ALS

ALS (Amyotrophic Lateral Sclerosis), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that affects nerve cells in the brain and spinal cord.

Aspect	Details
Symptoms	ALS leads to muscle weakness, atrophy, and eventual paralysis. Early symptoms often include muscle twitching, cramping, stiffness, or weakness, particularly in the arms and legs.
Cause	The exact cause is unknown in most cases. About 10% of cases are familial, linked to mutations in specific genes; the rest are sporadic, with complex genetic and environmental contributions.
Diagnosis	Diagnosis is primarily clinical, based on symptoms and disease progression, supported by electromyography (EMG) and nerve conduction studies (NCS).
Treatment	There is no cure. Approved treatments like Riluzole and Edaravone can modestly slow disease progression, but supportive care remains central.
Prevalence	ALS is rare. In the U.S., prevalence is 9.1 per 100,000 population (2018 data), with an estimated 32,893 cases in 2022 and projections of over 36,000 by 2030.
Prognosis	Average life expectancy after diagnosis is 2–5 years, though some individuals, such as Stephen Hawking, live much longer.
Famous Cases	Lou Gehrig (baseball player) and Stephen Hawking (physicist) are among the most well-known individuals with ALS.

Epidemiology and Prevalence

- **U.S. Prevalence:** 9.1 per 100,000 people (2018), with approximately 33,000 cases in 2022 and projections exceeding 36,000 by 2030.
- **Demographics:** ALS disproportionately affects Whites, males, and those over age 50.

Genetics and GWAS Findings

- **GWAS Studies:** As of 2025, the GWAS Catalog lists 44 genome-wide association studies (GWAS) on ALS, primarily in European populations.
- **Risk Loci:** The largest GWAS to date identified 15 risk loci associated with ALS susceptibility.
- **GWAS SNPs:** There are 353 genome-wide significant SNP associations for ALS reported in the GWAS Catalog.
- **Genetic Architecture:** Both common and rare variants contribute to ALS risk. About 10% of cases are familial, often with identifiable mutations (e.g., C9orf72, SOD1, KIF5A), while sporadic cases show complex heritability (estimated at 40–50%).

ALS GWAS Data Summary

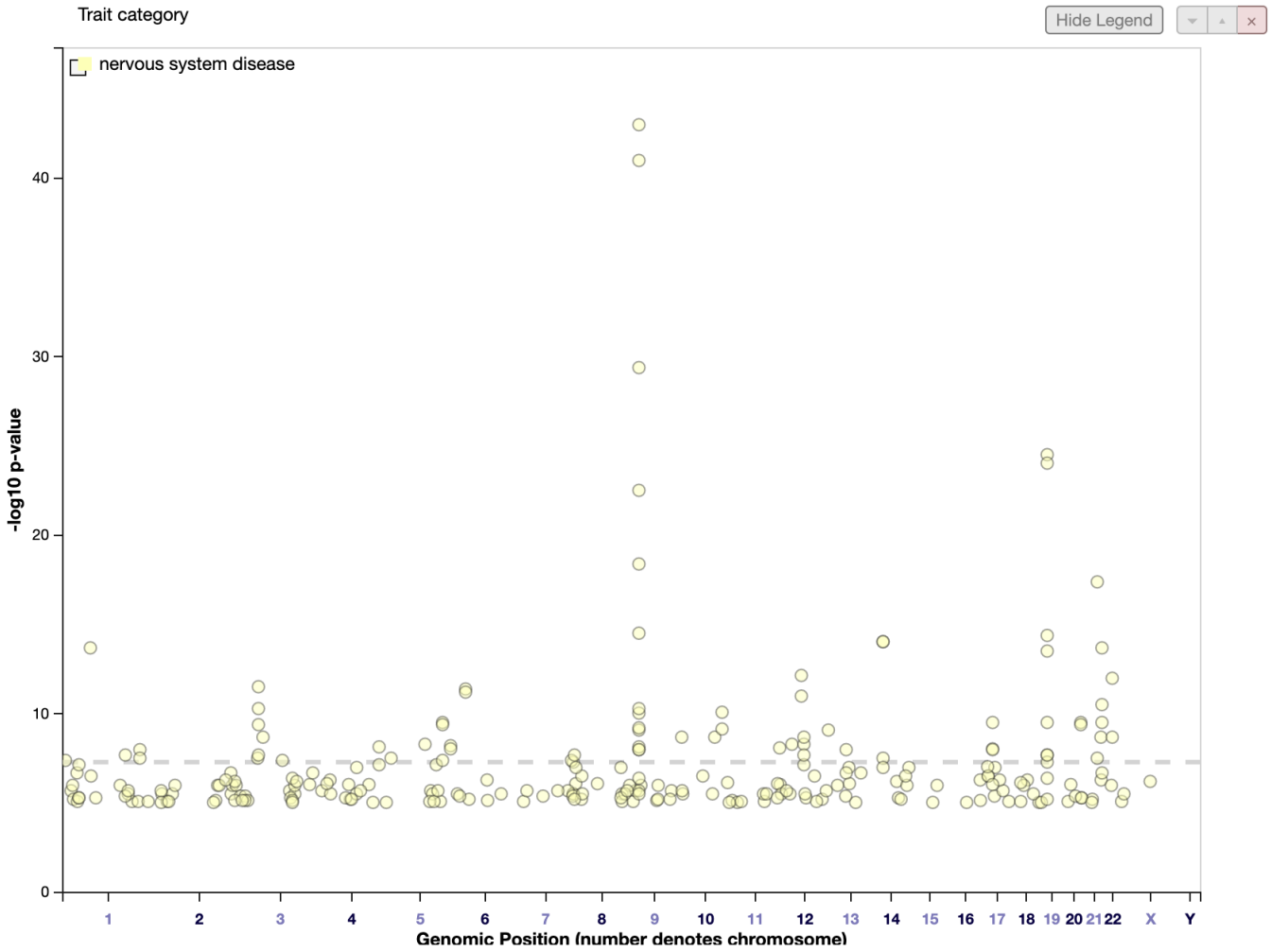
Metric	Value
Number of GWAS studies	44
Number of significant SNPs	353
Number of risk loci identified	15

Additional Notes

- **Lifetime Risk:** ALS has a lifetime risk of about 1 in 350 people.
- **Incidence:** In the U.S., the annual incidence is about 1.6–2 per 100,000 people.
- **Prognosis:** Most patients die within 3–5 years due to respiratory failure, but survival varies.

References:

- Prevalence: PMID: 37602649
- GWAS: PMID: 35042540



Early-Stage ALS Symptoms

- **Muscle twitching and cramps:** Often in the hands, arms, or legs (fasciculations).
- **Weakness:** Asymmetric limb weakness (e.g., difficulty gripping objects, stumbling).
- **Bulbar symptoms:** Slurred speech or swallowing difficulties (less common in early stages).
- **Fatigue and stiffness:** Increased muscle tone and reduced coordination.

Age of Onset:

- **Typical:** 40–70 years (average ~55 years).
- **Early-onset:** ~5% of cases before age 40; rare cases in 20s/30s.
- **Familial ALS:** Often diagnosed in late 40s/early 50s.
- **Sporadic ALS:** Typically diagnosed in late 50s/early 60s.

The GWAS also confirmed five previously identified ALS risk genes:

- **TNP1**
- **C9ORF72**
- **TBK1**
- **UNC13A**
- **C21ORF2**

C9orf72-ALS: Genetic, Epidemiological, and Clinical Insights

Genetic Overview

- **Mutation Type:** Hexanucleotide repeat expansion (HRE) in the *C9orf72* gene, typically involving hundreds to thousands of GGGGCC repeats.
- **Inheritance:** Autosomal dominant with incomplete penetrance. Penetrance increases with age, rarely manifesting before 35 years[2][9].
- **Founder Effect:** Originated from a single haplotype ~1,500–6,300 years ago, explaining its high prevalence in European populations[2][9].

Global Prevalence and Ethnic Variation

Population	Familial ALS	Sporadic ALS	Sporadic FTD
Europe/N. America	20%–86%[9]	6%–8%[1][3][7]	3%–6%[1][9]
Hispanic (USA)	-	8.3%[1]	-
African (USA)	-	4.1%[1]	-
Asian	0%–4.8%[4][9]	0.4%–5%[4][9]	Rare[4]

- **Regional Highlights:**
  - **Scandinavia:** Highest familial ALS rates (72%–86%)[9].
  - **Japan:** 0.4% of sporadic ALS cases carry *C9orf72* mutations[4].
  - **India/Pacific Islands:** No reported cases in sporadic ALS[1][4].

Clinical Features

- **Phenotypes:**
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia (FTD)
  - ALS-FTD overlap (30%–50% of carriers)[5][8].
- **Survival:** Similar to typical ALS (2–5 years post-diagnosis), though some reports suggest prolonged survival in subsets[9].
- **Non-Motor Symptoms:** Psychiatric/cognitive changes (e.g., disinhibition, apathy) often precede motor symptoms[5].

Genetic Architecture and Mechanisms

- **Pathogenesis:**

- **Toxic gain-of-function:** RNA foci and dipeptide repeats disrupt cellular processes[8].
- **Haploinsufficiency:** Reduced *C9orf72* expression may contribute to neurodegeneration[8].

- **Haplotype Instability:** The ancestral risk haplotype predisposes to repeat expansion due to inherent genomic instability[9].

Epidemiology in Key Populations

- **U.S. Estimates (2020):**
  - **Prevalent Cases:** 4,545 (26% familial, 74% sporadic)[3].
  - **Incident Cases:** 1,706 annually[3].
- **Europe:** Accounts for 46% of familial ALS and 8% of sporadic ALS cases[9].

Implications for Diagnosis and Research

- **Testing Recommendations:**
  - Prioritize *C9orf72* testing in all ALS/FTD patients, regardless of family history[6][7].
  - **Clinical Trials:** Target *C9orf72* due to its high contribution (up to 75% of pathogenic variants in U.S. cohorts)[5].
- **Challenges:**
  - Family history underestimates genetic burden (74% of *C9orf72*-ALS cases are sporadic)[3][6].
  - Non-penetrance complicates genetic counseling[4][9].

Comparison with Other ALS Genes

Gene	Familial ALS	Sporadic ALS
C9orf72	20%–86%[9]	6%–8%[1][7]
SOD1	24%–36%[4][9]	1.3%–2.3%[4]
FUS	4%–7.1%[4][9]	1.9%[4]

Key Citations:

- Prevalence: [PMID: 37602649][1], [PMID: 34247168][3]
- Genetics: [PMID: 35042540][2], [PMID: 22647138][9]
- Clinical Impact: [Nature (2017)][6], [Neurology (2020)][5]

Regulatory Elements of C9orf72

The expression and regulation of the **C9orf72** gene are influenced by several key genomic and epigenetic elements. Disruption of these elements, especially by hexanucleotide repeat expansions, is central to ALS and FTD pathogenesis.

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1. Promoter Region and G4C2 Repeat

- **Location:** 5' untranslated region (5' UTR) of *C9orf72*.
- **Key Feature:** Contains a GGGGCC (G4C2) hexanucleotide repeat.
- **Normal Function:**
  - Regulates transcription of *C9orf72*.
  - Normal alleles have 6–24 repeats.
- **Pathogenic Expansion:**
  - > 30 repeats leads to:
    - Epigenetic silencing (hypermethylation).
    - Reduced *C9orf72* mRNA and protein (haploinsufficiency).
    - Production of toxic RNA foci and dipeptide repeats (via RAN translation).

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2. CpG Islands and Epigenetic Modifications

- **CpG Islands:** Rich in cytosine and guanine nucleotides, flanking the repeat region.
- **Epigenetic Changes:**
  - **Hypermethylation** of CpG islands in carriers of the repeat expansion.
  - **Histone modifications** (e.g., H3K9me3, H3K27me3) that compact chromatin and silence gene expression.
- **Functional Impact:**
  - Silencing reduces *C9orf72* expression, contributing to neurodegeneration.
- **Therapeutic Angle:**
  - Demethylating agents (e.g., 5-aza-2'-deoxycytidine) can partially restore gene expression in cellular models.

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3. Conserved Non-Coding Sequences

- **Location:** Upstream and downstream of the G4C2 repeat.
- **Function:**
  - Bind transcription factors such as SP1 and CTCF.
  - Modulate basal transcriptional activity.
- **Genetic Variation:**
  - Structural variants in these regions may influence repeat stability and disease risk.

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4. Antisense Transcripts and Bidirectional Promoters

- **Bidirectional Promoter:** Drives both sense and antisense transcription at the *C9orf72* locus.
- **Antisense Transcripts:**
  - Produce C4G2 repeat RNAs, which can form toxic RNA foci.
  - Contribute to the pathology via RNA toxicity and abnormal protein products (RAN translation).

Summary Table: C9orf72 Regulatory Elements

Element	Location/Feature	Role/Impact
Promoter & G4C2 repeat	5' UTR	Transcription regulation, site of pathogenic repeat

Element	Location/Feature	Role/Impact
CpG islands	Flanking repeat region	Epigenetic silencing via methylation
Conserved non-coding seqs	Upstream/downstream	Transcription factor binding, repeat stability
Bidirectional promoter	Overlaps sense/antisense	Drives both sense and antisense transcripts

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References:

- DeJesus-Hernandez et al., Neuron, 2011
- Gijselinck et al., Human Molecular Genetics, 2016
- Zhang et al., Nature Communications, 2019
- PMID: 22658599

Enhancers and Regulatory Elements in C9orf72-ALS/FTD

Recent studies highlight the critical role of **enhancers** and other regulatory elements in modulating *C9orf72* expression and mitigating toxicity in ALS/FTD. Below is a synthesis of key findings:

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1. Super-Enhancers Protect Against PolyPR Toxicity

- **Mechanism**:
  Super-enhancers upregulate **KPNA2** and **KPNB1**, nuclear import proteins that sequester toxic **poly(proline-arginine) (PR20)** in the cytoplasm[2].
  - PR20 is a dipeptide repeat protein generated from *C9orf72* G4C2 repeat expansions.
  - Cytoplasmic retention of PR20 prevents nuclear entry and cell death[2].
- **Disruption**:
  Inhibiting super-enhancers with **JQ-1** or **Ivermectin** reduces KPNA2/KPNB1 levels, allowing PR20 nuclear translocation and triggering apoptosis[2].
- **Therapeutic Insight**:
  Enhancing KPNA2/KPNB1 expression could counteract PR20 toxicity[2].

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2. Enhancer-Promoter Interactions

- **General Function**:
  Enhancers are cis-regulatory elements that loop to promoters, recruiting transcription factors (e.g., CTCF) to modulate *C9orf72* expression[1][5].
- **Dysregulation in ALS/FTD**:
  Pathogenic G4C2 expansions disrupt chromatin architecture, impairing enhancer-promoter communication and reducing *C9orf72* transcription[3][5].

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3. Transposable Elements (TEs) and Chromatin Organization

- **Role of TEs**:
  Retrotransposons and transposons may alter enhancer activity or create new regulatory elements near *C9orf72*, influencing disease risk[5].

- **Topologically Associating Domains (TADs)**:
  TAD boundaries, marked by CTCF/cohesin, insulate *C9orf72* from aberrant heterochromatin spreading. Repeat expansions may destabilize these boundaries[5].

Key Regulatory Elements Summary

Element	Role in C9orf72-ALS/FTD	Impact
Super-enhancers	Upregulate KPNA2/KPNB1 to sequester PR20	Protects against cytoplasmic-to-nuclear PR20
Enhancers	Modulate *C9orf72* expression via chromatin looping	Dysregulated in repeat carriers
TAD boundaries	Maintain chromatin compartmentalization	Repeat expansions may disrupt insulation
Transposable elements	Potential source of novel regulatory sequences	May contribute to pathogenic rewiring

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Implications for Therapy:
Targeting enhancer activity (e.g., boosting KPNA2/KPNB1) or stabilizing TAD boundaries could mitigate *C9orf72*-linked toxicity[2][5].

References:
[1] Functional genomic approaches to elucidate enhancer roles[1]
[2] Super-enhancer-mediated protection from PR20 toxicity[2]
[5] Regulatory elements and chromatin organization[5]
[3] Cis-regulatory elements in C9orf72 models[3]

Summary Table: Key Cell Lines and Models

Cell Line/Model	Source	Key Features/Uses
iPSC-derived neurons	Human, patient/control	Disease modeling, drug screening, mechanistic studies
Knock-in iPSC lines	Engineered (e.g., KOLF2.1J)	Controlled genetic background, standardization
NSC34 (G4C2)102	Mouse, engineered	Motor neuron-like, RNA foci, DPRs, rapid assays
Lymphoblastoid cell lines	Human, patient/control	Mitochondrial studies, protein aggregation, signatures
Fibroblasts	Human, patient/control	Reprogramming, molecular studies
Primary mouse neurons	Mouse embryos	Axon growth, actin dynamics, mitochondrial function

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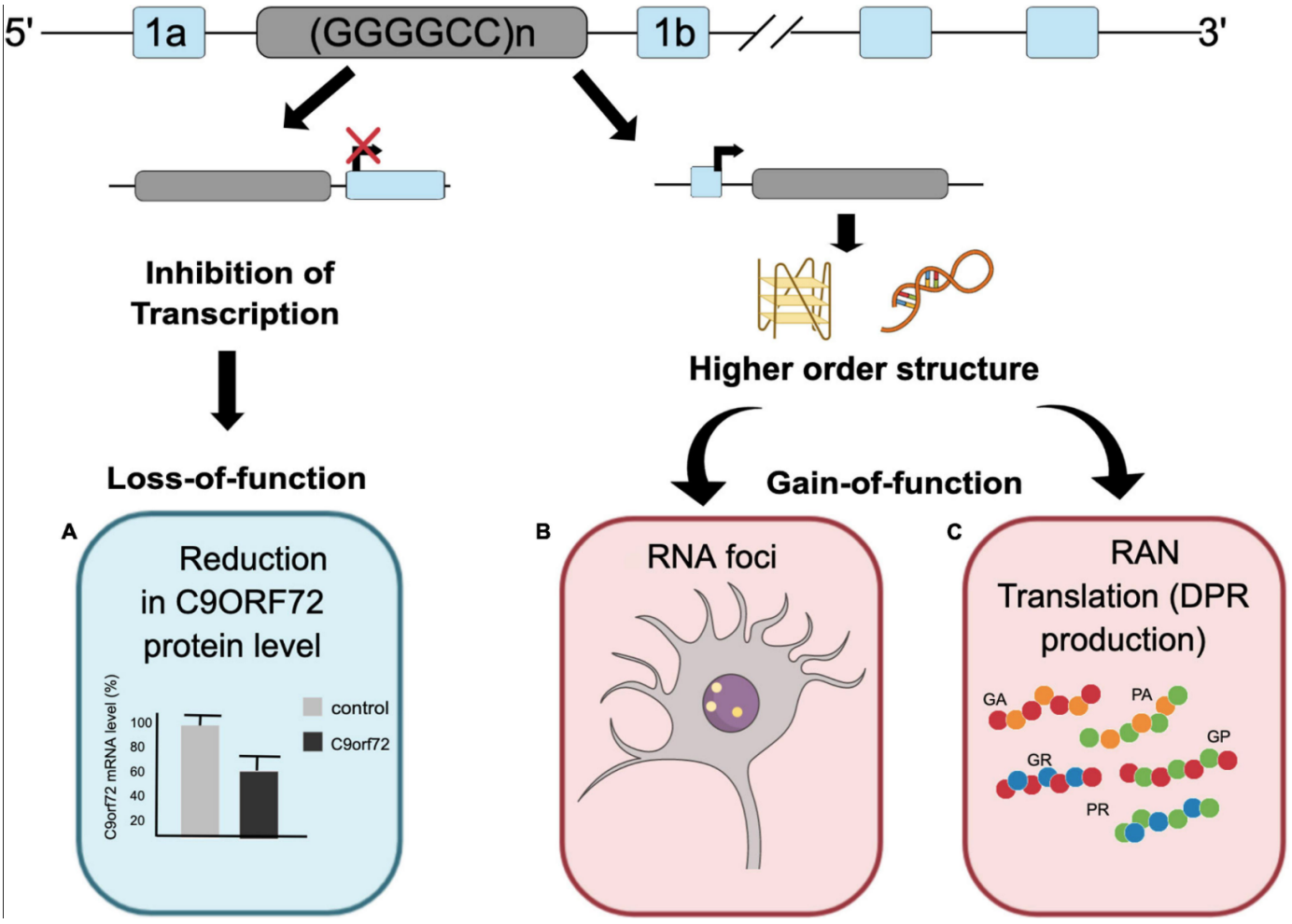
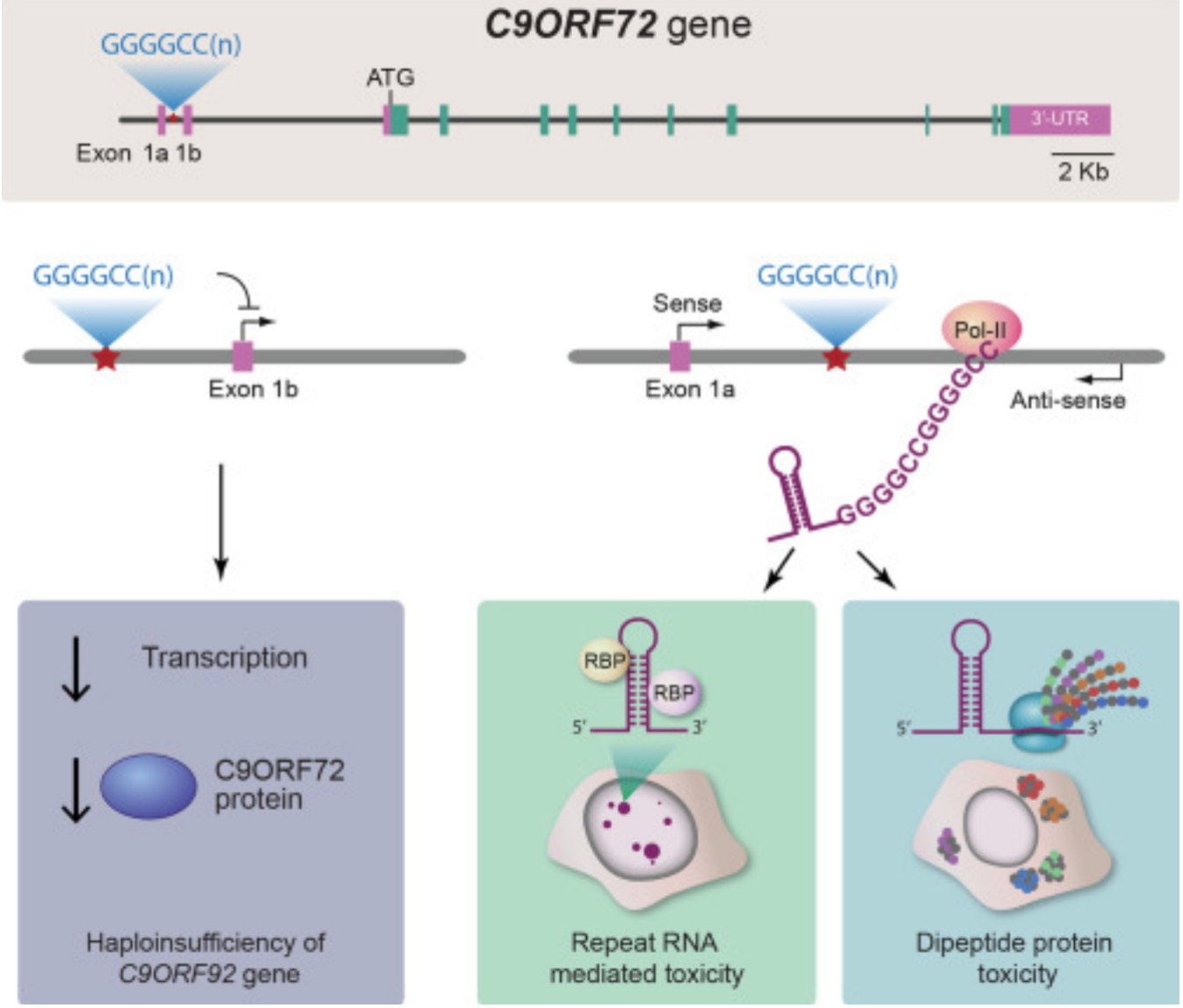
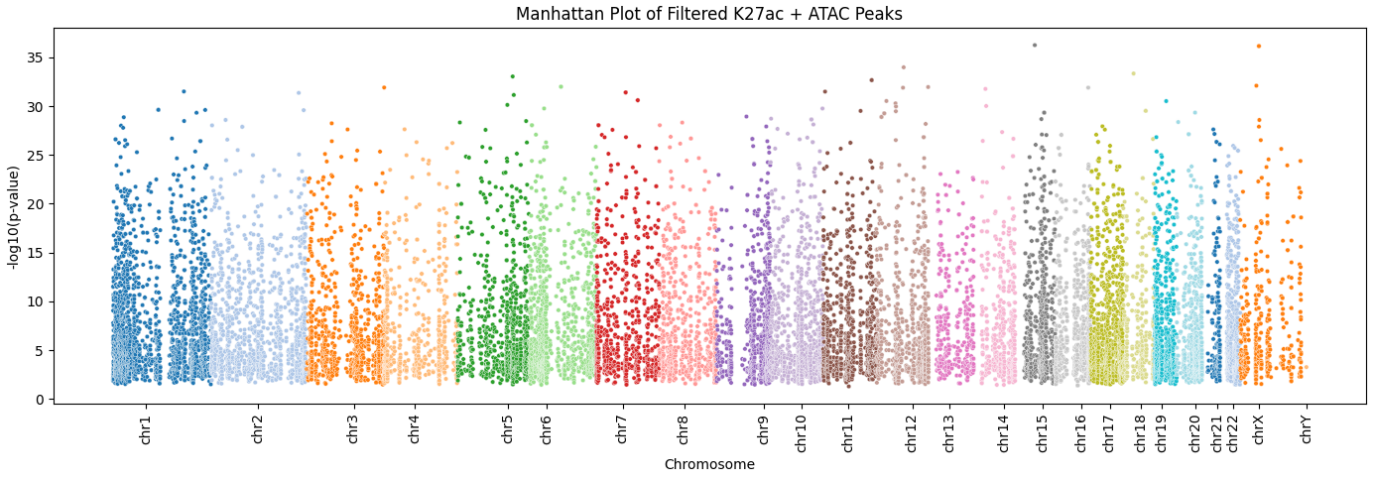

5'
1a
(GGGGCC)n
1b
3'
Inhibition of Transcription
Higher order structure
Loss-of-function
Gain-of-function
A
Reduction in C9ORF72 protein level
C9orf72 mRNA level (%)
100
80
60
40
20
control
C9orf72
B
RNA foci
C
RAN Translation (DPR production)
GA
PA
GP
GR
PR



NIH PIs ALS

- **Dr. Michael E. Ward, M.D., Ph.D.**: Leading a research team focusing on the cellular and molecular mechanisms of frontotemporal dementia (FTD) and ALS, Dr. Ward employs cell biology, proteomics, and functional genomics approaches using induced pluripotent stem cell (iPSC) neuron models to understand how familial mutations contribute to neurodegeneration. irp.nih.gov
- **Dr. Bryan J. Traynor, M.B., B.Ch., B.A.O., Ph.D.**: As Chief of the Neuromuscular Diseases Research Section at the National Institute on Aging (NIA), Dr. Traynor's work centers on identifying genetic causes of ALS and related disorders. He led the international consortium that discovered the pathogenic repeat expansions in the C9orf72 gene, a common cause of ALS and frontotemporal dementia

Enhancer in motor cell line


Manhattan Plot of Filtered K27ac + ATAC Peaks
-log10(p-value)
0
5
10
15
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chr1
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