

Genetic variation influences the severity of multiple phenotypes in Parkinson's Disease

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Phenotypic variability in Parkinson's Disease

Motor phenotypes:

- Tremor
- Bradykinesia
- Rigidity and freezing
- Posture and gait

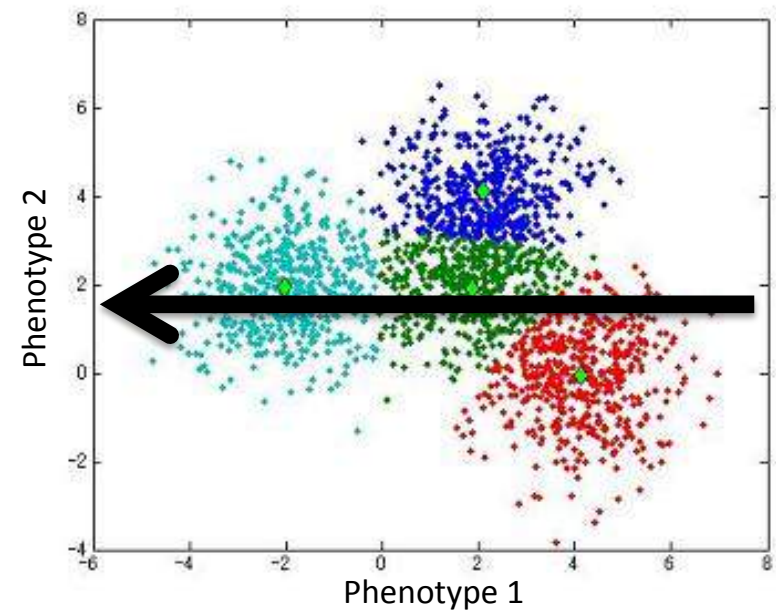
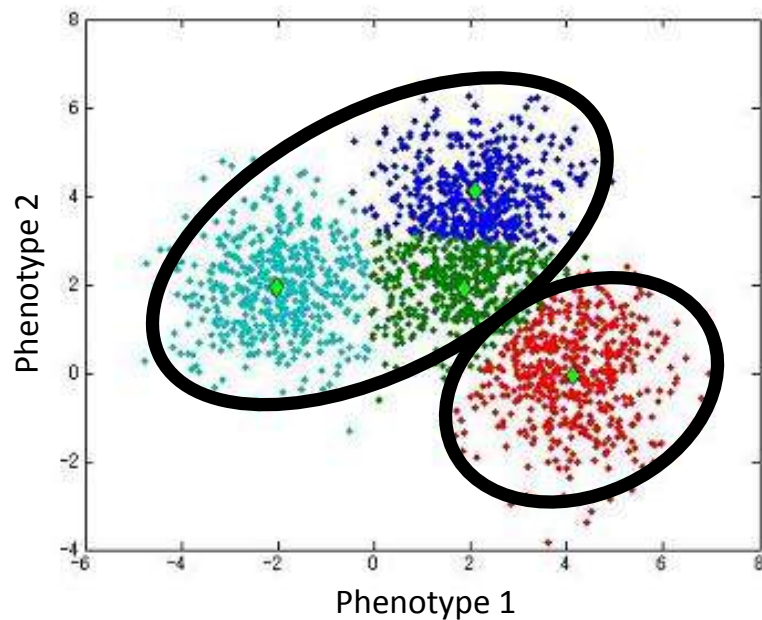
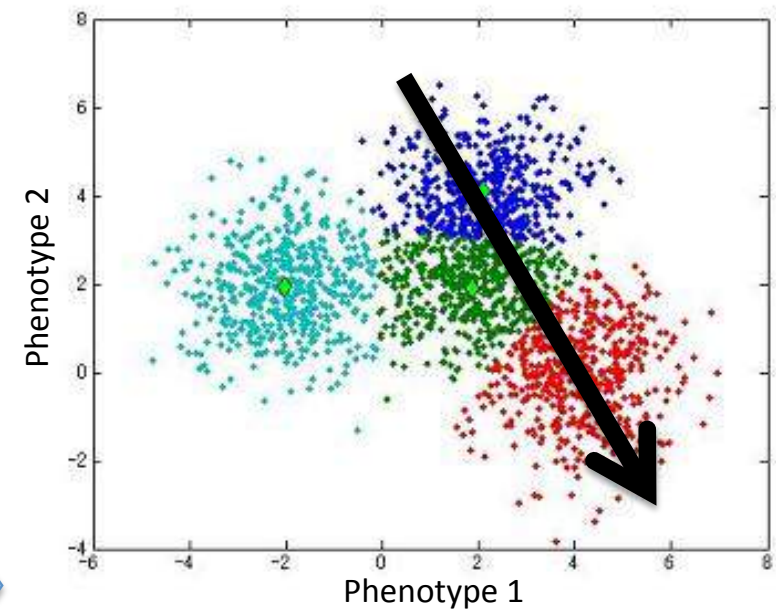
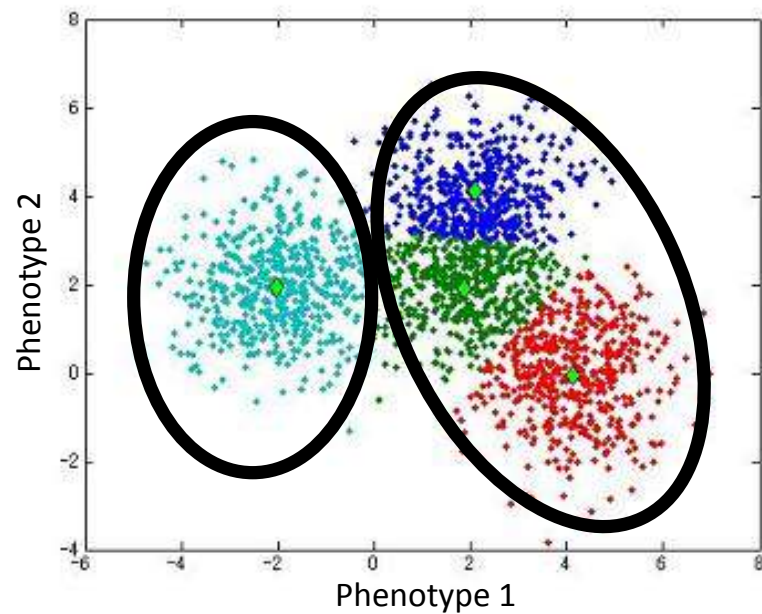
Neurological phenotypes:

- Anxiety
- Depression
- Cognitive decline

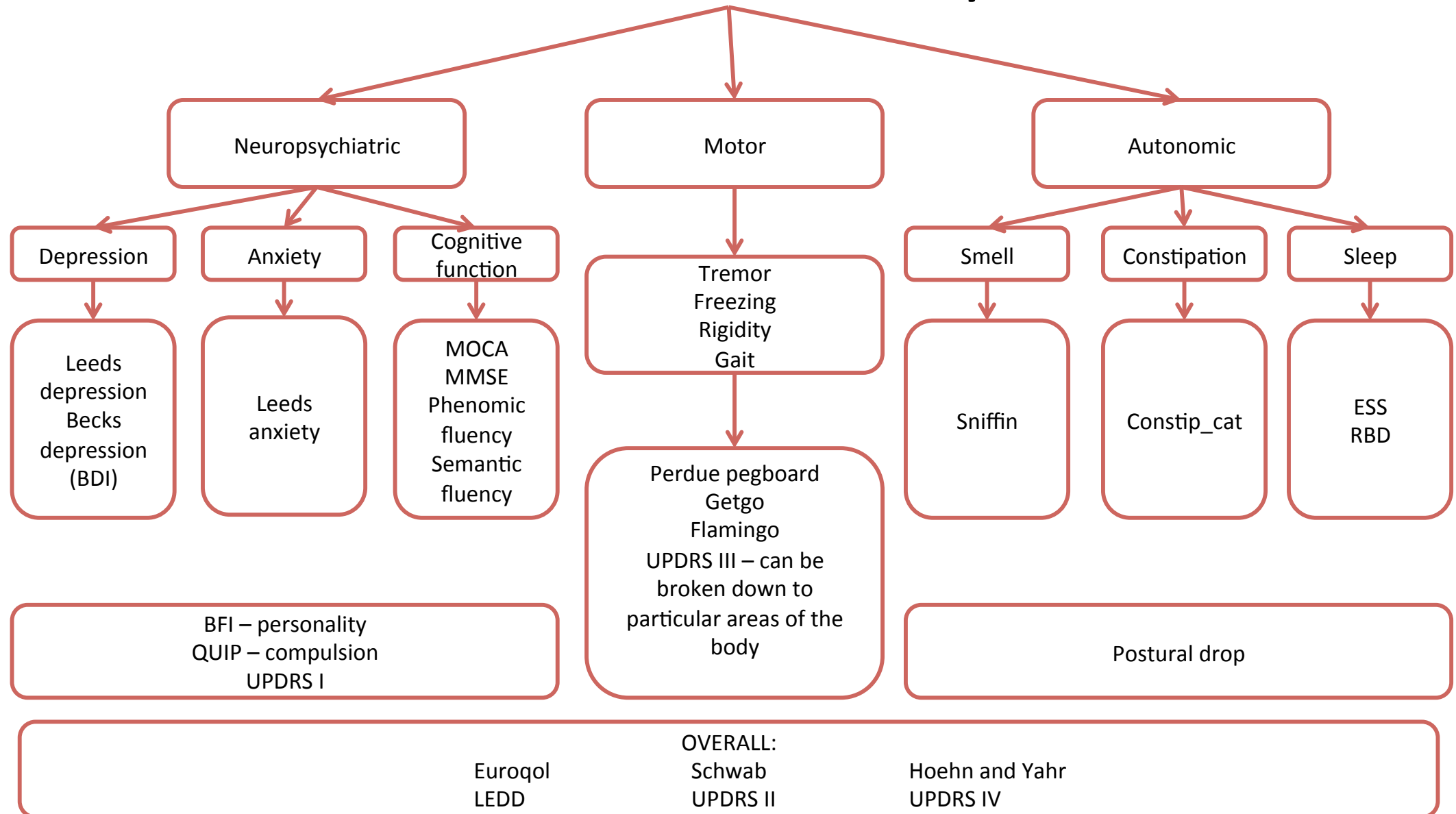
Autonomic phenotypes:

- Sleep disturbance
 - Smell loss
 - Constipation
- Response to medication

Concept: moving from discrete to continuous phenotypes



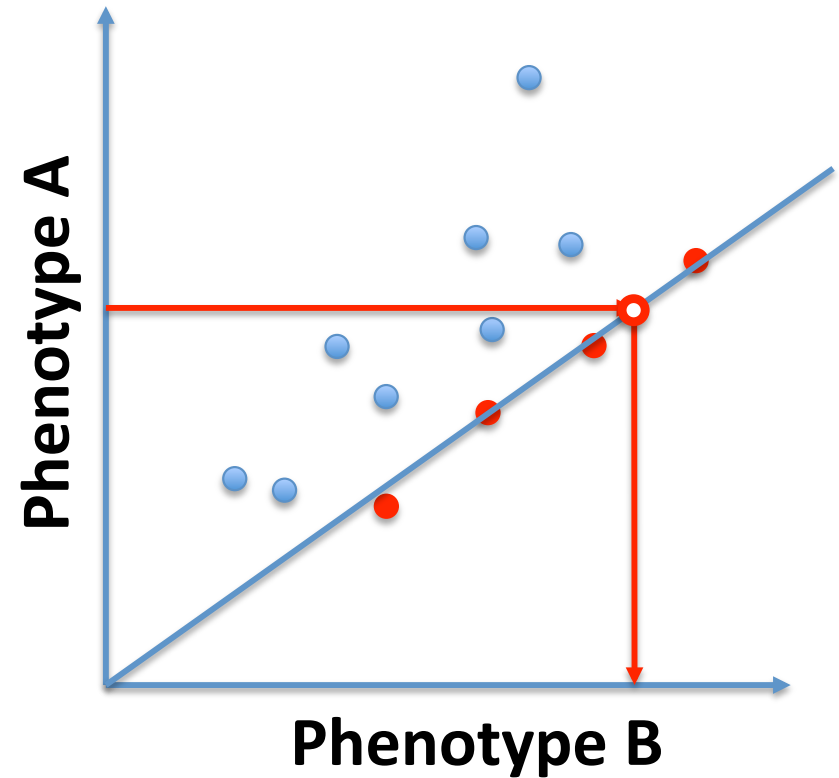
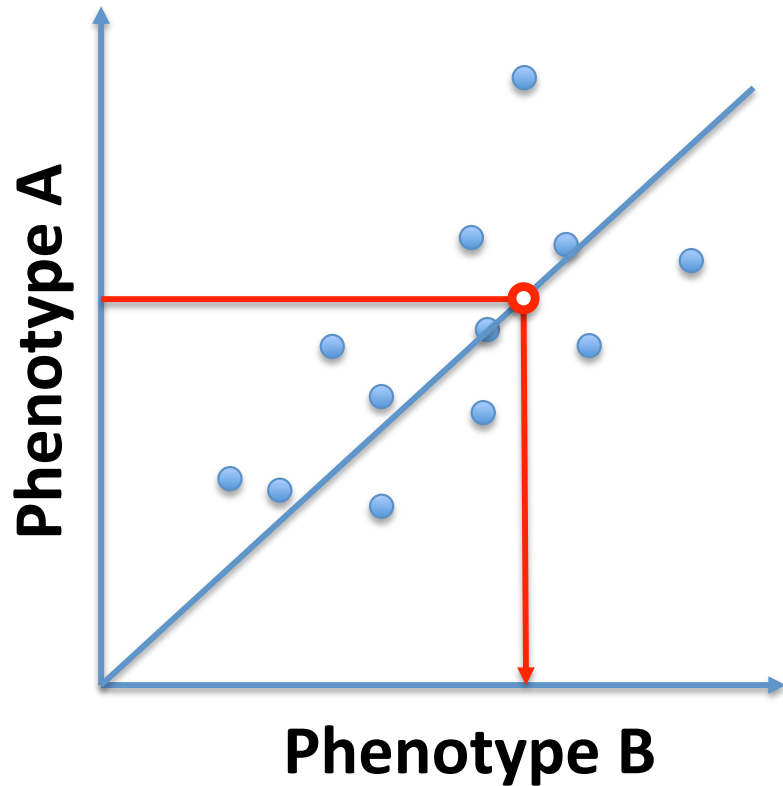
Phenotype measures in the Oxford Parkinson's Disease Centre Discovery Cohort



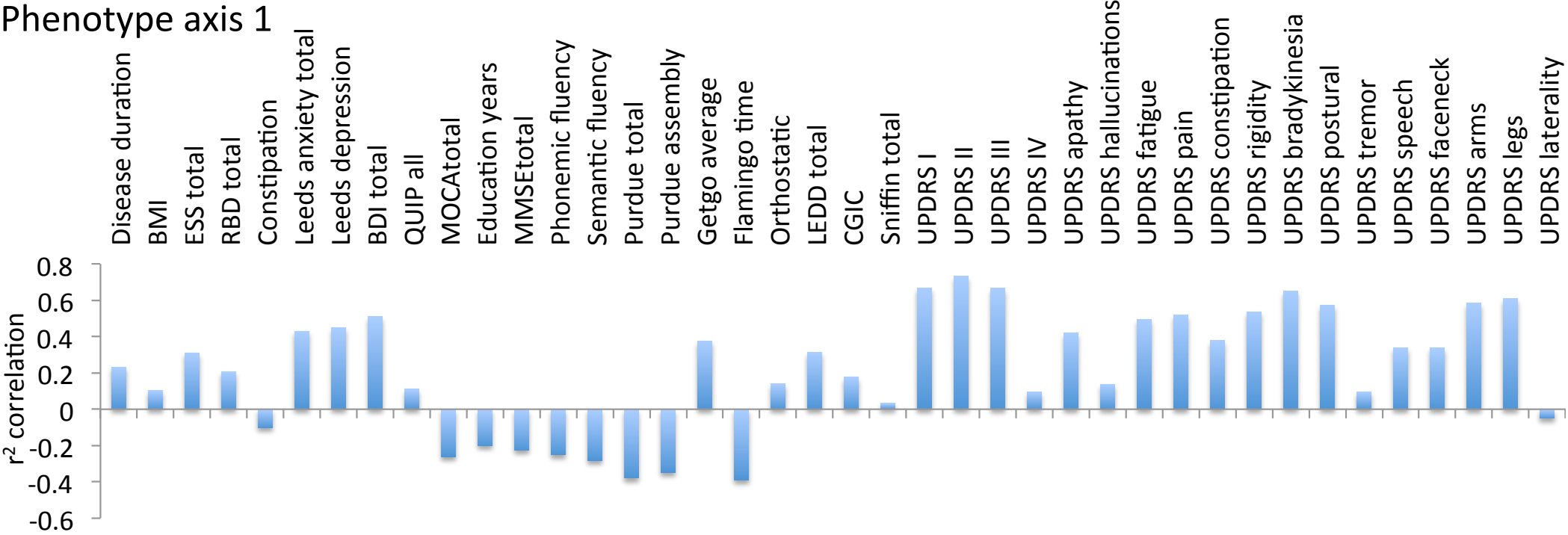
Dahl, A., et al., *A multiple-phenotype imputation method for genetic studies.*

Nature Genetics, 2016. **48**(4): p. 466-+

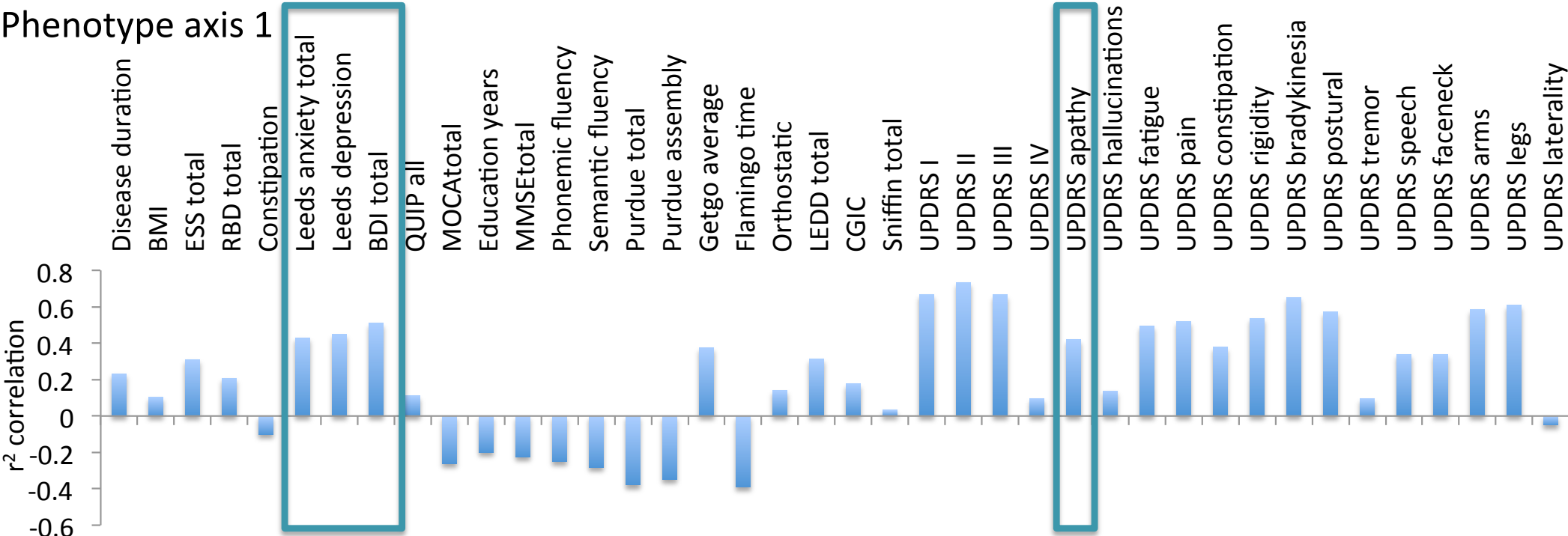
Identifying the underlying phenotypic axes,
incorporating genetic similarity using PHENIX.



Phenotype axis 1



Phenotype axis 1



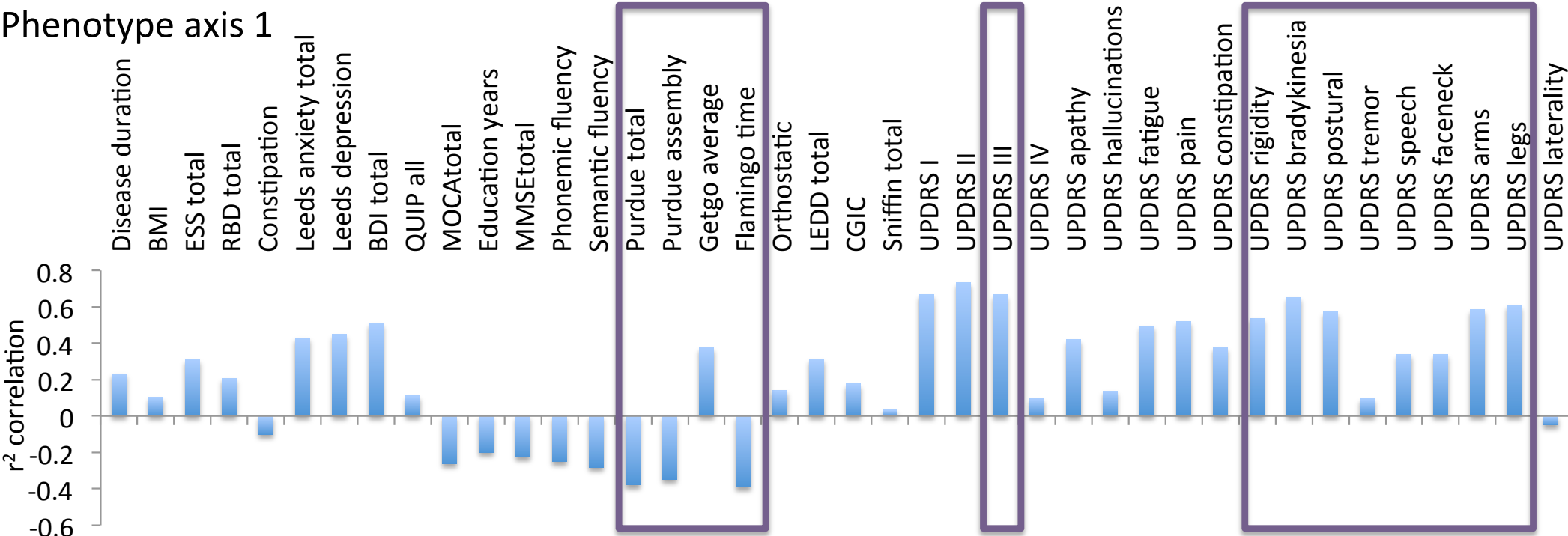
Increasing score



Anxiety and depression



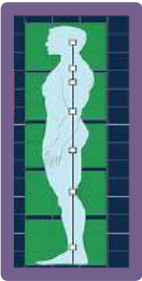
Phenotype axis 1



Increasing score →



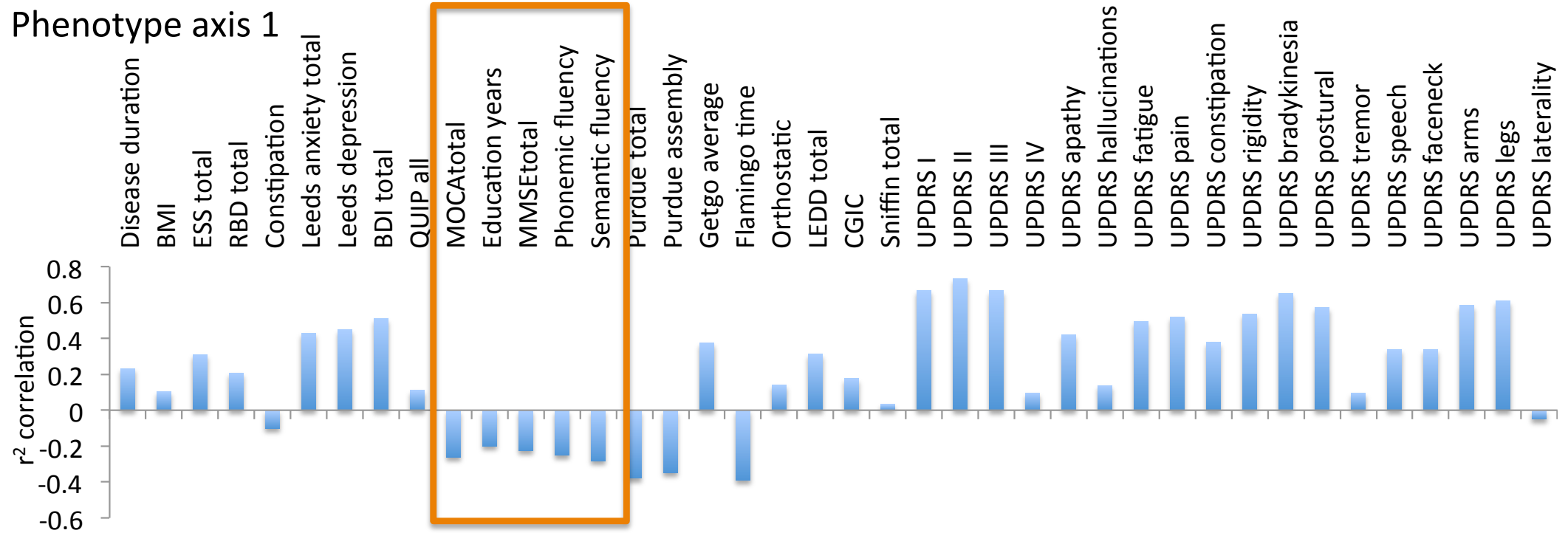
Anxiety and depression



Motor symptoms



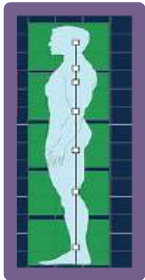
Phenotype axis 1



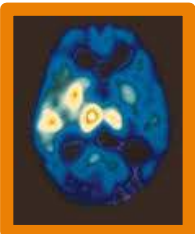
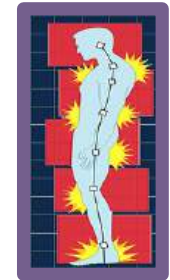
Increasing score →



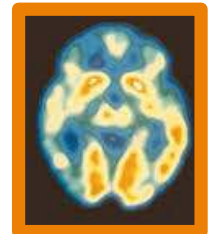
Anxiety and depression



Motor symptoms



Cognitive impairment



6 phenotypic axes identified

Phenotype axis 1

Worsening anxiety, depression and non-tremor motor but minimal cognitive decline

Phenotype axis 2

Worsening anxiety, depression and autonomic symptoms but minimal motor dysfunction

Phenotype axis 3

Rigidity, bradykinesia and tremor in limbs, face and neck

Phenotype axis 4

Tremor dominant, unilateral symptoms

Phenotype axis 5

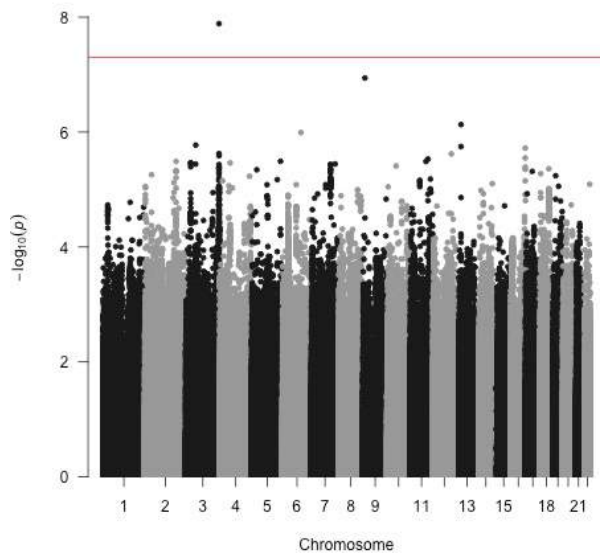
Worsening posture and speech but minimal tremor

Phenotype axis 6

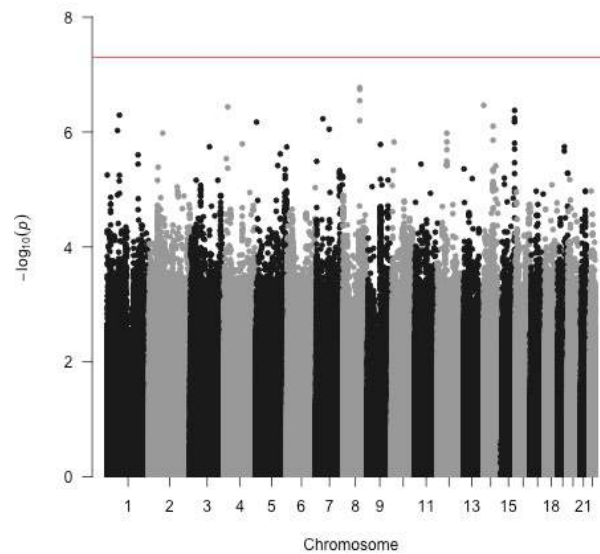
Worsening mobility and whole-body movement but minimal tremor or bradykinesia

Logistic regression along phenotype axes

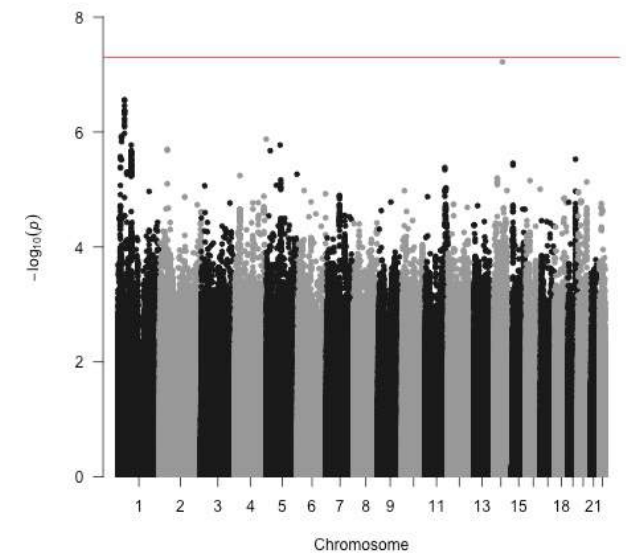
Phenotype axis 1



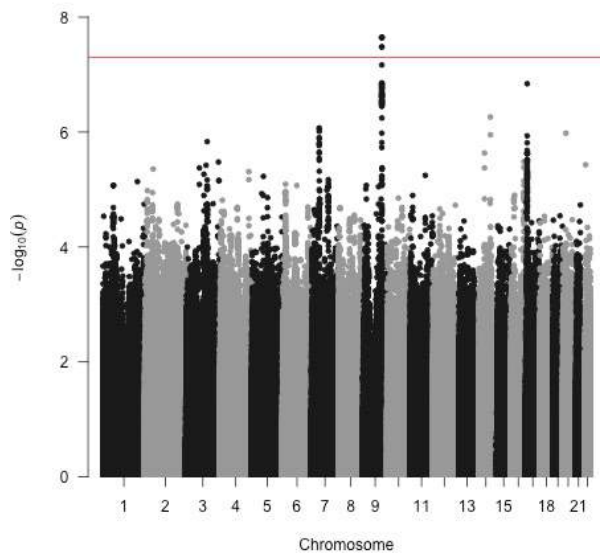
Phenotype axis 2



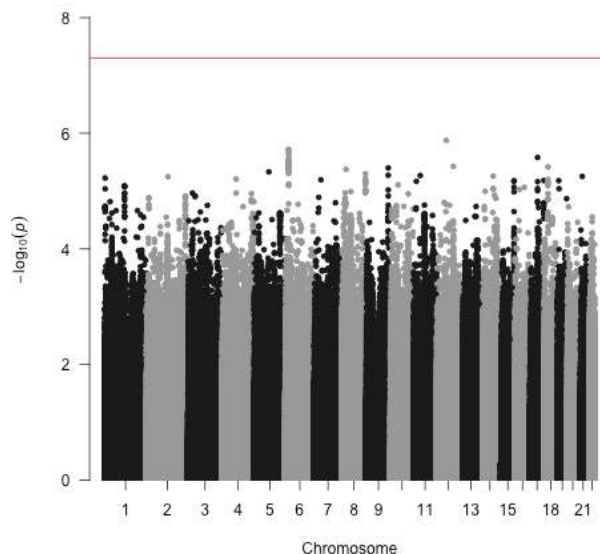
Phenotype axis 3



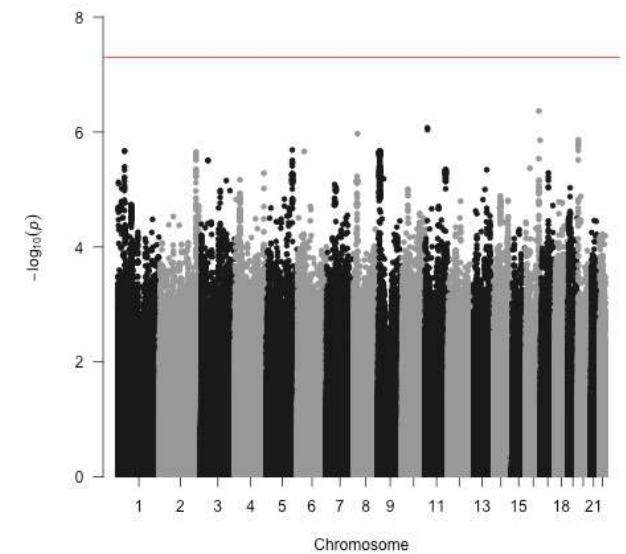
Phenotype axis 4



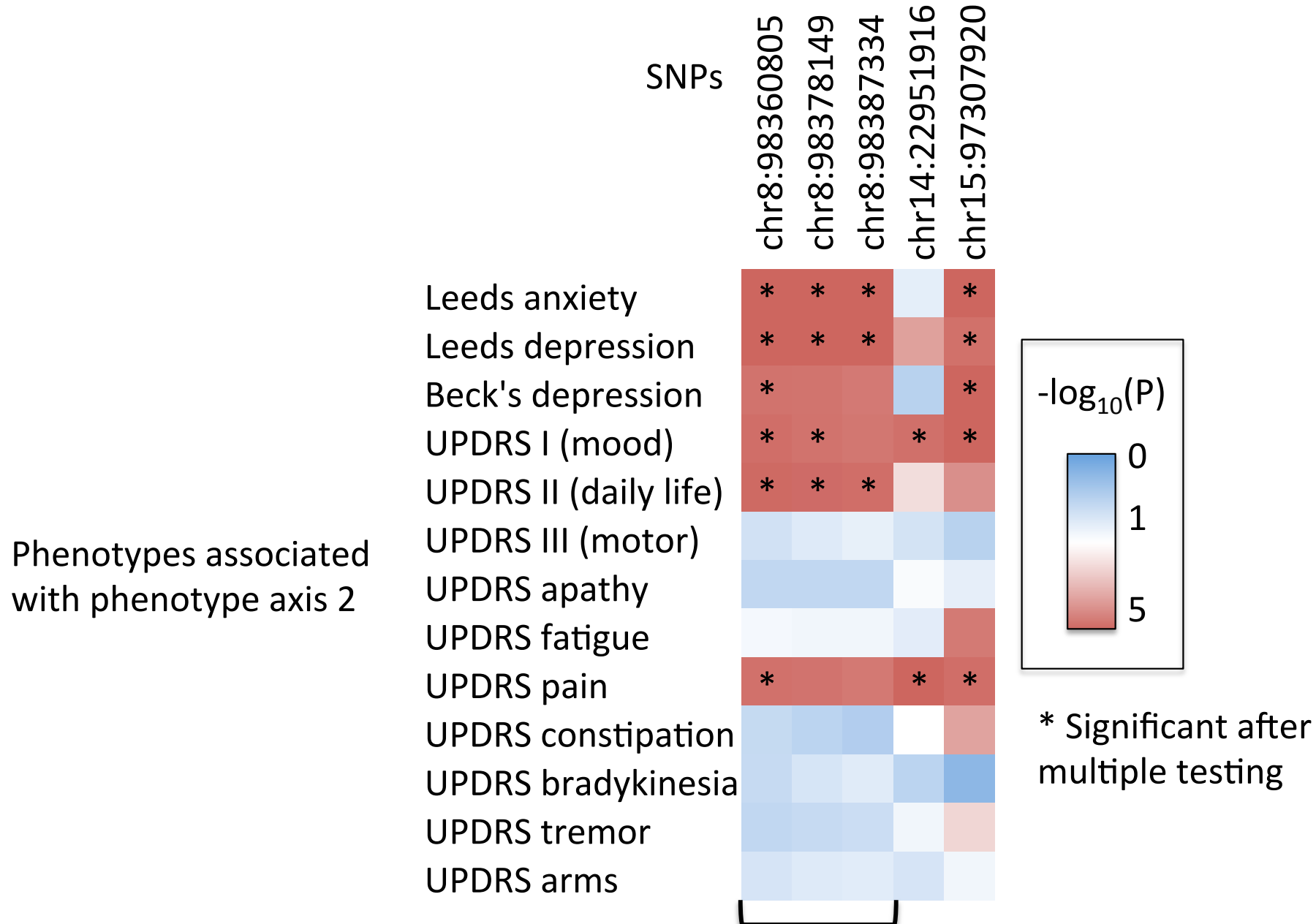
Phenotype axis 5



Phenotype axis 6



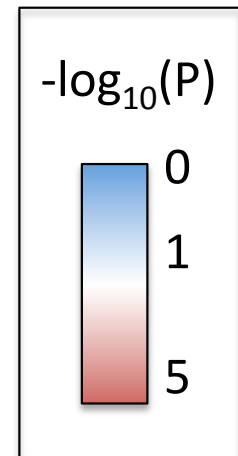
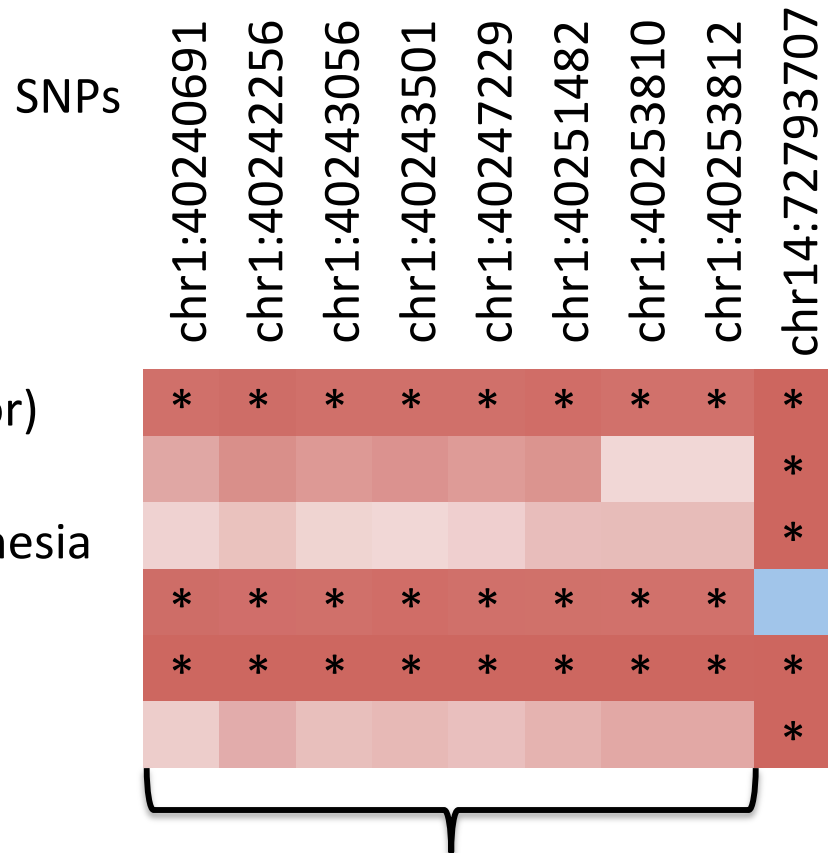
Genetic variants are associated with severity of clinical phenotypes



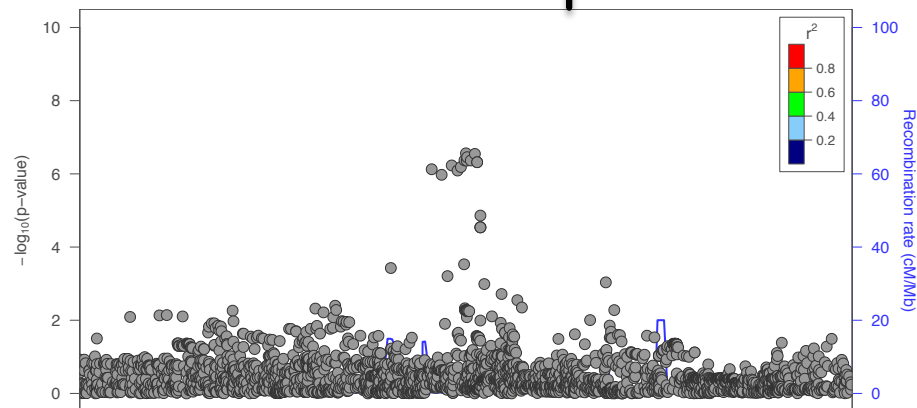
Genetic variants are associated with severity of clinical phenotypes

Phenotypes associated with phenotype axis 3

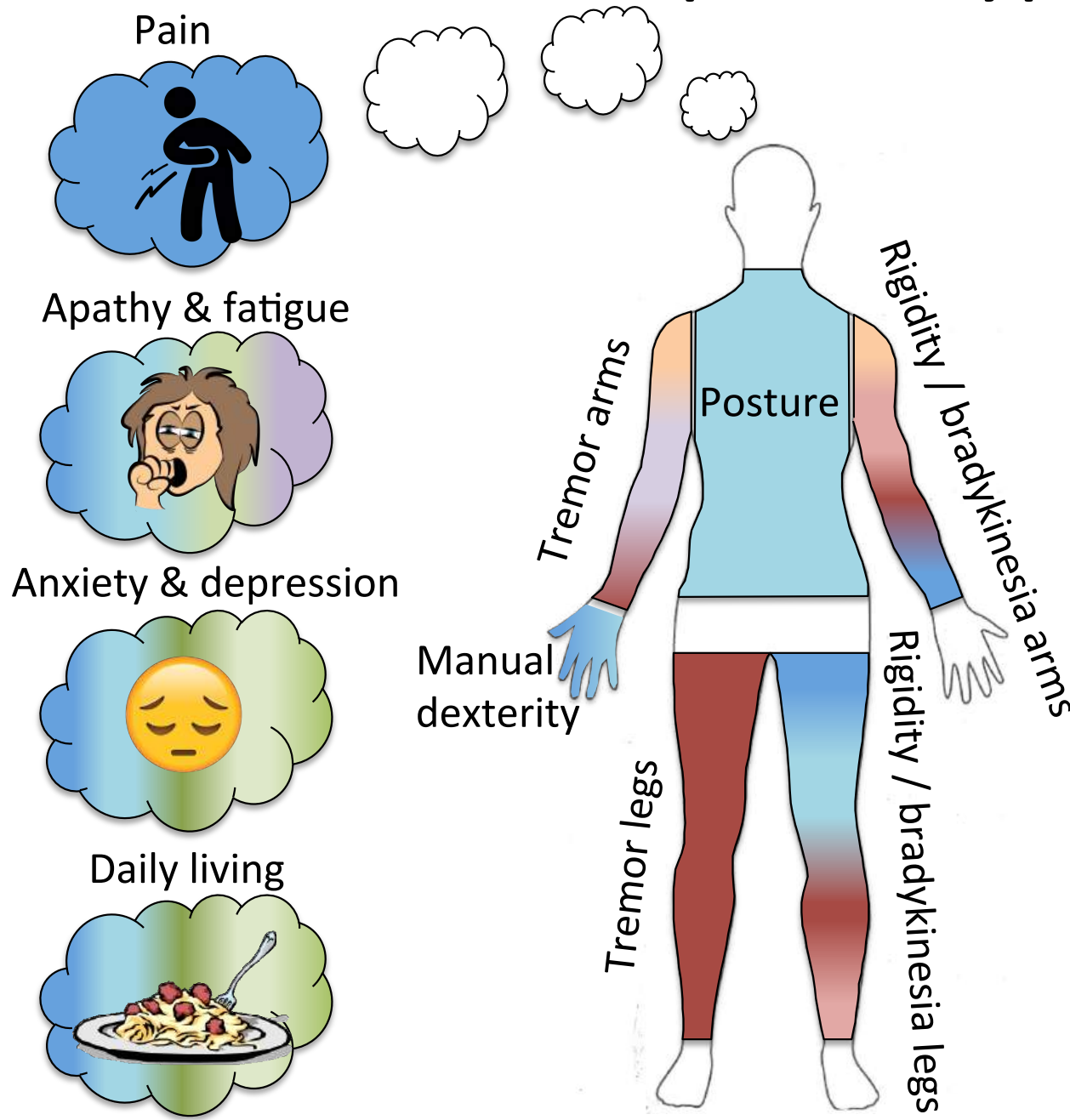
UPDRS III (motor)
UPDRS rigidity
UPDRS bradykinesia
UPDRS tremor
UPDRS arms
UPDRS legs



* Significant after multiple testing



Genetic regions affect distinct patterns of phenotypes



Genetic regions

Chr 3:194252539

Chr 9:9852889

**Chr 8:98360805-
98387334**

Chr 14:22951916

Chr 15:97307920

**Chr 1:40240691-
40253812**

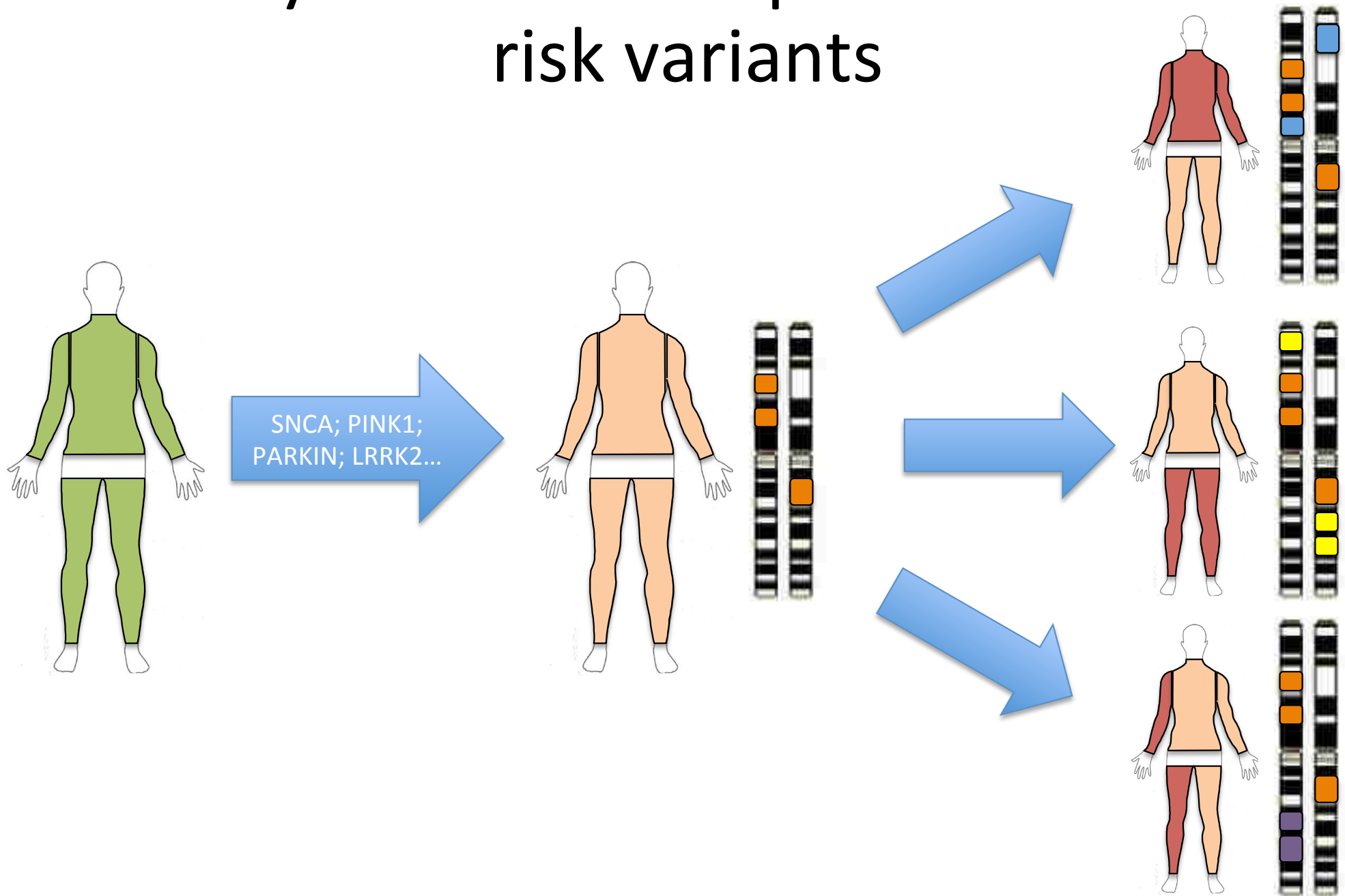
Chr 14:72793707

**Chr 9:109461301-
109489362**

Chr 17:7511934

Chr 16:78331954

Genetic regions affecting phenotype severity do not overlap with known PD risk variants



Conclusions

- The continuum of phenotypes observed in the clinic can be meaningfully represented by phenotypic axes
- 59 variants in 10 genomic regions were significantly associated with specific patient phenotypes with a modestly-sized cohort
- Genetic regions affecting phenotype severity do not overlap with known PD risk variants

Acknowledgements

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