Genome-wide assessment of genetic modifiers in ALS progression

Brain Center
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Introduction

- Largest genome-wide association study in amyotrophic lateral sclerosis (ALS) (n=29,612 patients), identified **15 SNPs significantly related to ALS risk** (1).
- The identified SNPs showed overall **little effect on ALS progression** individually or when used as constructed polygenic risk scores (PRS).
- This could imply **different biological mechanisms** are involved in ALS susceptibility compared to ALS progression which could have extensive therapeutic consequences.

Objectives and methods

We aim to **unravel the genetic architecture of disease progression** and more specifically to identify SNPs and biological processes associated with ALS progression

To achieve this we:
- Collected and harmonized clinical and genotyping data
- Adopted a **cox proportional hazards model in a mixed model framework** correcting for population structure, relatedness and added site of onset, cohort, platform, sex, and PC1-20 as covariates (2).

Results

Step 1: Phenotyping QC:
Biologically invalid values, extreme/inconsistent values.
Step 2: Genotype QC:
MAF> 0.01, remove duplicate samples, no imputation

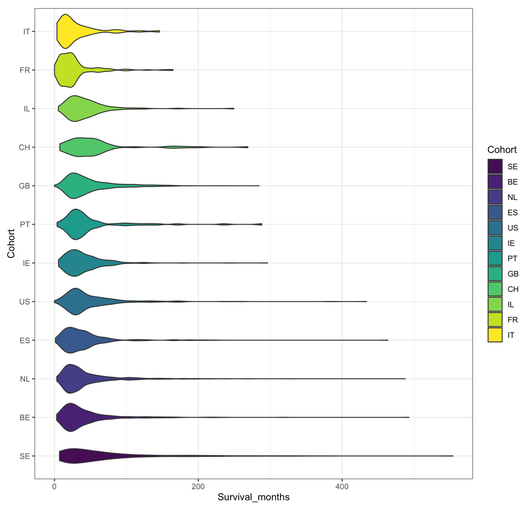

Figure 1: Survival of samples included in the pilot, separated by cohort.

Pilot WGS ((N=6124)	
Sex at birth	
female	2460 (40.2%)
male	3664 (59.8%)
Site of Onset	
bulbar	1693 (27.6%)
FTD	4 (0.1%)
generalized	215 (3.5%)
spinal	4028 (65.8%)
thoracic/respiratory	109 (1.8%)
Age at onset years	
Mean (SD)	60.4 (12.5)
Median [Min, Max]	61.8 [5.69, 100]
Survival (months)	
Mean (SD)	44.3 (42.7)
Median [Min, Max]	32.0 [0, 554]
Survival status	
alive	1532 (25.0%)
dead	4592 (75.0%)
C9ORF72 Status consensus	
expanded	354 (5.8%)
inconsistent	32 (0.5%)
intermediate	18 (0.3%)
normal	5719 (93.4%)

Table 1: Demographic and clinical characteristics of pilot.

Total sample overview		Remark
MinE WGS (17 cohorts)	6,124	analyzed
NYGC-GTAC	3,000	ready2go
MinE GWAS (13 cohorts)	6,940	Matched >4,000
MinE 2022	600	in progress
NL WGS	1,000	in progress
New collaborators?	?	
Total	**17,500+**	

Please contact us if you have data avialable

Table 2: Total overview of (expected sample size) separated by stratum. *included in the pilot

Step 3: Cox proportional hazards mixed model (SAIGE)

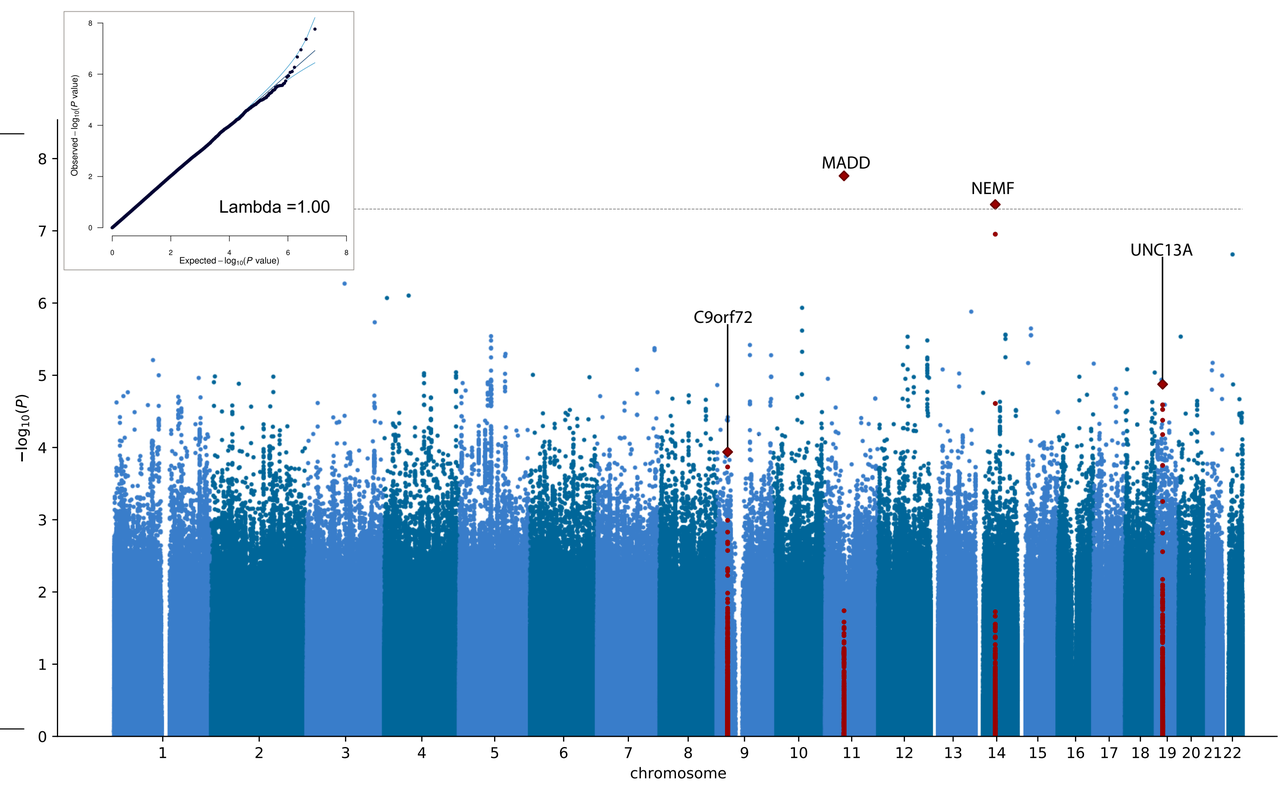

Figure 2: Manhattan from N=6,124 ALS patients with matching WGS and clinical data (no imputation, MAF>0.01). Nearest gene annotation (except for C9orf72). Identified two new low-frequency SNPs (MAF= 0.008/0.015).

Discussion

- This analysis **identified two significant low-frequency SNPs** on chromosomes 11 and 14 just passing genome-wide significance, not seen before in our case control GWAS
- **Confirmed previously identified signals** for C9orf72 and UNC13A (although not genome-wide significant).

- This motivates further increasing sample size for future analyses.

Future directions

- We are currently collecting clinical and genotype data for 10,000 ALS patients (17,500+ including pilot)
- Correct for SNPs known to influence survival (C9orf72)
- Combine with our repeat expansion imputation panel (under development)
- Investigate the genetic correlations with susceptibility GWAS
- Heritability

End goal: **Identification of new therapeutic targets specifically related to ALS progression**.

Literature:

1. van Rheenen et al., “Common and Rare Variant Association Analyses in Amyotrophic Lateral Sclerosis Identify 15 Risk Loci with Distinct Genetic Architectures and Neuron-Specific Biology.”
2. Dey et al., “An Efficient and Accurate Frailty Model Approach for Genome-Wide Survival Association Analysis Controlling for Population Structure and Relatedness in Large-Scale Biobanks.”

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project MinE Make it yours

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