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GOLGA8A repeat expansion redefines the genetic architecture of aFTLD-U

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INTRODUCTION

Frontotemporal lobar degeneration (FTLD) comprises clinically and neuropathologically heterogeneous neurodegenerative disorders and is an important cause of young-onset dementia[1,2]. Substantial progress has been made in defining the molecular basis of FTLD-tau and frontotemporal lobar degeneration with TAR DNA-binding protein 43 pathology (FTLD-TDP) through the identification of major causal genes such as *MAPT*, *GRN*, and *C9orf72*, whereas the genetic determinants of frontotemporal lobar degeneration with FET protein pathology (FTLD-FET) have remained largely unresolved[3,4]. In this context, the recent identification of a tandem repeat expansion within an intron of *GOLGA8A* as a major genetic risk factor for atypical FTLD with ubiquitin-positive inclusions (aFTLD-U) represents an important advance in subtype-specific neurodegenerative genetics[5]. The associated chr15q14 haplotypes were present in nearly 60% of pathologically confirmed aFTLD-U cases, providing a long-awaited entry point for investigating the molecular basis of FET-protein-associated neurodegeneration[5].

Neuropathology-driven genetic stratification of FTLD-FET

One of the most important conceptual contributions of this work is demonstrating the power of neuropathology-driven genetic stratification. FTLD-FET has historically been considered a predominantly sporadic condition without a clearly defined genetic architecture[5]. The identification of *GOLGA8A* repeat expansions in a substantial proportion of aFTLD-U cases challenges this view and illustrates that strong genetic risk factors may remain hidden when clinically or neuropathologically heterogeneous disease groups are analyzed together[5]. Importantly, the association appears specific to aFTLD-U, because comparable pathogenic expansions were not identified in neuronal intermediate filament inclusion body disease or basophilic inclusion body disease, the other major FTLD-FET subtypes[4,5]. These findings reinforce the importance of precise pathological subclassification for identifying disease-specific genomic determinants[6,7].

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Structural complexity of the GOLGA8A repeat expansion

Equally notable is the unusual structural architecture of the identified repeat. Repeat expansion disorders are often defined by expansion of a particular sequence motif, but interruptions and changes in motif composition can substantially influence repeat stability, penetrance, and clinical phenotype[8,9]. The *GOLGA8A* locus is remarkable for the extent of variation in repeat length, motif length, and sequence composition[5]. Most importantly, cytosine-thymine (CT) dimer was the only expanded motif observed exclusively on both disease-associated haplotypes A and B. Long CT-dimer-rich alleles were strongly enriched in aFTLD-U and were generally longer than CT-rich alleles observed in unaffected haplotype carriers, whereas CCTT and CCCTCT expansions were also found outside the affected group[5]. Consistent with this pattern, repeat-based classifiers using either an expansion > 450 bp with > 80% CT content or > 190 CT-dimer units showed stronger associations with aFTLD-U than the individual haplotype-tagging variants[5]. These observations indicate that pathogenicity is more likely to reflect a combination of repeat length and sequence composition than repeat length alone.

Mechanistic implications of intronic repeat expansions

The intronic localization of the expansion raises several mechanistic possibilities, including altered transcription, chromatin regulation, RNA processing, RNA-protein interactions, and repeat-associated translation[9]. Comparison with other non-coding repeat expansion disorders is informative. In *C9orf72*-related amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), the expanded G4C2 repeat contributes to disease through convergent mechanisms involving reduced *C9orf72* expression, accumulation of repeat-containing RNA, and production of dipeptide repeat proteins through non-canonical translation[10]. In neuronal intranuclear inclusion disease, a guanine-guanine-cytosine expansion in the 5′ region of *NOTCH2NLC* can be translated into a toxic polyglycine-containing protein[11]. No analogous pathogenic RNA species or translated product has yet been demonstrated for the CT-rich *GOLGA8A* expansion. Its intronic location and dinucleotide composition therefore leave open several possibilities that should currently be considered testable hypotheses rather than established mechanisms[5,9]. Given the roles of FET-family proteins such as fused in sarcoma and TAF15 in RNA metabolism and ribonucleoprotein organization, it will be particularly important to determine whether CT-rich DNA or RNA alters FET-protein localization, RNA handling, or phase-separated assemblies[12,13].

The genomic environment of the repeat creates an additional technical and biological challenge. *GOLGA8A* and its paralog *GOLGA8B* share approximately 98.9% sequence identity and lie within a region characterized by segmental duplications, copy-number variation, and evidence of recurrent genomic rearrangement[5,14]. This architecture complicates short-read mapping, transcript assignment, haplotype reconstruction, and gene-expression analysis. The original study itself reported that unique primers could not be designed for one haplotype-tagging variant because the paralogous *GOLGA8B* sequence was also amplified[5]. Possible paralog-related regulatory interference, including effects involving the broader GOLGA8 gene cluster, is therefore biologically plausible but remains unproven. Functional studies will require locus- and paralog-specific approaches that can distinguish true effects of the expanded *GOLGA8A* allele from signals originating from the closely related *GOLGA8B* locus.

Incomplete penetrance and modifying factors

Another important observation is that long CT-rich expansions can be inherited without concurrent clinical disease, indicating incomplete penetrance[5]. However, asymptomatic status at a single time point should not be interpreted as evidence of lifelong non-penetrance. Age-dependent penetrance is an important alternative explanation, as illustrated by other repeat expansion disorders such as Huntington's disease, in which the probability and timing of disease manifestation depend on repeat length and age[15]. This possibility is particularly relevant because the *GOLGA8A* repeat shows somatic length variation, predominantly within the

CT tract[5]. Additional genetic, epigenetic, environmental, or immune-related modifiers may also influence disease expression, but their contribution has not yet been demonstrated[5,16]. Longitudinal studies of age-stratified carriers will therefore be essential for distinguishing age-dependent penetrance from persistent resistance to disease and for identifying additional modifiers of clinical expression.

Sex-specific disease susceptibility

The male predominance observed in the study also requires cautious interpretation. Approximately 71% of aFTLD-U cases carrying the chr15q14 risk haplotypes were male, but a similar male predominance was present in the overall aFTLD-U cohort and among cases without the associated haplotypes[5]. The sex imbalance should therefore not currently be interpreted as a specific consequence of the *GOLGA8A* expansion. Instead, it may represent a broader feature of the aFTLD-U pathological subtype or a shared disease-modifying mechanism that operates in both expansion-positive and expansion-negative cases. Hormonal signaling, immune responses, and sex-dependent epigenetic regulation remain plausible modifiers of neurodegenerative disease susceptibility, but future studies will be needed to determine whether these mechanisms influence aFTLD-U generally or specifically modify penetrance among *GOLGA8A* expansion carriers[17,18].

Diagnostic implications

Beyond its mechanistic implications, identification of the *GOLGA8A* repeat has potential relevance for diagnostic stratification. The relationship between CT content, expansion length, and disease status suggests that repeat-based classifiers may ultimately contribute to molecular prediction of aFTLD-U during life[5]. However, the proposed thresholds were derived from the currently available cohorts and require independent validation, particularly across different populations and in prospectively characterized individuals. Age-dependent penetrance and the presence of long CT-rich expansions in some unaffected carriers must also be incorporated into future risk models[5]. Accordingly, *GOLGA8A* repeat profiling should currently be regarded as a promising candidate biomarker rather than an established diagnostic test within precision neurology[19].

Repeat expansions as a broader neurodegenerative mechanism

More broadly, this discovery expands the spectrum of repeat-mediated mechanisms implicated in neurodegeneration. Disease-associated tandem repeat expansions are increasingly recognized across Huntington's disease, *C9orf72*-associated ALS/FTD, neuronal intranuclear inclusion disease, and *ABCA7*-associated Alzheimer's disease risk[20,21]. The *GOLGA8A* finding adds a structurally unusual CT-dimer-dominated intronic expansion to this landscape and reinforces the principle that sequence composition can be as biologically relevant as repeat length[5,8]. At the same time, its marked motif heterogeneity and highly duplicated genomic context distinguish it from better-characterized repeat disorders. Repeat-containing RNAs can influence nuclear and chromatin organization in other settings, but whether this principle applies to *GOLGA8A* remains to be established experimentally[22].

Translational perspectives

The translational implications are intriguing but remain preliminary. Sequence-directed strategies, including antisense oligonucleotides and other RNA-targeting approaches, have created therapeutic opportunities for several repeat-associated disorders[23]. For *GOLGA8A*, however, therapeutic development will first require identifying the pathogenic molecular species and determining whether the relevant target is DNA, RNA, or a downstream pathway. The very high homology between *GOLGA8A* and *GOLGA8B* creates a major challenge for designing and validating paralog-specific oligonucleotides, whereas the low-complexity CT-rich sequence may introduce additional off-target and specificity constraints. Reliable measurement of target engagement will face the same locus-specificity problem. Furthermore, effective delivery to vulnerable cell populations in

the central nervous system remains a general challenge for oligonucleotide therapeutics[24]. Thus, the current discovery establishes a tractable genetic starting point for therapeutic research rather than an immediately actionable therapeutic target.

Future directions in aFTLD-U genetics

Finally, approximately 40% of aFTLD-U cases lacked the chr15q14-associated risk haplotypes, underscoring substantial genetic heterogeneity even within a neuropathologically well-defined disease entity[5]. These cases may harbor other repeat expansions, structural variants, or distinct pathogenic mechanisms. Long-read sequencing is particularly well suited to resolving tandem repeats and structurally complex genomic regions that remain difficult to characterize with conventional short-read approaches[25,26]. Extending these analyses to larger neuropathologically defined cohorts may identify additional genetic contributors to aFTLD-U. Equally important will be the development of paralog-specific functional assays, transcriptomic approaches capable of resolving *GOLGA8A* from *GOLGA8B*, and longitudinal studies of carriers to establish how repeat architecture, somatic variation, and age jointly influence disease expression.

CONCLUSION

Taken together, identifying a structurally complex CT-rich repeat expansion within *GOLGA8A* represents a major advance in defining the genetic architecture of aFTLD-U[5]. The findings highlight the importance of both repeat length and motif composition while also exposing fundamental questions concerning penetrance, somatic instability, paralog-specific regulation, and the molecular consequences of the expansion. Resolving these questions will be essential before the *GOLGA8A* locus can be translated from a strong genetic association into a validated mechanistic model, diagnostic biomarker, or therapeutic target. More broadly, the study illustrates how pathology-guided cohort stratification and long-read genomic technologies can reveal previously inaccessible forms of structural variation underlying neurodegenerative disease[25,26].

DECLARATIONS

Authors' contributions

Contributed to the conception and writing of the manuscript: Zhao P, Rozpędek-Kamińska W

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REFERENCES

1. Urso D, Giannoni-Luza S, Brayne C, Ray N, Logroscino G. Incidence and prevalence of frontotemporal dementia: a systematic review and meta-analysis. *JAMA Neurol.* 2025;82:1144. DOI PubMed PMC
2. Chu M, Wu L, Liu L, et al. Clinical, genetic, and pathological features of very early onset frontotemporal lobe degeneration: a systematic review. *Curr Alzheimer Res.* 2023;19:870-7. DOI
3. Van Langenhove T, Van Der Zee J, Van Broeckhoven C. The molecular basis of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum. *Ann Med.* 2012;44:817-28. DOI PubMed PMC
4. Mackenzie IRA, Munoz DG, Kusaka H, et al. Distinct pathological subtypes of FTLD-FUS. *Acta Neuropathol.* 2010;121:207-18. DOI
5. De Coster W, Van Den Broeck M, Baker M, et al. A repeat expansion in GOLGA8A is a major risk factor for atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions. *Nat Genet.* 2026;58:726-36. DOI
6. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol.* 2012;8:423-34. DOI PubMed PMC
7. Kovacs G. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. *Int J Mol Sci.* 2016;17:189. DOI PubMed PMC
8. Rajan-Babu I, Dolzhenko E, Eberle MA, Friedman JM. Sequence composition changes in short tandem repeats: heterogeneity, detection, mechanisms and clinical implications. *Nat Rev Genet.* 2024;25:476-99. DOI PubMed
9. Malik I, Kelley CP, Wang ET, Todd PK. Molecular mechanisms underlying nucleotide repeat expansion disorders. *Nat Rev Mol Cell Biol.* 2021;22:589-607. DOI
10. Gendron TF, Petrucelli L. Disease mechanisms of *C9ORF72* repeat expansions. *Cold Spring Harb Perspect Med.* 2018;8:a024224. DOI PubMed PMC
11. Boivin M, Deng J, Pfister V, et al. Translation of GGC repeat expansions into a toxic polyglycine protein in NIID defines a novel class of human genetic disorders: the polyG diseases. *Neuron.* 2021;109:1825-35.e5. DOI PubMed PMC
12. Mackenzie IR, Neumann M. FET proteins in frontotemporal dementia and amyotrophic lateral sclerosis. *Brain Res.* 2012;1462:40-3. DOI PubMed
13. Carey JL, Guo L. Liquid-liquid phase separation of TDP-43 and FUS in physiology and pathology of neurodegenerative diseases. *Front Mol Biosci.* 2022;9:826719. DOI PubMed PMC
14. Antonacci F, Dennis MY, Huddleston J, et al. Palindromic GOLGA8 core duplicons promote chromosome 15q13.3 microdeletion and evolutionary instability. *Nat Genet.* 2014;46:1293-302. DOI PubMed PMC
15. Mcdonnell EI, Wang Y, Goldman J, Marder K. Age of onset of huntington's disease in carriers of reduced penetrance alleles. *Mov Disord.* 2021;36:2958-61. DOI PubMed PMC
16. Kampmann M. Molecular and cellular mechanisms of selective vulnerability in neurodegenerative diseases. *Nat Rev Neurosci.* 2024;25:351-71. DOI PubMed
17. Shepherd R, Cheung AS, Pang K, Saffery R, Novakovic B. Sexual dimorphism in innate immunity: the role of sex hormones and epigenetics. *Front Immunol.* 2021;11:604000. DOI PubMed PMC
18. Vegeto E, Villa A, Della Torre S, et al. The role of sex and sex hormones in neurodegenerative diseases. *Endocr Rev.* 2020;41:273-319. DOI PubMed PMC
19. Hampel H, Gao P, Cummings J, et al. The foundation and architecture of precision medicine in neurology and psychiatry. *Trends Neurosci.* 2023;46:176-98. DOI PubMed PMC
20. Gall-Duncan T, Sato N, Yuen RK, Pearson CE. Advancing genomic technologies and clinical awareness accelerates discovery of disease-associated tandem repeat sequences. *Genome Res.* 2022;32:1-27. DOI PubMed PMC
21. Zhou Z, Jankovic J, Ashizawa T, Tan E. Neurodegenerative diseases associated with non-coding CGG tandem repeat expansions. *Nat Rev Neurol.* 2022;18:145-57. DOI PubMed
22. Trigiante G, Blanes Ruiz N, Cerase A. Emerging roles of repetitive and repeat-containing RNA in nuclear and chromatin organization and gene expression. *Front Cell Dev Biol.* 2021;9:735527. DOI PubMed PMC
23. Zhang Y, Liu X, Li Z, et al. Advances on the mechanisms and therapeutic strategies in non-coding CGG repeat expansion diseases. *Mol Neurobiol.* 2024;61:10722-35. DOI
24. Hammond SM, Aartsma-Rus A, Alves S, et al. Delivery of oligonucleotide-based therapeutics: challenges and opportunities. *EMBO Mol Med.* 2021;13:e13243. DOI PubMed PMC
25. Tanudisastro HA, Deveson IW, Dashnow H, Macarthur DG. Sequencing and characterizing short tandem repeats in the human genome. *Nat Rev Genet.* 2024;25:460-75. DOI PubMed
26. Logsdon GA, Vollger MR, Eichler EE. Long-read human genome sequencing and its applications. *Nat Rev Genet.* 2020;21:597-614. DOI PubMed PMC