Structural models of genome-wide covariance explain variation in autism spectrum disorder symptoms

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Why study heterogeneity in ASD symptoms with common genetic variation?

- 50% of ASD genetic variance due to **common variants**[1]
- Clinical ASD subcategories are **genetically heterogeneous**[2]
- Little characterization of genetic variance structures in ASD

Study design

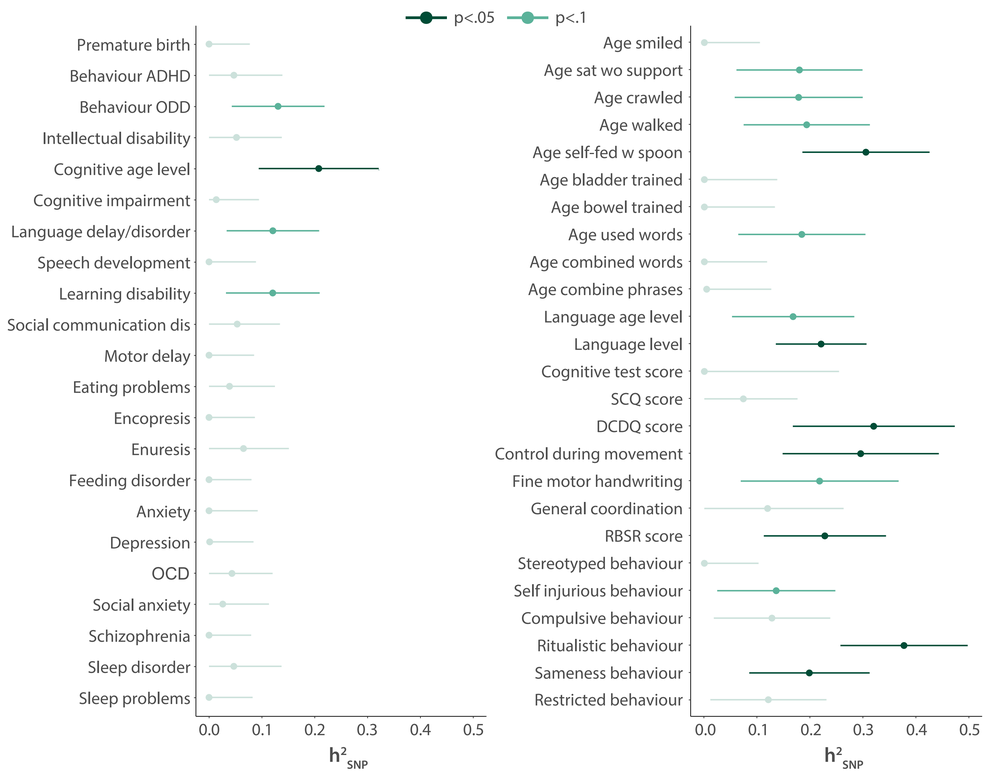
SNP-heritability analysis → select symptoms with trend for h^2_{SNP} (p<.1) → **Genetic correlation analysis** → cluster correlated phenotypes (r_G p<.1) → **Multivariate modelling analysis**

Sample

5,331 unrelated ASD probands (IBD<.05, Illumina N_{SNPs}=458,573) of European descent from the **SPARK**[3] cohort were included in the analysis. Individuals with non-genetic cognitive impairments were excluded.
47 co-ocurring developmental, cognitive and motor symptoms were selected from available SPARK symptoms (n=123). Among those, 17 phenotypes with a trend for h^2_{SNP} were subjected to GCTA-r_g and GRM-SEM analysis.

1 Which ASD symptoms show genetic heterogeneity?

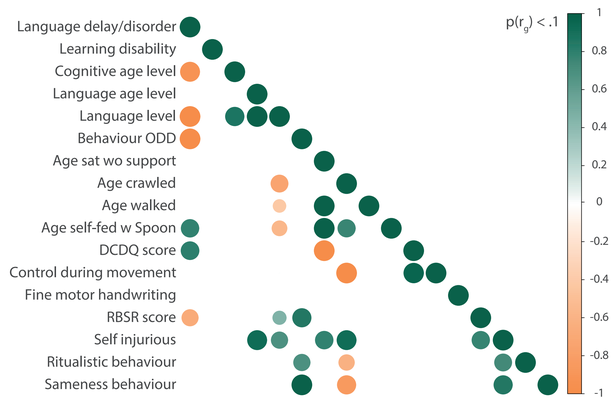
- **Strongest symptom heterogeneity in ASD: ritualistic behaviour (h^2_{SNP}=0.38 (SE=0.12), p=0.00093).**
- **Symptom heterogeneity was observed across the repetitive RBSR symptom spectrum and for multiple cognitive and developmental symptoms.**



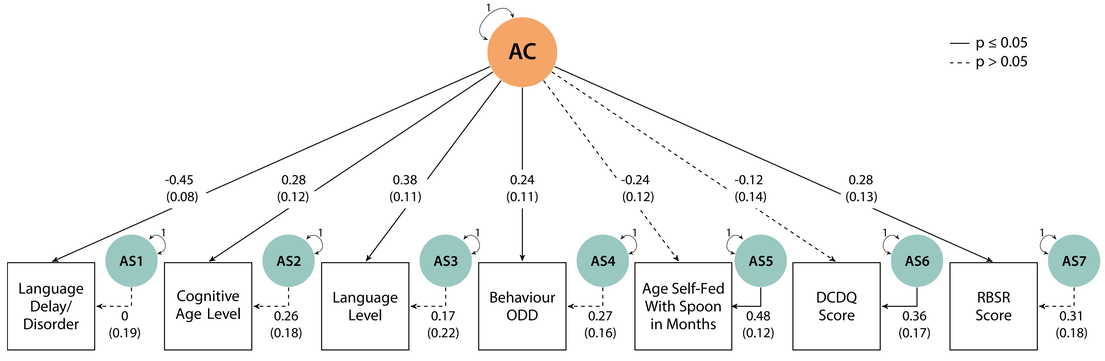
GCTA[4] SNP-heritability (h^2_{SNP}) captures polygenic heterogeneity in ASD.
21 categorical (prevalence > 5%) and 26 continuous phenotypes were examined (experiment-wide p<.0015). For categorical symptoms, deviance residuals were used and rank-transformed residuals for continuous symptoms.

2 Are there distinct overarching genetic factors in ASD?

- **A shared genetic factor in ASD links language delay/disorder symptoms inversely to higher cognitive age and language level as well as more oppositional behaviour and repetitive symptoms.**



	Cholesky	IPC
LL	-13,343.57	-13,348.88
$N_{PARAMETERS}$	56	42
df	0	14
AIC	26,799.13	26,781.76
BIC	27,167.14	27,057.76
LRT p-value		0.715



GCTA[4] genetic correlations (r_G) capture symptom correlations in ASD.
Multivariate genetic analyses of heritable and genetically interrelated symptoms (by trend, p<.1) were conducted with genetic-relationship-matrix structural equation modelling (grmsem[5]), using hybrid IPC (Independent Pathway: genetic part; Cholesky: residual part) models to identify shared genetic influences across symptoms.

(1) Gaugler et al. (2014) Nat Genet 46:881–885; (2) Lai et al. (2014) The Lancet 383:896–910; (3) https://sparkforautism.org/;
(4) Yang et al. (2011) Am J Hum Genet 88:76–82; (5) St Pourcain et al. (2018), Biol Psychiatry 83 (7): 598-606

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