Understanding Human Disease through Millions of Tandem Repeats across Millions of Genomes

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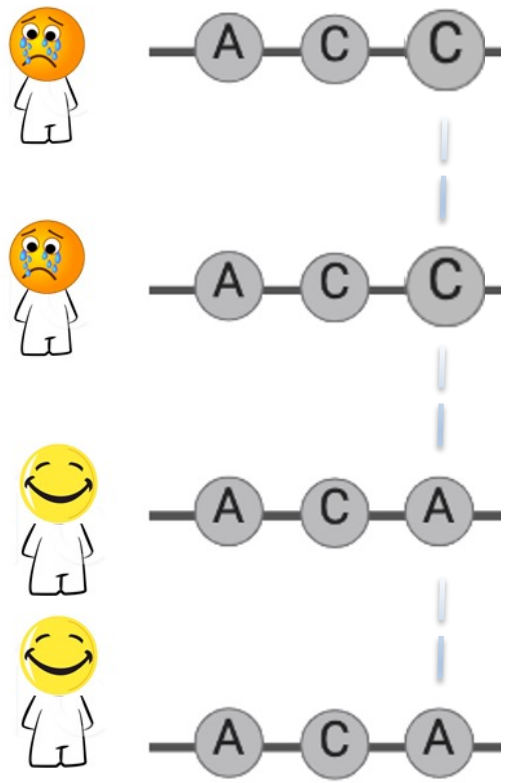
COI Disclosures: ChosenMed and Helio Genomics

Germline SNPs and Somatic Mutations Associated with Diseases



Challenges in SNP Association Studies

- **Missing Diagnosis**
  - **>60%** of rare genetic diseases remain undiagnosed.
- **Missing Heritability**
  - in common genetics disease like prostate cancer, breast cancer, and diabetes
  - **>50%** patients not explained by GWAS SNPs

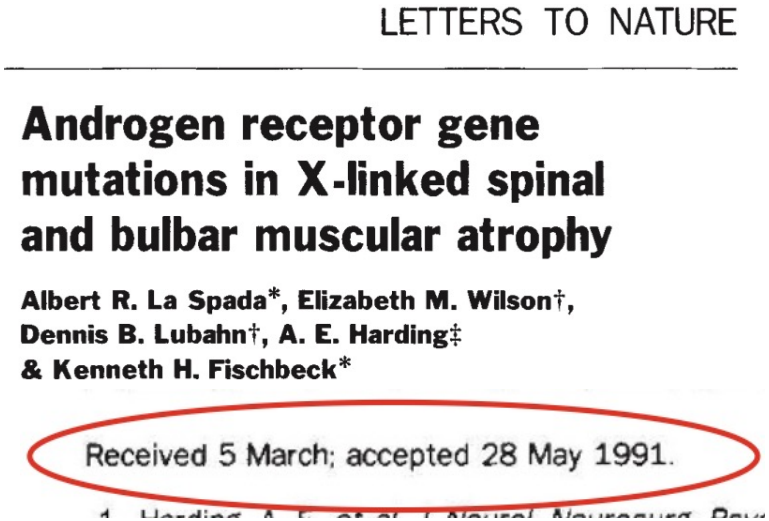
Missing diagnosis and heritability: a major barrier to precision medicine

Hypothesis: Tandem Repeats (TRs) are key genetic factors contributing to undiagnosed diseases and missing heritability

Rationale: beyond the ~60 well-known TRs linked to diseases like Huntington's Disease, ALS, and SBMA, millions more exist in the genome and have been largely **excluded** from clinical testing and GWAS.

Leslie Thompson

Albert La Spada



LETTERS TO NATURE

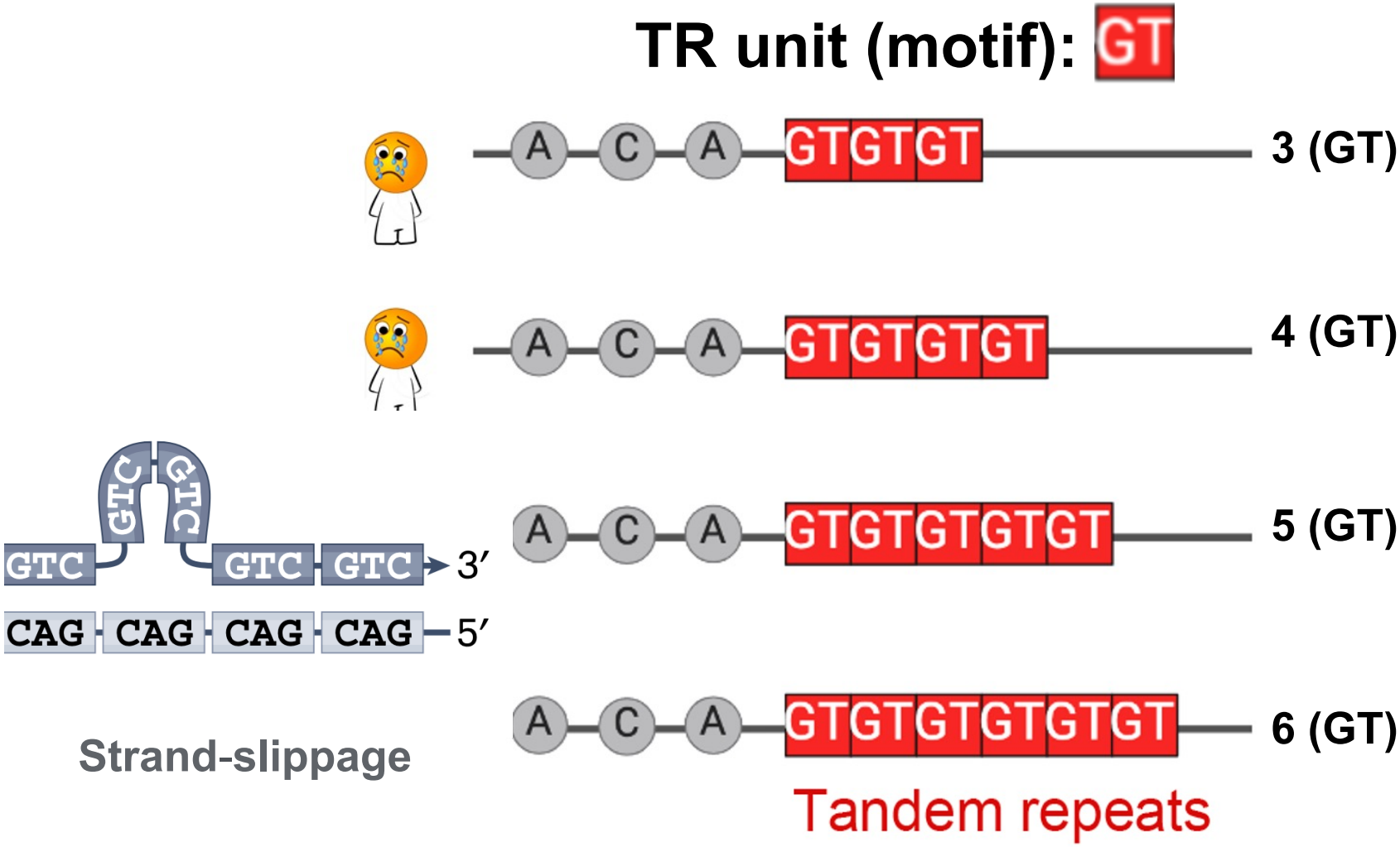
Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy

Albert R. La Spada*, Elizabeth M. Wilson†, Dennis B. Lubahn†, A. E. Harding‡ & Kenneth H. Fischbeck*

Received 5 March; accepted 28 May 1991.

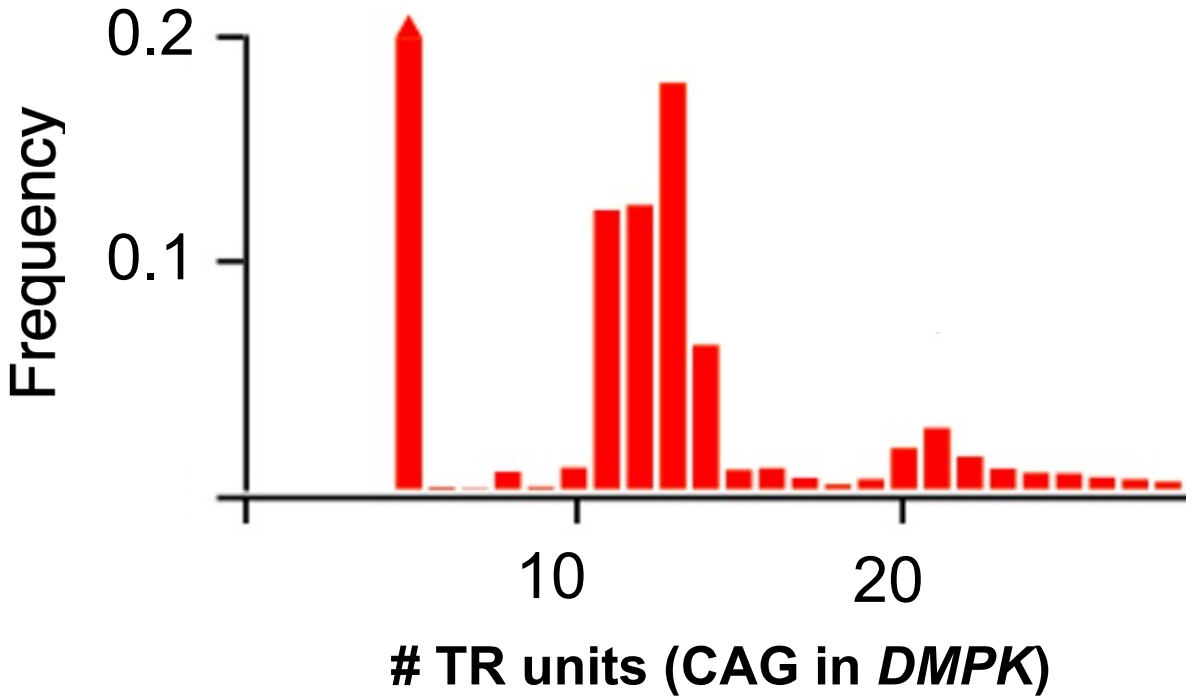
discovered the **FIRST** repeat expansion disorder in summer 1990

<u>Hypothesis</u>: Tandem Repeats (TRs), excluded from clinical testing and GWAS, are crucial genetic factors contributing to missing diagnosis & heritability



Tandem Repeat (TR) Variations

- TRs comprise ~8% of the genome across ~10 millions loci
- TR expansions or contractions generates 2-1,000 of alleles
- TR variation rate is ~1,000 times higher than SNPs
  - 1e-5 vs 1e-8 per locus per generation
- TRs are hard to impute with SNPs (A/T) and require whole genome sequencing

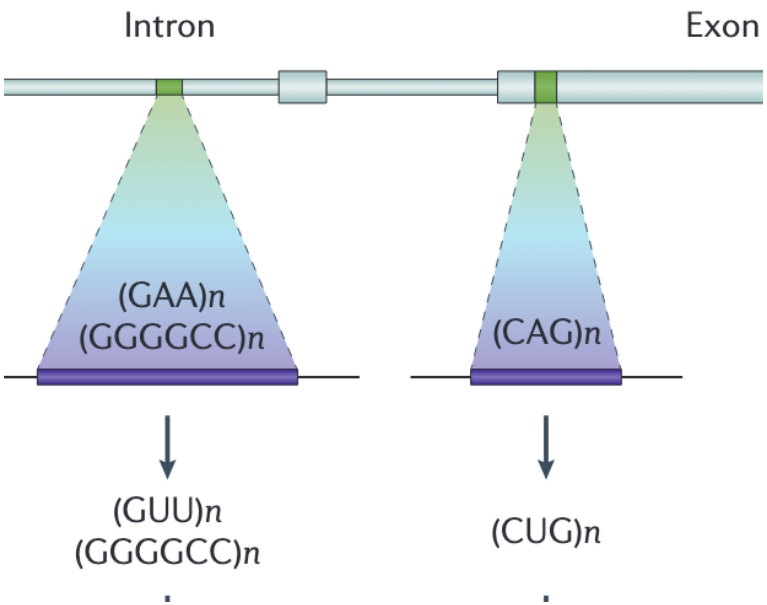


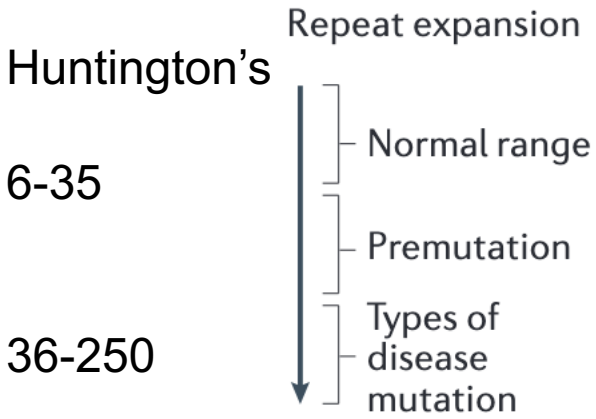
Knowledge Gaps: Tandem Repeats have been Implicated in only ~60/6,000 (1%) of Rare Genetic Diseases

primarily through family-based linkage analyses

Intronic TRDs
- FRDA
- C9ORF72 TRDs (includes subset of ALS and FTD)

Polyglutamine TRDs
- HD
- SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17
- SBMA (Kennedy disease)
- DRPLA



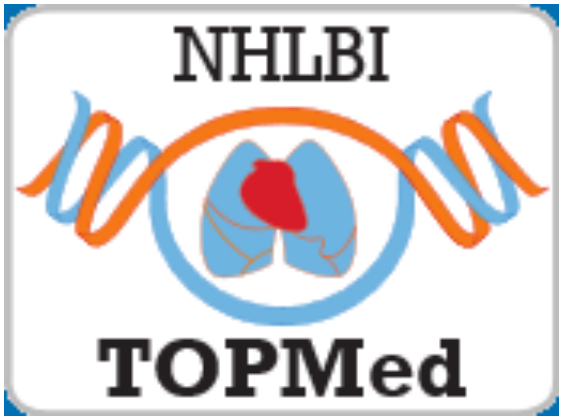


Hannan AJ, 2018

Whole Genome Sequencing (WGS) of Millions of Human

UK

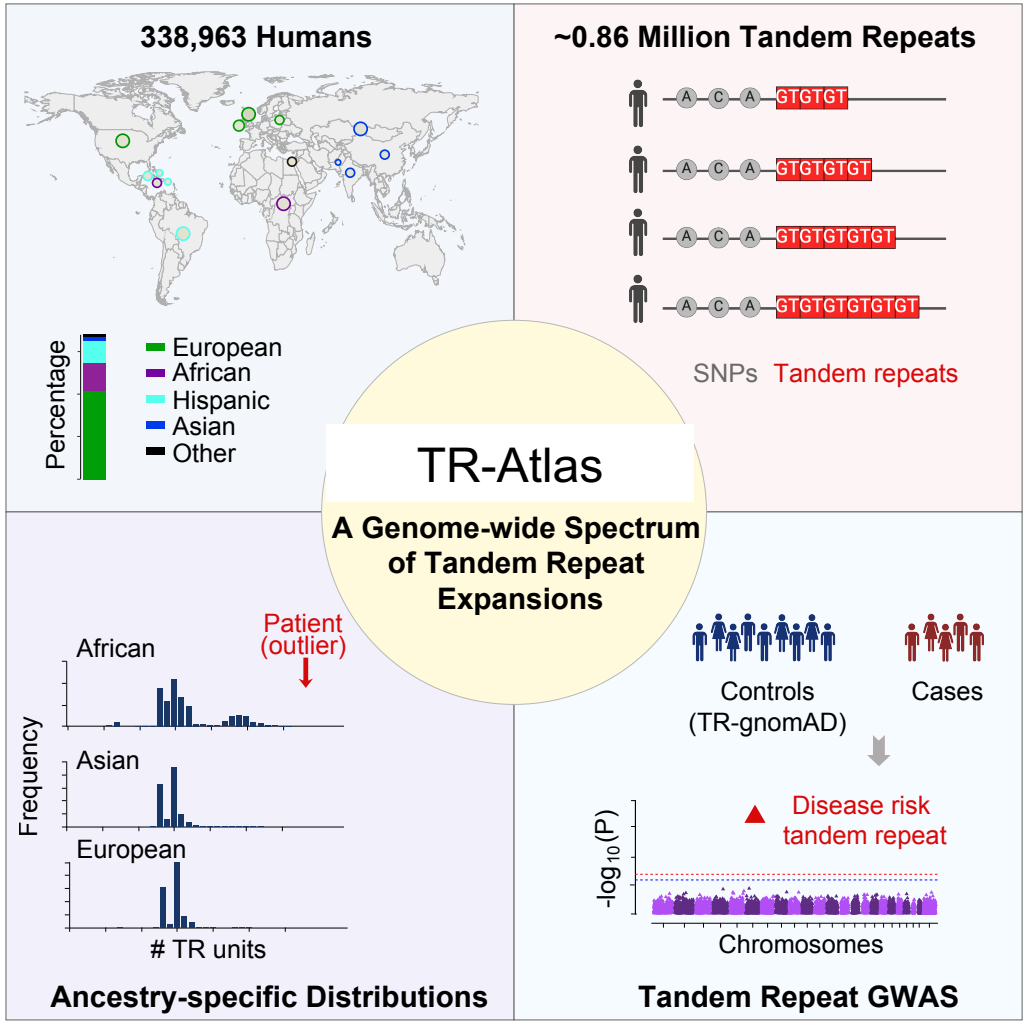
NIH



- Google/Amazon Cloud computing

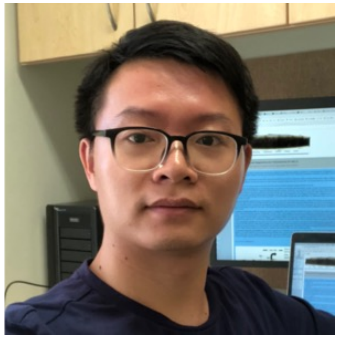
TR-Atlas: ~1 Million TR loci across 340K individuals -- built for $400K (Not $12M)

-- 100 times more than WebSTR



https://wlcb.oit.uci.edu/TRatlas/

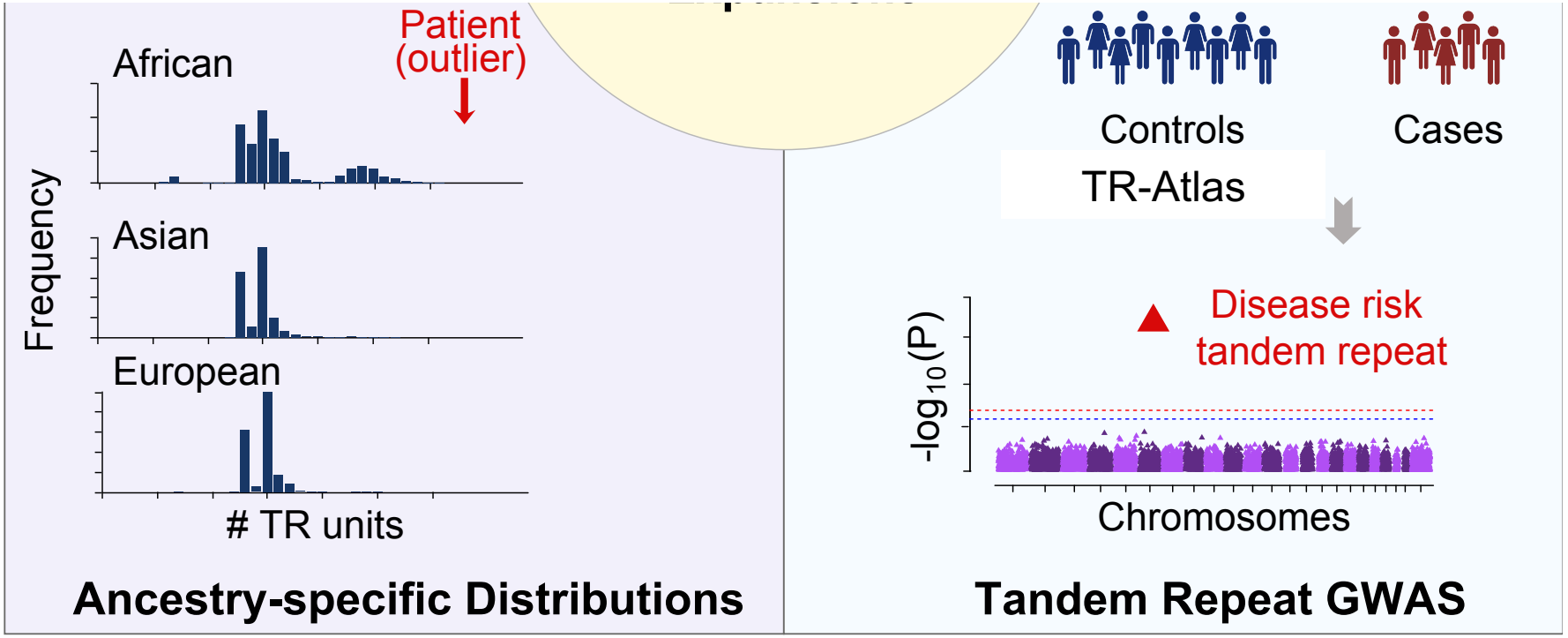
Short read WGS with TR genotypers: ExpansionHunter, GangSTR



Ya Allen Cui

Cui *et al.*, ***Cell*** *2024*

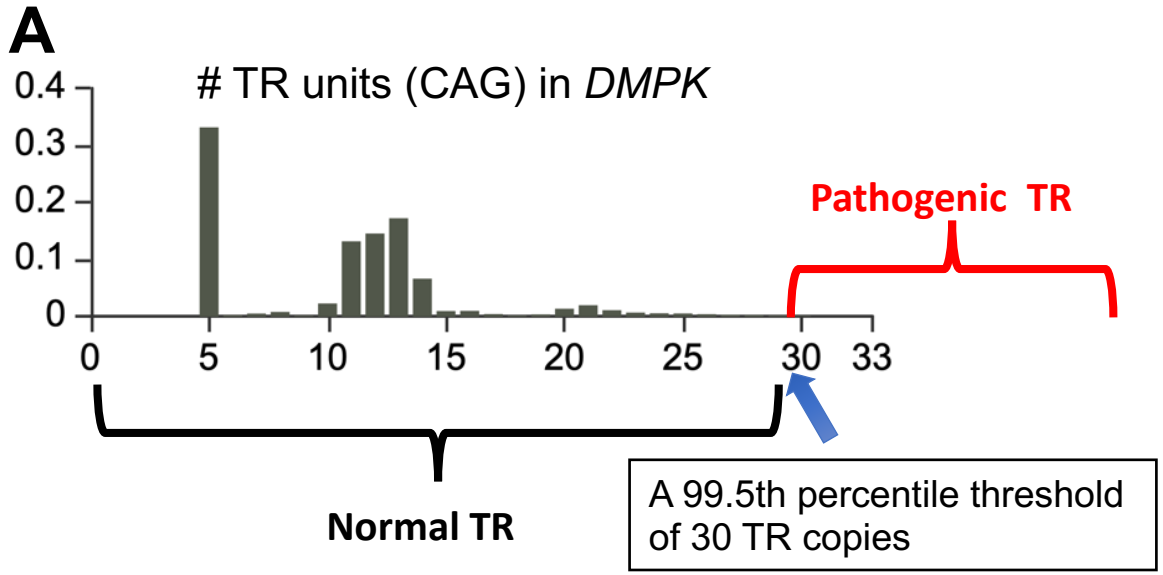
TR-Atlas



Cui et al., ***Cell*** *2024*

Threshold-Based Evaluation of TR Pathogenicity

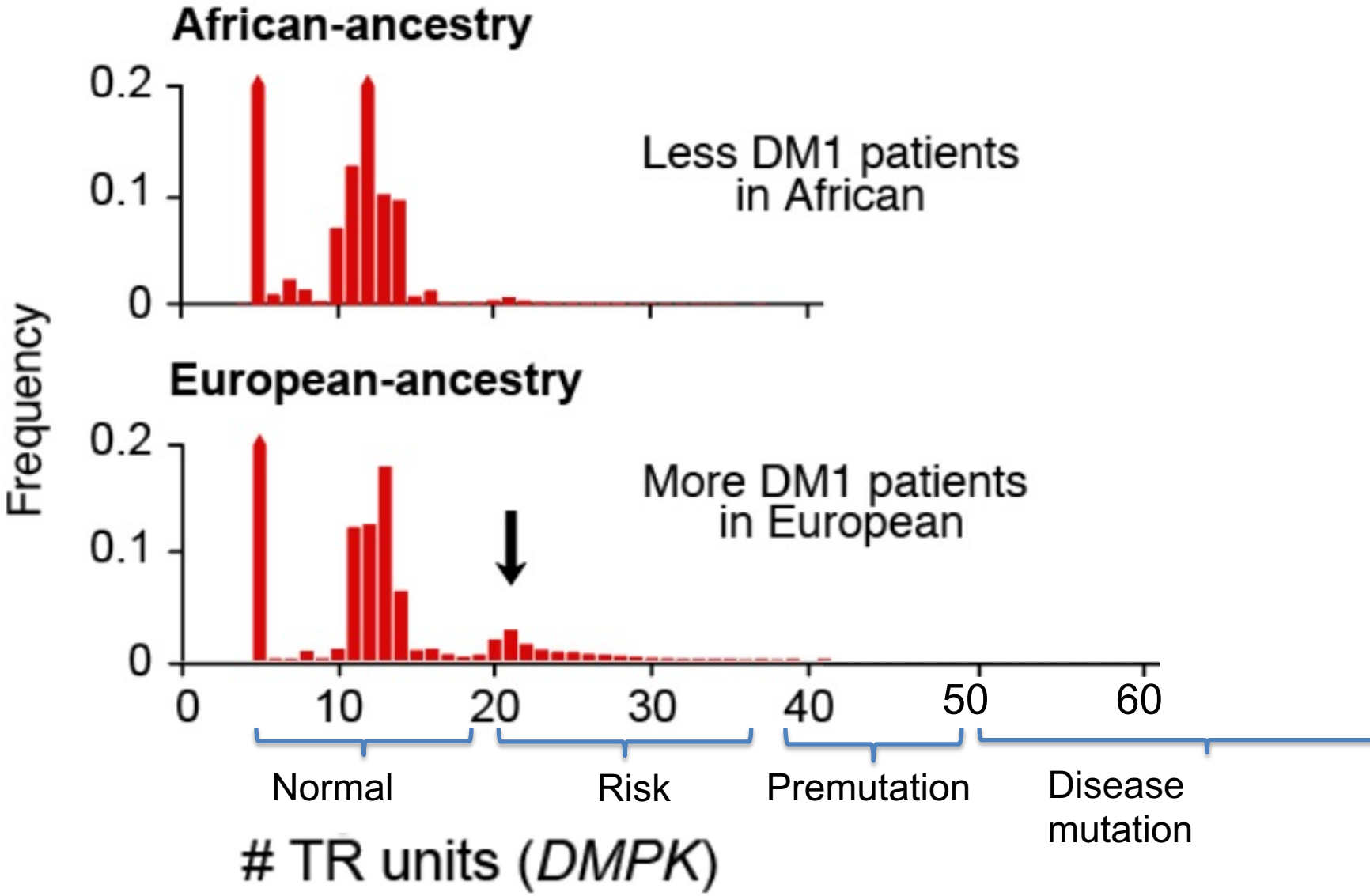
does not require precise allele length measurements



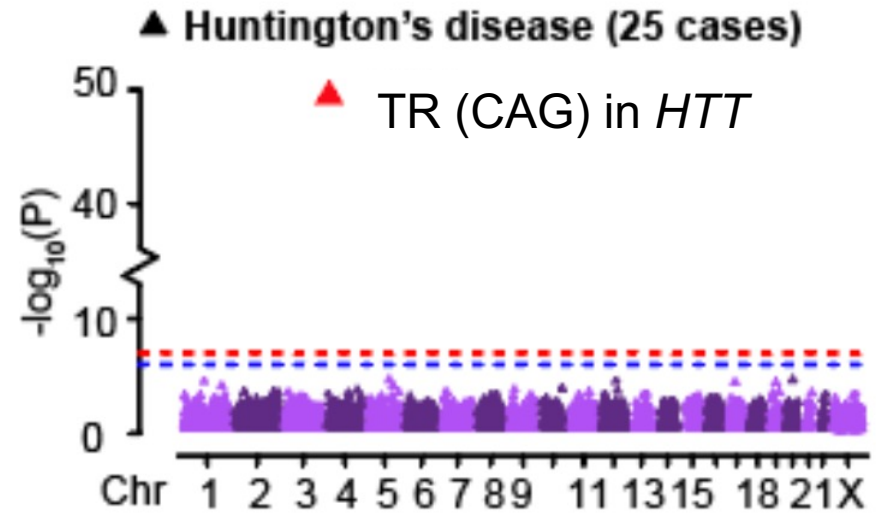
- short-read WGS with ExpansionHunter can successfully separate normal and risk TR groups **with 97.3% sensitivity and 99.6% specificity** in 404 patients across 13 disease-associated TR loci (including 4 loci with large repeat expansions) when compared to the gold-standard diagnostic method, PCR testing

THE LANCET Neurology 2022

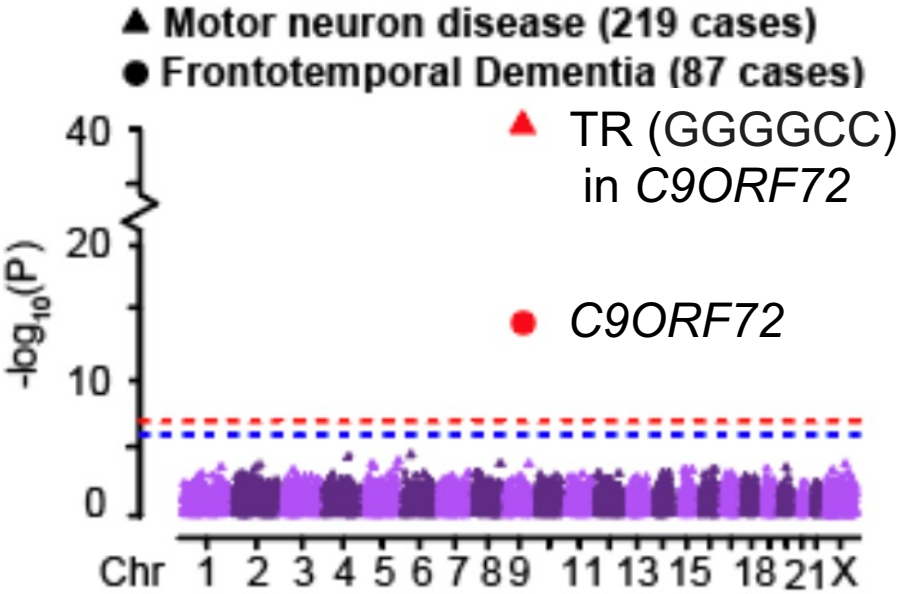
Tandem Repeat Expansions Explain Health Disparities



Tandem Repeat -based genome-wide association studies (TR GWAS)



vs. 18,000 healthy controls in TR-Atlas with matched ancestry



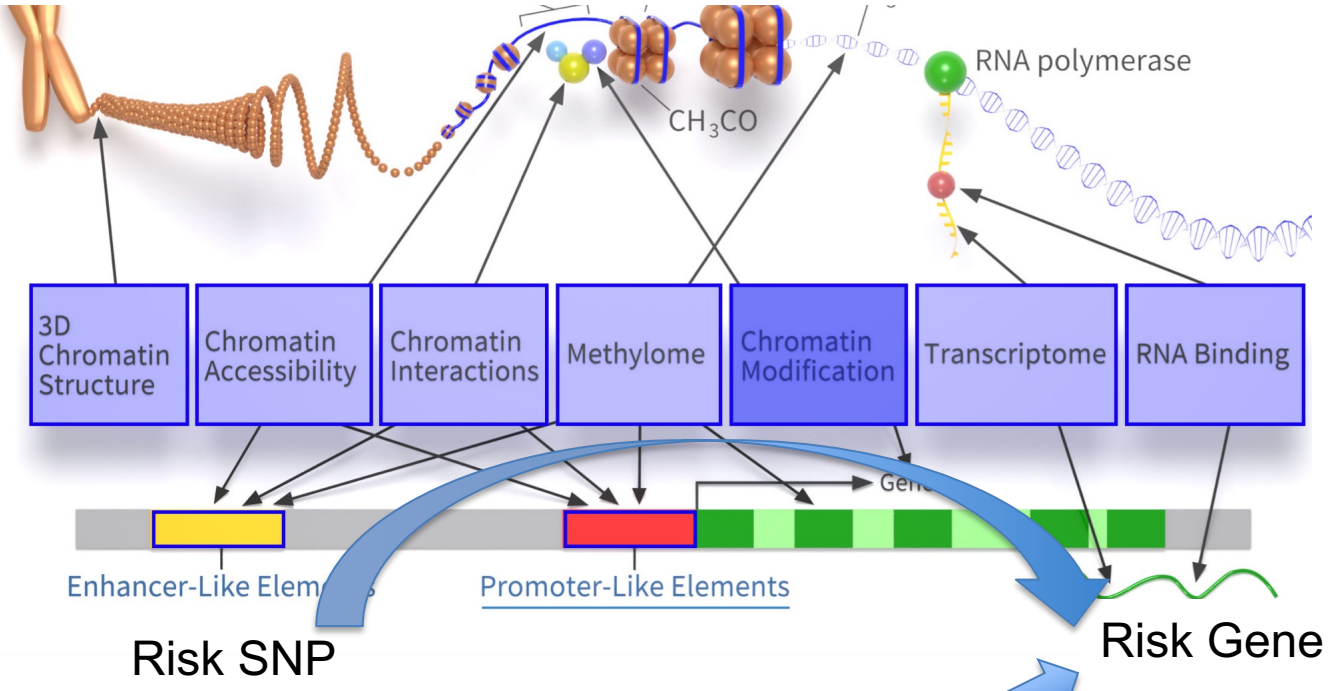
vs. 18,000 healthy controls in TR-Atlas with matched ancestry

Challenges in SNP Association Studies

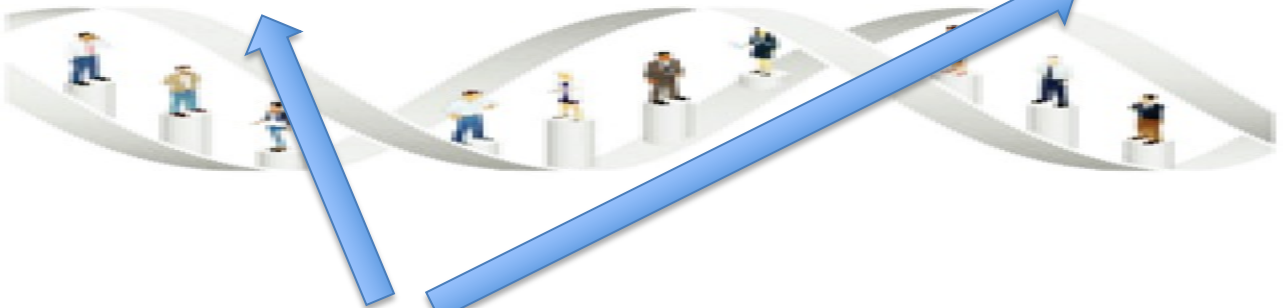
- **Missing Diagnosis**
  - ✓ **>60%** of rare genetic diseases remain undiagnosed.
- **Missing Heritability**
  - ✓ Genetics explain >**60%** of common diseases (e.g., prostate/breast cancer, diabetes).
  - ✓ **>50%** patients not explained by GWAS SNPs
- **Missing Mechanisms for Non-coding Variants (>95% total)**

eQTLs: SNPs associated with gene regulation

Molecular Phenotype



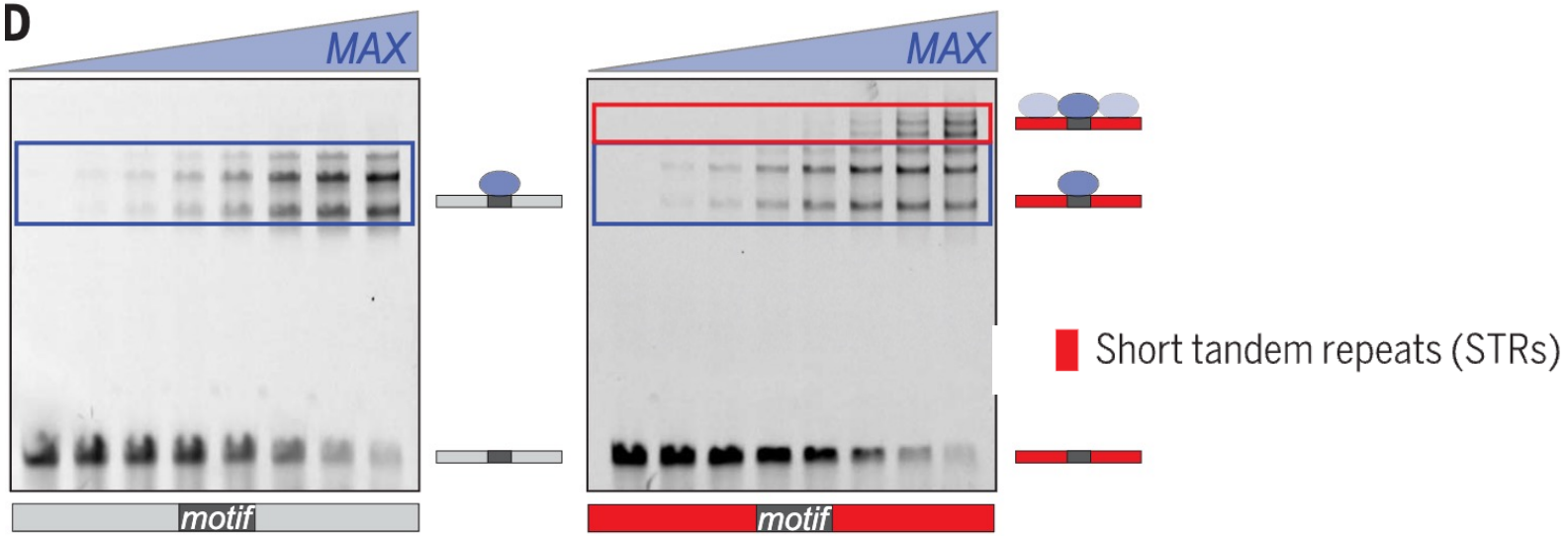
Genotype



Phenotype

Short tandem repeats bind transcription factors to tune eukaryotic gene expression

Horton et al., ***Science*** 2023



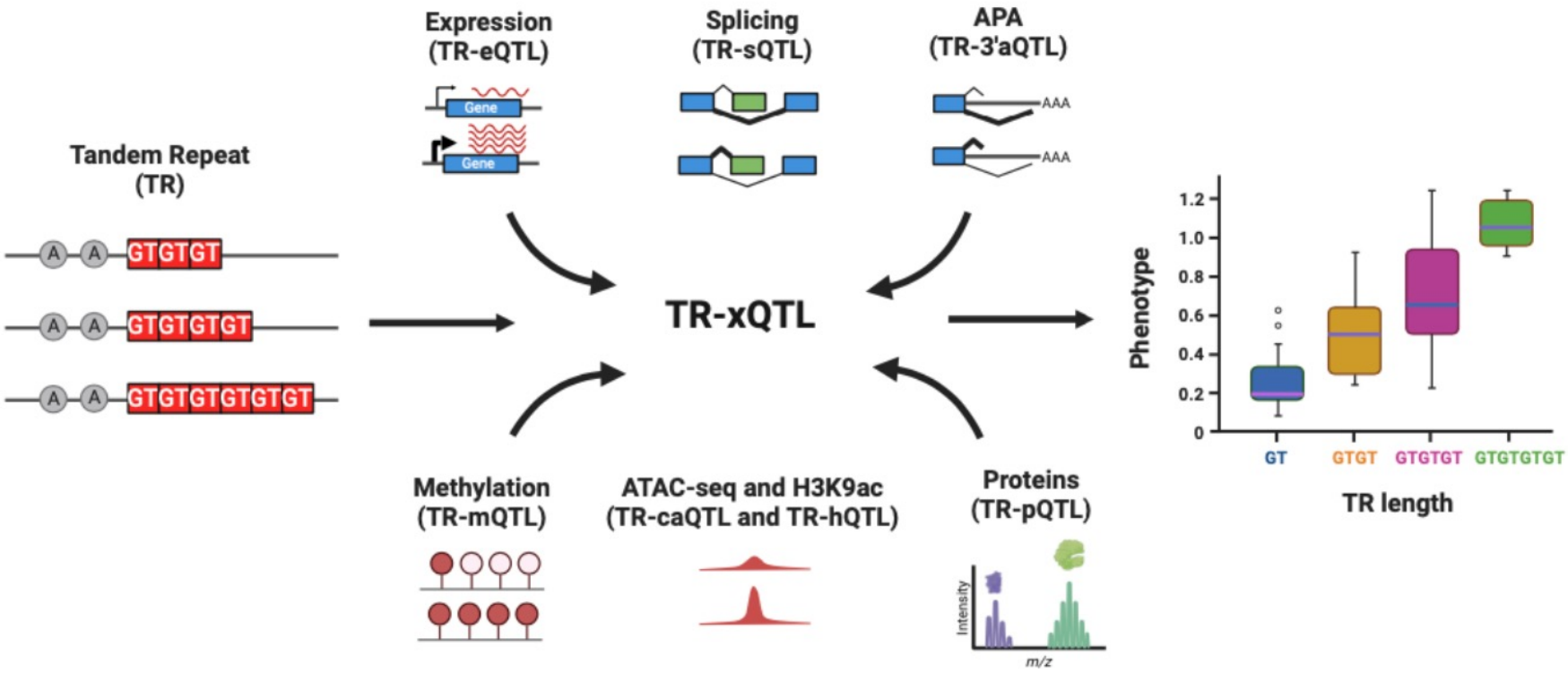
Analysis | Published: 01 November 2019

The impact of short tandem repeat variation on gene expression

Stephanie Feupe Fotsing, Jonathan Margoliash, Catherine Wang, Shubham Saini, Richard Yanicky, Sharona Shleizer-Burko, Alon Goren & Melissa Gymrek

Non-coding TR variations affect gene regulation, thereby mediating disease risk

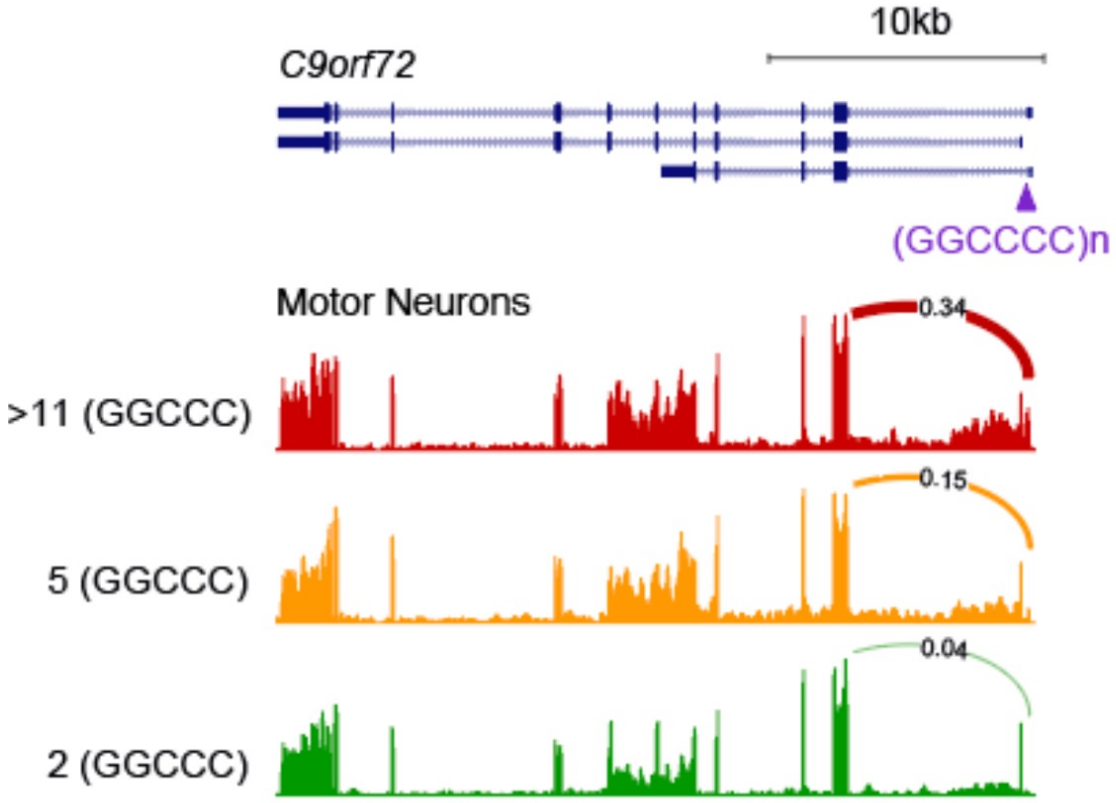
- TR quantitative trait loci (TR-xQTL) across ~4,000 multi-omics samples derived from ~1,600 unique donors
- ~2.2M TR-xQTLs linking ~139K unique TRs to gene regulation

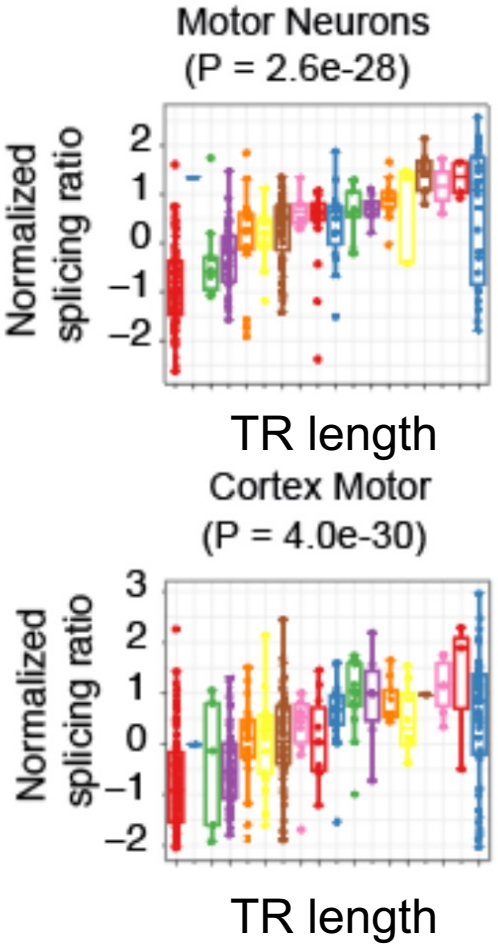


https://wlcb.oit.uci.edu/TRxQTL/

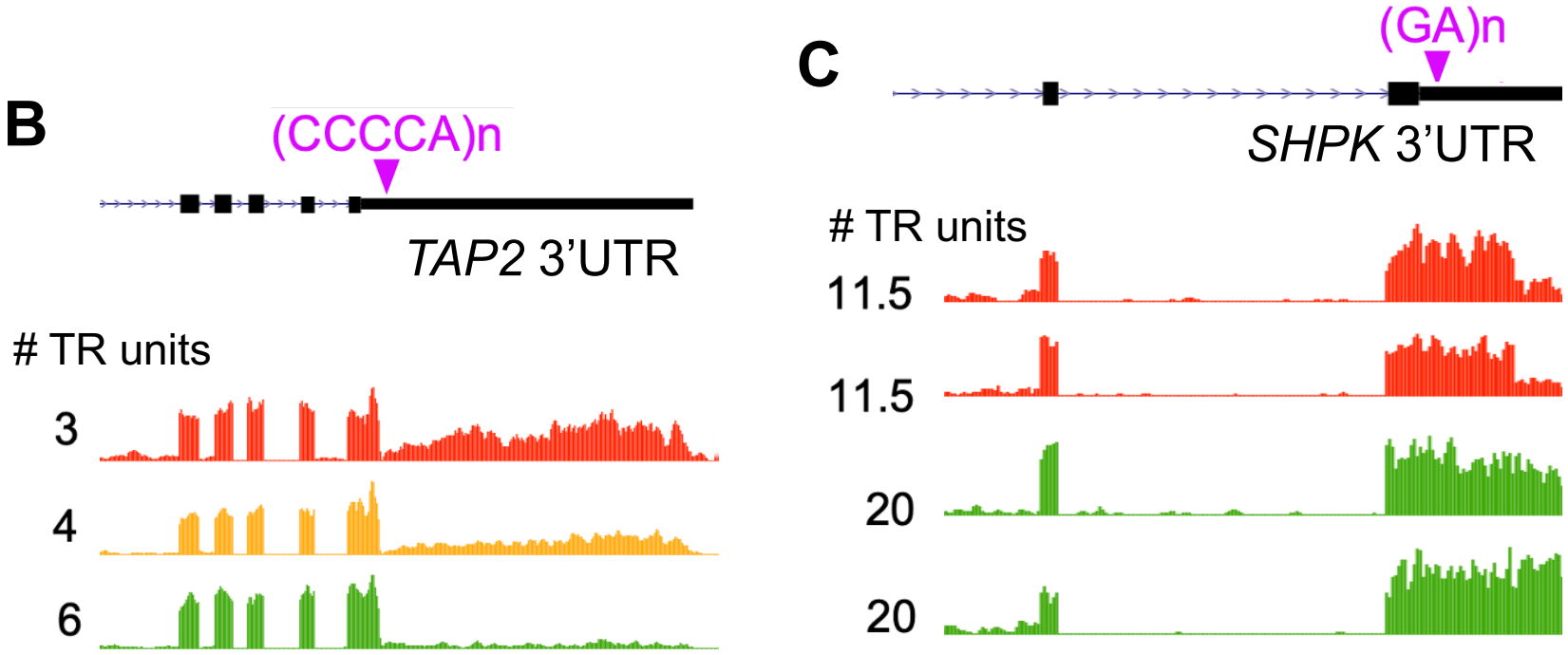
Cui et al., ***Nature Genetics,*** 2025

TR-sQTL of *C9orf72* in ALS



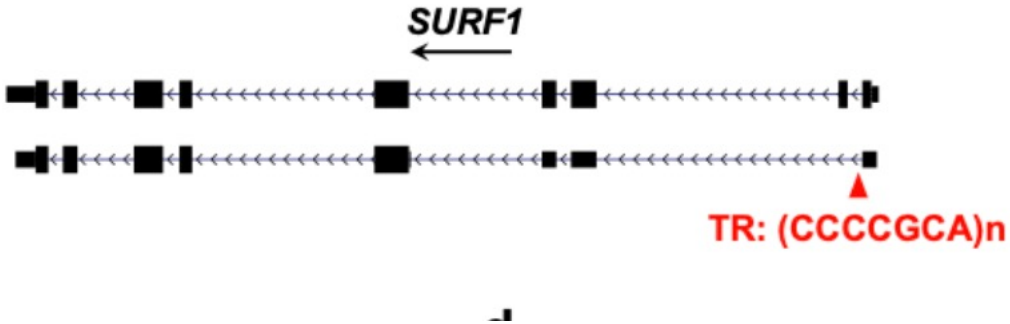


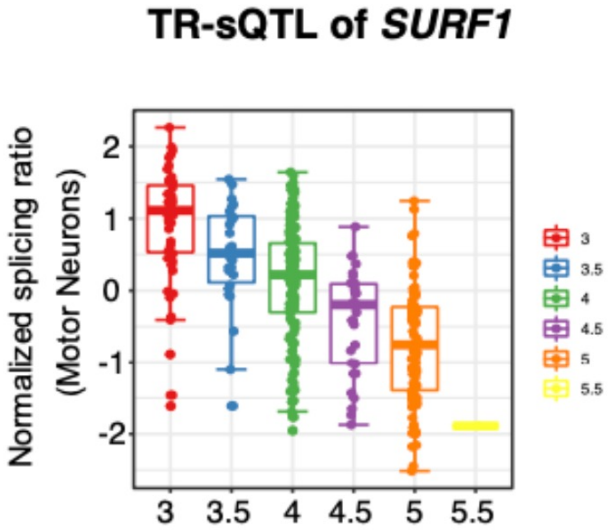
TR 3'UTR APA Quantitative Trait Loci (TR-3'aQTL):

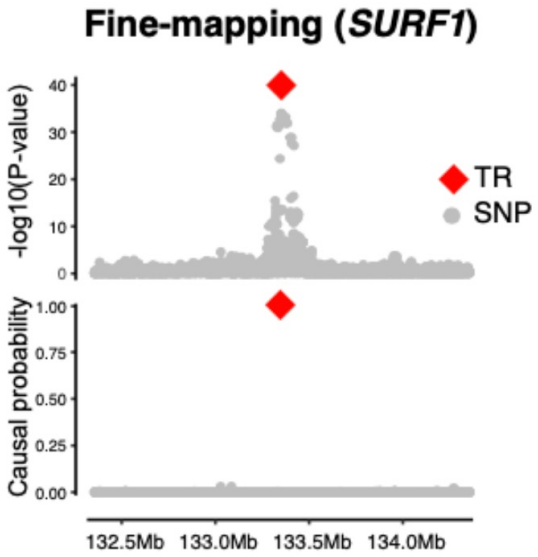


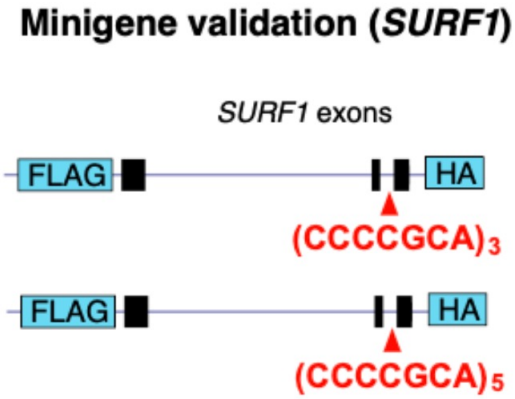
TRs are causal variants for gene regulation

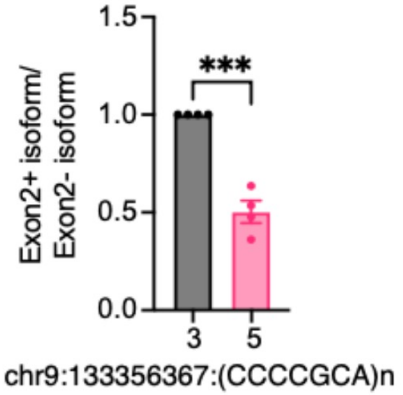
~13% of patients with Leigh syndrome





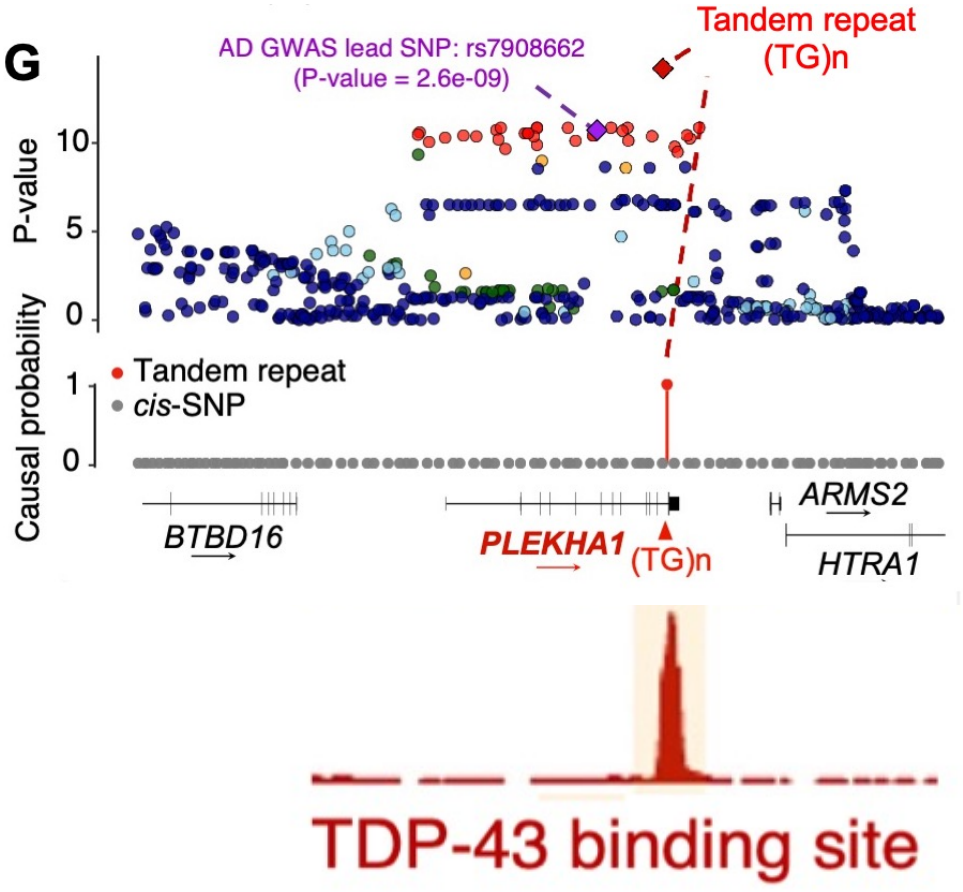


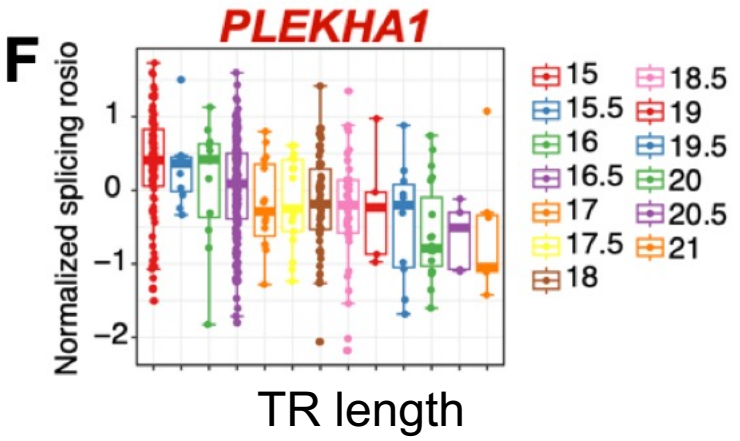


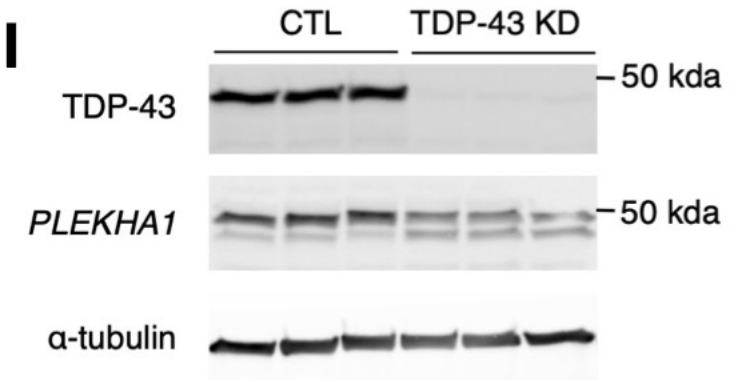


Albert La Spada

A potential risk TR for Alzheimer's disease (AD), primarily by altering TDP-43 binding affinity, leading to alternative splicing of *PLEKHA1*







Shift the focus from SNPs to the broader impact of TR variations

- **TR-Atlas**: ~1 Million TR loci across ~340K Humans (***Cell*** 2024), the world's largest reference map for TR variations
  - TR-GWAS: 2M genomes w/ 8,000 phenotypes: breast cancer, AD, diabetes, ALS
  - TR-outlier: 100K rare disease genomes
- **TR-xQTL**: how TR variants affect gene regulation, thereby mediating disease risk (***Nature Genetics*** 2025)
  - Genetically defined cis-elements for gene regulation beyond traditionally, biochemically defined promoters and enhancers
  - A single gene can be regulated by up to 10 distinct TR loci
- **Call to Collaborate** to unlock the TR's full potential
  - Experimental Biologists, Clinicians, Genomics Labs

Acknowledgements

Wei Li Lab Members

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Eric Wagner (Rochester)
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