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Awakening ancient mobile DNA drives aggressive lung cancer

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Lung adenocarcinoma remains one of the most genomically complex and lethal malignancies, and understanding how these tumors evolve, metastasize, and evade therapy continues to pose a major challenge in oncology. The field has long emphasized point mutations and copy-number alterations in well-established oncogenic drivers such as *KRAS*, *EGFR*, *ALK*, and *TP53*. Yet these events alone cannot fully explain why genetically similar tumors diverge so markedly in aggressiveness, metastatic behavior, and therapeutic response. Increasing evidence now shows that the non-coding genome and endogenous repetitive elements can influence cancer evolution as profoundly as protein-coding mutations.

In this context, leveraging one of the largest whole-genome sequencing (WGS) datasets of lung adenocarcinoma from the Sherlock-*Lung* study, we identified a single-base-pair deletion–associated mutational signature, ID2, as a dominant marker of aggressive tumor evolution, recently published in *Nature*.[1] Strikingly, we traced this signature to the reactivation of LINE-1 (L1) retrotransposons—ancient mobile DNA normally kept silent, yet capable of generating DNA breaks that fuel genomic instability when awakened. Together, these findings reveal a previously underappreciated mutational pathway—the L1–ID2 axis—that actively accelerates tumor diversification (Figure 1). This commentary highlights the conceptual and translational significance of the L1–ID2 axis, proposes mechanistic models linking endogenous retrotransposon activity to rapid tumor evolution, and outlines therapeutic opportunities targeting L1's ORF2 endonuclease as a novel strategy to slow cancer evolution. The emergence of L1 and ID2 reframes tumor evolution as a process shaped not only by somatic drivers but also by the awakening of mutagenic repetitive DNA.

A NEW LENS ON CANCER EVOLUTION

Mutational signatures—the characteristic patterns of DNA damage left behind by endogenous biological processes and environmental exposures—have become essential tools for interpreting cancer genomes. These signatures act as molecular footprints, revealing the underlying causes of mutations even when the initiating agents are cryptic. Because of their power to illuminate tumor etiology and evolutionary history, mutational signature analysis is now routine in cancer genomics. WGS, together with advanced computational methods, enables this approach by providing single-base-pair resolution across the entire genome, capturing both coding and noncoding alterations that define mutational processes.

Beyond their etiologic value, mutational signatures also offer an alternative lens through which to understand tumor evolution. Specifically, the clock-like signature SBS1, generated by spontaneous deamination of 5-methylcytosine, can serve as a molecular clock to map evolutionary time.[2] This allows estimation of tumor latency—the interval between a patient's age at diagnosis and the inferred age of the tumor's most recent common ancestor.

In our study, we leveraged one of the largest WGS datasets for lung adenocarcinoma to date, encompassing tumors from both smokers and never-smokers. This scale enabled a systematic evaluation of the genomic features that influence the speed and trajectory of tumor evolution, revealing clear divergence between etiologic subtypes. Tumors from smokers often begin with *KRAS* mutations induced by tobacco-related DNA damage. Once *KRAS* is activated, these tumors tend to evolve rapidly, accumulating genomic alterations that accelerate progression. By contrast, tumors from never-smokers typically initiate with *EGFR* mutations that arise in the absence of environmental mutagens, reflecting natural endogenous processes. These tumors often evolve slowly over many years and rarely exhibit aggressive phenotypes.

ID2 AS A HIDDEN MARKER OF AGGRESSIVE TUMOR PROGRESSION

Among the genomic features evaluated, ID2 emerged as a powerful determinant of evolutionary tempo. ID2 is characterized by single–base-pair thymine deletions occurring within long homopolymeric T tracts (≥5 bp).[3] Although widespread across tumors and frequently elevated in mismatch repair–deficient cancers, its biological origins have remained unclear. Prior studies attributed ID2 to polymerase slippage during DNA replication, yet this mechanism alone does not explain its impact on tumor development.

In our analysis, ID2 was tightly linked to short tumor latency, suggesting that this specific form of DNA damage actively shapes tumor evolutionary dynamics. Tumors with high ID2 burden exhibited a distinct and aggressive phenotype, marked by enhanced cell-cycle activation, increased genomic instability, elevated hypoxia, greater metastatic propensity, and poor overall survival. These findings position ID2 not as a passive endogenous artifact but as a dynamic marker of fast-evolving tumor states. Recognition of ID2 therefore expands our understanding of tumor heterogeneity and introduces a new biological axis—independent of canonical oncogenic drivers—through which aggressiveness can be interpreted. One contributor to this aggressive behavior is that ID2 exhibits the lowest neoantigen burden among mutational processes analyzed, consistent with enhanced immune evasion. However, additional mechanistic studies are needed to delineate how ID2-linked DNA damage remodels the genome and tumor microenvironment. Notably, in tumors from smokers, *KRAS* mutations and high ID2 burden frequently co-occur, providing dual mutational forces that accelerate progression. This convergence may partly explain why smoking-associated tumors often display particularly aggressive clinical behavior.

ANCIENT MOBILE DNA L1 CONTRIBUTES TO ID2

Long interspersed nuclear element–1 (LINE-1 or L1) retrotransposons comprise ~17% of the genome. Although most copies are inactive, ~100 evolutionarily young elements remain retrotransposition-competent. In healthy tissues, L1 is tightly silenced by DNA methylation, repressive chromatin, and post-transcriptional mechanisms. Under environmental or oncogenic stress—including tobacco exposure—this silencing erodes, enabling L1 reactivation. Activated L1 can generate DNA double-strand breaks, promote genomic instability, and drive large-scale structural alterations. However, its potential role in shaping small mutational processes had remained unknown.

Our study uncovered a strong correlation between L1 reactivation and ID2, with a clear dose–response relationship: tumors with more L1 insertions harbored a significantly higher burden of ID2 mutations. Tumors enriched for L1 activity also exhibited the most aggressive evolutionary trajectories. This suggests a mechanistic connection between L1 retrotransposition and the generation of ID2. Biologically, this is plausible. L1 encodes ORF1p and ORF2p; notably, ORF2p contains an endonuclease that cleaves genomic DNA at homopolymeric T motifs—the exact context in which ID2 deletions occur. This parallel suggests that ID2 could arise during L1 retrotransposition, when ORF2p introduces DNA nicks repaired by error-prone pathways. A recent study showed that ORF2p endonuclease activity is strongly stimulated by forked or flap DNA structures, explaining why L1 mobilization occurs during replication.[4] This aligns with ID2's replication-associated character. However, ID2 mutations and L1 insertions rarely map to the same genomic loci, suggesting an indirect or replication-stress–mediated link rather than direct colocalized damage. The precise mechanistic interplay remains unresolved and warrants further investigation.

CLINICAL IMPLICATIONS OF THE L1–ID2 AXIS

Although identified in lung adenocarcinoma, the L1–ID2 axis is likely relevant across many solid tumors, as both L1 activity and ID2 mutations occur broadly across cancers. Direct detection of L1 activity in tissue or liquid biopsy is technically challenging due to its repetitive nature and the need for

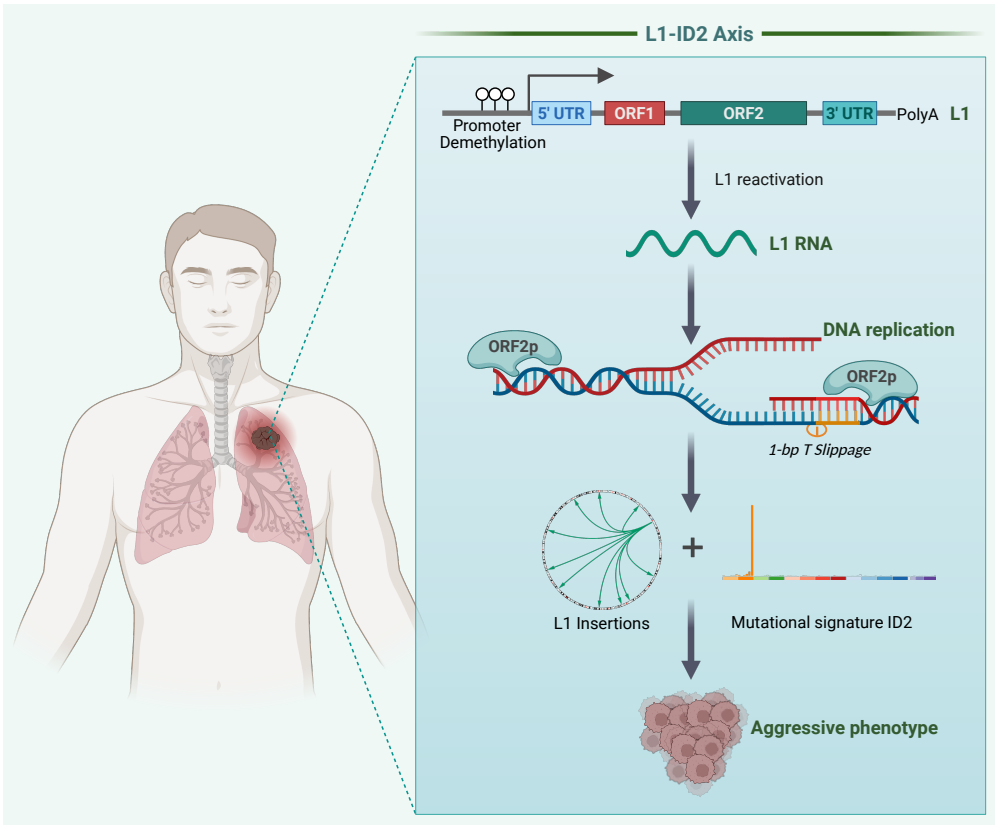

Figure 1. The L1–ID2 axis as a mutational pathway driving tumor aggressiveness The schematic illustrates how reactivation of LINE-1 (L1) retrotransposons fuels the generation of the ID2 mutational signature and contributes to aggressive tumor phenotypes. Promoter demethylation leads to L1 reactivation, resulting in the production of L1 RNA and translation of ORF1p and ORF2p. During DNA replication, the ORF2p endonuclease introduces DNA nicks at homopolymer thymine tracts, which may be resolved through DNA repair, contributing 1-bp T deletions characteristic of the ID2 mutational signature (shown as "one T slippage"). Tumors with active L1 show increased L1 insertions, and together with ID2 accumulation, exhibit aggressive biological phenotypes.

deep WGS. Alternatively, circulating ORF1p protein, shown to be detectable in plasma using ultrasensitive assays, may serve as a practical surrogate biomarker of L1 activity in liquid biopsy settings. ID2 is readily measurable from WGS or even whole-exome sequencing, enabling incorporation into clinical risk assessment. Tumors with high ID2 burden consistently exhibit poor outcomes independent of driver genotype, making ID2 a promising prognostic biomarker. Because ID2 reflects an active mutational process, it may better predict tumor trajectory than static genomic markers.

L1 activity also presents opportunities for early detection. L1-derived DNA fragments and ORF1p-associated signals in circulating tumor DNA may serve as biomarkers of aggressive tumor states, particularly in high-risk populations such as smokers.

Therapeutically, identification of L1 as a major contributor to ID2 opens new avenues for intervention. ORF2p, with both endonuclease and reverse transcriptase activity, represents a promising target.[5] Inhibiting ORF2p—through endonuclease inhibitors, reverse transcriptase inhibitors, or epigenetic silencing of L1 promoters—may reduce L1-induced DNA breaks, suppress ID2 generation, and slow tumor evolution. These approaches highlight the promise of targeting the mutational machinery itself rather than only downstream oncogenic consequences.

CONCLUSION

The discovery of ID2 as a dominant marker of rapid cancer evolution and the identification of L1 reactivation as its likely source represent a major conceptual advance. These findings illuminate how endogenous repetitive elements, once tightly silenced, can become engines of genomic instability when reawakened. While further experimental validation is required to establish direct causality, the L1–ID2 axis provides new opportunities for biomarker development, risk stratification, early detection, and therapeutic intervention.

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AUTHOR CONTRIBUTIONS

T.Z.: Visualization, conceptualization, writing, and supervision. M.T.L.: Manuscript revision. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.