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A REVIEW ON GENE THERAPY OF GENETIC DISORDERS

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Abstract

Numerous intricate and untreatable ailments are brought on by genetic diseases. Each person's unique DNA sequence is encoded, and the mitochondrial, nuclear, and microbial metagenomes all contain a wealth of disease-causing genes. The use of next-generation DNA sequencing has brought these disorders' diagnoses together. Nonetheless, one of the key objectives is still to convert particular genetic diagnosis into tailored genetic treatments. Genetic therapies can be divided into three main categories thus far: replacing the damaged genetic compartments in large quantities with a new exogenous genome; adding extra genetic material to compensate for genetic errors without targeting it; and, most recently, using gene editing to directly correct the alterations that are causing the problems. The development of new generations of curative genetic medicines will be accelerated by the use of generalized techniques for diagnosis, treatment, and reagent administration into each genetic compartment.

Keywords: Genetic disease, gene therapies, gene editing, genetic diagnostics, clinical genetics.

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Introduction

Genetic disorders occur when a mutation (a harmful change to a gene, also known as a pathogenic variant) affects your genes or when you have the wrong amount of genetic material. Genes are made of DNA (deoxyribonucleic acid), which contains instructions for cell functioning and the characteristics that make you unique.

Subtle changes to the genetic code can result in profoundly debilitating and diverse pathologies. The hereditary nature of human traits has been described since classical times. In the history of modern medicine, the first known genetic disorder, alkaptonuria, was described at the turn of the twentieth century, giving rise to the recognition of inborn errors of metabolism

(1).The first heritable alteration in a protein linked to disease was identified in sickle cell anemia in the late 1940s, with the discovery of altered shifts during electrophoresis, a change that corresponded with disease status among tested patients (5, 6). Subsequently, once the DNA code for amino acids was deciphered, scientists recognized the potential for alterations in DNA to cause alterations in enzymes and thus disease. Before the advent of DNA sequencing, the cause of Down syndrome, identified in 1959 as the chromosomal abnormality trisomy 21, was the first human genetic alteration found to be associated with disease (7).

The ethical issues around genetic testing have been discussed extensively and are out of the scope of this review. In short, a family history of disease reveals much about a patient's risk of disease, but the detailed nature of sequencing tests and the uncertainty of the interpretation raise concerns. As our understanding of genetic diseases improves and genetic testing becomes routine, it may well be possible to address those concerns so that patients can benefit from this remarkable technology(8).

Epidemiology:

One of the early proponents of genetic epidemiology, American geneticist Newton Morton, defined the field as one that addresses the etiology, distribution, and control of disease in groups of related individuals and the inherited causes of diseases in populations. That definition later was broadened to include the role of the environment, owing to the realization that genetic factors frequently interact with environmental factors to influence disease in human populations(9). In 2003, scientists Muin J. Khoury, Julian

Little, and Wylie Burke coined the term human genome epidemiology to encompass a system of study that uses the methods of epidemiology to understand the influence of genomic variation in both health and disease, thereby going beyond the influence of individual genes, which remained the primary focus of genetic epidemiology.

Categories of disease:

Rare and Mendelian disease:

Karangnesses that may have a genetic component and impact fewer than 2000 individuals in the United States In current combat practice genetic testing is confirmatory and takes place after anal syndrome has been identified rough discussion with the patient's parents in a typical case the suspected gene will be amplified and sequenced through Sanger The Online Mendelian Inheritance in Man (MIM database contains a complete rating of these genes and genetic disorders) (13).

Complex disease:

The vast majority of genetic diseases fall into this category. Some examples include Alzheimer's disease, scleroderma, asthma, Parkinson's disease, multiple sclerosis, osteoporosis, connective tissue diseases, kidney diseases, autoimmune diseases, and many more (14,15). NGS offers a comprehensive set of tools to study these complex diseases. Whole genome and exome Complex Disease sequencing can be combined with transcriptome sequencing (RNA-Seq) to assess expression levels and the expression of mutated transcripts and splice variants. Genome-wide association studies [GWAS]:

Disease or trait	% Variance explained by all GAWAS SNPs Combined
Type 1 diabetes	60 [includes per-GAWS loci with large effects
Type 2 diabetes	5-10
obesity [BMI]	1-2
Crohn's disease	10
Ulcerative colitis	5
Multiple sclerosis	10
Ankylosing Spondylitis	20
Schizophrenia	1
Bipolar disorder	2
Breast cancer	8
Von willebrand Factor	13
Height	10
Bone mineral density	5
QT interval	7
HDL cholesterol	10
Platelet count	5-10

Mitochondrial disease:

Mitochondrial diseases are caused by abnormal functioning of mitochondria. To date, more than 200 different molecular defects have been described in patients with mitochondrial diseases.(23) These abnormalities may be the result of spontaneous or inherited mutations in the mitochondrial genome (Medan) or in nuclear genes that code for mitochondrial components. The Medan encodes only 13 proteins of the respiratory chain, while most of the estimated 1,500 mitochondrial proteins are nuclear-encoded.

Histone Modifications:

The development of Chip-Seq with NGS enabled the first genome-wide mapping of histone modifications. This allowed the identification of activation marks such as mono- methylations of H3K27 H3K9, H4K20, H3K79, and H2BK." The epigenetic control of expression for both Poll and Polli has been mapped these are examples of the information that can be obtained using this approach DNA methylation

Undiagnosed genetic disease

It is estimated that up to half of the patients tested currently receive no molecular diagnosis, 33 The remarkable success of the National Institute of Health (NIH) Undiagnosed Diseases Program, which has led to the diagnosis of (13) rare diseases and the identification of two new diseases, has demonstrated the utility of whole-genome and whole-exome sequencing in the clinic.

Types of genetic disorders:

1. **Single gene inheritance:**

Single-gene inheritance is also called Mendelian or monogenetic inheritance. Changes or mutations that occur in the DNA sequence of a distinct gene affect this type of inheritance. There are thousands of known single-gene disorders. These disorders are known as monogenetic disorders (disorders of a single gene). Single-gene disorders have diverse patterns of genetic inheritance, including x autosomal dominant inheritance, in which only a single copy of a defective gene (from either parent) is crucial to basis the condition; x autosomal recessive inheritance, in which two copies of a defective gene (one from each parent) are necessary to effect the condition; and X-linked inheritance, in which the defective gene is present on the female, or X chromosome(9).

Multifactorial Genetic inheritance:

Multifactorial inheritance is also called intricate or polygenic inheritance. Multifactorial inheritance disorders are caused by a permutation of environmental factors and mutations in multiple genes. For example, unusual genes that control breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22. Multifactorial disorders also known as complex genetic disorders caused by genomic variations in one or more genes.

DNA and gene content of human chromosomes:

Chromosomes	Approximate length (bp)	Protein	Non-Protein	Pseudogenes
1	248956422	2047	1964	1233
2	242193529	1303	1605	1033
3	198295559	1075	1160	768
4	190214555	753	984	732
5	181538259	881	1200	710
6	170805979	1041	989	803
7	159345973	989	977	893
8	145138636	670	1041	629
9	138394717	778	786	678
10	133797422	728	880	568
11	135086622	1312	1053	815
12	133275309	1036	1197	627
13	114364328	321	586	378
14	107043718	820	857	519
15	101991189	613	986	513
16	90338345	867	1033	467
17	83257441	1185	1198	531
18	80373285	269	608	246
19	58617616	1474	895	514
20	64444167	543	594	250
21	46709983	231	403	183
22	50818468	492	513	332
X	156040895	843	604	872
Y	57227415	63	108	392
Mitochondrial	16569	13	24	

Although there could be several members of the family affected, the inheritance does not follow the Mendelian inheritance pattern. The disease may occur in one particular trait but it is not a sex-limited trait.

Mitochondrial Genetic inheritance:

This type of genetic disorder is caused by mutations in the non-nuclear DNA of mitochondria. Mitochondria are small round or rod-like organelles that are involved in cellular respiration and found in the cytoplasm of plant and animal cells. Each mitochondrion may contain 5 to 10 circular pieces of DNA. Since egg cells, but not sperm cells, keep their mitochondria during fertilization, mitochondrial DNA is always inherited from the female parent.

1. Single nucleotide variants:

The most frequent variants in our genome are substitutions that affect only one base pair (bp), referred to as single nucleotide variants (SNV) or as single nucleotide polymorphisms (SNP) depending upon the MAF. It has been estimated that there are at least 11 million SNPs in the human genome (averaging approximately 1 per 300 bp). It also seems likely that if we sequenced the genomes of everyone on the planet, for most positions in our genome we would discover at least one individual with an SNV, wherever such variation is compatible with life.

2. Structural variants:

Structural variants are defined as variants affecting segments of DNA greater than 1000 bp (1 kb)(22). They include translocations, inversions, large deletions, and copy number variants (CNV). CNVs are segments of our genome that range in size from 1000 to millions of bp, and which, in healthy individuals, may vary in copy number from zero to several copies

Repeat variations:

Human genomes contain large numbers of repetitive sequences. These include 'interspersed repeats' which constitute approximately 45% of our genome, and represent remnants of mobile DNA elements (transposons). There are also several classes of 'tandem repeats', in which the repeated units are side-by-side in a head-to-tail fashion forming arrays of repeats of the same (or very similar) sequence (13).

Manipulating other genomes:

A subset of somatic cells contains a unique addition to the nuclear genome, the T and B cells of the adaptive immune system, which generate new antigen receptor gene products after conception through somatic recombination. The immune receptor repertoire of a young adult contains, conservatively, on the order of 1011 unique antigenic receptors, generating almost six orders of magnitude more individual protein products than the nuclear genome (10–11), although repertoire diversity declines with age (8)

Diagnosis:

Single Gene Disorders

Worldwide frequencies of all monogenic disorders at birth are about 10/1000 (WHO, 2013). The "monogenic" diseases provide unique opportunities to dissect

components as they each have a single etiology and comparatively uniform treatments, and the role of the disease-causing gene is known to some extent (Antinatalism and Beckmann, 2006) Single gene disorders are passed on to successive generations in several ways. In autosomal dominant disorders, one copy of the mutated gene is involved.

Diagnosis and Prevention of Genetic Disorders Genetic:

For fetus or embryo information the use of all designed techniques during parental diagnosis. Before and after prenatal diagnosis some genetic counseling must be offered (Wrecker et al., 2010). Newborn screening identifies conditions that can affect a child's long-term health or survival. Early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential (CDCP, 2013).

Treatment:

Many genetic disorders result from gene changes that are present in essentially every cell in the body. As a result, these disorders often affect many body systems, and most cannot be cured(9). However, approaches may be available to treat or manage some of the associated signs and symptoms Gene therapy, along with many other treatment and management approaches for genetic conditions, are under study in clinical trials.

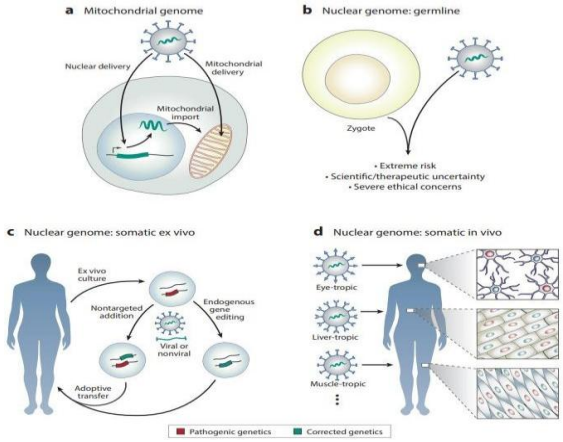

Figure no: 1 Gene therapies are based on nontargeted genetic addition or targeted gene editing.

(a) Direct delivery of genetic material to the mitochondrial genome poses a greater challenge. (b) Adding or editing genetic material in the nuclear genome of the human germline poses significant ethical concerns. (c) Nontargeted addition or targeted editing in somatic cells, such as cells cultured ex vivo(9) (e.g., hematopoietic stem cells and T cells). (d) Nontargeted addition or targeted editing in somatic cells in vivo, as in retinal cells, hepatocytes, or myocytes, critically depends on delivery platforms to carry DNA, RNA, and/or protein cargo to the cell type of interest.

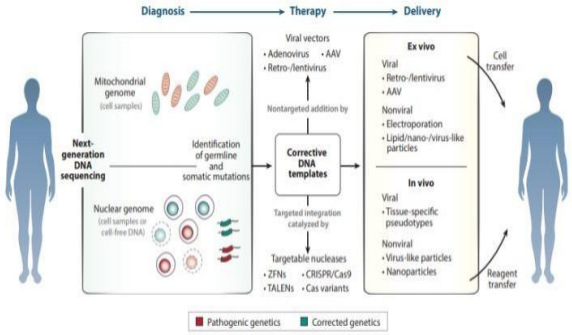

Figure number: 2

Conclusion

The size, complexity, diversity, and inheritance of the major human genetic compartments vary. Although the large expanse of the nuclear genome assures that the thousands of documented monogenic diseases occur in varied circumstances, developmental abnormalities are frequently caused by germline mutations in the mitochondrial and nuclear genomes (29). The availability of 16S and unbiased microbiological sequencing, clinical exome and whole-genome sequencing, and mitochondrial sequencing has increased due to advancements in next-generation DNA sequencing. These sequencing technologies have identified genetic abnormalities that gene treatments can fix.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Reference

1. Motulsky AG. History of human genetics. InVogel and Motulsky's Human Genetics 2010 (pp. 13-29). Berlin, Heidelberg: Springer Berlin Heidelberg.
2. Soler A, Morales C, Mademont-Soler I, Margarit E, Borrell A, Borobio V, Muñoz M, Sánchez A. Overview of chromosome abnormalities in first trimester miscarriages: a series of 1,011 consecutive chorionic villi sample karyotypes. Cytogenetic and genome research. 2017 Feb 1;152(2):81-9.
3. Baird PA, Anderson TW, Newcombe HB, Lowry R. Genetic disorders in children and young adults: a population study. American journal of human genetics. 1988 May;42(5):677.
4. Slack J, Evans KA. The increased risk of death from ischaemic heart disease in first degree relatives of 121 men and 96 women with ischaemic heart disease. Journal of medical genetics. 1966 Dec;3(4):239.
5. Ingram VM. A specific chemical difference between the globins of normal human and sickle-cell anaemia haemoglobin. Nature. 1956 Oct 13;178(4537):792-4.
6. Pauling L, Itano Ha, Et Al. Sickle Cell Anemia A

Molecular Disease. Science. 1949 Nov 25;110(2865):543-8. Doi: 10.1126/Science.110.2865.543. Pmid: 15395398.

7. LEJEUNE J, GAUTIER M, Turpin RA. Étude des Chromosomes Somatiques de Neuf Enfants Mongoliens (Study of the somatic chromosomes of nine mongoloid children). Landmarks in Medical Genetics: Classic Papers with Commentaries. 2004 Mar 11(51):73.
8. Vennela B, Shirisha V, Rao CB, Gullapalli V, Batsala M. Current and Future Strategies for Therapy of Pancreatic Cancer. International Journal of Research in Pharmacy and Medicine. 2012;2(3):728-40.
9. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, Chandu BR, Mitra A. Top-down and bottom-up approaches in 3D printing technologies for drug delivery challenges. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2015;32(1).
10. Jenkins MK, Chu HH, McLachlan JB, Moon JJ. On the composition of the preimmune repertoire of T cells specific for peptide–major histocompatibility complex ligands. Annual review of immunology. 2009 Apr 23;28:275-94.
11. Chowdary KP, Chandra DU, Mahesh N, Reddy TM, Gopaiah KV. Enhancement of dissolution rate and formulation development of pioglitazone-a BCS class II drug. J. Pharm. Res. 2011 Nov;4:3862-3.
12. Vennela M, Srinivas B, Reddy VR, Balram N. Studies on correlation and path coefficient analysis in hybrid rice (Oryza sativa L.) for yield and quality traits. International Journal of Bio-resource and Stress Management. 2021;12(5):496-505.
13. Gowri SP, Lakshmi HV, Bhanu VN, Brahmaiah B, Nama S, Rao CB. Proniosome: a novel approach to vesicular drug delivery system. The Pharma Innovation. 2013 May 1;2(3, Part A):166.
14. Qi Q, Liu Y, Cheng Y, Glanville J, Zhang D, Lee JY, Olshen RA, Weyand CM, Boyd SD, Goronzy JJ. Diversity and clonal selection in the human T-cell repertoire. Proceedings of the National Academy of Sciences. 2014 Sep 9;111(36):13139-44.
15. Walker LS, Abbas AK. The enemy within: keeping self-reactive T cells at bay in the periphery. Nature Reviews Immunology. 2002 Jan 1;2(1):11-9. https://www.nature.com/articles/nri701
16. Nemazee D. Mechanisms of central tolerance for B cells. Nature Reviews Immunology. 2017 May;17(5):281-94. https://www.nature.com/articles/nri.2017.19
17. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nature immunology. 2002 Nov 1;3(11):991-8.
18. Swart JF, Delemarre EM, van Wijk F, Boelens JJ, Kuball J, van Laar JM, Wulffraat NM. Haematopoietic stem cell transplantation for autoimmune diseases. Nat Rev Rheumatol. 2017 Apr;13(4):244-256. doi: 10.1038/nrrheum.2017.7. Epub 2017 Feb 23. PMID: 28228650. https://pubmed.ncbi.nlm.nih.gov/28228650/
19. Morgan RA, Dudley ME, Wunderlich JR, Hughes MS, Yang JC, Sherry RM, Royal RE, Topalian SL, Kammula US, Restifo NP, Zheng Z. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science. 2006 Oct6;314(5796):126-9. https://www.science.org/doi/abs/10.1126/science.1129003
20. June CH, Sadelain M. Chimeric antigen receptor therapy. New England Journal of Medicine.2018Jul5;379(1):64-73. https://www.nejm.org/doi/full/10.1056/NEJMra1706169
21. Friedmann T, Roblin R. Gene Therapy for Human Genetic Disease? Proposals for genetic manipulation in humans raise difficult scientific and ethical problems. Science.1972Mar3;175(4025):949-55. https://www.science.org/doi/abs/10.1126/science.175.4025.949
22. Merril CR, Geier MR, Petricciani JC. Bacterial virus gene expression in human cells. Nature. 1971 Oct 8;233(5319):398-400. https://www.nature.com/articles/233398a0
23. Rosenberg SA, Aebersold P, Cornetta K, Kasid A, Morgan RA, Moen R, Karson EM, Lotze MT, Yang JC, Topalian SL, Merino MJ. Gene transfer into humans—immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. New England journal of medicine. 1990 Aug 30;323(9):570-8.
24. Cline MJ, Stang H, Mercola K, Morse L, Ruprecht R, Browne J, Salser W. Gene transfer in intactanimals.Nature. 1980 Apr 3;284(5755):422-5. https://www.nature.com/articles/284422a0
25. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New England Journal of Medicine. 2017 Dec 28;377(26):2531-44.
26. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed M. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. New England Journal of Medicine. 2018 Feb 1;378(5):439-48.