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Artificial Intelligence-Driven Advances in Haemophilia Gene Therapy

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ABSTRACT: Hemophilia is the most frequent severe genetic haemorrhagic condition. Hemophilia A and B are caused by a lack or dysfunction of the factor VIII and factor IX proteins, respectively, and are distinguished by prolonged and heavy bleeding after minor trauma or even spontaneously. Treatments for hemophilia have been extremely expensive and required the infusion of plasma clotting factors throughout one's life. The last few years have brought major breakthroughs in gene therapy that now hold real promise for possible curative options. Artificial intelligence has the potential to transform all levels of hemophilia gene therapy, from vector design to predictive modeling and biomarker identification. This review highlights selected applications of AI towards precision medicine including viral vector design, predictive modeling for gene editing, and deep phenotyping in hemophilia gene therapy. It can greatly improve the efficacy and safety of gene therapy through off-target effects prediction, optimization designs of delivery vectors, and determination of personalized combinations of treatments. Consequently, this will also enable accelerated biomarker development for disease diagnosis and monitoring. In such a way, artificial intelligence in hemophilia gene therapy will revolutionize the framework of treatment and make it personalized or even curative for patients all over the world.

KEYWORDS: Hemophilia, gene therapy, viral vectors, gene editing, deep learning and machine learning.

INTRODUCTION

The integration of artificial intelligence (AI) into hemophilia management is in its nascent stages. This manuscript reviews advancements enabled by AI. Mechanically, robotic-assisted procedures, such as total knee arthroplasty and laparoscopic prostatectomy, have demonstrated success in hemophilia patients. Virtually, AI applications in hemophilia include CRISPR/Cas9 off-target prediction, severity estimation, and factor VIII/IX deficiency identification in hemophilia A and B, respectively.

Congenital bleeding disorders like hemophilia A and B are caused by absent or dysfunctional coagulation factors VIII or IX. Hemophilia A affects 1 in 5,000 male births, while hemophilia B affects 1 in 25,000. Clinical presentation depends on residual plasma factor levels. Severe phenotypes (≤1% FVIII/FIX activity) exhibit recurrent spontaneous bleeding and surgical complications.

We are just now beginning to use artificial intelligence (AI) in hemophilia. Topics addressed to access a better comprehension of the connection between hemophilia and AI, a review of the literature on the subject has been conducted in this work. In terms of the mechanical components of artificial intelligence (AI), successful outcomes have been achieved in haemophiliac patients through robotically assisted total knee arthroplasty and laparoscopic prostatectomy.[1] In terms of the virtual components of AI, the following applications of machine learning (ML) and deep learning (DL) in hemophilia have shown promising results such as calculation of cardiac rupture , developing a user-centered app centered around hemophilia, identifying CRISPR/Cas9 nuclease off-target for treatment, estimating the severity of the disease, and recognizing factor VIII and IX deficiency in mild to moderate hemophilia A and hemophilia B respectively, shown in figure 1.

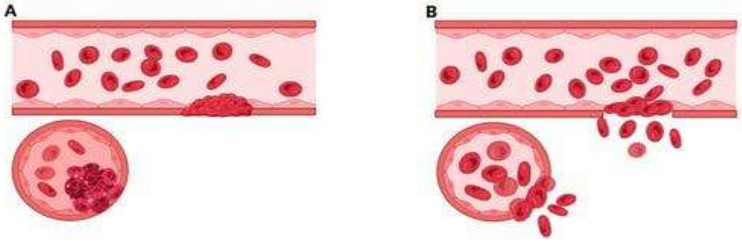

Fig 1: (A) Development of blood clots at normal factor VIII and factor IX levels. (B) Factor VIII insufficiency results in hemophilia type A, while factor IX deficiency causes hemophilia type B.[4]

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Congenital bleeding diseases such as Hemophilia A and B are brought on by coagulation factors (F) VIII or IX that are either absent or malfunctioning. Hemophilia A affects roughly one in every 5000 live male births, and hemophilia B affects one in every 25,000.[2] These illnesses are clinically indistinguishable despite their genetic and molecular differences, with symptoms that change depending on residual plasma coagulation factor levels. Patients with less than 1% (<1 IU/dL) FVIII or FIX activity have a severe phenotype, including recurrent spontaneous musculoskeletal, soft tissue, and other life-threatening bleeds including intracranial haemorrhage, as well as excessive bleeding during and after surgery or trauma.[3]

There are a variety of reasons gene therapy may represent a better alternative for the treatment of hemophilia. These cells produced short term low quantities of FVIII.[4] This ex vivo method of gene transfer onto autologous fibroblasts or hematopoietic stem cells was employed in earlier investigations, producing transient levels of FVIII production. More than 20 years ago, it was reported that individuals with hemophilia B might get FIX (rAAV-FIX) via intramuscular injection when a Adeno-associated virus (AAV)-based recombinant medical care was utilized.[5] Patients receiving this technique had coagulation factor expression for more than three years, and it was considered to be exceedingly safe. Regrettably, because most patients had levels less than 1%, it was unable to increase FIX expression at the necessary levels. Modern medications have the ability to release coagulation factors continuously for up to eight years.[6]

GENE THERAPY FOR HEMOPHILIA

While cell treatment involves putting living cells into an organism to aid in tissue repair or restore a function that is compromised, gene therapy entails introducing genetically modified cells into an organism to enable them to generate a functioning protein. Given that stem cells have the endless potential to self-renew and specialize into a variety of distinct cell lines, both tactics rely on their employment.

Hemophilia is a very curable condition that can be managed with non-viral vector transfer, autologous fibroblasts, platelets, or hematopoietic stem cells; lentiviral and adeno-associated vector gene therapy within adult stem cells; and chimeric oligonucleotide-assisted mutation repair .Although innate cellular T cells' toxicity to adeno-associated capsid protein and non-viral vectors' low efficacy are impeding and limiting their success, the majority of published studies to date have not mentioned any unfavorable events that resulted from the use of such strategies in clinical trials that were conducted.with reference to immune-mediated transgene rejection (factor VIII or IX expression).[7]

Gene therapy introduces functional proteins through genetically modified cells. Current strategies include:

- Non-viral vector transfer (e.g., lipid-based delivery systems).
- Viral vector-based therapies, such as adeno-associated and lentiviral vectors.
- Chimeric oligonucleotide-assisted mutation repair.

Most approaches face challenges, including immune-mediated rejection of transgenes. However, significant strides have been made to optimize delivery vectors and mitigate these issues.

Role of vectors in gene therapy:

Although gene therapy has the potential to treat a wide range of human illnesses, it encountered obstacles in the 1990s as a result of inexperience in planning clinical trials and an optimistic attitude toward viral vector safety concerns. Nearly 70% of these investigations are based on viral vectors. introduction of genetic information into cells may also be accompanied by non-viral vector-based delivery systems.[8]

AI CAN IMPROVE GENE THERAPY IN SEVERAL WAYS

VIRAL VECTOR DESIGN OPTIMISATION:

Adeno-Associated Virus Vectors:

AAV vectors remain the preferred choice for gene therapy in hemophilia due to their safety and efficacy. Seven AAV-based therapies are in clinical use (e.g., Luxturna, Zolgensma). AI-driven approaches now allow for the rational design of synthetic capsids with improved targeting and immune evasion properties. Recent innovations include machine learning algorithms that predict the optimal sequence modifications for capsid proteins, enhancing their specificity and reducing off-target uptake by non-hepatocyte cells like Kupffer and sinusoidal endothelial cells. Additionally, AI has facilitated the creation of split AAV vectors capable of delivering

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larger therapeutic payloads by reassembling in target cells, overcoming the inherent packaging limitations of traditional AAV systems.

Among the current widely used strategies for stable transduction of genes associated with therapy in somatic target cells, the method based on using viral vectors is considered to be one of the most efficient. For this reason, adeno-associated virus (AAV) vectors continue to be among the first options for gene transfer therapy for a variety of hereditary illnesses, including hemophilia seen in figure 2. Currently, seven AAV-based medications are authorised for commercial use and are being used in clinical trials: Leber's hereditary optic neuropathy (LHON) is represented by Lumevoq; Leber's congenital amaurosis (LCA) by Luxturna; spinal muscular atrophy (SMA) by Zolgensma; lipoprotein lipase deficiency by Glybera; hemophilia A and B by ROCTAVIAN; Duchenne cell dystrophy by Elevidys; and weak immunogenicity by BEQVEZ.[9] To repeat and productive infections it needs an aid of any satellite virus like adenovirus. Advanced and more potent synthetic capsids with increased packaging capabilities as well as with tissue specificity have been created by designing the AAV vectors bio genetically. But several different approaches have been devised to ensure that a huge therapeutic gene can be delivered, for instance, using a abbreviate gene that not only encodes for a compact but active protein.[10]

Numerous treatment approaches have been employed in the field of gene therapy.[11] the features of transduction in the context of histology should be taken into account when planning gene therapy using AAV vectors, particularly the role of Kupffer cells and sinusoidal endothelial cells in the liver, which together constitute the reticuloendothelial cells of the liver. Sinusoidal endothelial cells, which have a diameter of 7 to 9 µm, are scavengers that, under the right circumstances, can absorb particles as small as 0.23 µm in vivo. Larger particles are absorbed by Kupffer cells with a diameter of 10 to 15 µm. Hepatocyte-mediated gene transfer may be less successful if Kupffer cells and sinusoidal endothelial cells in the liver absorb the vectors, as the majority of gene transfer vectors have a diameter of less than 0.23 µm.[12]

Lentivirus Vectors:

Conversely, lentiviral vectors (LV) have the capacity to introduce their genetic material into the host cell's genome as shown in figure 2, and this remains stable even when the cell divides. This method can be useful for attaining specific levels of gene expression after a number of hours or days, but it has potential further drawbacks of insertional mutagenesis.[13] major benefits of these vectors are not very antigenic. The versatility that they exhibit in terms of being able to be incorporated making them ideal for gene therapy when divided into dividing and non-dividing cells.[14]

The results show that the most effective in vitro plasmid gene transfer method for delivering GFP to LSECs is electroporation (31%), as opposed to lipofection and calcium phosphate transfection (6% and 4%, respectively). Nonetheless, lentiviral transduction produced more stable and efficient gene expression than plasmid-based techniques.[4]

Non-viral delivery:

Using vectors based on lipid particles or synthetic polymers (liposomes and lipofectin, for instance) is known as non-viral delivery. reduced immunological problems mean increased safety in clinical usage; Long shelf life is possessed by synthetic materials. Numerous opportunities for increasing productivity and lowering final product prices.[15]

These products can, have trouble entering cells and can only express transgenes for a brief period of time. Despite the good outcome, there were some difficulties when testing on mice since transgenic expression quickly decreased, leading to epigenetic silencing or genetic material loss in dividing cells.[16]

The researchers suggested a design known as S/MAR (Scaffold Matrix Attachment Areas) to solve this issue. It speaks of the DNA sequences that, during interphase, link chromatin to the nuclear matrix. DNA vectors carrying the S/MAR sequence enable for improved mitotic stability of dividing cells and resist epigenetic silencing, consequently leading to sustained transgenic expression. S/MAR has not yet been put to the test in clinical trials, despite the fact that it was initially successful in preserving transgenic expression in the livers of mice and pigs.[17]

One popular technique to decrease nonspecific interactions is to shield the delivery vehicle interface with polyethylene glycol (PEG). Like DNA, mRNA, and short double-stranded RNA, RNA also needs to be protected from endo- and exo-ribonucleases that are found inside and outside cells to avoid degradation.[18] In addition, it is important to detect the immune escape and the endo/lysosomal escape, avoid non -specific chemistry biomolecules or non -target cells, prevent liver clearance, allow the tear to reach target tissues and improve cell penetration.[,23]

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Using these technologies, researchers are able to produce increasingly targeted, personalized treatments that are going to bring about comprehensive changes in human health.

PREDICTIVE MODELLING

Gene Editing:

Researchers are using viral vectors and editing programs such as CRISPR/Cas to deliver healthy copies of genes for homologous replacement. But preclinical research on CRISPR/Cas-based treatments for hemophilia B has ended, raising questions about unintended consequences. Since ex vivo editing necessitates continuous observation for unintended off-target effects, transplanting edited cells after editing them may be a safer and more controlled procedure. In this case, modifying cells in vivo and then transplanting them could be a safer and more regulated approach.[19]

In vivo or in cell lines, homologous recombination-based CRISPR/Cas editing shown in figure 2 has an efficiency of about 5% across several investigations. As a result, in order to produce effective knock-in, substantial doses of AAV containing Cas9 and donor DNA are typically needed, which carries a higher risk of off-target effects and increased production costs. There was no evidence of germ cell editing or off-target consequences. Anti-Cas and anti-AAV2/8 antibody titers were not statistically significant, as the combination of F9-Padova and the liver-specific LP1 promoter enabled for a 10-100-fold dose reduction in comparison to earlier investigations.[20] However, with this approach, hF9 insertions in the opposite direction and donor AAV without ires-hF9 were observed, but this was at a lower frequency and did not cause serious side effects.[21]

The following categories encompass their contributions: tools for creating gRNAs that can predict both on- and off-target editing, as well as instruments made expressly to forecast outcomes in advanced genome engineering.[22]

Base editing using AI:

Base modification is an effective GED approach that allows precise and very efficient conversion of individual genomic nucleotides without the need for double-strand breaks. With the main objective of improving editing outcomes, several ML and DL models have been built. in order to increase base editors' efficiency. BE-Hive is a machine learning model created by one researcher that predicts editing sequences and base effectiveness using a deep conditional autoregressive model. BE-Hive was eventually utilized to build base editing techniques to fix Several SNVs with ≥90% accuracy associated with the illness, some containing bystander nucleic acids.[23]

Prime editing using AI:

Prime editing is a revolutionary technique that uses reverse transcription to introduce preprogrammed modifications into DNA sequences. This versatile GED tool can perform a wide range of genetic modifications; nevertheless, to attain superior editing efficacy and product purity, experimental modification of the PED guide RNA (pegRNA) is required. It consists of three main components: a reverse transcriptase, a pegRNA, and a Cas9 nickase. Creating pegRNA is a more involved process than other CRISPR-based editing methods. We use tools like prime-design and Easy-prime to help us with this intricate design process.

This model considers the expression levels of TREX1 and TREX2, in addition to the length, structure, and secondary structure of the nucleic acid's insertion sequence. This is because TREX1 and TREX2 break down the DNA's tertiary lobe, which is necessary for primary editing insertions. Furthermore, a machine learning model was developed to predict the insertion efficiency of the prime editing method.

Genome editing using AI:

Epi-genome editing allows precise modifications to the regulation, on/off state, and regulation of specific genes without affecting the DNA sequence itself, in contrast to standard gene editing that modifies the genetic code. Researchers and medical professionals can precisely target and modify the expression of particular genes or signalling pathways implicated in a variety of diseases or cellular processes through the use of epigenome editing.

CRISPR-mediated epigenome editing can be predicted using DL (Deep Learning) EpiCas, a method created by Yang et al. Four categories of epigenetic variables are included to improve prediction accuracy: methylation, gene expression, chromatin accessibility, and distance between the transcription start site and the target site.[24]

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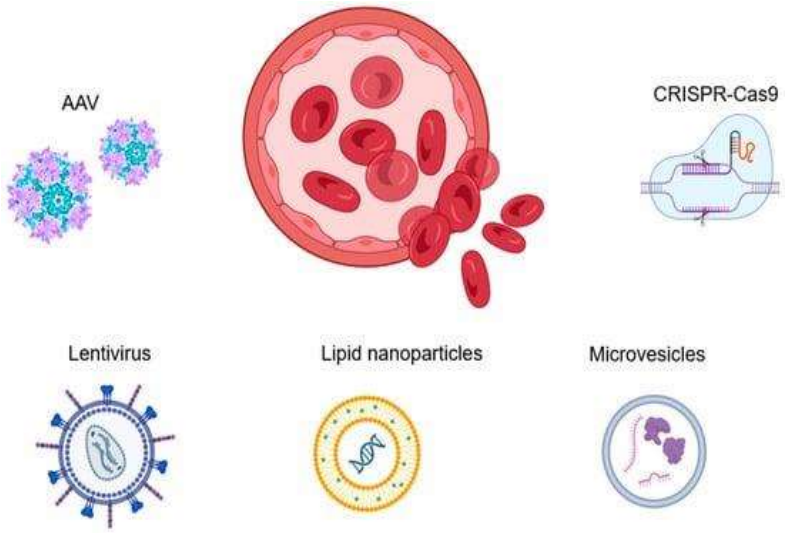

Fig 2: Types of treatment techniques for hemophilia therapy[4].

PRECISION MEDICINE

Over the past decade, Considerable capital has been invested in the development of novel medicines, comprehension of disease causes, and ultimately, illness prevention, as a means of advancing precision medicine. The goal of precision medicine has been to find efficient methods and individualized therapies based on a person's genetic, environmental, and lifestyle characteristics[25].

As previously stated, the results of the Human Functional Genomics Project (HFGP), which focused on 500 healthy adult participants, provide strong evidence of the biological variety of humans in both health and sickness.[26] Several studies have evidently demonstrated this by examining immune cells, or cytokines, as endpoints, demonstrating the dependence of cytokine types and quantities on genetic background, gut microbiota composition, and environmental conditions (such as season). the most recent HFGP investigation shown that in healthy patients, up to 67% of the interindividual variation in activated cytokine production might be attributed to 11 distinct types of host variables combined.[27]

As the figure 3 illustrates, an individual's health and risk of disease are largely determined by a variety of factors, including genetics, metabolism, gut microbiota, sleep patterns, stress, socioeconomic status, geography, early life experiences, and exercise habits[28].Thus, before interventions can be confidently implemented, each person's needs must be thoroughly assessed using deep phenotyping.[29]

Deep Phenotyping:

With AI, a drug combination can be developed based on the patient's biopsy and an N-of-1 drug recommendation can be made. Across many disciplines, AI-based algorithms have already demonstrated increases in diagnostic performance and accuracy.[30]Current research demonstrates how AI and technological advancements combine to achieve the goal of accurate and tailored medicine.[31]

Integrating multi-omics data requires machine learning, which is essential in areas where data types are merged and their connections examined. The UK Biobank project, one of the biggest prospective cohort studies, gathered detailed genetic and phenotypic information from 500,000 people, including biological measurements, lifestyle variables, blood and urine biomarkers, and brain imaging.[32]a precision drug screening study that included genomics, metagenomics, advanced imaging, metabolomics, clinical trials, and family history offered a thorough, predictive, and customized evaluation of people's health and conditions. This study also introduced an extensive quantitative multimodal phenotyping platform. danger of chronic illness.[33]

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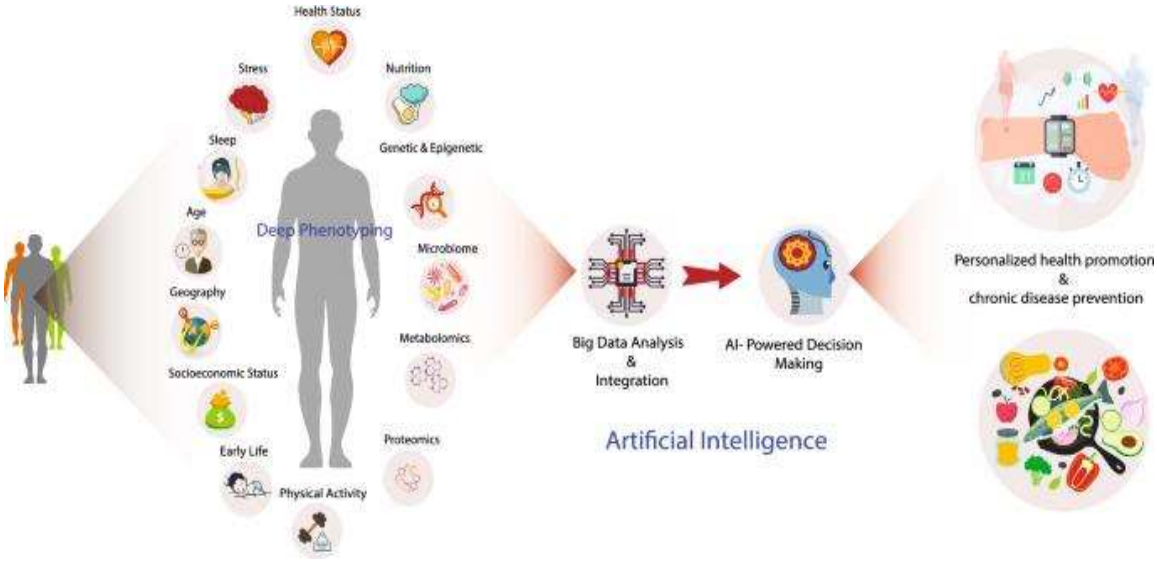

Fig 3: Deep phenotyping and artificial intelligence are being used to improve chronic illness prevention and health promotion by offering a detailed molecular profile of a person's physiological state, enabling early disease risk identification and prevention through big-data analysis and integration.[34]

BIOMARKER PREDICTION

A biomarker is a measurable characteristic that describes an organism's physiological or pathological status. These characteristics can be genes, proteins, metabolic pathways, etc., and can be used to diagnose diseases, monitor treatment outcomes, or predict disease progression. Biomarker discovery has been revolutionized by omics technologies, which enable high-throughput profiling of biological molecules in cells and tissues in all possible states and conditions. These platforms are capable of measuring millions of traits, including, to name a few, genotype, epigenetic state, and RNA, protein, and metabolite levels. This discovery capability has shifted research toward large collaborative projects and resources where sample size can also be maximized to improve performance and reduce costs at scale[35].

ML algorithms are powerful tools to find models in huge data sets to forecast the results or to classify groups according to input data such as transcriptome profiles in order to better our understanding of biology and allow a customized course of treatment based on each patient's unique biomolecular composition.[36] Supervised and unsupervised techniques are the two main categories of machine learning Interpretability is a major concern even if supervised learning systems have shown excellent results and offer many benefits. It is impossible for a human to comprehend how the most effective machine learning models generate individual predictions due to their complexity.[37,38,39]

CONCLUSION

In other words, AI employed in the treatment of hemophilia is a new frontier that has the potential to create seismic changes in many fields of lives. Thereby, genetic profiles of people suffering from hemophilia can be matched with personalized and effective treatment made available from the power-driven advancement in gene therapy, vector optimization, and predictive modelling. In recent approvals, gene therapies mark an important turning point in the treatment of hemophilia: away from very expensive, lifelong treatments toward potentially curative solutions. Further, continued development and refinement of machine learning and deep learning algorithms allow for biomarker identification, deep phenotyping, and the identification of optimal drug combinations. At the same time, these technologies have a potential that will enable researchers to minimize time and resources invested in developing effective therapies while reducing the possibility of intended consequences. This will require a continued collaboration of all the professionals within the health care ecosystem, from researchers and clinicians to patients and policymakers, that the innovations emerging in this area are translated responsibly and made available to all the patients with hemophilia, particularly in poor settings. This would allow improvements in quality of life and health outcomes.

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