Integrative analysis of mitochondrial changes in Parkinson's disease

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Outline

- Approach for algorithmic biospecimen selection & matching
- Overview of updated PD omics data collection
- Integrated meta-analysis of PD GWAS and transcriptomics data

Algorithmic biospecimen selection & matching

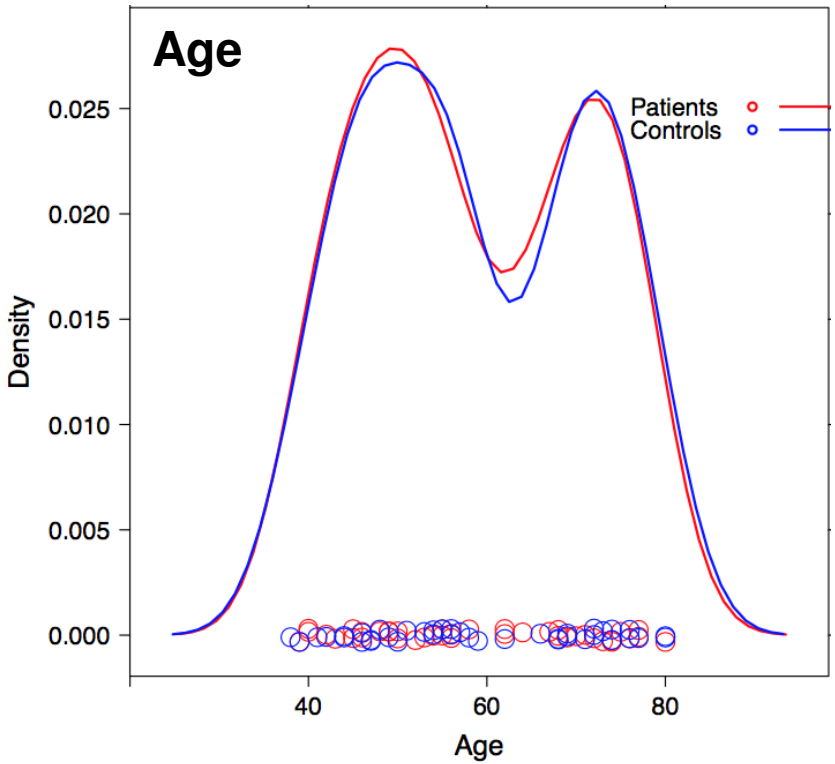
GOAL: Find a selection for a given number of IPD patients and controls, such that

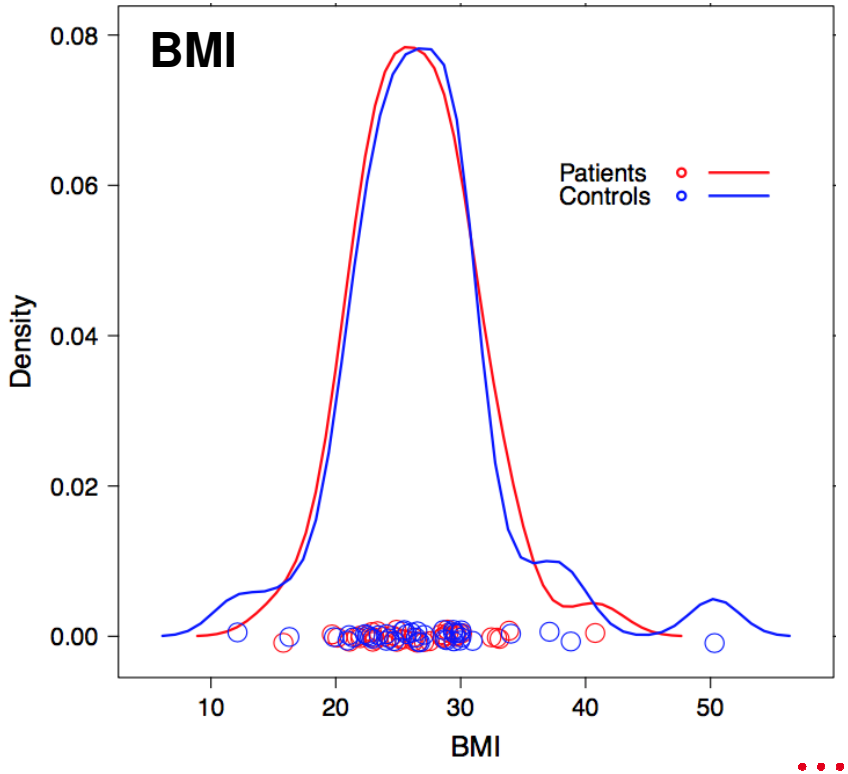
- **Genders** are matched and balanced
- **Age** distributions are matched
- **BMI** distributions are matched
- Occurrence of **hypertension** / use of **arterial medication** is balanced
- Occurrence of other **comorbidities** is reduced and approx. balanced
- Further optional criteria, e.g. focus on **de novo patients** or **early treatment period**

BENEFITS: → Reduces influence of confounding factors on omics analyses
→ Removes unwanted sources of variance

Matched sample selection (LuxPARK blood profiling study)

- **Gender representation**: PD (20 females, 20 males), controls (20 females, 20 males)
- **Arterial medication**: PD (7), controls (6 + 2 unknown)
- **Medication for other symptoms**: PD (6 unknown), controls (1 + 2 unknown)
- **Maximum number of de novo patients included**





Current collection of human PD datasets

Data type	Conditions	Data source
Transcriptomics (Whole blood)*	PD (298), control (331)	DeNoPa, GENEPARK, GEO
Transcriptomics (Substantia nigra)*	PD (92), control (88)	GEO
Metabolomics (Blood plasma)	GC-MS: PD (112), control (65), LC-MS: PD (89), control (90)	DeNoPa, PPMI, Cologne/Marburg
Metabolomics (CSF)	GC-MS: PD (44), control (43)	DeNoPa, PPMI
Resting-state fMRI + FDG/FDOPA PET subsets	PD (149), control (36)	PPMI, Cologne/Marburg
Clinical Data	PD (565), control (590), other (96); PD (159), control (110), other (3); PD (454), control (215), SWEDD (81);	LuxPARK, DeNoPa, PPMI
GWAS†	PD (28,818), control (1,039,955)	dbGAP
Exomes	PD (391), SWEDD (60), control (178)	PPMI

*after filtering out samples failing in ≥ 2 quality tests (ArrayQuality metrics software) †after quality filtering

Collection of PD GWAS datasets for meta-analysis

GWAS data overview:

Study	Conditions	Platform
TREND	PD (1, 298), control (883)	NeuroX chip
LANDSCAPE (Dutch cohort)	PD (772), control (2024)	Illumina Human660W-Quad beadchip
PPMI	PD (383), SWEDD (58), control (178)	NeuroX chip
Nalls et al., Nat. Genet., 2014 (pre-processed data from 15 independent GWAS datasets of European descent)	PD (13,708), control (95,282)	Multiple Illumina GWAS platforms

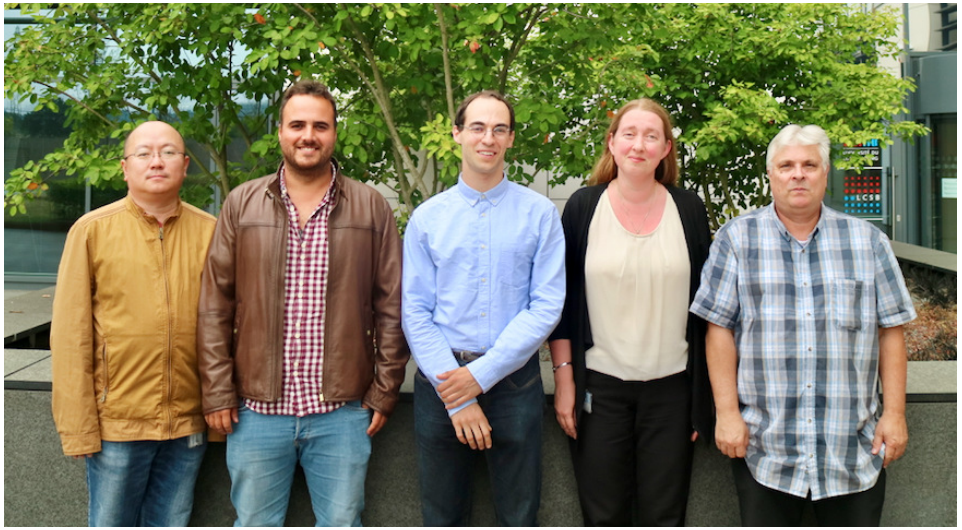
Mitochondrial genes in the meta-analysis of GWAS data

Determine mitochondrial genes containing SNPs with putative PD associations from the meta-analysis of GWAS datasets ($p < 1E\text{-}05$, MitoFDR < 0.3)

Gene Symbol	Description	MitoFDR
MCCC1*†	methylcrotonoyl-CoA carboxylase 1 (alpha)	0
MALSU1	mitochondrial assembly of ribosomal large subunit 1	0
SLC25A20	Solute Carrier Family 25 Member 20	0
NDUFAF2	NADH dehydrogenase (ubiquinone) complex I, assembly factor 2	0.01
SPATA19	spermatogenesis associated 19	0.012
ABCB9†‡	ATP-binding cassette, sub-family B (MDR/TAP), member	0.036
DNAH17	dynein axonemal heavy chain 17	0.071
QARS‡	Glutaminyl-TRNA Synthetase	0.077
NSF†‡	N-ethylmaleimide sensitive factor, vesicle fusing ATPase	0.101
PPT2‡	palmitoyl-protein thioesterase 2	0.119
NAGLU†	N-acetyl-alpha-glucosaminidase	0.15
TUBG1‡	Tubulin Gamma 1	0.199
C2	Complement C2	0.227
FDFT1†	farnesyl-diphosphate farnesyltransferase 1	0.232
VARS†‡	valyl-tRNA synthetase	0.239
FKBPL	FK506 binding protein like	0.267

*previously shown to contain genome-wide significant SNPs, Nalls et al., 2014
Differentially expressed in transcriptomics meta-analysis: †whole-blood, ‡brain

Acknowledgements



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- **Jens Schwamborn**
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