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VIRAL ELEMENTS IN THE HUMAN GENOME CONTRIBUTE TO ALS PATHOLOGY

Transcriptomics analysis revealed high retrotransposon expression as a consequence of TDP-43 loss in postmortem brain samples from ALS patients.

By Sejal Davla, PhD

Many transposable elements are ancient ancestral sequences that copy and paste themselves into the genome as they replicate within the host, and retrotransposon elements share an evolutionary history with viruses. Researchers at the Cold Spring Harbor Laboratory in New York identified the contribution of retrotransposon activation to the pathology of amyotrophic lateral sclerosis (ALS), a debilitating neurodegenerative disorder that remains incurable.1

TAR DNA-binding protein 43 (TDP-43) aggregates are common in tissues of patients with neurodegenerative diseases, such as ALS, frontotemporal dementia (FTD), and Alzheimer’s disease. Researchers have yet to uncover how TDP-43 aggregates make neurons vulnerable to cell death. Molly Gale Hammell, an associate professor in computational biology at the Cold Spring Harbor Laboratory in New York and the senior author of the study, described a link between TDP-43 pathology and elevated retrotransposon transcripts in postmortem brain tissue from ALS patients, unraveling a new mechanism that could accelerate diagnosis and drug targeting in ALS.

“One of the main things about TDP-43 in ALS is no matter whether it is a familial or sporadic mutation, about 97 percent of cases present TDP-43 pathology,” says Kessen Patten, professor and research chair in ALS at the Institut National de la Recherche Scientifique in Montreal, Canada, who was not part of the study. “TDP-43 is usually found in the nucleus but is completely mislocalized to the cytoplasm in ALS, and why the striking majority of ALS cases show the nuclear loss of TDP-43 still remains unknown,” he added.

“TDP-43 is an RNA binding protein, and a significant fraction of it binds to retrotransposons in cells,” said Hammell. Previous reports identified an increase in retrotransposon expression upon TDP-43 knockdown, suggesting that TDP-43 functions to silence transposons. “This led us to ask whether this was clinically relevant where patients who have dysfunctional TDP-43 protein would also show elevation of transposable elements,” added Hammell.

Hammell and her collaborators surveyed RNA sequencing data from ALS patients who had extensive TDP-43 pathology. “We found very, very high levels of transposable element expression, much higher than we would expect, as compared to controls and patients with other diseases,” reported Hammell. “Most of the time, the expression of transposable elements would be a nuisance for the cell. When they are activated, they can alert innate immune sensing pathways because they look like viral pathogens, and the cell tries to keep them off most of the time.”

Whether the transposons are just reporting on TDP-43 pathology or whether they are causative agents of disease pathology is unclear. “Are they contributing to inflammatory pathways? Are they neurotoxic in some way? If that’s true, then we could think about targeting them,” said Hammell.

ALS is a complex genetic disorder with nearly 50 causative genes; however, scientists have a limited understanding of the disease’s etiology. Despite previous efforts, researchers have not identified any biomarkers for ALS. All clinical hallmarks are seen in the central nervous system, and “that is not something available to us when the patients are diagnosed. What we would love to see is if there is a biomarker available in peripheral tissue,” explained Hammell. Elevated retrotransposon levels in the blood or cerebrospinal fluids could serve as biomarkers for ALS.

“We do know that at least about 45% of our genome is derived from transposable elements, and we know exactly what these elements are and where they came from.”

—Molly Gale Hammell, Cold Spring Harbor Laboratory

A biomarker is not just valuable for diagnosis, but can be valuable in clinical trials. Most ALS clinical trials fail because disease progression is complex with diverse clinical manifestations in patients. “I think stratification using molecular signatures could be very helpful as a potential biomarker for clinical trials,” said Patten.

“It is funny that transposons are often called alien DNA. I suppose in a sense, it is true. They are not properly human genes, but they have been with us. I think we have to acknowledge that they are a part of us, even though most of what it is doing is not for the benefit of the human body,” said Hammell.

See references on the last page.
Hidden within the human genome are the remnants of our ancestors’ viral infections. Scientists initially considered these stowaway sequences as junk DNA that served no purpose, but genetic remnants such as endogenous retroviruses (ERVs) comprise about eight percent of the human genome and may be expressed through epigenetic mechanisms. ERV expression spills double-stranded RNA (dsRNA) into the cytoplasm, which mimics viral infection and spurs the immune system into action.

Previously, researchers showed that the expression of ERV-containing transcripts may be a source of neoantigens that trigger an immune response in some cancers. In fact, increased ERV expression correlated with greater patient response and survival while on immunotherapy. To explore the connection between ERVs and immunotherapy response, researchers from institutions including Pancreas Centre BC, the University of British Columbia, and Vancouver General Hospital recently collaborated to measure ERVs in tumor samples from different cancer types.

“We want to identify biomarkers or some predictive signature that we could [use] to say, this person is likely to respond to immunotherapy,” said James Topham, a bioinformatician at Pancreas Centre BC and lead author on the study.

Immunotherapy uses the host’s anti-tumor immune response to eliminate cancer cells, but not all patients respond to the treatments. Predicting which patients would benefit from immunotherapy would help clinicians choose the best treatment course. The presence of ERV transcripts could highlight tumors that are especially immunogenic with the ability to induce an immune response that slows their growth.

The ERV cancer study took advantage of patient samples collected as part of the Personalized Oncogenomics (POG) program of British Columbia Cancer. The researchers did a retrospective analysis of ERV transcripts in whole transcriptome sequencing data from 199 patients with metastatic breast, colorectal, and pancreatic ductal adenocarcinoma (PDAC) tumors collected over four years. In each cancer type, the researchers found distinct subgroups with a viral mimicry phenotype, which included increased ERV transcript abundance and signatures of immunogenicity and antiviral response, such as genes associated with infiltrative immune cell types. However, the pattern of ERV loci expression was different for each cancer.

“It was a validation of a lot of ideas that were going around at the time, that these ERVs would be associated with some biological response in different tumor types.”

—James Topham, Pancreas Centre BC

It was a validation of a lot of ideas that were going around at the time, that these ERVs would be associated with some biological response in different tumor types. Most of the patients in the study did not receive immunotherapy as part of their cancer care, so the researchers could not compare ERV abundance with immunotherapy response or survival. The next step is to test ERV levels in a cohort that is receiving immunotherapy and to obtain RNA-seq data from fresh tissues.

Topham is optimistic that ERVs could be useful in cancer clinics. “[ERV biomarkers] could be used not alone, but in combination with other things like tumor mutational burden or T cell scores...to say that this patient should receive immunotherapy,” said Topham.

See references on the last page.
Hunting for Ancient Coronaviruses

Ancient signatures of genetic adaptation signal the presence of past coronavirus epidemics.

By Tiffany Garbutt, PhD

Humans have battled viruses for centuries, leaving genomic scars in the form of altered gene expression patterns. In a recent study published in *Current Biology*, a team of researchers from the University of Arizona, University of California, San Francisco, and the University of Adelaide in Australia identified genomic signatures from an ancient coronavirus-like epidemic 20,000 years ago.¹

“Our immune system is in constant balance with surrounding pathogens and adapts accordingly. If there is anything that can drive evolution, even in shorter time frames, it is infectious diseases,” said Hugo Zeberg, an assistant professor at Karolinska Institutet in Stockholm, Sweden who was not involved in the recent study, but whose research group identified ancient DNA from Neanderthals that affect COVID-19 susceptibility.²

Ancient DNA from past ancestors or viruses does not always have to integrate into DNA to cause long-lasting changes in gene expression patterns. David Enard, an assistant professor at the University of Arizona and senior author of the recent study noticed that there were numerous signals of past adaptations in human and mammalian genomes.

“From biology, I knew of genes that were known to adapt in response to viruses. I saw that viruses were a really excellent candidate to explain, at least partly, the very large amount of adaptation that we can see in the genomes of any species,” said Enard. He explored this phenomenon for years with other viruses in humans and mammals prior to the COVID-19 pandemic and had all the methodology and tools needed to investigate if there was an ancient coronavirus epidemic.

As the COVID-19 pandemic progressed, researchers identified proteins that interacted with SARS-CoV-2. With the gene sequences of these proteins in hand, Enard and his team scoured data from the 1000 Genomes Project, the largest public catalog of common human genetic variation, in search of changes in human genes that coded for SARS-CoV-2-interacting proteins.

“It was really important to not have a preconceived idea about where coronaviruses might have caused ancient epidemics in the world,” said Enard. His team searched the genome databases of 26 different populations for selective sweeps. Selective sweeps occur when a mutation or genetic variant is so advantageous that it and the genes surrounding it persist across generations without recombining, essentially sweeping genetic variation away.

Enard and his team identified 42 genetic variants at the center of historical genetic sweeps, more than would be expected by chance. Interestingly, not all of these genes were related to immune function. When a virus enters the cell, they hijack the host machinery to replicate, which includes genes encoding the basic machinery needed for common housekeeping functions such as transcription and translation.

By mapping these signatures, Enard and his team determined that a past coronavirus-like epidemic likely occurred in five East Asian populations approximately 20,000 years ago. Their finding is consistent with another study where researchers mapped the emergence of the sarbecoviruses to approximately 20,000 years ago in East Asia.³

“The genetic effects today of those past adaptations are probably pretty moderate. It’s very important to put this in perspective compared to the very strong effects that have been observed with social economics, wearing a mask, or being vaccinated,” said Enard.

“I saw that viruses were a really excellent candidate to explain, at least partly, the very large amount of adaptation that we can see in the genomes of any species.”

—David Enard, University of Arizona

The results of Enard’s study may help scientists better understand how humans have adapted to ancient viral infections. “The most important take-away message is that in the history of mankind we have always battled infections and these battles have left traces in our genome,” said Zeberg.

Enard continues to investigate past interactions between hosts and viruses, except now he is expanding his research to include viruses that have yet to infect humans. He envisions sequencing viruses in the wild to better understand impending threats to human health. “It could be an early line of defense that we don’t have today that could help us at least know more about what the dangers are that are lurking in the world that we don’t know about yet,” said Enard.

See references on the last page.
A WINDOW INTO THE PAST: HOW ANCIENT HUMANS SHAPED MODERN GENOMES

A deep learning-based methodology reveals Neanderthal and Denisovan DNA that benefits modern-day humans

By Nele Haelterman, PhD

The evolutionary processes that shaped the modern-day human intrigued scientists long before Charles Darwin postulated his evolutionary theories. Modern humans diverged from Neanderthals about half a million years ago, but there is evidence of interbreeding between the two species as recently as 50,000 years ago. Such admixture events introduced ancient human DNA into the genome of our modern human ancestors.

Most ancient DNA disappeared from the gene pool because it was not beneficial to contemporary human fitness. However, natural selection favored the retention of some Neanderthal genes through adaptive introgression, an evolutionary process by which some foreign DNA fragments are retained in the genome because they benefit the organism. A typical modern European or Asian genome contains two to four percent Neanderthal DNA, but not every individual has the same combination of fragments. “We find many regions of the genome where perhaps you have a Neanderthal fragment, but that fragment is not very frequent in a population. So, finding these interesting regions where a lot of people have Neanderthal fragments, those are quite rare,” said Fernando Racimo, associate professor at the GLOBE Institute at the University of Copenhagen.

To identify ancient DNA fragments that benefit modern-day humans, scientists have to first identify genomic regions where Neanderthal and contemporary populations match significantly while assuming that the genome evolved neutrally. Next, they must assess whether the regions occur more frequently than expected in modern humans. To tackle both steps at once, Racimo’s group developed a deep learning-based methodology called Genomattn. “The innovation here is that we’re jointly modeling the admixture event and the selection on the fragments. The other cool feature of it is that...we’re not giving the algorithm any prior information. So, what we’re doing is just simulating data under different scenarios—like a scenario of admixture, of admixture with selection, a scenario with no admixture, [a scenario with] no selection—and then we’re letting what’s called a convolutional neural network learn to distinguish between these different scenarios,” said Racimo. Previous methods allowed researchers to identify such events based on a priori expectations of what the DNA fragment should look like. “In this case, we’re letting the algorithm learn that by just feeding it simulations of genomic data,” Racimo added.

While most DNA from fossils is low quality and reveals only a snapshot of the genome, researchers have built several high-quality ancient human genomes. Racimo’s postdoctoral fellow, Graham Gower, compared two Neanderthal and one Denisovan genome to a global reference panel of present-day human genomes from across the world to test Genomattn’s adaptive introgression recognition ability.

Gower showed that the algorithm identifies known introgressed regions. He also found new fragments involved in immunity and pigmentation, pathways that are prone to introgression as they present an easy way for an immigrating species to adapt to the region. What surprised the team was the identification of genes with functions related to the blood and metabolism. “We’re not sure what those could be doing in modern human or Neanderthal biology, but it’s definitely something to pursue,” said Racimo. “It’s just interesting in terms of human biology, trying to understand what these regions are doing, why we got them from [Neanderthals], and why they were so beneficial to us.”

“This paper provides a very solid methodology to infer events of adaptive introgression,” says Diego Ortega-del Vecchyo, group leader at the International Laboratory for Human Genome Research at the National Autonomous University of Mexico, who was not involved in the study. “This method will likely accelerate discovery in evolutionary genetics, as it can disentangle more complex evolutionary scenarios that include multiple admixture or selection events without specifying DNA features a priori.

A typical modern European or Asian genome contains two to four percent Neanderthal DNA, but not every individual has the same combination of fragments.

See references on the last page.
SECRET SUPPORT: ENDOGENOUS RETROVIRUSES AS CANCER ENHANCERS

The activation of endogenous retrovirus sequences may enhance cancer onset and impact disease progression and prognosis.

By Nathan Ni, PhD

Many cancers are characterized by genetic and epigenetic changes that deregulate transcriptional networks and result in aberrant cellular behavior. Despite the advent of next-generation sequencing techniques, potential contributors to transcriptional networks such as endogenous retroviruses (ERVs) remain understudied. Recently, Özgen Deniz and Miguel Branco from Queen Mary University of London identified six ERV families as potentially oncogenic enhancers of acute myeloid leukemia (AML). Their work, published in Nature Communications, underscores the importance of studying neglected genomic elements.

ERVs represent an ideal source of novel regions that potentially regulate AML.

Retroviruses replicate by inserting their genome into host cells. Retroviral genomes persist in the germline, undergoing mutations and recombination events, and are inherited via Mendelian mechanisms. This endogenization process, over millions of years, creates ERVs—elements in the host genome with retroviral origins that are no longer recognized by the body as viral. “Our genomes are littered with [ERVs] at every stage of genomic integrity,” according to George Kassiotis, head of the laboratory of Retroviral Immunology at the Francis Crick Institute and who was not affiliated with Deniz’s study.

For Deniz, now running her own laboratory as a Research Fellow at Imperial College London, ERVs represent an ideal source of novel regions that potentially regulate AML. “These elements, like most non-coding DNA regions, have not been studied in detail because they were classified as ‘junk DNA’ until the ENCODE project [started in 2003],” Deniz said. “But because they retain regulatory regions and exhibit regulatory function in biological contexts, they are quite important for genomic evolution.”

Using DNase I hypersensitive sites sequencing—a sequencing technique specifically designed to identify regulatory regions—Deniz and her colleagues identified six ERV families that were enriched in both AML-model cell lines and patient samples. They found that these ERV elements bore chromatin signatures indicative of enhancer elements, and by linking chromatin status with short-range gene expression levels noted that ERV elements gained gene-regulatory activity in AML cells and bound AML-related transcription factors. Finally, genetically or epigenetically inactivating one of these ERV-derived enhancers resulted in suppressed growth and elevated apoptosis in AML cell lines.

A major question stemming from this study and facing the field at large is whether ERVs can induce oncogenesis by themselves. Many, if not all, of the properties of disease-causing exogenous retroviruses have been lost in ERVs, and Kassiotis noted that while ERVs are historically closely linked with cancer, no human ERV has ever been shown to cause cancer itself by producing infectious virus or inserting new copies of itself in the genome. “I believe that ERVs are activated by epigenetic dysregulation in cancer cells [arising due to oncogenesis], and then contribute to disease progression or aggressiveness afterward. It is difficult to definitively say this with the information we have now, but I hope to be able to shed more light on this throughout my career,” concurred Deniz.

ERVs may also potentially serve as biomarkers or clinical risk factors for specific diseases. “I would like this field to go in a direction where we can use information on ERV sequences, chromatin structures, and DNA methylation status to aid prognosis, determine patient outcome, anticipate therapy resistance, and so on,” said Deniz. She acknowledges that a better understanding of ERV variation is required to reach that objective. Some ERVs are not present in some individuals. “In our study, we noted ERV epigenetic heterogeneity from patient to patient, which was not surprising because AML is quite a heterogeneous disease. Even if the sequence and chromatin structures are identical, an ERV sequence can still be bound by different transcription factors depending on the tissue and cell type. There are many layers involved.”

Deniz plans to probe the functional phenomena she observed in this study further “We did all of the functional experiments in cell lines, and I think we need to go further and check for them in patient cells,” said Deniz. “Do these elements have oncogenic effects in vivo, and how do these effects manifest from a disease perspective? We need to establish that in order to potentially target them for therapeutic reasons.”

See references on the last page.
References

**Article 1: Viral Elements in the Human Genome Contribute to ALS Pathology**


**Article 2: Measuring Viral Infections from the Past to Inform Future Cancer Therapies**


**Article 3: Hunting for Ancient Coronaviruses**


**Article 4: A Window into the Past: How Ancient Humans Shaped Modern Genomes**


**Article 5: Secret Support: Endogenous Retroviruses as Cancer Enhancers**