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Enrichment of nuclear DNA of organelle origin may shape genome evolution in *Plasmodium malariae*

Abstract

Plasmodium malariae is an understudied human malaria parasite with reduced but essential mitochondrial and apicoplast genomes. Transfer of organellar DNA into the nuclear genome generates nuclear DNA of organellar origin (NUOTs), including nuclear mitochondrial DNA segments (NUMTs) and nuclear plastid DNA segments (NUPTs), which can influence genome architecture and evolution. Although NUOTs have been described in several apicomplexans, their contribution to *Plasmodium* genome evolution remains poorly defined. We hypothesize that *P. malariae* contains a higher abundance of NUOTs than *Plasmodium falciparum*, reflecting species-specific differences in organellar DNA integration dynamics and nuclear genome evolution. Using comparative genomic analyses of publicly available nuclear genome assemblies, this study aims to assess NUOT abundance and distribution in both species. Elucidating NUOT content may reveal evolutionary features associated with genome stability and long-term persistence in human malaria parasites.

Keywords: *Plasmodium malariae*, nuclear DNA of organellar origin, NUMTs, NUPTs, genome evolution

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Introduction

Malaria is caused by protozoan parasites of the genus *Plasmodium*, with *Plasmodium falciparum* and *Plasmodium vivax* responsible for the majority of human disease worldwide and *Plasmodium malariae* representing an understudied but widespread human malaria parasite.[1] Like other apicomplexans, *Plasmodium* species retain two endosymbiont-derived organelles: the mitochondrion and the apicoplast. The mitochondrial genome of *Plasmodium* is among the smallest known, at approximately 6 kb with a limited set of protein-coding genes and fragmented ribosomal RNAs.[2] Similarly, the apicoplast genome is a reduced circular DNA molecule of approximately 30–35 kb that encodes functions critical for parasite survival and metabolism.[2,3] Both organellar genomes are indispensable for processes including electron transport, ATP production, and essential metabolic pathways.

Transfer of organellar DNA into the nucleus is a widespread evolutionary process in eukaryotes, giving rise to nuclear mitochondrial DNA sequences (NUMTs) and nuclear plastid DNA sequences (NUPTs) that together are referred to as nuclear DNA of organellar origin (NUOTs).[4] In apicomplexan parasites such as *Toxoplasma gondii*, NUMTs and NUPTs have been shown to constitute a substantial fraction of the nuclear genome, and ongoing organellar DNA transfer contributes to genomic variation and structural dynamics.[2] In contrast, reports suggest a relatively lower abundance of NUOTs in *Plasmodium* genomes, and systematic comparative analyses across species remain limited.

Given differences in genome architecture and evolutionary history among human malaria parasites, we hypothesize that *P. malariae* harbors a higher abundance of NUOTs compared with *P. falciparum*, reflecting species-specific differences in genome evolution and organellar DNA integration dynamics.

Importantly, *Plasmodium malariae* is distinguished from other human malaria parasites by its exceptional capacity to establish long-term, low-density infections that may persist for years or even decades in the human host. While the biological basis of this chronicity remains incompletely understood, genomic features that promote stability, adaptability, and immune evasion are likely contributors. Integration of organellar DNA into the nuclear genome, manifested as NUMTs and NUPTs, may represent an underappreciated mechanism supporting this phenotype. Increased NUOT content could enhance genomic plasticity, influence local chromatin organization, or modulate transcriptional regulation of adjacent nuclear genes, thereby facilitating subtle adaptive responses under sustained immune pressure. In this context, a higher abundance of NUOTs in *P. malariae* relative to *P. falciparum* may reflect evolutionary selection for genome architectures that favor persistence rather than rapid proliferation, providing a potential genomic substrate for the chronicity characteristic of *P. malariae* malaria.

Discussion

The present hypothesis proposes that Plasmodium malariae harbors a greater abundance of nuclear DNA of organellar origin (NUOTs), including NUMTs and NUPTs, than Plasmodium falciparum. If validated, this would suggest that organellar DNA transfer contributes in a species-specific manner to nuclear genome architecture among human malaria parasites. Such differences may reflect variation in DNA repair mechanisms, rates of organellar DNA release, chromosomal recombination dynamics, or long-term evolutionary pressures linked to parasite life history traits.

In eukaryotes, integration of mitochondrial and plastid DNA into the nucleus is an ongoing evolutionary process. Studies across diverse taxa indicate that double-strand break repair via non-homologous end joining represents a principal mechanism facilitating organellar DNA insertion into nuclear chromosomes.[5] The frequency and retention of these insertions are influenced by genome size, recombination landscape, and selective constraints. In apicomplexans, extensive organellar DNA integration has been demonstrated in Toxoplasma gondii, where NUMTs and NUPTs significantly shape genome organization and contribute to structural plasticity.[2] In contrast, Plasmodium species generally possess compact genomes with strong AT bias and streamlined intergenic regions, factors that may limit tolerance for large insertions. Therefore, any relative enrichment of NUOTs in P. malariae would imply distinct evolutionary dynamics compared with P. falciparum.

Comparative genomic data indicate that P. falciparum exhibits highly dynamic subtelomeric regions enriched in multigene families involved in antigenic variation, including var, rifin, and stevor genes.[6] These regions undergo frequent recombination and rearrangement, contributing to immune evasion and virulence. If NUOT insertions preferentially accumulate in subtelomeric or recombination-prone regions, differences in chromosomal architecture between species could partly explain divergent NUOT abundance. P. malariae, which lacks the extensive var gene repertoire characteristic of P. falciparum, may accommodate alternative genomic elements—such as organellar DNA fragments—within its nuclear chromosomes without compromising essential gene density.

Another important consideration is the relationship between NUOT accumulation and parasite chronicity. P. malariae is notable for its ability to maintain low-level parasitemia for prolonged periods. Chronic infection may impose selective pressures favoring genomic stability rather than rapid expansion of antigenic variation gene families. NUOT insertions, particularly if fragmented and transcriptionally inert, could serve as neutral or near-neutral elements contributing to chromosomal structural buffering. Alternatively, they may influence nearby gene regulation through effects on local chromatin conformation or epigenetic modification patterns. In P. falciparum, nuclear organization and gene expression are tightly linked to epigenetic regulation and three-dimensional genome architecture.[7] Similar mechanisms in P. malariae could interact with NUOT-derived sequences, potentially affecting transcriptional plasticity under immune pressure.

From a mechanistic standpoint, differences in organellar genome maintenance may also influence NUOT formation rates. The mitochondrial genome of Plasmodium species is linear and concatenated, while the apicoplast genome remains circular and multicopy. Variations in replication stress, reactive oxygen species exposure, or organelle turnover could alter the likelihood of DNA fragments escaping into the cytosol and becoming substrates for nuclear integration. Furthermore, species-specific divergence in DNA repair pathways, particularly those governing double-strand break repair, may determine insertion frequency and retention.

It is also essential to consider potential methodological confounders. Apparent differences in NUOT abundance may reflect assembly artifacts, especially in highly AT-rich genomes such as that of P. falciparum. Improved long-read sequencing and chromosome-level assemblies for P. malariae will be critical to accurately quantify organellar-derived insertions and distinguish genuine integrations from assembly misplacements. Rigorous filtering strategies, including alignment stringency thresholds and validation across independent assemblies, will be necessary to ensure reliable comparative analysis.

If confirmed, enrichment of NUOTs in P. malariae would broaden our understanding of genome evolution in malaria parasites by highlighting organellar DNA integration as an additional layer of genomic diversification beyond gene family expansion and recombination. This could open new avenues for investigating how structural genomic features correlate with parasite persistence, host adaptation, and evolutionary history. Moreover, NUOT mapping may provide phylogenetic markers or molecular signatures reflecting lineage-specific integration events.

In conclusion, differential accumulation of nuclear DNA of organellar origin represents a plausible and testable mechanism contributing to interspecies genomic diversity within Plasmodium. Integrating comparative genomics, structural variation analysis, and functional assays will be essential to clarify whether NUOT enrichment in P. malariae constitutes a neutral byproduct of genome maintenance or an adaptive feature linked to its distinctive biological phenotype.

Conclusion

This study advances the hypothesis that nuclear DNA of organellar origin contributes differently to genome architecture among human malaria parasites. We propose that *Plasmodium malariae* contains a higher abundance of NUMTs and NUPTs within its nuclear genome than *Plasmodium falciparum*, potentially reflecting distinct evolutionary pressures acting on genome stability, plasticity, and long-term persistence. Validation of this hypothesis would highlight NUOTs as an underexplored component of *Plasmodium* genome evolution and provide a framework for future comparative analyses aimed at linking organellar DNA integration with parasite biology, adaptation, and chronic infection phenotypes.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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