Industry Focus

November 2024

Genetics & Genomics

A curated collection of top articles, Thought Leaders and Insights from Industry

NEWS MEDICAL LIFE SCIENCES

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Foreword

Welcome to this edition of Genetics and Genomics where we present a diverse and insightful collection of articles, interviews, and news that highlight the latest advancements in genetics and genomics. This edition covers a wide array of topics that reflect the growing impact of genetic science on human health, disease prevention, and treatment.

This edition starts with groundbreaking research on genetic risk factors for long-COVID, offering valuable insights into how specific genetic variants and chronic conditions, like depression and fibromyalgia, increase susceptibility to this lingering condition. Following this, we dive into the expanding field of epigenetics, exploring its critical role in disease development and potential new treatments through gene regulation mechanisms.

The potential of gene editing technologies is more exciting than ever, as discussed in our feature on breakthroughs in gene editing, where recent innovations promise to unlock new therapeutic approaches for genetic disorders. Staying in the realm of cutting-edge treatment, we also feature an insightful interview on how Aventa Genomics is transforming cancer care with advanced genomic testing, offering hope for more personalized and effective cancer treatments.

In addition, this edition highlights important findings about the genetic links between smoking, high BMI, and dementia risk, along with protective factors such as education and physical activity.

Similarly, we look at research revealing a genetic connection between Alzheimer's disease and lipid metabolism, which may open new avenues for understanding and treating these conditions.

For those interested in the practical applications of genomic research, we take an inside look at Azenta Life Sciences' new Oxford Genomics Laboratory, which is advancing genomics research and offering critical support to the scientific community. We also feature a compelling interview with an Illumina software expert, who shares insights into the evolving role of software in driving genomic progress.

Lastly, we discuss the growing understanding of clonal hematopoiesis, a condition linked to aging and the risk of blood cancers, which adds yet another layer to our understanding of how genetics influence health throughout life.

As you explore these topics, you will discover how each development contributes to a broader understanding of the genetic and genomic landscape.

Whether you're a researcher, clinician, or simply passionate about science, we hope this edition informs and inspires you as we continue to explore the future of genetics and genomics.

Enjoy reading!

Danielle Ellis
Editor
News Medical Life Sciences

Genetic risk factors for long-COVID uncovered in a large multi-ethnic study

By Hugo Francisco de Souza

Reviewed by Susha Cheriyedath, M.Sc.

Oct 16 2024

New research reveals how specific genetic variants and chronic conditions like depression and fibromyalgia increase the risk of long-COVID, offering insights into potential treatments.

Study: Multi-ancestry GWAS of Long COVID identifies immune-related loci and etiological links to chronic fatigue syndrome, fibromyalgia and depression. Image Credit: Lightspring / Shutterstock

In a recent research paper uploaded to the *medRxiv* preprint* server, researchers at 23andme

conducted the largest meta-analysis of genome-wide association studies (GWAS) comprising more than 174,000 participants from ethnically diverse backgrounds, including European, Latinx, and African-American cohorts, to identify genetic loci or phenotypic traits demonstrating an increased risk of long-COVID.

Study findings revealed that three specific genetic loci, HLA-DQA1–HLA-DQB1, ABO, and BPTF–KPAN2–C17orf58, and three phenotypes were at significantly heightened risk, highlighting high-priority populations for interventions against this poorly understood disease.

Background

Long-COVID is the condition of prolonged coronavirus disease of 2019 (COVID)-like symptoms that persist or develop for months or even years following survival from a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.

> ***Long COVID symptoms vary widely, including neurological issues like brain fog and post-exertional malaise, which worsens after mental or physical effort***

An estimated 10-80% of COVID survivors suffer from the condition, whose symptoms include severe fatigue, cognitive 'brain fog,' and constant breathlessness.

More than 65 million people have been confirmed as long-COVID patients. Unfortunately, while recent genome-wide association studies have provided an understanding of the immune responses underpinning acute SARS-CoV-2 infections, little is known about the biology and risk factors contributing to long-COVID.

Long-COVID is a multiorgan condition, with several patients reporting multiple, frequently unrelated symptoms, complicating studies aimed at validating the roles of autoimmune responses, viral load, and inflammation in long-COVID incidence.

Epidemiological investigations have established links between long-COVID occurrence and population phenotypes, suggesting that preexisting diseases may increase long-COVID risk. The study identified 13 phenotypes linked to long-COVID, including chronic pain, chronic fatigue, and fibromyalgia, with varying association strengths.

Leveraging large, multi-ethnic genome-wide association study (GWAS) datasets provides a means to test this hypothesis while further allowing for identifying genetic predispositions (loci) at heightened risk.

About the study

The present study leverages extensive genotype data from the 23andMe database (n = 174,432) across diverse ethnic backgrounds to identify genetic variants at heightened risk of long-COVID and elucidate phenotypic clusters with similar hierarchies in disease susceptibility.

Additionally, it employs Mendelian randomization models to explore causal relationships between genetics and phenotypes (e.g., COVID-19 severity) and their combined impacts in determining a COVID-19 survivor's long-COVID risk.

Study participants were identified from online repositories recording confirmed COVID-19 survivors. Potential participants were invited via email and requested to provide demographics, socio-behavioral, and health characteristics.

Additionally, detailed medical reports on participant age, sex, chronic disease, education level, and health behaviors (smoking and alcohol consumption) were obtained from participants or previous 23andMe publications.

> ***Studies suggest that vaccination reduces the likelihood of developing long COVID but does not eliminate it.***

Participants without medically diagnosed SARS-CoV-2 infections or those reporting first COVID-19 infections in the preceding three months before recruitment were excluded from the study cohort.

Participant genotyping was carried out using saliva-derived DNA by the Laboratory Corporation of America, with data used for participant genetic ancestry classification (hidden Markov model [HMM] classifier) and GWAS loci characterization.

All analyses were run separately for each genetic ancestry category (European, Latinx, African-American). Identified genetic variants were clustered based on human leukocyte antigen (HLA)-imputed allelic similarity, and age- and sex-adjusted logistic regression were carried out to establish associations with long-COVID.

Finally, genetic causal liability between phenotypes and long-COVID was computed using two-sample Mendelian randomization (MR). The study also explored a more specific "Long-COVID Impact" phenotype, focusing on cases where long-COVID significantly impaired daily living activities.

> *"To limit our analyses to unrelated individuals, we selected participants such that no two individuals shared more than 700cM of DNA identical by descent. In a scenario where a case and a control have at least 700cM of DNA identical by descent, we removed the control from the analytical sample. After excluding unrelated individuals while prioritizing the retention of cases, the analytical cohort for GWAS consisted of 53,764 cases and 120,688 controls for long-COVID, and 32,087 cases and 121,298 controls for long-COVID Impact."*

Study findings

Initial database screening revealed 332,638 COVID-19 survivors, of which 179,167 met the study inclusion criteria and were included in subsequent analyses.

Most participants were identified as being of European ancestry (78.9%), with Lantinx (16.6%) and African-American (4.5%) comprising the other ethnic cohorts.

Participants from other ancestry groups were excluded from further analyses due to insufficient sample size for robust statistical analyses.

Comparisons between long-COVID (cases) and non-long-COVID (controls) survivors revealed that females (66.7%) and non-tobacco consumers (37%) were more likely to develop the condition compared to their male and tobacco-using counterparts.

After adjusting for covariates (age, ancestry, sex), preexisting high blood pressure (odds ratio [OR] = 1.52), depression (OR = 1.98), autoimmune conditions (OR = 1.55), and cardiometabolic conditions (OR = 1.60) were more frequently observed in cases compared to controls.

GWAS analyses using ~110 million imputed genetic variants revealed three distinct loci—HLA-DQA1–HLA-DQB1, ABO, and BPTF–KPAN2–C17orf58—significantly associated with long-COVID across all three ancestry cohorts. Additionally, the rs78794747 variant was found to be significant in participants of European ancestry.

Notably, analyses of phenotype-long-COVID associations revealed 13 phenotypes with varying association strengths, with chronic pain, chronic fatigue, and fibromyalgia being the most common co-occurrences observed. Since chronic pain is a participant-provided, non-specific 23andMe database definition, it was excluded from MR modeling.

> *"We found strong evidence of a potential causal effect to each of these three conditions on long-COVID (chronic fatigue: OR=1.59 (95%CI: 1.51, 1.66), fibromyalgia: OR=1.54 (95%CI: 1.49, 1.60), and depression: OR=1.53 (95%CI: 1.46, 1.61); estimates from IVW-MR). These effects persisted when employing robust MR approaches including weighted median and MR Egger."*

Conclusions

The present study utilizes the largest multi-ethnicity GWAS dataset hitherto used in long-COVID investigations and provides evidence that individuals with genetic predispositions to chronic fatigue, depression, and fibromyalgia, as well as other phenotypes such as autoimmune conditions and cardiometabolic conditions, are at significantly higher risk of long-COVID than individuals without these conditions.

The study's two-tier approach, focusing on both general long-COVID and a more severe "Long-COVID Impact" phenotype, helps refine our understanding of long-COVID's broader and more debilitating forms.

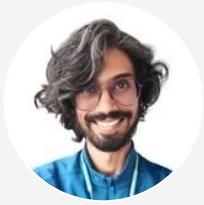
Since these conditions also result in higher probabilities of hospital visits following COVID-19 infections, it corroborates reports highlighting higher long-COVID rates in hospitalized COVID-19 patients.

> *"Together, these findings can help identify at-risk individuals for Long COVID, as well as provide novel insights that support developing therapeutic options for both long-COVID and symptomatically similar conditions."*

Journal reference:

- **Preliminary scientific report.** Chaudhary, N. S., Weldon, C. H., Nandakumar, P., Holmes, M. V., & Aslibekyan, S. (2024). Multi-ancestry GWAS of Long COVID identifies immune-

related loci and etiological links to chronic fatigue syndrome, fibromyalgia, and depression . Cold Spring Harbor Laboratory, **DOI** – 10.1101/2024.10.07.24315052, https://www.medrxiv.org/content/10.1101/2024.10.07.24315052v1



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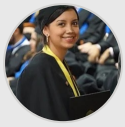
Hugo Francisco de Souza

Hugo Francisco de Souza is a scientific writer based in Bangalore, Karnataka, India. His academic passions lie in biogeography, evolutionary biology, and herpetology. He is currently pursuing his Ph.D. from the Centre for Ecological Sciences, Indian Institute of Science, where he studies the origins, dispersal, and speciation of wetland-associated snakes. Hugo has received, amongst others, the DST-INSPIRE fellowship for his doctoral research and the Gold Medal from Pondicherry University for academic excellence during his Masters. His research has been published in high-impact peer-reviewed journals, including PLOS Neglected Tropical Diseases and Systematic Biology. When not working or writing, Hugo can be found consuming copious amounts of anime and manga, composing and making music with his bass guitar, shredding trails on his MTB, playing video games (he prefers the term 'gaming'), or tinkering with all things tech.

The Role of Epigenetics in Human Disease



By Deliana Infante

Reviewed by Danielle Ellis, B.Sc.

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Epigenetics plays a critical role in human health by regulating gene expression without the direct modification of DNA sequence. Aberrant epigenetic modifications mediated by changes in DNA and histone methylation and acetylation patterns, in addition to non-coding RNAs, can disrupt normal cellular function and lead to chronic conditions such as cancer and neurological disorders.

Image Credit: VectorMine/Shutterstock.com

Understanding epigenetics

Epigenetic modifications induce or suppress gene expression without altering the DNA sequence.[1] Such modifications include DNA methylation, post-translational histone

modifications, and gene expression regulation by ncRNAs.[1]

The histone proteins, in conjunction with the chromatin, constitute the nucleosomes.[1] When the N-terminal tails of histone undergo acetylation or methylation, alterations in chromatin structure and function are observed, which subsequently impact gene expression.[1]

A variety of extrinsic and intrinsic environmental factors, including nutrition, exposure to toxins, inflammation, aging, exercise, medication, social stress, and metabolic or hormonal disorders, have been linked to influence epigenetic patterns in germ cells.[2]

These modifications can then be inherited by subsequent generations.[2] When epigenetic modifications are transmitted from parents to their direct offspring, it is referred to as intergenerational epigenetic inheritance.[2] When these modifications persist beyond the first generation, it is defined as transgenerational epigenetic inheritance.[2]

The scientific community continues to debate the existence of transgenerational epigenetic inheritance in mammals.[2] However, the postulated mechanisms of epigenetic inheritability involve DNA methylation, which commonly acts to repress gene expression, and histone modifications, which can either activate or repress gene expression but are often context-dependent.[1-2]

Non-coding RNAs, on the other hand, are involved in both transcriptional and post-transcriptional regulation of gene expression, as well as chromatin remodeling through ncRNA-dependent recruitment of chromatin remodeling complexes.[1,3]

It is noteworthy that research has demonstrated the capacity of acquired epigenetic signatures at specific regions of the mouse genome to be inherited across generations.[1] Additionally, during gametogenesis, not all methylated cytosines (5-mC) in primordial germ cells undergo demethylation; a significant proportion of these epigenetic marks exhibit resistance to complete erasure.[1]

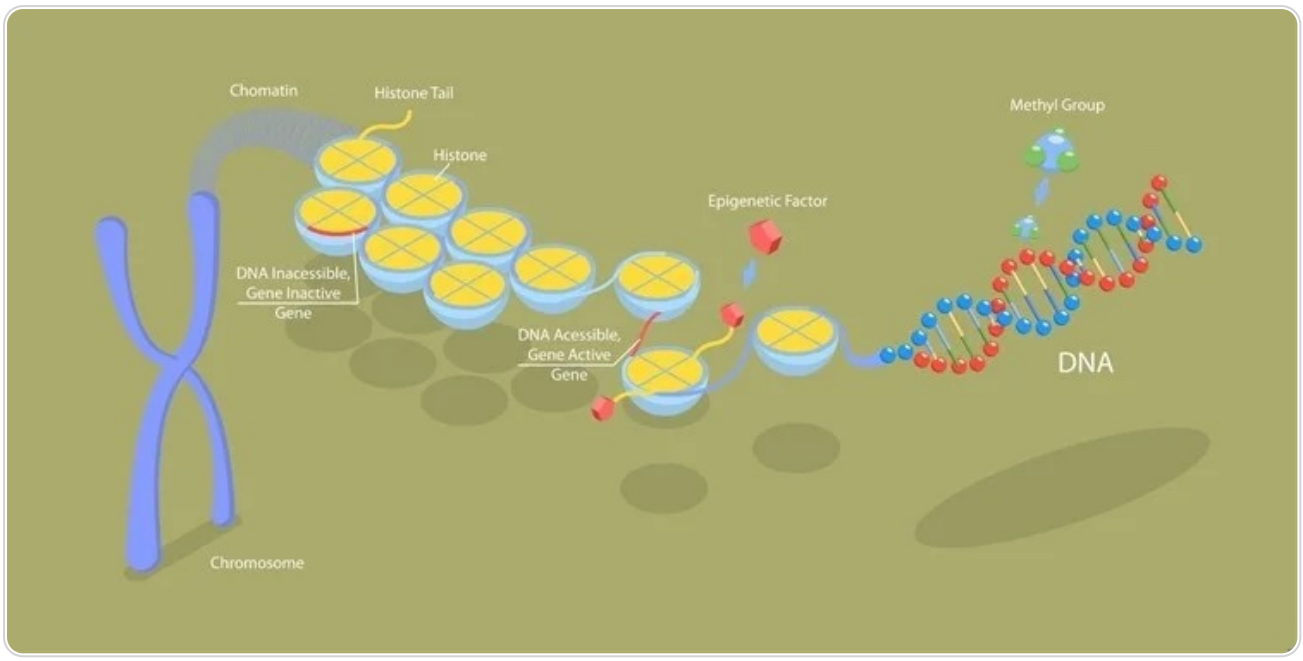

Image Credit: TarikVision/Shutterstock.com

Approximately 40% of 5-mC and its derivatives persist following extensive epigenetic reprogramming during meiosis.[1] Consequently, sperm and oocytes retain an important part of the parental DNA methylation patterns.[1]

Epigenetics and development

During human embryogenesis, chromatin undergoes extensive remodeling, altering its accessibility at key developmental stages.[4] These changes support gene regulatory network rewiring and the establishment of new developmental programs. Regions gaining accessibility are mainly compromised in promoters, CpG islands, and enhancers.[4]

Over 8,000 promoters open in zygotes, remaining accessible through preimplantation; these genomic regions are enriched with specific metabolic and biosynthetic functions.[4]

It is important to note that epigenetics plays a significant role in both embryo development and the development of primordial germ cells (PGC), which are precursors of the embryo.[5]

During their development, mammalian PGCs undergo a distinctive and comprehensive epigenetic remodeling process, coinciding with their transition toward totipotency.[5] It is observed that there are differences in the rates of OXPHOS and glycolysis, as well as sexual dimorphism.[5]

In order to ensure genomic stability during the differentiation process, certain genomic regions retain higher DNA methylation, resisting global demethylation.[5] Histone remodeling involves changes in the methylation patterns of H3K9me2, H3K27me3, and H2A/H4R3me2s.

These changes are coordinated to safeguard the genome during the transition to totipotency.[5]

Gene expression is also affected by ncRNAs that interfere with transcription by modulating chromatin. They play roles in dosage compensation and imprinting, crucial for normal development through epigenetic chromatin state modulation.[6]

Environmental factors that act during the process of embryogenesis, including dietary intake and exposure to toxins, have the potential to alter the uterine environment and fluid composition.[7] This, in turn, can affect epigenetic modifications in embryos, influencing their development and potentially leading to structural and functional alterations in the offspring.[7]

These changes can impact systems such as the immune and cardiovascular systems.[7] The effect of these factors causes important metabolic and endocrine changes that can predispose the fetus to certain postnatal diseases.[8] This concept is known as fetal programming.[8]

Epigenetics and disease

A variety of studies have highlighted the significant role of environmental factors in influencing epigenetic mechanisms, contributing to the pathophysiology of different diseases.

Exposure to neurotoxins, pesticides, and heavy metals has been shown to alter epigenetic patterns linked to Parkinson's disease (PD).[9] These changes include increased histone acetylation and DNA methylation, affecting genes associated with PD such as *PINK1*, *PARK2* and *TH*.[9]

Hypermethylated patterns have been identified in tumors, frequently located in gene promoter regions of tumor suppressor genes, in contrast to the overall hypomethylated regions observed in cancer cells.[10] These hypermethylation patterns have been linked to the development of breast cancer, liver cancer, prostate cancer, and small-cell bladder cancer.[10]

Additionally, dysregulation of histone deacetylases has also been observed in various cancers, as well as the influence of ncRNAs effect on the expression of protooncogenes like c-Myc in colorectal cancer (CRC).[10]

Epigenetics plays a crucial role in major depressive disorder and schizophrenia research, with DNA methylation significantly influenced by environmental stressors like childhood adversity.[11]

These stressors lead to lasting methylation changes, affecting neuroendocrine responses, neuroplasticity, neurotransmission, and neural development in both brain and peripheral tissues.[11]

Histone modifications, especially lysine acetylation, are linked to stress responses and antidepressant effects in depression.[11] Additionally, ncRNAs, including circRNAs, miRNAs, and lncRNAs, regulate gene expression, impacting synaptic transmission, insulin resistance, immune responses, and inflammation in these disorders.[11]

Epigenetics and lifestyle

Diet, exercise, and stress significantly impact the epigenome by influencing DNA methylation, histone modifications, and ncRNAs.[12]

A healthy diet and regular exercise promote beneficial epigenetic changes, such as DNA demethylation and histone modifications, which can help prevent chronic diseases like cancer, diabetes, and cardiovascular disorders.[12]

Conversely, chronic stress can lead to detrimental epigenetic changes, contributing to disease progression.[12] Early-life nutrition is crucial for inducing lifelong epigenetic modifications, while regular physical activity and stress management are essential for maintaining positive epigenetic health.[12]

Epigenetic therapies hold promise for treating diseases, including cancer and neurodegenerative disorders.[13] The reversible nature of the epigenome allows for reprogramming through environmental and pharmacological interventions, enhancing therapeutic strategies.[13]

However, ethical implications, such as privacy concerns and potential discrimination based on epigenetic profiles, necessitate careful consideration in research and clinical applications, emphasizing the need for equitable access and public policy measures.[14]

References

1. Trerotola, M., Relli, V., Simeone, P., & Alberti, S. (2015). Epigenetic inheritance and the missing heritability. *Human Genomics*, 9(1). https://doi.org/10.1186/s40246-015-0041-3
2. Khatib, H., Townsend, J., Konkel, M. A., Conidi, G., & Hasselkus, J. A. (2024). Calling the question: what is mammalian transgenerational epigenetic inheritance? *Epigenetics*, 19(1). https://doi.org/10.1080/15592294.2024.2333586
3. Kaikkonen, M. U., Lam, M. T. Y., & Glass, C. K. (2011). Non-coding RNAs as regulators of gene expression and epigenetics. *Cardiovascular Research*, 90(3), 430–440. https://doi.org/10.1093/cvr/cvr097
4. Wilkinson, A. L., Zorzan, I., & Rugg-Gunn, P. J. (2023). Epigenetic regulation of early human embryo development. *Cell Stem Cell*, 30(12), 1569–1584. https://doi.org/10.1016/j.stem.2023.09.010
5. Verdikt, R., & Allard, P. (2021). Metabolo-epigenetics: the interplay of metabolism and epigenetics during early germ cells development†. *Biology of Reproduction*, 105(3), 616–624. https://doi.org/10.1093/biolre/ioab118
6. Pauli, A., Rinn, J. L., & Schier, A. F. (2011). Non-coding RNAs as regulators of embryogenesis. *Nature Reviews Genetics*, 12(2), 136–149. https://doi.org/10.1038/nrg2904
7. Lamberto, F., Peral-Sanchez, I., Muenthaisong, S., Zana, M., Willaime-Morawek, S., & Dinnyés, A. (2021). Environmental Alterations during Embryonic Development: Studying the Impact of Stressors on Pluripotent Stem Cell-Derived Cardiomyocytes. *Genes*, 12(10), 1564. https://doi.org/10.3390/genes12101564
8. Kwon, E. J., & Kim, Y. J. (2017). What is fetal programming?: a lifetime health is under the control of in utero health. *Obstetrics & Gynecology Science*, 60(6), 506. https://doi.org/10.5468/ogs.2017.60.6.506
9. Tsalenchuk, M., Gentleman, S. M., & Marzi, S. J. (2023). Linking environmental risk factors with epigenetic mechanisms in Parkinson's disease. *Npj Parkinson S Disease*, 9(1). https://doi.org/10.1038/s41531-023-00568-z
10. Yu, X., Zhao, H., Wang, R., Chen, Y., Ouyang, X., Li, W., Sun, Y., & Peng, A. (2024). Cancer epigenetics: from laboratory studies and clinical trials to precision medicine. *Cell Death Discovery*, 10(1). https://doi.org/10.1038/s41420-024-01803-z
11. Yuan, M., Yang, B., Rothschild, G., Mann, J. J., Sanford, L. D., Tang, X., Huang, C., Wang, C., & Zhang, W. (2023). Epigenetic regulation in major depression and other stress-related disorders: molecular mechanisms, clinical relevance and therapeutic potential.

Signal Transduction and Targeted Therapy, 8(1). https://doi.org/10.1038/s41392-023-01519-z

12. Epigenetics and Diet: How Food Influences Gene Expression. (2024, June 26). Rupa Health. https://www.rupahealth.com/post/epigenetics-and-diet-how-food-influences-gene-expression
13. Majchrzak-Celińska, A., Warych, A., & Szoszkiewicz, M. (2021). Novel Approaches to Epigenetic Therapies: From Drug Combinations to Epigenetic Editing. *Genes*, 12(2), 208. https://doi.org/10.3390/genes12020208
14. Santaló, J., & Berdasco, M. (2022). Ethical implications of epigenetics in the era of personalized medicine. *Clinical Epigenetics*, 14(1). https://doi.org/10.1186/s13148-022-01263-1

Further Reading

- All Epigenetics Content
- Epigenetics and Epigenomics
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- Epigenetics and Forensics
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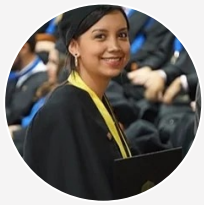


Written by

Deliana Infante

I am Deliana, a biologist from the Simón Bolívar University (Venezuela). I have been working in research laboratories since 2016. In 2019, I joined The Immunopathology Laboratory of the Venezuelan Institute for Scientific Research (IVIC) as a research-associated professional, that is, a research assistant.

Breakthrough in gene editing: Enhanced virus-like particles promise new era in genetic disease treatment

By Pooja Toshniwal Paharia

Reviewed by Susha Cheriyedath, M.Sc.

Jan 9 2024

In a recent study published in the journal *Nature Biotechnology*, researchers engineered prime editor (PE)-engineered virus-like particles (eVLPs) delivering PE proteins, PE guide ribonucleic acids (pegRNAs), and nicking single guide ribonucleic acids (ngRNAs) as ribonucleoprotein (RNP) complexes.

Study: Engineered virus-like particles for transient delivery of prime editor ribonucleoprotein complexes in vivo. Image Credit: Andrii Yalanskyi / Shutterstock

Background: The Promise of Prime Editing

Prime editing is a promising technology for changing genomic deoxyribonucleic acid (DNA) that has the potential to be used to cure genetic diseases in individuals. Prime editors are

proteins that can replace a specific deoxyribonucleic acid sequence with another. PE systems necessitate three distinct nucleic acid hybridizations and are not dependent on double-strand deoxyribonucleic acid breaks or donor deoxyribonucleic acid templates.

Researchers must devise efficient and safe techniques to deliver prime editors in tissues in the *in vivo* settings to fulfill PE's objective. While viral delivery techniques such as adenoviruses and adeno-associated viruses (AAVs) can transport PE *in vivo*, non-viral delivery techniques like lipid nanoparticles can sidestep these concerns by packaging PEs as temporarily expressing messenger ribonucleic acids.

Developing the PE-eVLP System

In the present study, researchers developed a prime editor-engineered VLP system to deliver prime editors, including ngRNAs and pegRNAs as ribonucleoproteins.

The team evaluated the PE-eVLP system in HEK293T cells, Neuro-2a cells, and Gesicle Producer 293T cells for cell culture tests. The researchers created v3 and v3b PE-eVLPs with 65- to 170-fold greater editing effectiveness in human cells than a previously reported base editor eVLP design. They used v1.2 prime editor-eVLPs with engineered PE guide ribonucleic acids (epegRNAs) and replaced the PE protein with PEmax2.

Optimizing for Efficiency: The v1.2 and v2.3 PE-eVLPs

The team used v1.2 PE-eVLPs with engineered pegRNAs to replace the prime editor protein with PEmax2, an enhanced PE that includes SpCas9 amino acid substitutions, an optimized linkage molecule between the RT domain, Cas9 nickase, nuclear localization signal (NLS) optimization, and codon optimization. They sought to identify mechanistic bottlenecks in v1 PE-eVLPs, solving the problem by relocating the nuclear export signals (NES) within the Gag protein and inserting three nuclear export signals before the site of protease cleavage of every Gag protein subdomain with two additional regions that could tolerate large insertions into the MMLV Gag-Pol.

The researchers observed that cellular mismatch repair (MMR) pathways can reduce PE efficiency and that avoiding or inhibiting MMR enhances PE efficiencies. To investigate this potential for eVLP-delivered primary editing systems, they used the v2.3 prime editor-eVLP system to insert additional close alterations at the HEK3 and Dnmt1 loci.

The researchers investigated whether the ngRNA could be packaged in the same or a different particle from the epegRNA to find the best all-in-one particle v3 PE3-eVLP system. They

additionally examined whether these changes improved eVLP-mediated BE delivery. The transient introduction of PE via eVLPs reduced the capacity of v3 and v3b PE-eVLPs to facilitate in vivo prime editing in the mouse central nervous system.

Results: Advancements in PE-eVLP Technology

The research aims to create third-generation PE-eVLPs with clinically relevant levels of primary editing in the retina, protein expression restoration, and partial visual function rescue. The researchers found and designed prime editors and engineered VLP architectures, resulting in a PE efficiency boost of 79-fold in murine neuro-2A (N2A)-type cells and an improvement of 170-fold in human HEK293T cells compared to v1 PE-eVLPs. One subretinal v3 PE-eVLP injection corrected a 4.0-bp Mfrp deletion in the rd6 murine retinal degeneration model (mean efficiency of 15%) and an Rpe65 mutation to partially release visual functions in the rd12 model (mean efficiency of 7.2%).

Key Innovations in PE-eVLP Design

The nuclear export signals promote Gag-cargo protein localization in the cytoplasm, and the p= four additional MMLV protease cleavage regions in the Gag protein enhance incomplete cleavage possibility, leading to the retaining of some Gag and nuclear export signals by PE cargo. In the human embryonic kidney 293T cells, inserting three nuclear export signals between the CA and p12 domains of Gag (nuclear export signal position number 5) resulted in the highest PE efficiency, generating v2.2 prime editor-eVLP.

The researchers used the v2.3 prime editor-eVLP technique to insert extra adjacent replacements at the human embryonic kidney (HEK3) and Dnmt1 loci, which enhanced primary editing efficiency in both cases. Inadequate epegRNA packing hampered PE-eVLP efficiency, whereas epegRNA supplementation increased PE-engineered VLP editing efficiencies by more than 8.0-fold. With v3 PE3-eVLPs, the researchers achieved 2.3% bulk cortex editing and 36% editing among GFP+ nuclei.

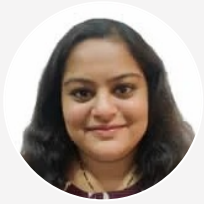
Conclusion: Future Directions for PE-eVLPs

Overall, the study findings showed that optimized PE-eVLPs enable transitory in vivo administration of prime editor ribonucleoproteins, improving safety and inhibiting oncogenic transgene integration. In both culture and in vivo, these virus-like particles transport PE RNPs into mammalian cells. Recent advancements in primary editing systems, including epegRNAs, PEmax design, and MMR avoidance, have resulted in better results. In vivo, the improved v3 and v3b PE-eVLPs systems corrected pathogenic deletions in the mouse retina and achieved

editing levels equivalent to triple-vector AAV-PE systems in genetic blindness models. Next-generation PEs and enhanced eVLP systems will need further technical work.

Journal reference:

- An, M., Raguram, A., Du, S.W., *et al.* Engineered virus-like particles for transient delivery of prime editor ribonucleoprotein complexes in vivo. *Nat Biotechnol* (2024). **DOI:** https://doi.org/10.1038/s41587-023-02078-y, https://www.nature.com/articles/s41587-023-02078-y



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Pooja Toshniwal Paharia is an oral and maxillofacial physician and radiologist based in Pune, India. Her academic background is in Oral Medicine and Radiology. She has extensive experience in research and evidence-based clinical-radiological diagnosis and management of oral lesions and conditions and associated maxillofacial disorders.

Transforming Cancer Care: Aventa Genomics and the Future of Genomic Testing

Sponsored Content by Aventa Genomics Feb 16 2024

In this interview, Chris Roberts of Aventa Genomics highlights the groundbreaking Aventa FusionPlus test, detailing its superior ability to detect gene fusions in cancer diagnostics and its pivotal role in advancing personalized oncology treatments.

Could you give us a brief overview of Aventa Genomics, including its founding vision and primary mission in the field of genomics?

Many patients with cancer undergo testing to identify genomic variants that can be targeted by personalized cancer drugs. Unfortunately, traditional next-generation sequencing-based and FISH tests often miss gene fusions and rearrangements present in cancer that can a) resolve diagnostic dilemmas or b) be targeted with therapies on the market or in clinical trials. Aventa Genomics was founded to develop and commercialize 3D genomics-based tests to improve upon conventional methods.

Aventa Genomics is a joint venture between Arima Genomics and Protean BioDiagnostics. What synergies between these two companies led to the formation of Aventa Genomics, and how do these synergies drive the company's innovation and research?

The two companies have complementary competencies. Arima Genomics is fundamentally a technology company, and Protean BioDiagnostics is a clinical laboratory testing company.

Image Credit: Kittyfly/Shutterstock.com

How does Aventa Genomics aim to transform patient care in oncology? What specific gaps in the current healthcare system is Aventa addressing with its technologies?

Aventa Genomics has commercialized the Aventa FusionPlus test, which enables any oncologist or pathologist, whether in a highly specialized comprehensive cancer center or a community hospital, to offer patients access to a genomic test able to identify gene fusions and other rearrangements that may be missed by conventional NGS and FISH tests.

Aventa FusionPlus is a genome-wide test and bioinformatically filters to report variants in 361 genes that are potentially actionable in solid tumors.

Can you describe how the Aventa FusionPlus test differs from traditional gene sequencing methods like FISH and RNA sequencing, particularly in its approach to detecting gene fusions, translocations, and rearrangements?

Both RNA sequencing and FISH methods can be utilized for the detection of gene fusions and rearrangements, but each method has limitations. RNA sequencing is limited to identifying gene fusions and rearrangements that produce a fusion transcript. However, in many cases, the breakpoint for a potentially actionable variant is in a non-coding region, and therefore no fusion transcript is produced. Another limitation of RNA, as a molecule, is that it is labile and

often degraded in clinical specimens and can result in an insufficient quantity for sequencing.

Image Credit: CrizzyStudio/Shutterstock.com

FISH tests typically identify only one gene rearrangement at a time, and it is not practical, from a tissue availability perspective, or economical, to perform more than three or four FISH tests on a single specimen.

In our experience, when RNA sequencing or FISH finds a gene fusion or rearrangement, we find it as well. The power of the Aventa test is that it also identifies the gene fusions and rearrangements that RNA sequencing or FISH either did not or cannot detect.

The Aventa FusionPlus test utilizes 3D genomics technology. Could you explain the significance of preserving the spatial proximity of fused and rearranged genes and how this contributes to the 100 to 1000-fold signal amplification in detecting gene variants?

The Aventa FusionPlus test works by first crosslinking DNA in intact nuclei and then wherever two strands of DNA are in close proximity to each other, ligating them together, creating a molecule that has DNA from each of the two strands. When two genes are rearranged, we see

hundreds or even thousands of contact points where the genes are in close spatial proximity. In contrast to conventional sequencing methods, which only see the breakpoint, we see the breakpoint plus these additional, informative signals that enable the identification of a fusion.

In previously characterized tumor specimens with no known actionable driver, the Aventa FusionPlus test detected potentially actionable variants in half of the cases. How does this increase in diagnostic yield translate into clinical benefits for patients?

The patients whose test results indicate potentially actionable variants can access targeted therapies or be enrolled in clinical trials that their oncologists might not have been able to identify without this testing.

How does the Aventa FusionPlus test improve upon the limitations of existing genomic testing methods? Are there specific types of cancers or stages where this test is particularly beneficial?

Physicians are using the Aventa FusionPlus test to a) resolve diagnostic dilemmas in translocation-driven cancers like sarcoma and b) identify targetable fusions in genes like NTRK and ALK. The majority of the cases we see are advanced cancers.

What do you foresee as the future role of 3D genomics in patient diagnosis and therapy selection?

We expect 3D genomics-based tests to become an integral part of the standard workup for patients with advanced cancers.

How accessible is the Aventa FusionPlus test for physicians and patients? Are there any geographical or logistical limitations in its availability?

Oncologists and pathologists can order the Aventa FusionPlus test. We are pursuing reimbursement in the U.S. via Medicare and commercial insurance payers, akin to other genomic-based cancer tests. Test requisition forms are available at www.aventagenomics.com.

How do you see the Aventa FusionPlus test contributing to the field of personalized medicine and improving patient outcomes?

We believe the test will be able to identify new biomarkers of response, as well as resistance, to on-market therapeutics. We also see this test as a mechanism to accelerate clinical trial enrollment due to the additional diagnostic yield of gene fusions and rearrangements.

What are the future goals for Aventa Genomics, and can we expect any new tests or technologies in the near future?

The Aventa FusionPlus test is indicated for solid tumors. We are in the process of developing a test for hematological malignancies.

Where can readers find more information?

- *www.aventagenomics.com*

About Chris Roberts

Chris Roberts is the Executive Director of Aventa Genomics, where he is responsible for the management of the organization. He is also the SVP of Corporate Strategy for Arima Genomics, which is one of the parent companies of Aventa Genomics (along with Protean BioDiagnostics).

Prior to this role, Chris held leadership positions at Decipher Biosciences (acquired by Veracyte), HTG Molecular, Caris Life Sciences, and Ventana Medical Systems (acquired by Roche).

Genetic analysis shows smoking and high BMI increase dementia risk, but education and exercise protect

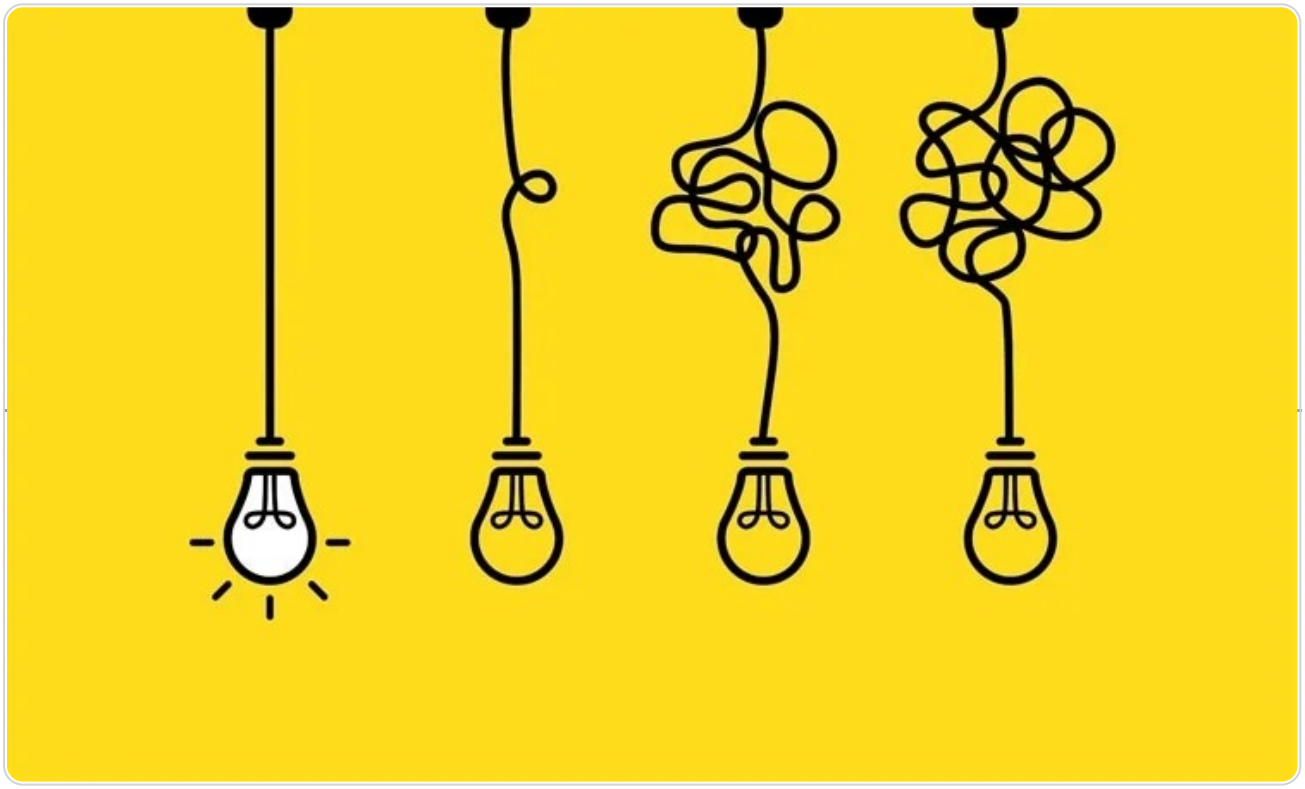
By Hugo Francisco de Souza

Reviewed by Susha Cheriyedath, M.Sc.

Oct 17 2024

100/100

New research from the University of Copenhagen links genetic predispositions to smoking and high BMI with elevated dementia risk while highlighting the protective power of education and physical activity.



Study: Modifiable Risk Factors for Dementia: Causal Estimates on Individual-Level Data. Image Credit: Bagel Studio / Shutterstock

Dementia is a chronic and severely debilitating disease with no known cure, underscoring the importance of its prevention and early detection. In a recent research paper* published on the *Preprints with The Lancet* server, researchers at the University of Copenhagen used extensive, individual-level genomic data from more than 400,000 European participants to establish causal relationships between modifiable risk factors and the disease.

Polygenic risk scores (PRS) were calculated for each participant to estimate the genetic predispositions to these risk factors. Mendelian randomization (linear and non-linear) revealed that genetically predicted smoking, high body mass index (BMI), high blood pressure, type 2 diabetes (T2D), high low-density lipoprotein (LDL) cholesterol concentrations, and high triglycerides significantly increased all-cause dementia risk.

> ***Triglycerides as a key risk factor: The study identified high triglycerides, often overlooked in dementia research, as significantly increasing the risk of all-cause and vascular dementia.***

In contrast, more extended education was found to demonstrate a protective effect against vascular- and all-cause dementia and Alzheimer's disease. No non-linear associations were detected, meaning that the genetic risk associated with these factors was consistent across different exposure levels.

These findings validate the World Health Organization (WHO) and the Lancet Commission for Dementia Prevention, Intervention, and Care's reports suggesting alteration in dementia-associated modifiable risk factors and inform future research on high-priority genetic targets for dementia interventions.

Background

Dementia is a serious and potentially lethal age-associated neurological condition characterized by a substantial gradual decline in cognitive functions such as memory, thinking, and judgment. It is one of the most prevalent causes of non-communicable disability and death and, unfortunately, remains without cure.

Alarming increases in global dementia prevalence have prompted the World Health Organization (WHO) and the Lancet Commission for Dementia Prevention, Intervention, and Care to release guidelines highlighting the role of modifiable risk factors in dementia incidence, emphasizing how the cessation of smoking (for example) can help prevent dementia during old age.

The most recent Lancet Commission report (2024) estimates that 45% of dementia can be prevented by eliminating modifiable risk associations, including smoking and high body mass index (BMI), resulting in a safer, healthier tomorrow.

> ***Physical activity impact on Alzheimer's: Genetically predicted higher physical activity levels showed a particularly strong protective effect against Alzheimer's disease, reducing the risk by 42%.***

Despite decades of research, causal associations between modifiable risk factors and dementia outcomes remain vague and often confounding. Studies have attempted to elucidate the mechanisms underpinning these associations, but the current lack of discrete-age datasets and analyses leads to several studies, even using identical datasets, providing contrasting outcomes.

The aforementioned reports are, therefore, based predominantly on observational evidence with limited clinical validation. Importantly, the present study uses Mendelian Randomization to provide stronger evidence for causal relationships between these risk factors and dementia outcomes.

About the Study

The present study leverages Mendelian Randomization (MR) analyses and an extensive, United Kingdom (UK) BioBank-derived genomic dataset to evaluate the individual-specific genetic odds ratios (ORs) of dementia. MR is a research method that uses genetic variation to study the causal effect of exposures (herein, genetic predispositions to dementia-related modifiable risk factors) on an outcome (herein, dementia manifestation).

Study data was obtained from the UK BioBank and consisted of 408,788 British participants of European ancestry. Data collection included archived genome-wide association study (GWAS), baseline anthropometric measurements (obtained at participants' initial screening), and self-reported behavioral data (e.g., smoking status and weekly physical activity). Preexisting medical records were obtained from UK BioBank records and were annotated using International Classification of Diseases (ICD) codes.

The main outcomes of interest are the manifestation of dementia (all-cause) or its two most prevalent subtypes – Alzheimer's disease and vascular dementia. Polygenic risk scores (PRSs), which estimate the number of genetic variants a person carries that may increase their risk for these conditions, were generated for each participant and used in the MR analysis.

> ***No evidence of alcohol impact: Unlike other risk factors, the study found no significant genetic association between alcohol consumption and dementia, despite prior observational studies suggesting otherwise.***

To establish the shape of the genetic association between identified continuous risk factors and subsequent dementia manifestation, both linear and non-linear MRs were employed. Logistic and linear regressions were further utilized to account for covariates (age, sex) across both categorical and continuous risk factor datasets. However, no evidence of non-linear effects was detected in the association between the risk factors and dementia.

Study Findings

The study cohort (n = 408,788) comprised 53.7% women with a median age of 59. Baseline observations revealed a higher dementia risk in men compared with their female counterparts. At baseline examinations, 13.2% of participants reported ischemic heart disease, followed by all-cause dementia (1.7%), Alzheimer's disease (0.9%), and vascular dementia (0.4%).

GWAS MR predictions revealed that of the 14 factors listed in the Lancet Commission report, genetic predispositions to high BMI resulted in dementia (OR = 1.04) most frequently. Similarly, frequent smoking (OR = 1.18), high systolic (OR = 1.14) and diastolic blood pressure (OR = 1.10), high LDL cholesterol (OR = 1.12), high triglycerides (OR = 1.19), and T2D (OR = 1.04) substantially increased future dementia risk.

In contrast, genetic predispositions to higher physical activity levels (OR = 0.58) and longer education times (OR = 0.72) were found to confer a protective effect against Alzheimer's disease and all-cause dementia, respectively. The study also highlighted that some of these findings, such as the link between cardiovascular conditions and dementia, may be impacted by survival bias, as individuals with severe cardiovascular diseases often die before receiving a dementia diagnosis.

Conclusions

The present study identifies populations with genetic predispositions for smoking, high BMI, high blood pressure, T2D, and high triglycerides as high-risk individuals requiring immediate behavioral interventions to reduce future dementia risk.

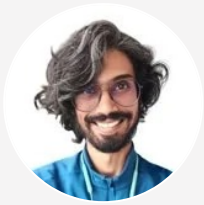
Contrasting previous reports, more extended education was found to confer protection against all-cause dementia. Increased physical activity levels were similarly observed to keep the condition at bay. Importantly, no non-linear associations were found in these genetic relationships, which means that the risk from these factors remained consistent across different exposure levels.

The study authors suggest that some of the factors listed in the Lancet Commission report, such as cardiovascular conditions, cannot currently be verified since people with severe cardiovascular diseases (CVDs) often die before the natural onset of dementia, preventing their inclusion in dementia testing study cohorts.

This limitation notwithstanding, the present work provides insights into the genetic underpinnings of dementia and its main risk factors, highlighting preventive measures and educating clinicians and policymakers on steps to curb this debilitating disease.

Journal reference:

- **Preliminary scientific report.** Luo, Jiao and Juul Rasmussen, Ida and Thomassen, Jesper Qvist and Frikke-Schmidt, Ruth, Modifiable Risk Factors for Dementia: Causal Estimates on Individual-Level Data, DOI – 10.2139/ssrn.4986344, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4986344



Written by

Hugo Francisco de Souza

Hugo Francisco de Souza is a scientific writer based in Bangalore, Karnataka, India. His academic passions lie in biogeography, evolutionary biology, and herpetology. He is currently pursuing his Ph.D. from the Centre for Ecological Sciences, Indian Institute of Science, where he studies the origins, dispersal, and speciation of wetland-associated snakes. Hugo has received, amongst others, the DST-INSPIRE fellowship for his doctoral research and the Gold Medal from Pondicherry University for academic excellence during his Masters. His research has been published in high-impact peer-reviewed journals, including PLOS Neglected Tropical Diseases and Systematic Biology. When not working or writing, Hugo can be found consuming copious amounts of anime and manga, composing and making music with his bass guitar, shredding trails on his MTB, playing video games (he prefers the term 'gaming'), or tinkering with all things tech.

Advancing genomics research: An inside look at Azenta Life Sciences' new Oxford Genomics Laboratory

Sponsored Content by GENEWIZ from Azenta Life Sciences

Jul 8 2024

Reviewed by Andrea Salazar

This interview delves into the capabilities and services of Azenta Life Sciences' new Oxford Genomics Laboratory, discussing its role in advancing genomics research in the UK, the unique setup process, and future expansion plans.

Can you provide an overview of GENEWIZ Multiomics & Synthesis Solutions from Azenta Life Sciences and the new Oxford Genomics Laboratory, as well as the services and technologies it offers?

David: GENEWIZ from Azenta Life Sciences is much more than just a sequencing service provider. With a global presence and numerous laboratories, we offer a range of genomics solutions including next generation sequencing, gene synthesis, Sanger sequencing, molecular genetics, and cloning. We cater to researchers who require minimal support as well as to those who want to work in a more collaborative manner and use us as an extension of their lab. Although not every site offers all services, GENEWIZ as a whole provides an extensive portfolio of genomics and analytical services to our customers.

The Oxford Genomics Laboratory is dedicated exclusively to next generation sequencing (NGS). Initially, we are focusing on whole genome sequencing, RNA sequencing, and run-only services, rather than offering our entire portfolio from the start. This phased approach prevents operational overload and ensures quality service delivery.

The demand for run-only services is notably high. This is likely because the latest sequencing technologies are prohibitively expensive for traditional core or small research labs.

Outsourcing these services to GENEWIZ from Azenta makes them accessible and affordable for these labs.

With a Sanger sequencing facility already operational in the UK, why was it important for Azenta Life Sciences to open a separate facility for next generation sequencing in the UK?

David: The primary reason for expanding into next generation sequencing (NGS) was the growing demand for this service. Our Sanger lab is highly efficient and serves as a logistics hub. We have been offering NGS to our customers for some time, but this required shipping materials from the UK to Leipzig. After Brexit, this process became a logistical challenge.

Azenta had a great opportunity when the Oxford Genomics Centre (OGC) was closing. The lab had a large customer base accustomed to working with a talented team that I built over 14 years. Although the OGC lab itself was closing, there was still a strong desire among the former OGC team and its customers to continue providing exceptional services.

Some might argue that combining everything on one site would have been more cost-effective. However, we would have lost the strong customer connections in the Oxford region. As the former head of the OGC, I was able to bring five key members of my management team to this new venture at Azenta, making the transition both exciting and rewarding.

This background highlights why Azenta's Oxford lab focuses exclusively on NGS, ensuring we maintain the high level of service our customers expect while navigating the logistical challenges posed by Brexit.

What was unique about the process of setting up this lab?

David: Labs are being established around the world regularly, but what made our setup unique was the expertise of the people we hired— my former team from the Oxford Genomics Centre (OGC). Their extensive experience in the field was invaluable.

Another remarkable aspect of this setup was the transformation process. Although we didn't fully appreciate it until the project was completed, it took only 10 weeks to convert a high-end gym into a next generation sequencing facility.

Can you discuss the role of Azenta's new laboratory in advancing genomics research in the UK?

David: The most important aspect of our facility is our cutting-edge technology, including advanced sequencing platforms and automation. We also have sophisticated internal LIMS systems and a wealth of experience. Our team includes Ph.D.-level project managers who interact directly with our customers at every step of their project, providing deep scientific understanding and guidance.

Having this facility in the UK is crucial. As a scientist who previously worked with service providers like GENEWIZ, I know the importance of being able to communicate directly with the scientists handling your work and ensuring that your samples are processed locally. This not only keeps your samples within the UK but also ensures that your data remains secure and close to home.

How do you see NGS services, like those offered at the new Oxford Genomics Laboratory, helping to overcome some of the current limitations or challenges faced in the medical field?

John: Genomics is absolutely crucial to the government's life science initiatives. It is a key part of letting the NHS evolve into molecular medicine and disease prevention. At the heart of that is sequencing DNA.

There are many advances in genomics and that allows major studies, like UK Biobank and Our Future Health, to move forward rapidly and gain all sorts of insights into human health and disease prevention.

What measures are in place to ensure the reliability and high accuracy of the data produced by the laboratory?

David: Our commitment to validating the effectiveness of everything we do is paramount. We have stringent controls in place to ensure our processes work properly. Automation is crucial in a high-throughput environment, and we strive to automate as many processes as possible to guarantee reliability and reproducibility.

We utilize cutting-edge technologies, such as the latest MagPip Star V system from Hamilton Robotics, which represents state-of-the-art automation. To maintain our high standards, we only hire individuals who understand the science behind our operations. Even then, they must undergo a rigorous training process to ensure they meet our exacting standards.

What impact do you anticipate the new Oxford Genomics Laboratory from Azenta Life Sciences to have on the local scientific community?

John: The Oxford ecosystem is one of the leaders in human health and disease prevention in the UK and worldwide. Having an amazing sequencing facility like this on our doorstep allows us to work faster, more accurately and achieve more at a lower cost. This can significantly enhance discovery in medical research, ultimately benefiting patients.

What feedback have you received from the scientific community about the Oxford lab?

David: When the OGC facility closed down, I had to notify its customers about the facility's closure, which left a significant wave of unhappiness as they relied heavily on the services offered at OGC.

Now, these customers are overjoyed to have local access to genomics capabilities once again with the opening of Azenta's Oxford lab. They can continue working with the same team they've trusted for the past 14 years. Being able to visit us locally and discuss projects in person is a major selling point. They appreciate knowing that their samples and data will remain within the UK and that they can consult with highly qualified experts about their projects.

How does Azenta Life Sciences plan to expand or evolve its services in the future for the UK?

David: The most important thing is that we provide services that our customers want and need. It is essential to be the fastest, most cost-effective, and knowledgeable, but just because you build something does not necessarily mean the customer will use it. Therefore, when expanding any operation, it is crucial to consider what the customer base wants.

So far, we have started with whole genome sequencing, RNA sequencing, and run-only sequencing services offered at the Oxford lab. We are also planning to add a locally based extraction service in the near future.

Regarding the next step for the Oxford Genomics Lab, there are many ideas. We have numerous suppliers who want us to add their technology to our sequencing portfolio. Although I would love to incorporate all these technologies, our expansion must be realistic and driven by customer demand.

What excites you most about the future possibilities enabled by the new Oxford Genomics Laboratory from Azenta Life Sciences?

David: We are passionate about high-throughput genomics and supporting the incredible scientific research happening at Oxford, throughout the UK, and around the world. As an experienced team including Ph.D.-level experts, our focus is on advancing science by generating data faster than anyone else globally.

In addition to data generation, we offer analytical support when requested. Our services cater to various needs, providing multiple layers of support including consultations, real-time updates, and post-delivery assistance.

Customers who prefer a hands-off approach can simply go online, place an order, send their samples, and collect the data without any additional interaction. On the other hand, we also offer comprehensive analytical support for those who need it. We aim to meet our customers' needs at every level.

About David Buck

David Buck, Ph.D., is the Director of Operations at Azenta Life Sciences in the UK. He has over three decades of leadership in molecular biology, excelling in complex restructuring, global expansion, and pioneering DNA sequencing technology to enhance scientific performance and productivity.

About John Todd

John Todd, Ph.D., is a Professor of Precision Medicine at the University of Oxford and Director of the Wellcome Centre for Human Genetics. He is renowned for pioneering genome-wide genetic studies and researching type 1 diabetes genetics and disease mechanisms to develop clinical interventions. Currently, his research focuses on ultra-low doses of

interleukin-2 and the role of the microbiome in T1D.

About Azenta Life Sciences

Azenta is a leading provider of life sciences solutions worldwide, enabling impactful breakthroughs and therapies to market faster. Azenta provides a full suite of reliable cold-chain sample management solutions and multiomics services across areas such as drug development, clinical research and advanced cell therapies for the industry's top pharmaceutical, biotech, academic and healthcare institutions globally. Our global team delivers and supports these products and services through our industry-leading brands, including GENEWIZ, FluidX, Ziath, 4titude, Limfinity, Freezer Pro, Barkey and B Medical Systems.

Azenta is headquartered in Burlington, MA, with operations in North America, Europe and Asia. For more information, please visit www.azenta.com.

Study reveals genetic link between Alzheimer's disease, lipid metabolism, and coronary artery disease

By Vijay Kumar Malesu

Reviewed by Lily Ramsey, LLM

Aug 20 2024

100/100

In a recent study published in the International Journal of Molecular Sciences, a group of researchers systematically evaluated the genetic overlap between Alzheimer's disease (AD) (a neurodegenerative disorder causing memory loss and cognitive decline), lipid profiles, and coronary artery disease (CAD) traits using large-scale genetic data and robust analytical methods.

Study: Investigating Genetic Overlap between Alzheimer's Disease, Lipids, and Coronary Artery Disease: A Large-Scale Genome-Wide Cross Trait Analysis. Image Credit: angellodeco/Shutterstock.com

Background

AD is a leading neurodegenerative disorder, with cases expected to exceed 139 million globally

by 2050. In Australia, it is the primary disease burden among older adults. AD is associated with tau tangles and beta-amyloid (Aβ) plaques in the brain.

Research suggests links between lipid disorders, CAD, and AD, with genetic studies indicating potential overlapping mechanisms.

However, the precise relationships and underlying biology remain unclear, highlighting the need for further research to understand these complex connections better.

About the study

The relationship between AD and various lipid traits, representing eight major lipid classes, was thoroughly examined.

These lipid classes included fatty acyls, glycerophospholipids, high-density lipoproteins (HDL) and low-density lipoproteins (LDL), neutral lipids (triglycerides), medium-chain fatty acids, steroids (total cholesterol), and sphingolipids.

The study utilized Genome-Wide Association Study (GWAS) summary data from large-scale research consortia, including Cooperative Health Research in the Region of Augsburg (KORA), Twins United Kingdom (TwinsUK), and the Global Lipids Genetics Consortium, among others.

The analysis also considered the relationship between AD and seven CAD traits, using data sourced from the Lee Lab for Statistical Genetics and the CARDIoGRAMplusC4D consortium.

To explore the genetic relationships, the study employed linkage disequilibrium score regression (LDSC) and local analysis of [co]variant association (LAVA) methods at both Single Nucleotide Polymorphism (SNP) and gene levels.

Additionally, the study conducted gene-based association analyses to identify overlapping genes between AD, lipids, and CAD traits, employing multi-marker analysis of genomic annotation (MAGMA) within the Functional Mapping and Annotation (FUMA) platform.

The research identified significant global genetic correlations between AD and specific lipid traits such as LDL, triglycerides, and total cholesterol and a positive correlation between AD and various CAD traits.

However, Mendelian randomization analyses did not support a causal link, suggesting shared genetic susceptibility as a more plausible explanation. Local genetic correlation analyses

pinpointed specific genomic loci contributing to these associations, offering further insight into the complex genetic landscape linking AD with cardiovascular health.

Study results

Initially, the researchers utilized LDSC to assess and quantify SNP-level global genetic correlations across 13 lipid traits, seven CAD traits, and AD.

This analysis revealed significant global genetic correlations between AD and specific lipid traits, particularly triglycerides, LDL, and total cholesterol.

Similarly, strong correlations were found between AD and several CAD traits, including angina pectoris (chest pain due to reduced blood flow to the heart), cardiac dysrhythmias (abnormal heart rhythms), and coronary arteriosclerosis (hardening and narrowing of heart arteries). These results suggested that shared genetic components might predispose individuals to both AD and certain lipid and CAD traits.

The study applied bi-directional two-sample Mendelian randomization (2SMR) analyses to test for potential causal associations between these traits. However, the 2SMR analyses did not provide evidence for a causal relationship between AD, lipids, and CAD traits, indicating that the observed correlations might be due to shared genetic susceptibility rather than direct causal links.

The researchers conducted gene-based analyses to delve deeper into the genetic overlap, identifying genome-wide significant (GWS) genes shared by AD, lipids, and CAD traits. Notably, genes such as Apolipoprotein E (APOE), APOC1, and Translocase of Outer Mitochondrial Membrane 40 (TOMM40) overlap AD and several CAD traits, reinforcing the genetic connection between these disorders.

Additionally, Fisher's combined p-value (FCP) method was employed to identify shared genes that reached GWS across AD, lipids, and CAD traits, highlighting genes that might play a critical role in the pathogenesis of these conditions.

Furthermore, local genetic correlation analysis using the LAVA method was conducted to identify specific genomic regions contributing to the genetic correlations observed at the global level. This analysis pinpointed several loci, particularly on chromosomes 6, 8, 17, and 19, significantly associated with AD and various lipid and CAD traits.

Among these, the locus on chromosome 19 was notably implicated across multiple traits,

suggesting a hotspot for shared genetic influences.

Finally, the study compared the results obtained from LDSC and LAVA to assess the consistency of the findings. While both methods identified significant genetic correlations, some discrepancies were observed, particularly in the direction of effects, emphasizing the importance of using multiple analytical approaches to understand genetic relationships comprehensively.

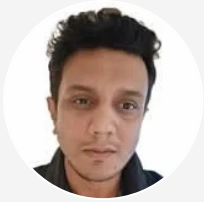
Conclusions

This study systematically assessed genetic correlations between AD, 13 lipid traits, and seven CAD traits using advanced statistical tools. Significant correlations were found between AD and specific lipids (LDL, triglycerides, total cholesterol) and all CAD traits, indicating shared genetic susceptibility.

However, Mendelian randomization analyses found no causal relationships, suggesting these associations may stem from shared genetics rather than direct causality. Local genetic analysis identified key loci on chromosomes 6, 8, 17, and 19 contributing to these associations.

Journal reference:

- Kirby A, Porter T, Adewuyi EO, Laws SM. (2024) Investigating Genetic Overlap between Alzheimer's Disease, Lipids, and Coronary Artery Disease: A Large-Scale Genome-Wide Cross Trait Analysis. International Journal of Molecular Sciences. **doi**: https://doi.org/10.3390/ijms25168814. https://www.mdpi.com/1422-0067/25/16/8814



Written by

Vijay Kumar Malesu

Vijay holds a Ph.D. in Biotechnology and possesses a deep passion for microbiology. His academic journey has allowed him to delve deeper into understanding the intricate world of microorganisms. Through his research and studies, he has gained expertise in various aspects of microbiology, which includes microbial genetics, microbial physiology, and microbial ecology. Vijay has six years of scientific research experience at renowned research institutes such as the Indian Council for Agricultural Research and KIIT University. He has worked on diverse projects in microbiology, biopolymers, and drug delivery. His contributions to these areas have provided him with a comprehensive understanding of the subject matter and the ability to tackle complex research challenges.

Ancient DNA traces multiple sclerosis origins to 5,000-year-old migrations

University of Cambridge

Jan 13 2024

100/100

Researchers have created the world's largest ancient human gene bank by analyzing the bones and teeth of almost 5,000 humans who lived across Western Europe and Asia up to 34,000 years ago.

By sequencing ancient human DNA and comparing it to modern-day samples, the international team of experts mapped the historical spread of genes – and diseases – over time as populations migrated.

The 'astounding' results have been revealed in four trailblazing research papers published in the same issue of *Nature* and provide a new biological understanding of debilitating disorders.

The extraordinary study involved a large international team led by Professor Eske Willerslev at the Universities of Cambridge and Copenhagen, Professor Thomas Werge at the University of Copenhagen, and Professor Rasmus Nielsen at the University of California, Berkeley, and involved contributions from 175 researchers from around the globe.

The new study has found the genes that significantly increase a person's risk of developing multiple sclerosis (MS) were introduced into north-western Europe around 5,000 years ago by sheep and cattle herders migrating from the east. Image Credit: SayoStudio

The scientists found:

- The startling origins of neurodegenerative diseases, including multiple sclerosis
- Why northern Europeans today are taller than people from southern Europe
- How major migration around 5,000 years ago introduced risk genes into the population in north-western Europe – leaving a legacy of higher rates of MS today
- Carrying the MS gene was an *advantage* at the time as it protected ancient farmers from catching infectious diseases from their sheep and cattle
- Genes known to increase the risk of diseases such as Alzheimer's and type 2 diabetes were traced back to hunter-gatherers
- Future analysis is hoped to reveal more about the genetic markers of autism, ADHD, schizophrenia, bipolar disorder, and depression

Northern Europe has the highest prevalence of multiple sclerosis in the world. A new study has

found the genes that significantly increase a person's risk of developing multiple sclerosis (MS) were introduced into north-western Europe around 5,000 years ago by sheep and cattle herders migrating from the east.

By analyzing the DNA of ancient human bones and teeth found at documented locations across Eurasia, researchers traced the geographical spread of MS from its origins on the Pontic Steppe (a region spanning parts of what are now Ukraine, South-West Russia, and West Kazakhstan Region).

They found that the genetic variants associated with a risk of developing MS 'travelled' with the Yamnaya people - livestock herders who migrated over the Pontic Steppe into North-Western Europe.

These genetic variants provided a survival advantage to the Yamnaya people, most likely by protecting them from catching infections from their sheep and cattle. But they also increased the risk of developing MS.

> *"It must have been a distinct advantage for the Yamnaya people to carry the MS risk genes, even after arriving in Europe, despite the fact that these genes undeniably increased their risk of developing MS," said Professor Eske Willerslev, jointly at the Universities of Cambridge and Copenhagen and a Fellow of St John's College, an expert in the analysis of ancient DNA and Director of the project.*
>
> *He added: "These results change our view of the causes of multiple sclerosis and have implications for the way it is treated."*

The age of specimens ranges from the Mesolithic and Neolithic through the Bronze Age, Iron Age, and Viking period into the Middle Ages. The oldest genome in the data set is from an individual who lived approximately 34,000 years ago.

The findings provide an explanation for the 'North-South Gradient,' in which there are around twice as many modern-day cases of MS in northern Europe than in southern Europe, which has long been a mystery to researchers.

From a genetic perspective, the Yamnaya people are thought to be the ancestors of the present-day inhabitants of much of North-Western Europe. Their genetic influence on today's population of southern Europe is much weaker.

Previous studies have identified 233 genetic variants that increase the risk of developing MS.

These variants, also affected by environmental and lifestyle factors, increase disease risk by around 30 percent. The new research found that this modern-day genetic risk profile for MS is also present in bones and teeth that are thousands of years old.

> *"These results astounded us all. They provide a huge leap forward in our understanding of the evolution of MS and other autoimmune diseases. Showing how the lifestyles of our ancestors impacted modern disease risk just highlights how much we are the recipients of ancient immune systems in a modern world," said Dr. William Barrie, a postdoc in the University of Cambridge's Department of Zoology and co-author of the paper.*

Multiple sclerosis is a neurodegenerative disease in which the body's immune system mistakenly attacks the 'insulation' surrounding the nerve fibers of the brain and spinal cord. This causes symptom flares, known as relapses, as well as longer-term degeneration, known as progression.

> *Professor Lars Fugger, a co-author of the MS study professor and consultant physician at John Radcliffe Hospital, University of Oxford, said: "This means we can now understand and seek to treat MS for what it actually is: the result of a genetic adaptation to certain environmental conditions that occurred back in our prehistory."*

> *Professor Astrid Iversen, another co-author based at the University of Oxford, said: "We now lead very different lives to those of our ancestors in terms of hygiene, diet, and medical treatment options and this combined with our evolutionary history means we may be more susceptible to certain diseases than our ancestors were, including autoimmune diseases such as MS."*

The Lundbeck Foundation GeoGenetics Centre – the resource underpinning the discoveries

The new findings were made possible by analyzing data held in a unique gene bank of ancient DNA created by researchers over the past five years with funding from the Lundbeck Foundation.

This is the first gene bank of its kind in the world. It has already enabled fascinating new insights into areas from ancient human migrations to genetically determined risk profiles for the development of brain disorders.

By analyzing the bones and teeth of almost 5,000 ancient humans, held in museum collections across Europe and Western Asia, the researchers generated DNA profiles ranging across the Mesolithic and Neolithic through the Bronze Age, Iron Age, and Viking period into the Middle Ages. They compared the ancient DNA data to modern DNA from 400,000 people living in Britain, held in the UK Biobank.

> *"Creating a gene bank of ancient DNA from Eurasia's past human inhabitants was a colossal project, involving collaboration with museums across the region," said Willerslev.*
>
> *He added: "We've demonstrated that our gene bank works as a precision tool that can give us new insights into human diseases, when combined with analyses of present-day human DNA data and inputs from several other research fields. That in itself is amazing, and there's no doubt it has many applications beyond MS research."*

The team now plans to investigate other neurological conditions, including Parkinson's and Alzheimer's diseases, and psychiatric disorders, including ADHD and schizophrenia.

They have received requests from disease researchers across the world for access to the ancient DNA profiles, and eventually aim to make the gene bank open access.

The research was funded by a €8M grant from the Lundbeck Foundation and conducted at the Lundbeck Foundation Geogenetics Centre at the University of Copenhagen.

> *Jan Egebjerg, Director of Research at the Lundbeck Foundation, said: "The rationale for awarding such a large research grant to this project, as the Lundbeck Foundation did back in 2018, was that if it all worked out, it would represent a trailblazing means of gaining a deeper understanding of how the genetic architecture underlying brain disorders evolved over time. And brain disorders are our specific focus area."*

> *Making the news*
> *Florey Director Prof Trevor Kilpatrick tells @RadioNational why some people are susceptible to multiple sclerosis. Factors include genetics, exposure to the Epstein-Barr Virus, smoking, low vitamin D levels and childhood obesity. Listen: https://t.co/cgkxbmjODf pic.twitter.com/ll4BsieSi5*
>
> *— The Florey (@TheFlorey) January 11, 2024*

> *New research has looked at the origins of some genes using ancient human DNA.*
>
> *We take a closer look into the new research that's been making the headlines and what this means for people with MS.*
>
> *Read more https://t.co/9x80Ngll38#MSResearch pic.twitter.com/Hdn1ZWJkql*
>
> *— MS Society UK (@mssocietyuk) January 11, 2024*

Source:

- University of Cambridge

Journal references:

- Barrie, William, et al. "Elevated Genetic Risk for Multiple Sclerosis Emerged in Steppe Pastoralist Populations." *Nature*, vol. 625, no. 7994, 2023, pp. 321-328, https://doi.org/10.1038/s41586-023-06618-z, https://www.nature.com/articles/s41586-023-06618-z
- K., Evan, et al. "The Selection Landscape and Genetic Legacy of Ancient Eurasians." *Nature*, vol. 625, no. 7994, 2023, pp. 312-320, https://doi.org/10.1038/s41586-023-06705-1, https://www.nature.com/articles/s41586-023-06705-1
- Allentoft, Morten E., et al. "Population Genomics of Post-glacial Western Eurasia." *Nature*, vol. 625, no. 7994, 2023, pp. 301-311, https://doi.org/10.1038/s41586-023-06865-0, https://www.nature.com/articles/s41586-023-06865-0
- Allentoft, Morten E., et al. "100 Ancient Genomes Show Repeated Population Turnovers in Neolithic Denmark." *Nature*, vol. 625, no. 7994, 2023, pp. 329-337, https://doi.org/10.1038/s41586-023-06862-3, https://www.nature.com/articles/s41586-023-06862-3

Nutrigenomics: How Your Genes Influence Your Nutritional Needs and Health

By Marzia Khan

Reviewed by Danielle Ellis, B.Sc.

Nutrigenomics or nutritional genomics comprises the study of how genes and nutrition interact, with gene variants predicting how an individual's body will respond to specific nutrients.[1] Gene-diet interactions are a two-way axis and can affect health and disease status in individuals; approaches that determine these interactions at both the cellular and molecular levels can aid in developing nutritional interventions personalized to each person's genome.[2]

Image Credit: alicja neumiler/Shutterstock.com

The genetic blueprint of nutrition

Nutrigenomics involves using various scientific fields, including biochemistry, physiology, nutrition, genomics, proteomics, metabolomics, transcriptomics, and epigenomics in order to investigate and understand the bi-directional interactions between different genes and nutrients at the molecular level.[2]

Identifying these interactions between genes and nutrients can assist with producing prescribed customized diets corresponding to each person's genotype.[3] This comprehension and development of a personalized diet has the potential to mitigate the symptoms of both existing diseases as well as prevent future diseases, especially for non-transmissible chronic diseases (NTCDs), which is a significant world public health problem.[3]

An example of gene interaction with food can be seen with genes responsible for digestion and absorption of carbohydrates and fats.[4] Two gene polymorphisms, rs1042714 and rs1042713, related to the ADRB2 gene that encodes the β2-adrenergic receptor cause a decrease in carbohydrate output rate in cells, and this subsequently can result in the development of disorders including type 2 diabetes mellitus, obesity, and metabolic syndrome.[4]

Additionally, the gene that encodes the nuclear receptor (gamma receptor) known as PPARG induces the proliferation of peroxisomes; this regulates the transcription of different genes involved in the metabolism of lipids and carbohydrates in muscle tissue and inflammatory processes.[4]

A portion of the PPARG gene that consists of the oligonucleotide polymorphism, rs1801282, is believed by researchers to increase sensitivity to insulin, total cholesterol, high-density lipoprotein as well as increased glucose utilization, which acts as a protective mechanism against both obesity and diabetes mellitus.[4]

Image Credit: MiniStocker/Shutterstock.com

Personalized diets

The translation of nutrigenomics can result in a more personalized approach to both diet and health, with diet playing a significant environmental role in health, from benefits including the prevention of diseases to performance and overall quality of life.[5]

Individuals have been known to have different responses to the same dietary intake. For example, for the past 20 years, dietary cholesterol has been believed to lead to changes in plasma cholesterol; however, this can be dependent on the individual. Additionally, some differences in response to dietary cholesterol are also dependent on genotype. [5]

Personalizing the overall diet may not be as simple as personalizing essential nutrient intake, which can be delivered through supplements.[5] The goal of personalizing nutrition is dependent on an individual's genotype and metabolic variations that first require identifying responders and non-responders to personalized diets. [5]

The practical implication for creating personalized diets can be difficult, with each person having different needs and responses to the components of a diet; this subject is being actively researched in nutrigenomics in order to identify which difference is a result of heritable genetic sequence variation.[5]

Challenges and controversies

Dietary health challenges have evolved over the years, from finding solutions for nutrient

deficiencies as a result of poor food choices to dealing with caloric imbalances that are caused by poor diets.[5] This has changed the food concerns of consumers from fearing acute safety to being afraid of long-term health deterioration.[5]

Achieving tailor-made diets and personal health will require entire diets to be personalized instead of just occasional foods, which means nutritional needs will have to be integrated into all foods consumed.[5]

This approach of developing entire diet plans that deliver all meals and foods to an individual every day in order to correspond to their nutritional need may have the unfortunate consequence of destroying the traditional joy that individuals have from the diversity of an open food marketplace. Subsequently, this may not be a sustainable approach for every person.[5]

However, approaches that combine the ability to match dietary needs while also allowing for personal choice may be more palatable.[5] Additionally, the development of diets that are based on metabolic, performance, and cognitive requirements may be the first step into aiding those who choose to eat healthier with food products and devices that already exist on the market to meet consumer demand.[5]

The ethical considerations of personalized diets led by nutrigenomics, which encapsulate genetic testing in order to gain nutritional advice, include the lack of knowledge of the risks, as it may be difficult to avoid unknown risks.[6] The precautionary principle states to exercise caution and avoid actions when risks cannot be foreseen, and personalizing diets based on genotypes is not something that can be stated as being absolutely safe or without risk.[6]

From research to reality

One of the first dietary intervention studies included the use of proteomics technology in order to identify biomarkers that demonstrate the response of peripheral blood mononuclear cells (PBMCs) to dietary isoflavone extract in postmenopausal women.[7]

Proteomics in PBMCs was used to identify proteome-diet interactions during the postprandial state after different types of meals, which demonstrated how some meals increased or decreased proteins that respond to oxidative stress and DNA damage.[7] This can demonstrate the impact of using approaches to regulate diet in order for more favorable outcomes in individuals with health conditions.[7]

With various studies being researched, including using metabolomics, due to metabolites being products of dietary intake and metabolism, these analytical tools can evaluate biochemical and physiological pathways of related dietary or disease metabolite biomarkers.[7]

Interestingly, individuals who are obese or have type 2 diabetes have specific metabolomic signatures dependent on lipid species and amino acids, and identifying these in individuals can aid in personalizing a diet that consists of low-glycemic index foods as opposed to high-glycemic index foods for more favorable health outcomes.[7]

Overall, nutrigenomics in healthcare may be an innovative approach for preventive medicine and may aid in better management of chronic conditions, including type 2 diabetes and obesity.[7]

References

- Cleveland Clinic. How nutrigenomics may impact the way you eat. Cleveland Clinic. December 14, 2023. Accessed January 5, 2024. https://health.clevelandclinic.org/how-does-nutrigenomics-work.
- Ahluwalia MK. Nutrigenetics and nutrigenomics—a personalized approach to nutrition. Advances in Genetics. Published online 2021:277-340. doi:10.1016/bs.adgen.2021.08.005
- Sales NM, Pelegrini PB, Goersch MC. Nutrigenomics: Definitions and advances of this new Science. Journal of Nutrition and Metabolism. 2014;2014:1-6. doi:10.1155/2014/202759
- Vesnina A, Prosekov A, Kozlova O, Atuchin V. Genes and eating preferences, their roles in personalized nutrition. Genes. 2020;11(4):357. doi:10.3390/genes11040357
- German JB, Zivkovic AM, Dallas DC, Smilowitz JT. Nutrigenomics and personalized diets: What will they mean for food? Annual Review of Food Science and Technology. 2011;2(1):97-123. doi:10.1146/annurev.food.102308.124147

- Görman U, Mathers JC, Grimaldi KA, Ahlgren J, Nordström K. Do we know enough? A scientific and ethical analysis of the basis for genetic-based personalized nutrition. Genes & Nutrition. 2013;8(4):373-381. doi:10.1007/s12263-013-0338-6
- Brennan L, de Roos B. Nutrigenomics: Lessons learned and future perspectives. The American Journal of Clinical Nutrition. 2021;113(3):503-516. doi:10.1093/ajcn/nqaa366

Further Reading

- All Nutrition Content
- The Role of Nutrition in Health
- What Are the Positive Health Effects of Eating Meat?
- What Are the Negative Health Effects of Eating Meat?
- Macrominerals and Trace Minerals in the Diet

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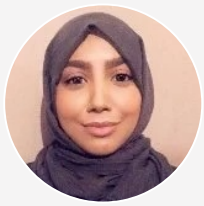


Written by

Marzia Khan

Marzia Khan is a lover of scientific research and innovation. She immerses herself in literature and novel therapeutics which she does through her position on the Royal Free Ethical Review Board. Marzia has a MSc in Nanotechnology and Regenerative Medicine as well as a BSc in Biomedical Sciences. She is currently working in the NHS and is engaging in a scientific innovation program.

Pioneering Genomic Progress: An Interview with Rami Mehio, Illumina's Software and Informatics Expert

Sponsored Content by Illumina, Inc. Jan 15 2024

In this interview, Rami Mehio, head of software and informatics at Illumina, shares his experiences and contributions to major genomic projects like the UK Biobank's whole genome sequencing. He discusses the challenges and innovations in genomic data analysis, highlighting Illumina's role in advancing genetic research and precision medicine.

Please could you introduce yourself and give us a brief description of your professional background?

My name is Rami Mehio. I lead the Software and Informatics development at Illumina. I joined Illumina in 2018 as part of the Edico Genome acquisition and have since been responsible for overseeing Bioinformatics, sequencer software, cloud data platforms, and clinical software across Illumina's portfolio. Prior to joining Illumina, I was at Edico and spearheaded the development of the DRAGEN BioIT processor and aided in its commercialization.

Could you describe Illumina's specific role and contributions in the UK Biobank's whole genome sequencing project, especially in terms of the technology and expertise provided?

Illumina is the sequencing technology partner for the project, meaning that the whole-genome sequencing (WGS) was done with Illumina sequencers. Illumina was also chosen as a bioinformatics partner in the analysis of each genome and their joint calling into a cohort. As such, the secondary analysis was performed using DRAGEN's award-winning germline pipeline with its multi-genome graph mapping and variant calling. To keep up with the computational and storage tasks of 500,000 WGS, the aggregation was performed with DRAGEN iterative

gVCF genotyper (IGG) on Illumina Connected Analytics (ICA) cloud platform and employed ML-based filtering allowing for improved sensitivity and precision of variants.

Image Credit: ESB Professional/Shutterstock.com

Handling and analyzing such an extensive dataset must have presented unique challenges. What were these challenges, and how did Illumina's technology address them?

The main challenge was ensuring that we had the right computational infrastructures in place to support analyzing 500,000 genomes. The secondary analysis of the 500,000 genomes was done in about six weeks on Amazon Web Service (AWS). We had to put quality assurance processes in place to make sure the analysis jobs for the rest of our customers were not starved of compute nodes.

Another challenge that we experienced was with aggregation, particularly with the number of files, the number of API calls, the size of the data, and the cost. This exercise allowed us to architect and tune DRAGEN IGG and ICA to make it a product that is unparalleled and able to aggregate millions of genomes with high precision and low cost. The architecture also allowed for solving the N+1 problem. This means, that if we were to aggregate an additional thousand genomes, we would be able to do it incremental and not do the 510,000 job.

How does Illumina's technology improve the identification of less frequent genetic variants, and what impact does this have on genetic research?

The DRAGEN pipeline has unique features that improve the sensitivity and precision of the data, meaning we can detect variants that other pipelines have difficulty identifying. DRAGEN does this by using multireference genome technology that better matches the reference to the samples. This allows for accurate detection and mapping in difficult and highly polymorphic regions of the genome. We also introduced machine learning into our later versions of DRAGEN enabling us to significantly reduce false positives while improving sensitivity. DRAGEN's precision and sensitivity have been put to the test and corroborated with two PrecisionFDA awards in germline disease, inherited disease, and oncology.

In what ways does your technology ensure that the data from this project is compatible and comparable with other large-scale population health studies?

Credit for this goes to the UK Biobank and its pharma Consortium members, some of the leaders in the All of Us program and its associated sequencing centers, and the leadership at Genomics England. They agreed on adopting the same version of the DRAGEN pipeline, and Illumina was able to support and remove obstacles. We provided details of the pipeline and the configurations on our centralized location and worked closely with each program to ensure consistency across the groups. A common pipeline is a key necessity for the data to be compatible and increase the statistical power of the cohorts.

What advancements in software and informatics have emerged from this project, and how do they push the boundaries of genomic research?

This is probably the biggest aggregation of whole-genome sequencing in the world at this time. Usually, aggregating large cohorts is quite difficult. From our experience, projects often tend to struggle when dealing with more than 10,000 samples. DRAGEN IGG on ICA is now able to scale to hundreds of thousands of samples while also solving the N+1 problem - adding another 10,000 samples to the cohort of 500,000 does not require the user to restart the joint calling from the beginning.

Based on the outcomes of this project, what are the broader implications for future research and healthcare, particularly in the context of precision medicine?

WGS data will enable researchers to identify rare non-coding variants that contribute to disease onset and progression. It will also identify mutations that protect against disease. By combining the WGS data with the rich clinical and lifestyle data of UK Biobank participants, researchers are now uniquely equipped to answer questions about why some individuals develop particular diseases but others do not and why certain conditions worsen in some individuals over time.

Image Credit: Mongkolchon Akesin/Shutterstock.com

It will also help accelerate drug discovery and development by allowing researchers to identify new drug targets. This is important because pharmaceutical companies have found that potential drug targets supported by clear genetic evidence are twice as likely to result in effective medicines.

Can you discuss the importance of collaboration and partnership, like that seen in the UK Biobank project, in advancing genomic research?

Through collaboration, this partnership has enabled the dream of sequencing and analyzing a large number of genomes for the purpose of improving healthcare to become a reality.

The UK Biobank's vision for producing and making these cohorts of data publicly available is commendable. It opens the door for polygenic risk score evaluations and more precise drug discoveries.

Through this collaboration, Illumina's software has matured, and our capabilities have grown. We've established our capabilities in the informatics space and it enabled us to bring more precise meaning to data.

Where can readers find more information?

- https://www.illumina.com/products/by-type/informatics-products/dragen-secondary-analysis.html
- https://www.illumina.com/products/by-type/informatics-products/connected-analytics.html

About Rami Mehio

Rami is the global head of software and Informatics development at Illumina. He joined Illumina in 2018 as part of the Edico Genome acquisition and has continuously expanded his leadership, which now includes overseeing all of instrument software, cloud platforms, bioinformatics, and clinical software across Illumina's entire portfolio. Over the past few years, Rami's organization has helped establish Illumina as a leading provider in informatics, delivering innovative, reliable software products developed in deep collaborations with KOLs.

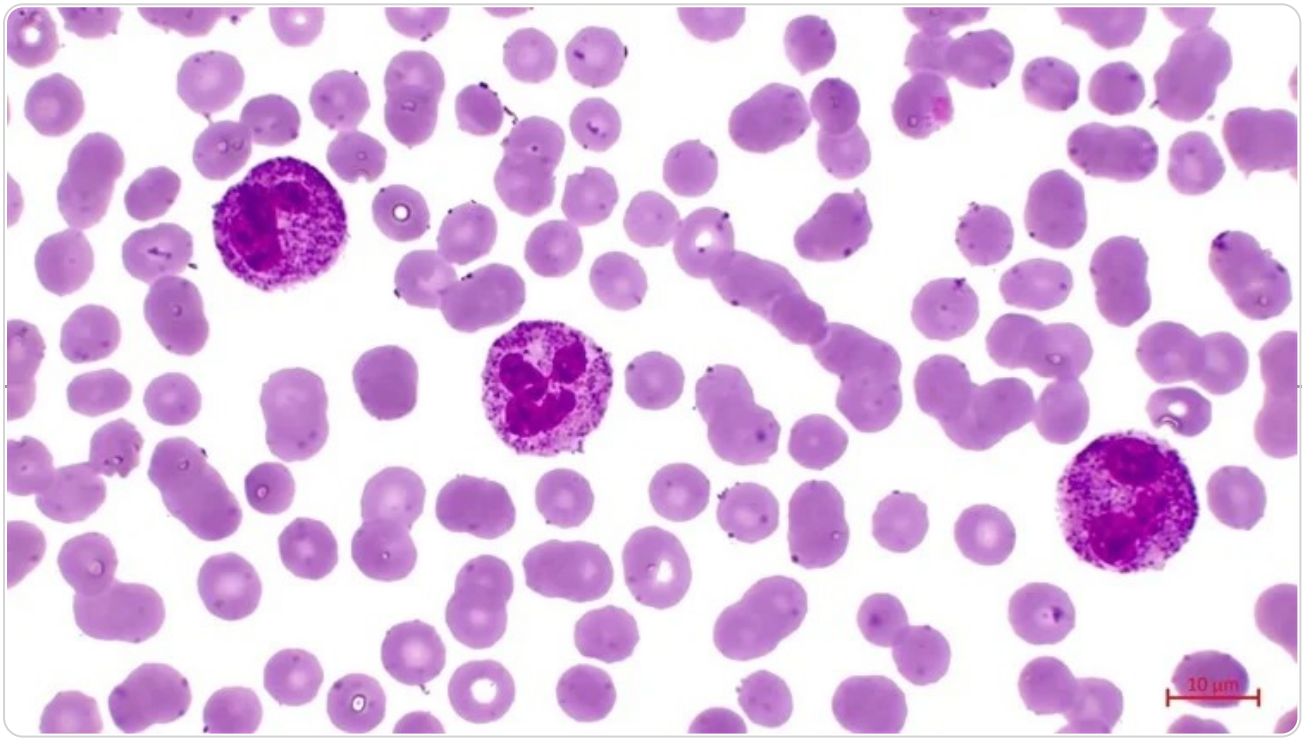
New study uncovers 17 genes driving clonal hematopoiesis and links to aging and disease

By Dr. Chinta Sidharthan

Reviewed by Susha Cheriyedath, M.Sc.

May 15 2024

In a recent study published in the journal *Nature Genetics*, a team of researchers from the United Kingdom (U.K.) and the United States (U.S.) analyzed whole blood samples from a large cohort of U.K. Biobank participants to discover 17 genes that are being positively selected at the population level and driving clonal hematopoiesis.



Study: Analysis of somatic mutations in whole blood from 200,618 individuals identifies pervasive positive selection and novel drivers of clonal hematopoiesis. Image Credit: BioFoto / Shutterstock

Background

Clonal hematopoiesis is the clonal expansion of dividing cells in the blood, carrying accumulated somatic mutations, leading to an assortment of clones that evolve with age. The emergence of clonal hematopoiesis and similar clonal expansions in other dividing tissues is often considered a hallmark of human aging. Given that some of these somatic mutations provide a fitness benefit, these clones often come under positive selection. However, some of the mutations in these clones can not only drive cancer but also contribute directly and

indirectly to other diseases, such as chronic liver disease.

Genomic sequencing studies on blood samples have identified that the occurrence of clonal hematopoiesis is higher among elderly individuals. Furthermore, retrospective studies among large cohorts have also identified an association between clonal hematopoiesis and cardiovascular disease, hematological cancers, and mortality. However, most approaches to detect clonal expansion either fall short, such as bulk approaches that can detect only a few small clones, or detect a large number of clones, with most of them lacking the specific driver mutations, as in the case of single-cell sequencing.

About the study

In the present study, the researchers attempted to find better methods to map clonal hematopoiesis drivers, understand how these clones undergo selection, and determine the phenotypes of aging in blood. They obtained whole blood samples from a large cohort (200,618) of U.K. Biobank participants and studied the exomes from these samples to determine the drivers of clonal hematopoiesis.

The researchers worked on the principle that nonsynonymous mutations within a gene would be enriched compared to synonymous mutations if the gene was under positive selection. Therefore, the exomes from the buffy coats, which are the residual units enriched with leukocytes obtained when whole blood is centrifuged, were examined to determine the genes under positive selection.

The participants from the U.K. Biobank included in this study were between 40 and 70 years old. A method of somatic variant calling was used to filter out the germline variants and artifacts from the whole blood exomes. Subsequently, the non-synonymous to synonymous mutations ratio was used to identify specific mutations and genes under negative, positive, and neutral selection.

To verify that the genes identified to be under positive selection were not an unintended result of the somatic mutation calling method, the researchers used a method called Shearwater, which is used for calling subclonal variants, to call the somatic mutations in newly identified and classical clonal hematopoiesis genes.

Additionally, published whole-genome sequences from healthy individuals as well as patients with hematological cancers were examined for corresponding mutations to validate these fitness-inferred drivers of clonal hematopoiesis. Furthermore, the updated health records available through the U.K. Biobank were used to determine the clinical associations of these

fitness-inferred clonal hematopoiesis drivers at the population level.

Results

The study identified 17 additional genes involved in clonal hematopoiesis that were positively selected at the population level. The 17 newly identified clonal hematopoiesis genes were *ZNF318*, *ZNF234*, *ZBTB33*, *YLPM1*, *SRFS1*, *SRCAP*, *SPRED2*, *SIK3*, *SH2B3*, *MYD88*, *MTA2*, *MAGEC3*, *IGLL5*, *CHEK2*, *CCL22*, *CCDC115*, and *BAX*.

This finding was further validated by comparing these genes with those in close to 11,000 whole genomes obtained from hematopoietic lymphoid and myeloid colonies derived from single cells. Furthermore, the prevalence of clonal hematopoiesis increased by 18% in the U.K. Biobank cohort when the mutations in these fitness-inferred clonal hematopoiesis genes were included in the analysis.

When the researchers examined the fitness effects specific to these mutations, they found that the fitness conferred by some of these mutations was substantial. Mutations in the *MTA2*, *SPRED2*, and *SRFS1* genes were found to confer a clonal advantage to hematopoietic stem cells by providing an excess division rate of 15% to 20% per year. Surprisingly, the most common mutation found in the *MYD88* gene was not found to be one of the sites under strong selection, and the researchers believe that recurrent mutations in this gene might be better explained by high mutation rates rather than selection.

Conclusions

Overall, the findings reported 17 additional clonal hematopoiesis genes under positive selection that conferred fitness and were being selected for at the population level. The study found that clonal populations carrying mutations in these genes increased in size and frequency with age and could be compared to the classical drivers of clonal hematopoiesis. These mutations also showed significant correlations with increased risks of hematological cancers, and infection.

Journal reference:

- Bernstein, N., Chapman, S., Nyamondo, K., Chen, Z., Williams, N., Mitchell, E., Campbell, P. J., Cohen, R. L., & Nangalia, J. (2024). Analysis of somatic mutations in whole blood from 200,618 individuals identifies pervasive positive selection and novel drivers of clonal hematopoiesis. *Nature Genetics*. DOI: 10.1038/s41588024017551, https://www.nature.com/articles/s41588-024-01755-1

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Chinta Sidharthan is a writer based in Bangalore, India. Her academic background is in evolutionary biology and genetics, and she has extensive experience in scientific research, teaching, science writing, and herpetology. Chinta holds a Ph.D. in evolutionary biology from the Indian Institute of Science and is passionate about science education, writing, animals, wildlife, and conservation. For her doctoral research, she explored the origins and diversification of blindsnakes in India, as a part of which she did extensive fieldwork in the jungles of southern India. She has received the Canadian Governor General's bronze medal and Bangalore University gold medal for academic excellence and published her research in high-impact journals.