

GENETIC DISEASES THEIR ORIGINS AND THERAPY

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Abstract: This article discusses chromosomal diseases in the field of genetics, including their pathogenesis, development, and origin. It analyzes the main types of chromosomal disorders, their genetic basis, effects on the body, and clinical manifestations. Additionally, the article provides detailed information on the mechanisms of development of these diseases and the factors that contribute to their occurrence. Furthermore, it examines methods for diagnosing chromosomal disorders and scientific approaches to their prevention.

Keywords: Genome, DNA, Gametes, Therapy, Mutation, Autosome, Disease Diagnose, Nuclear, Cells, System Gene,

INTRODUCTION

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). Diseases with their basis in mutations and alterations of the human genetic code represent a massive burden, and recognized genetic disorders affect more than 5% of live births and more than two-thirds of miscarriages (2, 3). Beyond highly penetrant monogenic disorders and large-scale chromosomal alterations, the heritability of many common diseases has long suggested a genetic basis for more prevalent disorders such as cardiovascular disease (4). The prospect of passing genetic afflictions on to the next generation adds to the fear of these disorders.

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. Prior to 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). Beginning in the 1960s, hereditary metabolic disorders such as phenylketonuria could be screened for biochemically without the need to know the causative gene's location or sequence (8). The advent of Sanger sequencing and recombinant molecular biology in the 1970s and 1980s made the determination of DNA sequences widely accessible for the first time. The following decades, prior to the completion of the Human Genome Project in 2003, saw gene mapping consortia undergo herculean efforts to discover the causative genes in some of the most debilitating diseases, including the first mapped human genetic disorder, Huntington's disease, in 1983 (9). With the diminishing costs of exome and whole-genome sequencing over the past 2 decades, genetic diagnosis has become



increasingly feasible, even for conditions that were not previously recognized as genetic diseases.

Human Genomic Compartments

The genetic material in an adult human can be divided into compartments that differ in size, heritability, and diversity. The mitochondrial genome, the smallest (only 16.5 kb) but by far the most abundant, is inherited maternally and varies little among the human population. The traditional human genome contained in the nucleus is significantly larger and harbors mutations that cause the majority of traditional genetic diseases. The nuclear and mitochondrial genomes are determined at conception, although somatic mutations can drive mosaic disorders, cancer, and even aging.

More broadly, the adaptive immune receptor repertoire, which is a distinctive subset of the nuclear genome, and the microbial metagenome are determined only after conception, and their genetic complexity, at least as measured by the diversity of unique protein coding sequences, dwarfs that of the rest of the nuclear genome. The T and B cells of the adaptive immune system undergo somatic recombination, generating orders of magnitude more unique protein products than are possessed by the other genes of the nuclear genome, and together constitute the adaptive immune receptor repertoire. Finally, the nonhuman cells of the microbiome make up potentially the most dynamic and diverse genomic compartment of all, with a litany of different species, predominantly bacterial and viral, occupying structured niches across human skin, sexual organs, and gastrointestinal and respiratory tracts. Both the adaptive immune receptor repertoire and the microbial metagenome vary significantly more among individuals, and increasing research aims to understand how genetic alterations in immune receptor repertoires and the microbiome contribute to disease pathology.

Modes of Genetic Therapy



Disruptions in any of these compartments, interacting in many cases with environmental factors, can contribute to different classes of genetic disease. The simplicity of the DNA code has enticed researchers and clinicians since the 1960s with the curative promise of correction of genetic alterations, or gene therapy ([10](#)). Since the first successful ectopic expression of a foreign gene in human cells in the early 1970s ([11](#)), successive generations of gene therapy technology have increased the efficiency, specificity, and safety of gene transfers. These advances led to the first human gene therapy trials at the National Cancer Institute, National Institutes of Health, in the late 1980s ([12](#)), following a handful of unregulated and ultimately unpublished gene therapy attempts earlier that decade ([13](#)).

The rapid proliferation of gene therapies in the 1990s, with more than 500 trials initiated, came to a halt in the early 2000s following patient deaths in clinical trials for severe combined immunodeficiency (SCID) and a metabolic liver disorder. Further improvements in the safety and efficacy of gene transfer in the 2000s and 2010s ultimately led to the resurgence of new generations of gene therapy approaches and approval by the US Food and Drug Administration (FDA) of the first ex vivo chimeric antigen receptor T cell (CAR T)–based gene therapies in B cell malignancies in 2017 ([14](#), [15](#)), as well as the first in vivo gene therapy for vision loss caused by Leber’s congenital amaurosis in 2017 ([16](#)).

In a broad context, genetic mutations can be altered in three general modes: bulk replacement or selection of the entire genomic compartment containing the mutation, nontargeted insertion into the genome of additional genetic material restoring enough functionality to compensate for the genetic defect (nontargeted addition), or specific correction of only the causative mutation or genetic alteration (gene editing). Bulk replacement represents the most basic form of gene therapy ([Figure 1](#)). Selective reproduction and, more recently, preimplantation diagnostics offer the chance to preemptively avoid germline mutations in the nuclear genome.



Mitochondrial replacement therapy followed by in vitro fertilization can effectively correct mitochondrial mutations by replacing a child's entire mitochondrial genome with a "third parent." Similarly, somatic mutations resulting in tumors can be removed in bulk from the body by surgery. Portions of the microbial metagenome are increasingly being therapeutically altered via fecal or microbial community transplants (17).

Gene therapies based on bulk replacement or selection of genetic compartments. (a) The mitochondrial genome of an affected mother's oocyte can be replaced through transfer of its nucleus into a donor mother's oocyte, which contains mitochondria unaffected by the mutation. (b) The nuclear genome can be selected through preimplantation diagnosis of in vitro-fertilized zygotes.

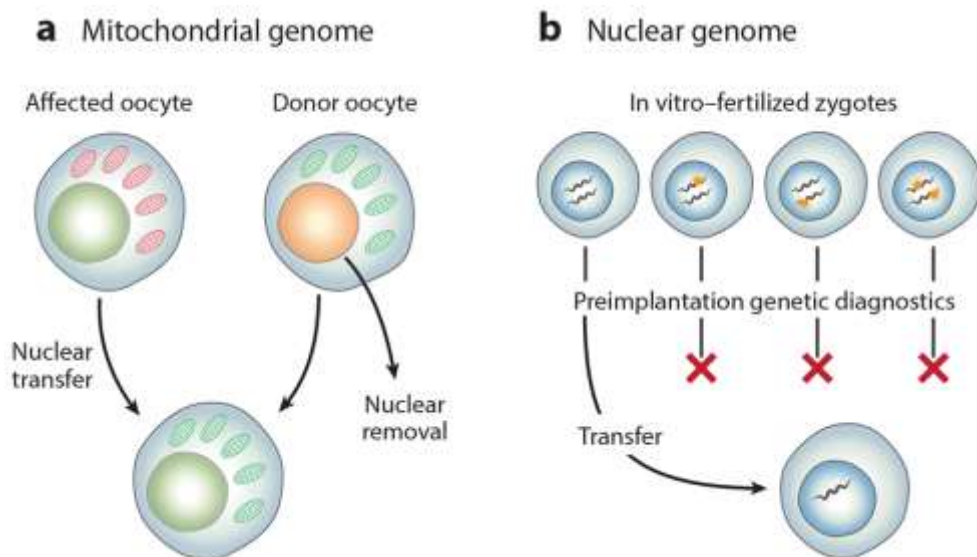


Figure 1

In many patients, however, a more practicable gene therapy is the nontargeted introduction of new genetic material to make up for the lost or deleterious function of mutated sequences (Figure 2). This nontargeted addition of genetic material is common in the germline transgenesis of model organisms, but important ethical concerns have, appropriately, prevented additive gene therapies in the human germline. In the more therapeutically relevant somatic cells, successive generations of viral vectors, ranging from SV40 to retroviruses, adenoviruses, and now,

prominently, adeno-associated virus (AAV) pseudotypes, have enabled ever greater control over the in vivo cell types receiving new, corrective genetic material, culminating in the recent FDA approval of an AAV2 vector specific for rod and cone photoreceptors ([16](#)). A separate line of technical development based on γ -retroviruses and lentiviruses has led to efficient ex vivo manipulation of the nuclear genome of hematopoietic stem cells (HSCs), as well as the adaptive repertoire of T cells, resulting in the similarly recently approved CAR T-based therapies ([14](#), [15](#)).

Gene therapies based on nontargeted genetic addition or targeted gene editing. (a) Mutated genes in the mitochondrial genome can be integrated into the nuclear genome, with their protein products targeted for import into the mitochondria. 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 (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 cargos to the cell type of interest.



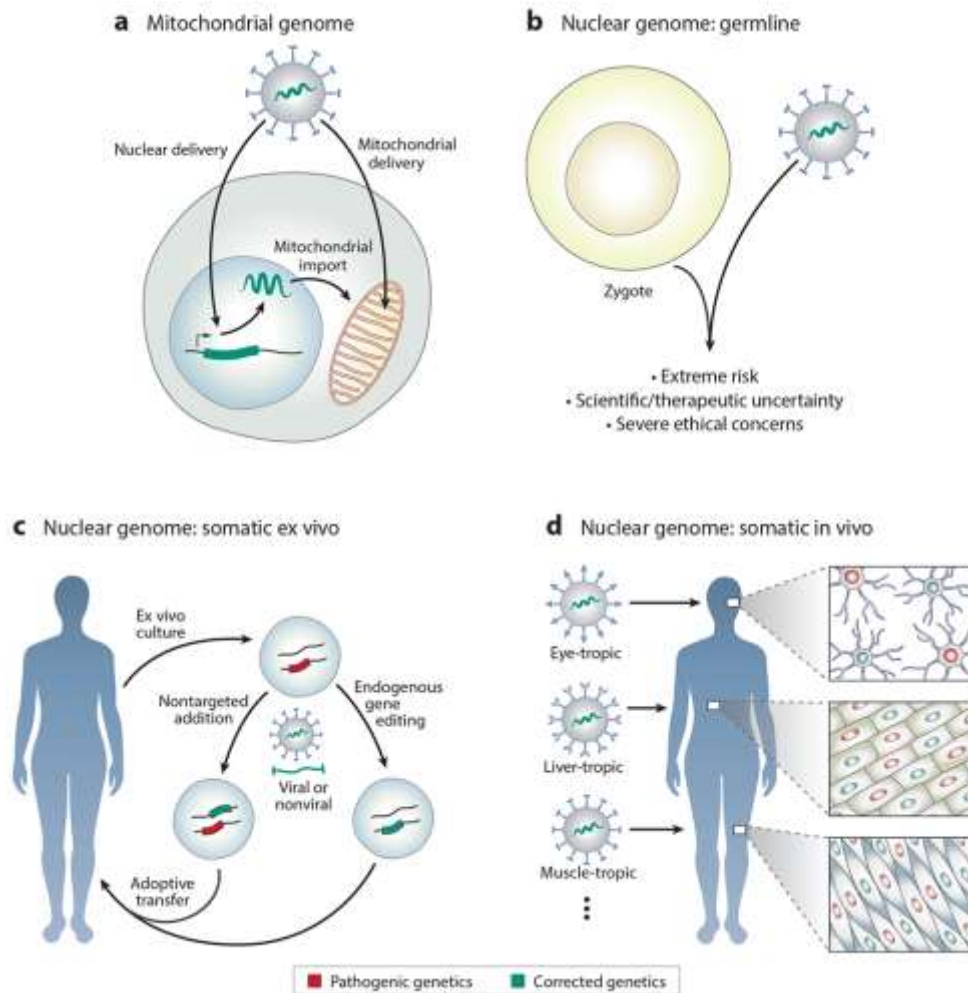


Figure 2

CONCLUSION

The major genetic compartments in humans differ in genomic size, complexity, heritability, and diversity. Germline mutations in the mitochondrial and nuclear genomes often cause developmental disorders, although the great size of the nuclear genome ensures that the thousands of identified monogenic diseases present in diverse contexts. Accumulation of somatic mutations in the nuclear genome underlies the development of cancer, and somatic mutations in mitochondria may contribute to aging. More broadly, the microbial metagenome develops largely after birth and is characterized by much greater diversity among humans and variation over the course of life. Advances in next-generation DNA

sequencing have made mitochondrial sequencing, clinical exome and whole-genome sequencing, and 16S and unbiased microbial sequencing widely available.

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