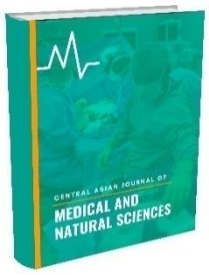
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 04 Issue: 06 | Nov-Dec 2023 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

# Investigation Association between Line-1 And MORC2 Expression in Different Types of Cancers

**1. Wisam Abdan Wawi AL-Abdullah**

*Received 2nd Oct 2023,*
*Accepted 19th Nov 2023,*
*Online 21st Dec 2023*

[1] Al-Qadisiyah University / College of Education

**Abstract:** Line-1 elements act as an engine in alteration human genomic DNA. These elements continue to insert new insertions facilitating genomic diversity and sometimes causing disease including cancer. Mobilization of line-1 could act as mutagenesis and exon skipping. However, there are different mechanisms can regulate mRNA transcript of line-1 elements.. MORC2 gene was suggested to be a novel participant in regulation line-1 transcription, acting by binding HUSH complex and suppress active line-1 element. Thus, in current project we are interested to evaluate the level expression of line-1 and MORC2 in some cases of cancer compared with healthy group as well as evaluating the correlation between line-1 and MORC2 expression to investigate how regulatory factors affect line-1 expression in several cases of cancer. This study was first assay conducted in Iraq. However, this study started with collecting whole blood samples of patients and healthy group. Then, RNA was extracted and created cDNA to set up RT-qPCR, which used to analyze mRNA level of both genes line-1 and MORC2. Most cases of cancer expressed line-1 including testicular, breast, colon, pharyngeal, stomach, prostate, rectal, pancreatic, brain, lung, and bone respectively at different levels of p-value. Brain cancer was highly expressed line-1. MORC2 gene was expressed in rectal, pancreatic, brain, lymphoma, testicular, cervical, ovarian, pharyngeal, bone, lung, and leukemia at p-value 0.05. Line-1 is substantially more elevated than MORC2 in several cancer types, and Line-1 expression has a significantly negative correlation with MORC2 expression in cancer patients.

**Key words:** line-1, MORC2, Cancer, gene expression.

## Introduction

Genetic materials could be repetitive including copies of DNA fragments dispersed in genomic DNA repeats elements (retrotransposones) represent dynamic expansion of genomic DNA, some types of repeats can mobilize and duplicate to composed more than 50% of human DNA material (Nurk *et al*., 2022). DNA polymorphisms have play a vital role in human DNA alterations. These include SNPs, deletion of DNA, new insertion, microsatellite and young elements of retrotransposones (Kidd *et al*., 2008; Seleme *et al*., 2006). One of these elements is line-1, which is only an active elements that can mobilized and cause variability in human DNA by exon shuffling or by changing expression levels of some patterns of genes (Goodier and Kazazian, 2008; Moran *et al*., 1999). Active line-1 has been showed in most somatic tissues like epithelial tissues of cancer cells (Scott and Devine, 2017). Line-1 considered as a hallmark of several genomic instability and chromosomal instability in addition. It becomes as an indicator of cancer occurrence (Zhang *et al*., 2020). The first report identified tumorigenic role of line-1 elements insertions adenocarcinoma ductal cells in the second intron of *myc* oncogene (Morse *et al.*, 1988). 750bp of line-1 ended with A tail (150bp) was inserted in colon tumor tissues during tumorigenesis while it was absent from normal tissues (Miki *et al.*, 1992). Several studies showed line-1 insertions in several human epithelial cancer such as novel insertions were detected by using transposon-sequence approach in human lung tumor and the researchers proposed line-1 ability to drive carcinogenesis (Iskow *et al.*, 2010). However, these studies encouraged us to study alterations line-1 expression in some types of Iraqi patients cancer. Epigenetic modifications can organize line-1 movement. Repetitive genes and repeats activity was regulated when repetitive elements is companied with diseases and genomic instability (Burns, 2022; Jönsson *et al*., 2020).

Packaging of repetitive elements into specific chromatin represents a converted method to control their replication and transcription (Pandiloski *et al.*, 2023). Human silencing Hub complex (HUSH) is an epigenetic repressor considered as a critical defense pathway. It safe guards genomic DNA form the invasion of retrotransposones and controls the information (DNA-RNA) in mammalian genomic DNA (Das *et al.*, 2022; Seczynska and Lehner, 2023). HUSH complex recruits two main factor genes: MORC2 gene compacts chromatin and SETDB gene deposits H3Kgme3 at interested loci to silence active integrated retrotransposons (Seczynska *et al*., 2022). Some evidences proposed vital role of MORC members family in regulating repetitive DNA and retrotransposons transcription. Through targeting DNA methylation and histone as part of silencing transcription genes (Moissiard *et al*., 2012). MORC2 gene is member of MORC family and this gene expressed in colon, gastric, brain, testis and ovary (Kikuno *et al*., 1999; Wang *et al.*, 2010). According to identify zin fing motif (cw) in MORC2 gene structure, it has been expected contributing role of MORC2 in proteins interaction or DNA binding to affect transcription levels of genes. MORC2 has been identified to silence active young copies of line-1 retrotransposones by binding HUSH complex to MORC2 protein (Liu *et al*., 2018; Robbez-Masson *et al*., 2018). Above review encouraged us to ask are there is changes in line-1 expression in some types of tumors and find if there is a positive or negative association between line-1 and MORC2 expressions as well as to highlight which type of cancer highly expressed line-1 and which one is less in Iraqi patients of cancer.

## Materials and methods

100 blood samples were collected from cancer patients. They attended to consult in the cancer department in Al-Diwaniyah hospital. 100 blood samples were drawn from non-cancer people acting as the control. They were a contributor to current studying. Cancer cases were selected according to the clinical and laboratory examination. To isolate mRNA, 2 ml blood samples were collected in EDTA tubes.

**RNA isolated and created of cDNA:** Total RNA was extracted from blood cells by adding 1ml of Trizol (Bioneer Acuzol, Irans Zolvp, Trans). NanoDrop was used to measure the RNA concentration,

and the 260/280 nm ratio was utilized to assess the RNA's purity. RNA was reverse transcribed into cDNA using 2µof total RNA 3µ based on the manufacturer's information of the transcription kit (TransScript® All-in-One First-Strand cDNA, trans) into a 2µl reaction system

**Real-Time PCR assay:** qPCR was done using the bright-green qPCR master mix kits (applied biological materials Inc, USA) in a Light cycler system RT-qPCR system (Roche, Mannheim, Germany). Oligonucleotides sequencing were used as following line-1 F: 5'-TGCGGAGAAATA GGAACATTTT-3', R: 5'-TGAGGAATCGCCACACTGACT-3' MORC2 F: 5'-TCGGAAGCGG AGTGTC-3', R: 5'-CGTCGTGCAGCCCTTTATCT-3', GAPDH F: 5'-GTCAAGGCTGAGAAC GGGAA-3', R: 5'-TCGCCCCACTTGATTTTGGA-3'. The transcript levels were normalized to GAPDH expression. Relative expression was determined utilizing $2^{\wedge -\Delta\Delta CT}$ method.

**Statistical analyses:** Results were analyzed by the Graph Pad Prism version 9 (Inc., San Diego, CA, USA). The difference between patient and control groups was examined using T-tests. A one-way ANOVA (Tukey multiple comparisons) was used to analyze the data between control and different types of cancer. Pearson correlation was used to analysis relation between line-1 and MORC2 expression. Data are shows as the mean ± standard error using $p \leq 0.05$.

**Results**

Upregulation of line-1 and MORC2 genes expression were evaluated in whole blood of cancer cases compared with the control group. Line-1 mRNA expression showed an increase in cancer cases with 3.930-fold changes at p-value 0.01, Table (1), Figure (1A). MORC2 gene expression elevated to 2.03 fold change in patients compared to control group. This exhibitions significant variation between the cancer cases and non-cancer group at p-value 0.05, Table (1), Figure (1B).

| Genes | Groups | $C_T$ of GAPDH | $C_T$ of Target | $\Delta C_T$ Mean | $\Delta\Delta C_T$ | Fold change |
|---|---|---|---|---|---|---|
| Line1 | Healthy | 28.62±0.49 | 18.80±0.52 | -9.54±0.82 | -1.53 | 3.930 |
| | Cancer | 27.85±0.33 | 16.77±0.35 | -11.08±0.18 * | | |
| MORC2 | Healthy | 26.28±0.52 | 36.28±0.14 | 10.00±0.47 | -1.02 | 2.03 |
| | Cancer | 25.46±1.05 | 33.28±0.25 | 9.17±0.55* | | |

**Table 1. Line-1 And Morc2 Mrna Transcript Levels In Human Healthy And Cancer Patients. Data Represents Ct Means, ΔCt, ΔΔCt And Fold Change Values. A Lower ΔCt Value Shows Higher Expression Of The Tested Gene. Results Are Showed As Mean ±Sem, *P≤0.05.**

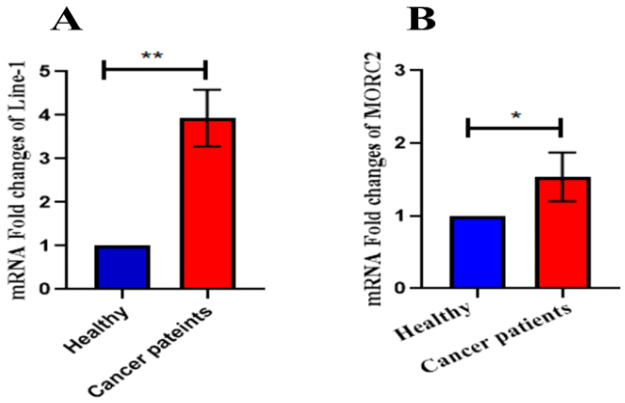



***Figure (1) Relative genes expression including (A) line-1 and (B) MORC2 for cancer patients and control groups.*** ** referred a significant difference ($p \leq 0.05$), **($p \leq 0.01$).*

mRNA of line-1 was highly amplified in all cancer patient samples. It was upregulated significantly in diverse types of cancer including testicular, breast, colon, pharyngeal, stomach, prostate, rectal, pancreatic, brain, lung, and bone respectively according to its level in non-cancer group Figure (2). Conversely, there was no significant mRNA expression of line-1 at $p \geq 0.05$ in these types of cancers leukemia, lymphoma, ovarian, cervical, and bladder compared with control. Brain and lung cancer patients were highly expressed line-1 then stomach patients that was expressed at $p \leq 0.0001$. While bladder and ovarian cancer patients were lowest expression of line-1 element compared with non-patient samples.

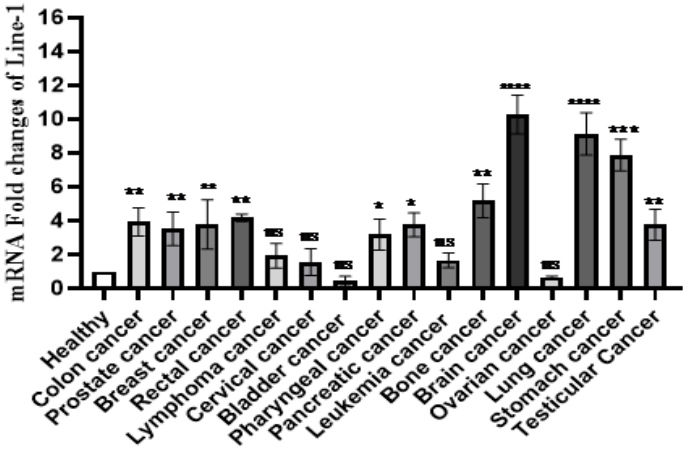



***Figure (2) Relative expression genes of line-1 for cancer patients and control groups***.

Relative expression of MORC2 in bladder, stomach, breast, colon, and prostate when compared with the group of control Figure (3). In several cancer types (rectal, pancreatic, brain, lymphoma, testicular, cervical, ovarian, pharyngeal, bone, lung, and leukemia) the relative MORC2 mRNA expression was not expressed significantly ($p \geq 0.05$), Figure (3). However, MORC2 was highly expressed at $p \leq 0.05$ in bladder cancer in contract the lowest expression of MORC2 was in ovarian cancer patients compared with healthy group.

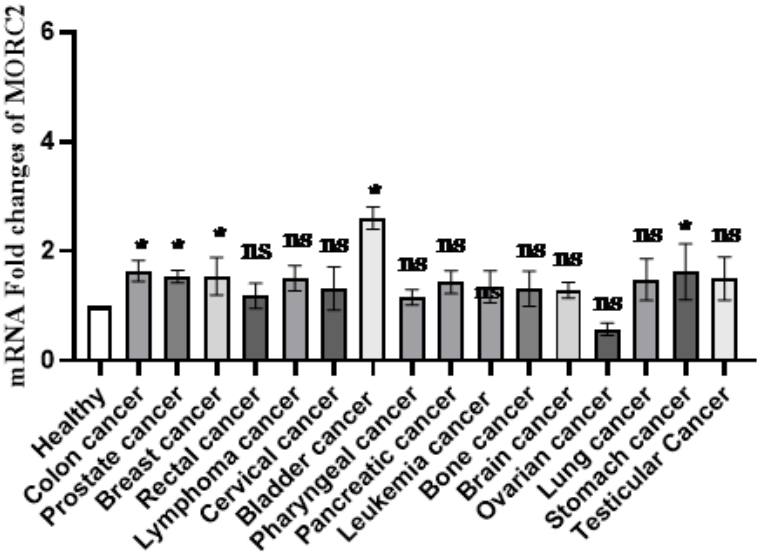



***Figure (3) Relative expression genes of MORC2 for cancer patients and control groups.***

Regarding to investigate gene expression differences between line-1 and MORC2 genes, it is clear from Table (2) and Figure (4) there are no significant differences at $p \geq 0.05$ between transcript level of these genes in leukemia, cervical, ovarian and lymphoma. However, data showed a significant difference in gene expression between line-1 and MORC2 at the level of probability at $p \leq 0.05$ in breast, colon, prostate and pharyngeal. It also noticed that there were significant at $p \leq 0.001$ and $p \leq 0.001$ of mRNA expression of line-1 Table (2) and Figure (4). Correlation analysis between line-1 and MORC2 expression for cancer patients is shown in Figure (5), the data found a significantly negative association between the expression of line-1 and MORC2 r = - 0.3615 at $p \leq 0.05$.

| Samples | N | mRNA folding change | | P - value |
|---|---|---|---|---|
| | | Line-1 | MORC2 | |
| **Colon cancer** | 7 | 3.937±0.484 | 1.604±0.190 | 0.0110 |
| **Prostate cancer** | 7 | 3.533±0.571 | 1.533±0.117 | 0.0266 |
| **Breast cancer** | 8 | 3.791±0.729 | 1.541±0.172 | 0.0239 |
| **Rectal cancer** | 7 | 4.182±0.132 | 1.182±1.182 | **<0.0001** |
| **Lymphoma cancer** | 6 | 1.939±0.413 | 1.206±0.210 | 0.1513 |
| **Cervical cancer** | 7 | 1.568±0.399 | 1.318±0.1982 | 0.5950 |
| **Bladder cancer** | 7 | 0.447±0.166 | 2.603±0.620 | 0.0002 |
| **Pharyngeal cancer** | 6 | 3.189±0.526 | 1.156±0.815 | 0.0188 |
| **Pancreatic cancer** | 6 | 3.765±0.409 | 1.431±0.121 | 0.0054 |
| **Leukaemia** | 6 | 1.678±0.252 | 1.344±0.168 | 0.3341 |
| **Bone cancer** | 6 | 5.179±0.577 | 1.313±0.185 | 0.0031 |
| **Brain cancer** | 6 | 10.29±0.659 | 1.287±0.823 | 0.0002 |
| **Ovarian cancer** | 6 | 0.672±0.040 | 0.572±0.067 | 0.2713 |
| **Lung cancer** | 7 | 9.146±0.723 | 1.479±0.220 | 0.0005 |
| **Stomach cancer** | 7 | 7.887±0.535 | 1.620±0.296 | 0.0005 |
| **Testes cancer** | 6 | 3.766±0.532 | 1.499±0.228 | 0.0173 |

**Table 2. the level of mRNA for Line-1 gene and MORC2 gene in different types of cancer. Data are presented as mean±S.E.M.**

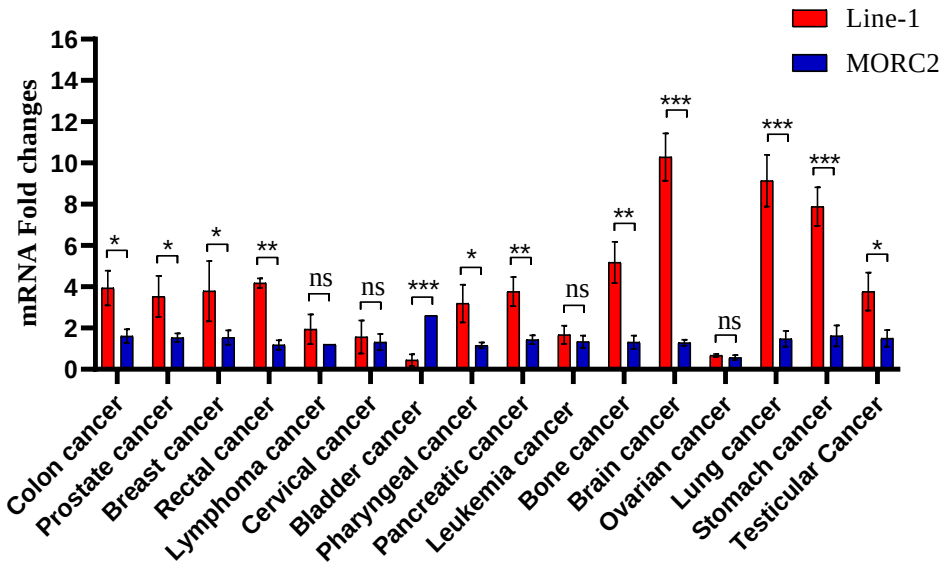



***Figure (4) transcription levels of line-1 gene compared with transcerpition level of MORC2 gene in patients cancers.***

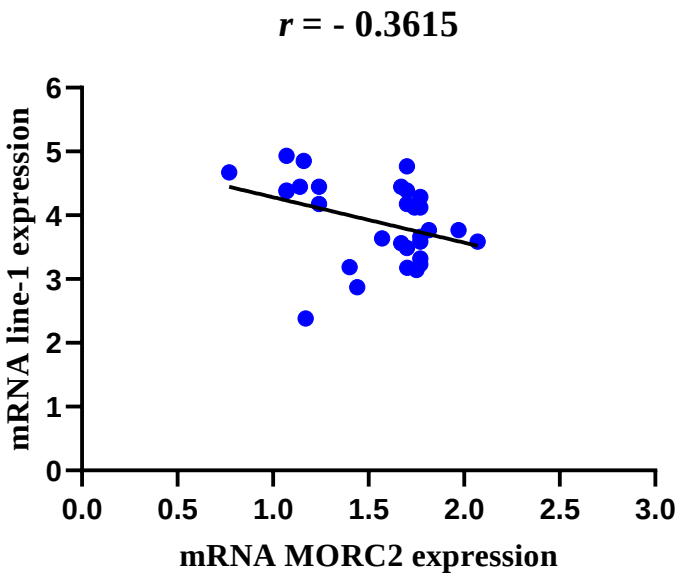



***Figure (5) Correlation mRNA line-1 expression and mRNA MORC2 expression in cancer patients.***

**Discussion:**

Transposable elements including (line-1) have a significant role in genome evolution causing genomic DNA instability, homologues recombination and oncogenesis (Kazazian and Moran, 2017). line-1 element is a main contributor in human DNA variation that can cause various types of diseases (Beck *et al.*, 2011). Present study clarifies the high level of line-1 in several cancers. ORF1 primers was used to determine line-1 expression studied samples. ORF1 offline-1 produces an RNA-binding protein. A high mRNA level of ORF1 was identified to be more expression in most kinds of cancer thus line-1 was utilized as a characterization marker. line-1 mRNA was widespread and identified as a hallmark in several cases of cancer including prostate, colon, breast, neuroendocrine and hepatocellular cancer (Rodić *et al*., 2014). Suggesting line-1 transcript contributes in breaking double strand of genomic DNA (Gasior *et al*., 2006) or possibly, line-1 expression contributes in cancer cases progression (Belancio *et al.*, 2015). However, different ways could control line-1 expression like siRNA causing degradation of ORF line-1 mRNA (Soifer, 2006). APOBEC3 gene represents another mechanism to control line-1 mobilization (Wissing *et al*., 2011). Line-1 promoter methylation could inhibit line-1 activity (Hancks and Kazazian Jr, 2012). MPP8 gene expression elevated in several kinds of tumors, MPP8 is a member of HUSH complex (Abdullah, 2023). This is lead us to test if the effector MORC2 of HUSH complex associate with line-1 elements. HUSH complex described as a gatekeeper via epigenetic regulation of line-human specific (Tunbak *et al*., 2020). HUSH complex cooperates with next complex to dissect the expression of transposable elements (Garland *et al*., 2022).

Using widescreen analysis identified more than 100 novel genes that characterized to activate or inhibit line-1 activity (Liu *et al*., 2018) some of novel candidate genes functionally contribute in repairing DNA pathways, DNA damage, RNA processing and transcriptional regulation (Liu *et al.*, 2018). These candidate includes interesting gene in present study which is MORC2 gene (Liu *et al.*, 2018). However, in present study MORC2 transcript was significantly evaluated in some cases of cancer including bladder, prostate, stomach, breast and colon. These results supported previous study that identified MORC2 expression in diverse cancers such as stomach, colon, pancreas, lung, kidney, esophagus, bladder, ovary, breast, skin, liver, prostate and endometrium (Ding *et al.*, 2018) as well as MORC2 implicated reprogramming metabolism rate of cancer (Guddeti *et al*., 2021). Accumulated evidence has determined that MORC2 gene not restricted to chromatin remodeling or gene

transcription but also contribute in tumor developing via regulating tumor suppressors expression or downstream oncogenes (Zhang *et al*., 2023). MORC2 expression alterations in current study could be related with gene mutation. Growing evidence has suggested that MORC2 gene mutations could be associated with developing several types of cancer (Zhang *et al.*, 2023). Present study found a negative association between line-1 and MORC2 expression. These results support the study of Liu et al. (2018). They identified that knockout novel regulating genes including MORC2 lead to increase line-1 expression. Present results identified that line-1 highly expressed in most types of cancer compared with MORC2 gene expression as shown figure 4. For example brain cancer was highly expressed line-1 figure 2 while MORC2 was not significantly expressed in this type of cancer. However, MORC2 plays an effective role in transcription regulation and repair system of DNA (Li *et al*., 2013), MORC2 prefers to bind active young line-1 element at the 5end and enhanced the deposition of H3K9me3 to inhibit line-1 mobilization and expression (Robbez-Masson *et al*., 2018)

**Conclusion**

Current study determined level expression of line-1 gene in Iraqi cancer patients and study MORC2 expression level in carcinomas cells in addition, we heighted correlation of retrotransposone elements line-1 and MORC2 which they are expressed in multiple kinds of cancer therefore, these genes has become a new therapeutic target and they are considered as a diagnostic mark for some types of mechanism. Therefore, MORC2 detection application in cancer cells are still worth to discover it.

**References**


1. Abdullah WAWA (2023) L1Hs and MPP8 genes expression correlation with several types of carcinoma tumors. *International Journal of Medical Science and Clinical Research Studies* **3**:2445-2450.
2. Beck CR, Garcia-Perez JL, Badge RM and Moran JV (2011) LINE-1 elements in structural variation and disease. *Annual review of genomics and human genetics* **12**:187-215.
3. Belancio VP, Blask DE, Deininger P, Hill SM and Jazwinski SM (2015) The aging clock and circadian control of metabolism and genome stability. *Frontiers in genetics* **5**:455.
4. Burns KH (2022) Repetitive DNA in disease. *Science* **376**:353-354.
5. Das A, Vijayan M, Walton EM, Stafford VG, Fiflis DN and Asokan A (2022) Epigenetic silencing of recombinant adeno-associated virus genomes by NP220 and the HUSH complex. *Journal of Virology* **96**:e02039-02021.
6. Ding Q-s, Zhang L, Wang B-c, Zeng Z, Zou X-q, Cao P-b, Zhou G-m, Tang M, Wu L and Wu L-l (2018) Aberrant high expression level of MORC2 is a common character in multiple cancers. *Human Pathology* **76**:58-67.
7. Garland W, Müller I, Wu M, Schmid M, Imamura K, Rib L, Sandelin A, Helin K and Jensen TH (2022) Chromatin modifier HUSH co-operates with RNA decay factor NEXT to restrict transposable element expression. *Molecular Cell* **82**:1691-1707. e1698.
8. Gasior SL, Wakeman TP, Xu B and Deininger PL (2006) The human LINE-1 retrotransposon creates DNA double-strand breaks. *Journal of molecular biology* **357**:1383-1393.
9. Goodier JL and Kazazian HH (2008) Retrotransposons revisited: the restraint and rehabilitation of parasites. *Cell* **135**:23-35.
10. Guddeti RK, Chutani N and Pakala SB (2021) MORC2 Interactome: Its Involvement in Metabolism and Cancer. *Biophysical Reviews* **13**:507-514.

11. Hancks DC and Kazazian Jr HH (2012) Active human retrotransposons: variation and disease. *Current opinion in genetics & development* **22**:191-203.

12. Iskow RC, McCabe MT, Mills RE, Torene S, Pittard WS, Neuwald AF, Van Meir EG, Vertino PM and Devine SE (2010) Natural mutagenesis of human genomes by endogenous retrotransposons. *Cell* **141**:1253-1261.

13. Jönsson ME, Garza R, Johansson PA and Jakobsson J (2020) Transposable elements: a common feature of neurodevelopmental and neurodegenerative disorders. *Trends in Genetics* **36**:610-623.

14. Kazazian HH and Moran JV (2017) Mobile DNA in Health and Disease. *New England Journal of Medicine* **377**:361-370.

15. Kidd JM, Cooper GM, Donahue WF, Hayden HS, Sampas N, Graves T, Hansen N, Teague B, Alkan C and Antonacci F (2008) Mapping and sequencing of structural variation from eight human genomes. *Nature* **453**:56-64.

16. Kikuno R, Nagase T, Ishikawa K-i, Hirosawa M, Miyajima N, Tanaka A, Kotani H, Nomura N and Ohara O (1999) Prediction of the coding sequences of unidentified human genes. XIV. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. *DNA research* **6**:197-205.

17. Li D-Q, Nair SS and Kumar R (2013) The MORC family: new epigenetic regulators of transcription and DNA damage response. *Epigenetics* **8**:685-693.

18. Liu N, Lee CH, Swigut T, Grow E, Gu B, Bassik MC and Wysocka J (2018) Selective silencing of euchromatic L1s revealed by genome-wide screens for L1 regulators. *Nature* **553**:228-232.

19. Miki Y, Nishisho I, Horii A, Miyoshi Y, Utsunomiya J, Kinzler KW, Vogelstein B and Nakamura Y (1992) Disruption of the APC gene by a retrotransposal insertion of L1 sequence in a colon cancer. *Cancer research* **52**:643-645.

20. Moissiard G, Cokus SJ, Cary J, Feng S, Billi AC, Stroud H, Husmann D, Zhan Y, Lajoie BR and McCord RP (2012) MORC family ATPases required for heterochromatin condensation and gene silencing. *Science* **336**:1448-1451.

21. Moran JV, DeBerardinis RJ and Kazazian Jr HH (1999) Exon shuffling by L1 retrotransposition. *Science* **283**:1530-1534.

22. Morse B, Rotherg PG, South VJ, Spandorfer JM and Astrin SM (1988) Insertional mutagenesis of the myc locus by a LINE-1 sequence in a human breast carcinoma. *Nature* **333**:87-90.

23. Nurk S, Koren S, Rhie A, Rautiainen M, Bzikadze AV, Mikheenko A, Vollger MR, Altemose N, Uralsky L and Gershman A (2022) The complete sequence of a human genome. *Science* **376**:44-53.

24. Pandiloski N, Horvath V, Karlsson OE, Christoforidou G, Dorazehi F, Koutounidou S, Matas J, Gerdes P, Garza R and Jönsson ME (2023) DNA methylation governs the sensitivity of repeats to restriction by the HUSH-MORC2 corepressor. *bioRxiv*:2023.2006. 2021.545516.

25. Robbez-Masson L, Tie CH, Conde L, Tunbak H, Husovsky C, Tchasovnikarova IA, Timms RT, Herrero J, Lehner PJ and Rowe HM (2018) The HUSH complex cooperates with TRIM28 to repress young retrotransposons and new genes. *Genome research* **28**:836-845.

26. Rodić N, Sharma R, Sharma R, Zampella J, Dai L, Taylor MS, Hruban RH, Iacobuzio-Donahue CA, Maitra A and Torbenson MS (2014) Long interspersed element-1 protein expression is a hallmark of many human cancers. *The American journal of pathology* **184**:1280-1286.

27. Scott EC and Devine SE (2017) The role of somatic L1 retrotransposition in human cancers. *Viruses* **9**:131.

28. Seczynska M, Bloor S, Cuesta SM and Lehner PJ (2022) Genome surveillance by HUSH-mediated silencing of intronless mobile elements. *Nature* **601**:440-445.

29. Seczynska M and Lehner PJ (2023) The sound of silence: mechanisms and implications of HUSH complex function. *Trends in Genetics*.

30. Seleme MdC, Vetter MR, Cordaux R, Bastone L, Batzer MA and Kazazian Jr HH (2006) Extensive individual variation in L1 retrotransposition capability contributes to human genetic diversity. *Proceedings of the National Academy of Sciences* **103**:6611-6616.

31. Soifer HS (2006) Do small RNAs interfere with LINE-1? *Journal of Biomedicine and Biotechnology* **2006**.

32. Tunbak H, Enriquez-Gasca R, Tie CH, Gould PA, Mlcochova P, Gupta RK, Fernandes L, Holt J, van der Veen AG and Giampazolias E (2020) The HUSH complex is a gatekeeper of type I interferon through epigenetic regulation of LINE-1s. *Nature communications* **11**:5387.

33. Wang GL, Wang CY, Cai XZ, Chen W, Wang XH and Li F (2010) Identification and expression analysis of a novel CW-type zinc finger protein MORC2 in cancer cells. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology* **293**:1002-1009.

34. Wissing S, Montano M, Garcia-Perez JL, Moran JV and Greene WC (2011) Endogenous APOBEC3B restricts LINE-1 retrotransposition in transformed cells and human embryonic stem cells. *Journal of biological chemistry* **286**:36427-36437.

35. Zhang S, Guo A, Wang H, Liu J, Dong C, Ren J and Wang G (2023) Oncogenic MORC2 in cancer development and beyond. *Genes & diseases*.

36. Zhang X, Zhang R and Yu J (2020) New understanding of the relevant role of LINE-1 retrotransposition in human disease and immune modulation. *Frontiers in cell and developmental biology* **8**:657.