A framework to integrate genome-wide CRISPR functional genomics screens with human genetics to nominate novel therapeutic targets in ALS

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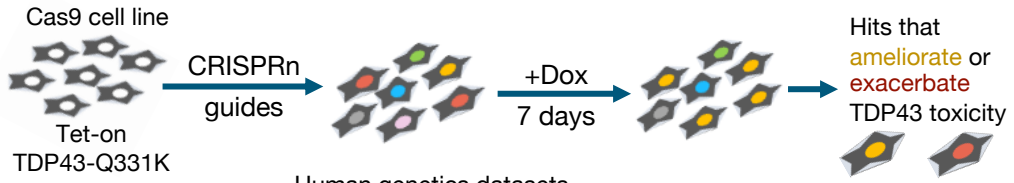
ASHG VIRTUAL MEETING 2020 OCTOBER 27-30

Background

- Human genetic analyses and functional genomic screens represent two powerful, orthogonal approaches for drug target discovery
- Both approaches have caveats : arbitrarily defined statistical thresholds to define 'hits', limits in power, difficulty in prioritizing hits as targets
- Integrating both approaches requires a statistical framework that is generalizable across any CRISPR screen – human genetics analysis pair

Approach

- Focus on amyotrophic lateral sclerosis (ALS)
- tractable cellular models
- publicly available human genetics data
- genetic modifiers previously identified in screens
- TDP43 cytoplasmic aggregates observed in 97% of all ALS patients



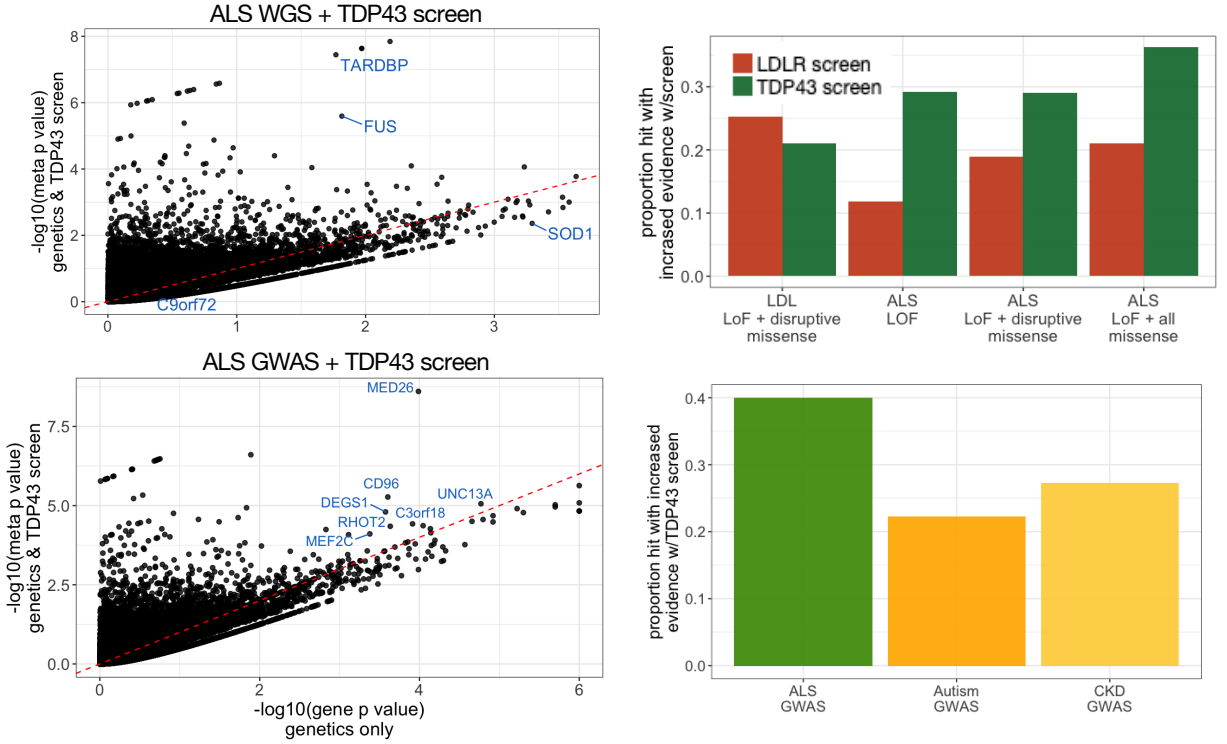
Human genetics datasets

Non-ALS datasets for calibration

	ALS WGS[1]	Sporadic ALS GWAS[2]	LDL-C WGS[3]	Autism GWAS[4]	CKD GWAS[5]	LDLR CRISPR screen[6]
N Case :	4,366	20,806	16,324	18,381	64,164	Published FACS-based screen
N Ctrl :	1,832	59,804	NA	27,969	625,219	

Results

- Integration of TDP43 screen with ALS rare variant analysis re-identifies known ALS risk genes and additional putative targets
- Comparison of relevant human genetics – CRISPR screen pairs captures more putative targets than the inverse



Next steps

- Follow up on putative targets : validation and counter screen
- Incorporating more human genetics data
- Incorporating effect size and directionality
- Additional biologically relevant CRISPR screens

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References:
1. Project Mine ALS Sequencing Consortium *EJHG* (2019)
2. Nicolas et al *Cell* (2018)
3. Natarajan et al. *Nature Communications* (2018)
4. Grove et al *Nature Genetics* (2019)
5. Wuttke et al *Nature Genetics* (2019)
6. Smith et al *bioRxiv* (2020)

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