen Array
  - - 1344 samples, 653,142 SNPs

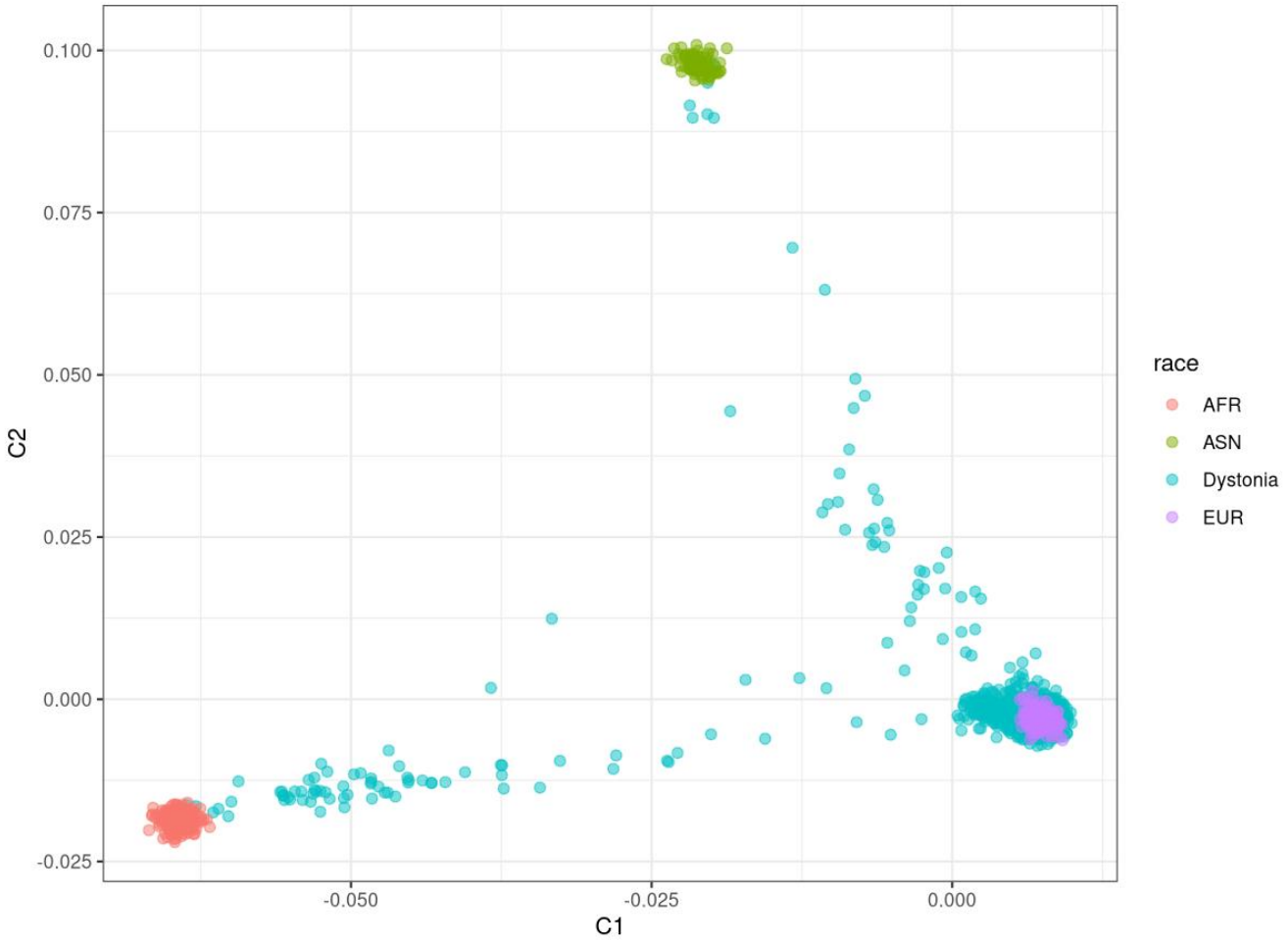
**Genotype data QC**
- Filtered for ≥ 98% call rate, HWE $P<10^{-6}$
  - 8 samples failed

**Imputation**
- TOPMed Imputation Server
- A total of 41,499,784 variants passe QC

**IBD and sex checks**
- 12 samples with IBD issues
- 18 have sex mismatches

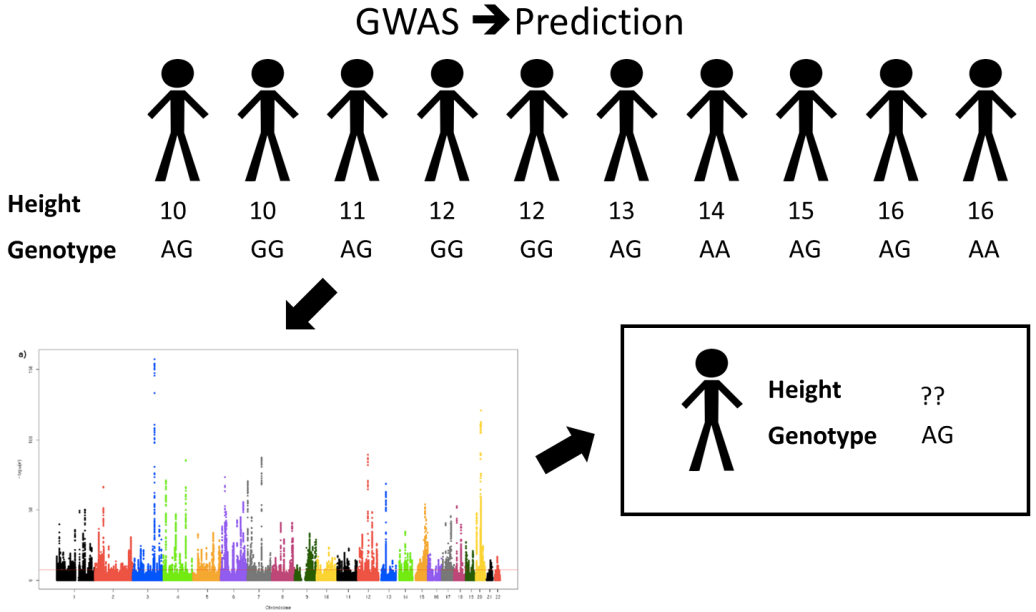
**Final QC'ed data**
- A total of 2225 samples
- and 41,499,784 variants

## Genetic ethnicity




Data by Priyanka Gorijala

# Polygenic risk scores for Dystonia




1. Obtain GWAS summary statistics (p-values and β's) in largest possible **discovery sample**
    1. Alzheimer's disease: Bellenguez et al 2023
    2. Parkinson disease: Kim et al 2022

2. Obtain independent **target sample (this is the Dystonia samples)** with Genome-wide data
    1. Use **SNPs in common** between the two samples.
       Deal with **association redundancy due to LD**.
    2. Restrict to **SNPs with p <** $5x10^{-8}$ for the disease GWAS
        1. We calculated PRS for AD, PD and FTD
    3. **Construct PRS** = Sum of Risk Alleles weighted by β from regression.

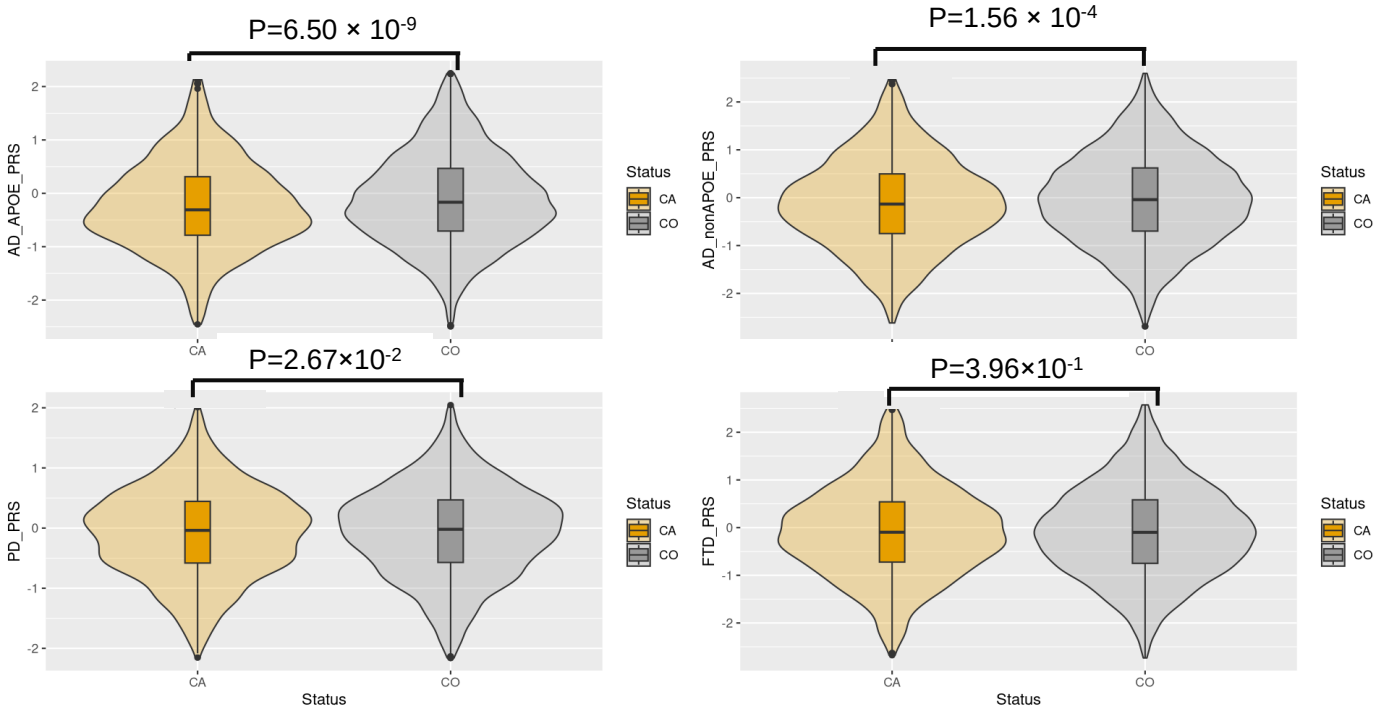
Data by Priyanka Gorijala

# Polygenic Risk Score Analysis

**Association results of extreme tertiles of the PRS at genome-wide threshold derived for each of the AD, PD, and FTD categories and compared to Dystonia Vs controls.**

| Variable | Odds Ratio | 2.50% CI | 97.50% CI | P value | N Cases | N Controls |
|---|---|---|---|---|---|---|
| **AD with APOE PRS** | 0.698 | 0.618 | 0.788 | $6.505 \times 10^{-9}$ | 2024 | 7607 |
| **AD without APOE PRS** | 0.789 | 0.698 | 0.892 | $1.567 \times 10^{-4}$ | 2024 | 7607 |
| **PD PRS** | 0.872 | 0.773 | 0.984 | $2.675 \times 10^{-2}$ | 2024 | 7607 |
| **FTD PRS** | 1.054 | 0.933 | 1.190 | $3.961 \times 10^{-1}$ | 2024 | 7607 |

N – Number of samples in each category, CI – Confidence interval, PRS – Polygenic risk score, APOE – Apolipoprotein.
AD - Alzheimer's disease, PD- Parkinson's disease, FTD – Fronto temporal dementia.




1. Dystonia cases are depleted for AD risk variants, independently of APOE
2. Dystonia cases are depleted for PD risk variants
3. No differences for FTD

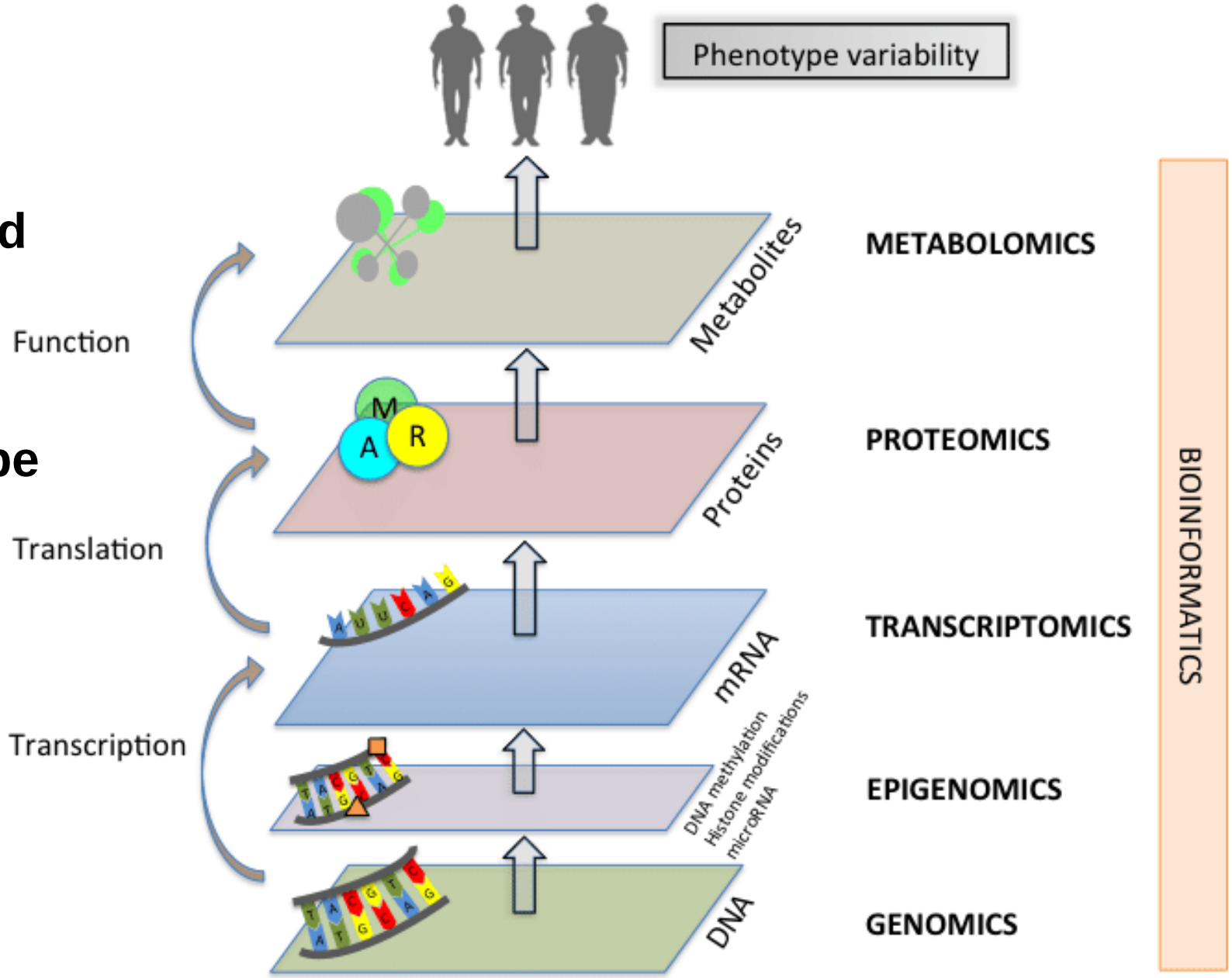
Data by Priyanka Gorijala

# Genome-Wide Association studies

- Obtaining GWAS data for all samples.
  - Previous studies by Sun et al, 2021 already identified one genome-wide significant
    - 919 cases and 1,491 controls
    - Chromosome 3 signal is close upstream of *COL8A1*
    - Defects in *COL8A1* are associated with corneal dystrophy and age-related macular degeneration.
- A larger GWAS in collaboration with Dr. Klein is ongoing with > 5K cases
- PRS analyses suggest very low overlap with AD, but some overlap with PD

# Goal: identify causal and druggable targets

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

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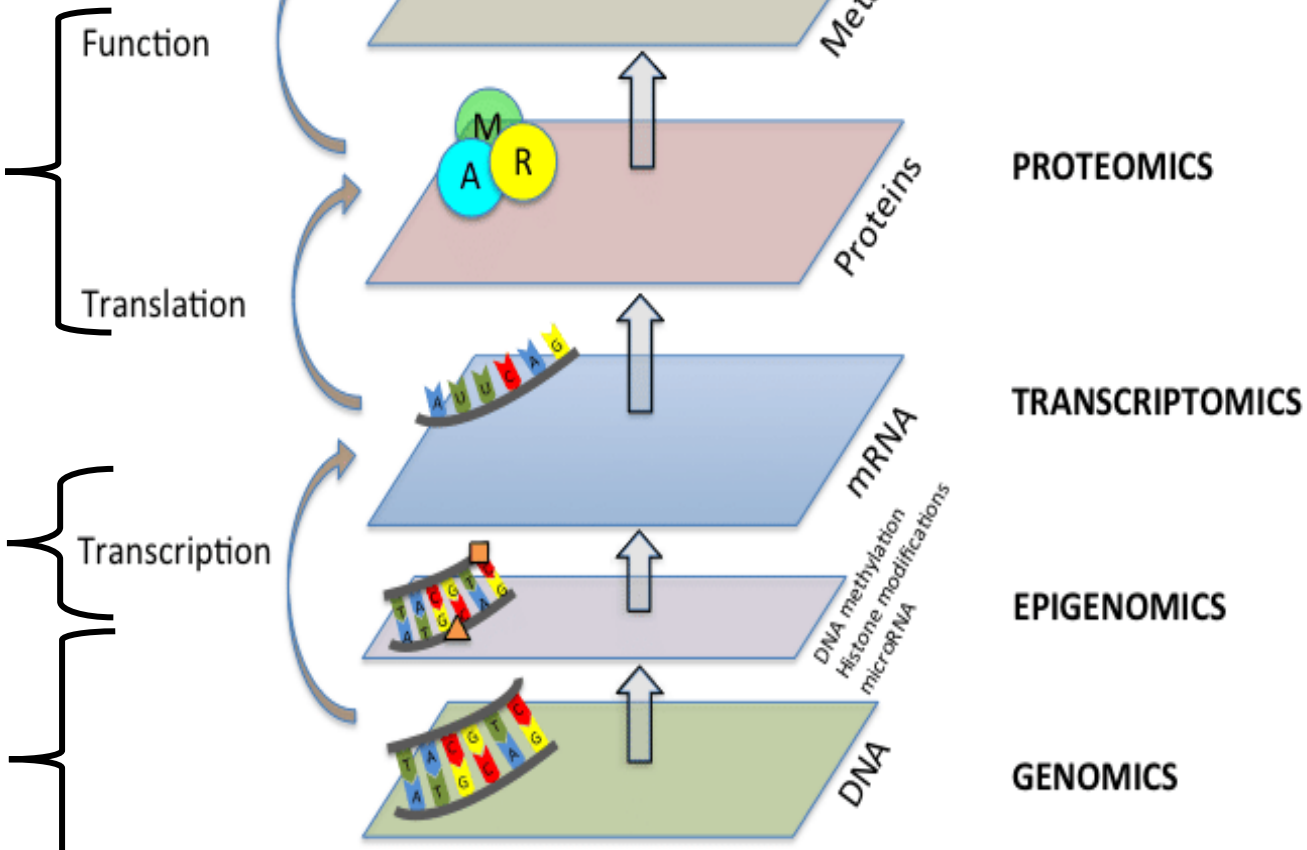
# Genetics is just the first layer

**Plasma**

**Blood-RNA**

**Blood-DNA**

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# 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,*]

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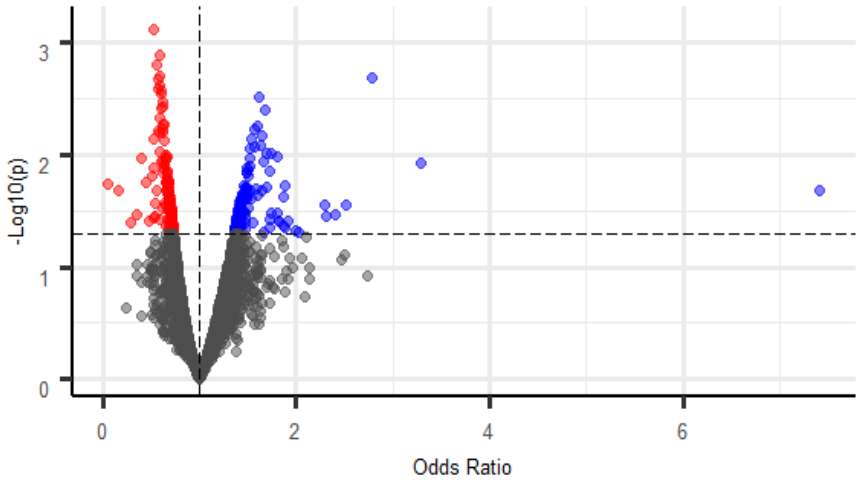


- Plasma samples from 100 cases with idiopathic cervical dystonia and 100 controls
- 7,346 metabolic features remained after quality control
- 289 significantly associated with case-control status

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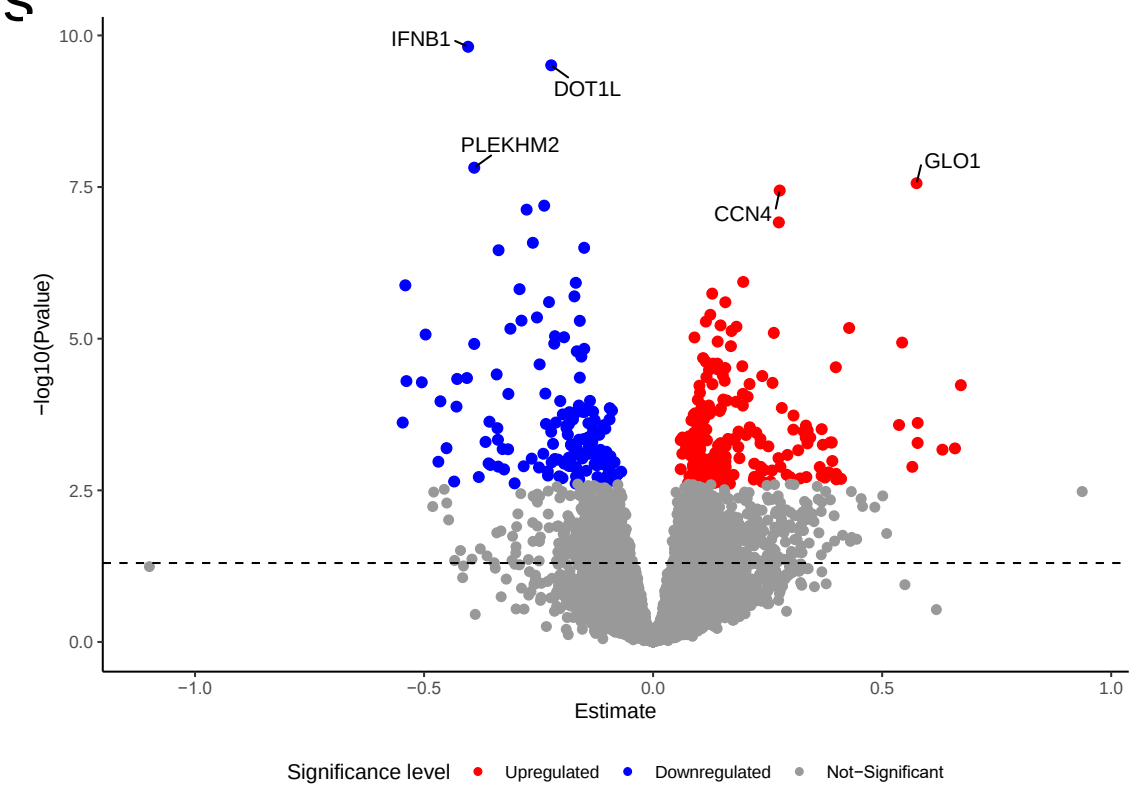
# Other omic studies

- Proteomics:
  - 50 controls and 150 dystonia cases
    - See poster by **Jigyasha Timsina**
    - Emory-WU collaboration
    - Manuscript being drafted
- Transcriptomics
  - RNA available for all new samples
- Methylation
  - Biological vs chronological clocks
  - Differential methylation

**Proteins dysregulated in LD**

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# Summary

- **The goals is to obtain samples that will allow deep molecular characterization 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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