Gene Therapy Perspective of Autosomal Recessive & Dominant Disorders

(Dr. Archana Kumari Srivastava[1], Senior Executive; Mr. Vijayanand K[1], Deputy General Manager; Mr. Sudip Kumar Majumder[1], Vice President)

[1]Department of Biotechnology, Jodas Expoim Pvt. Ltd

Genetic disease in humans usually results from either chromosomal aberrations, or defects associated with single-gene Mendelian or single-gene non-Mendelian inheritance. Our body cell carries 22 pairs of chromosomes known as autosome and the genes located on these autosomes are inherited biologically in specific pattern. Disorders associated with single-gene Mendelian inheritance are categorized as autosomal recessive, autosomal dominant or sex-linked.

Autosomal dominant disorder inherits a single copy of the defective gene from any of the parents and is enough for the manifestation of the disorder. Some of the autosomal dominant cardiovascular disorders are familial hypercholesterolemia and Marfan's syndrome (Figure 1A). On the other hand, an autosomal recessive disorder needs two copies of the defective gene for its manifestation. A person who inherits only a single copy of the mutated gene is called as "carrier" of the trait or disease. Examples of autosomal recessive disorders include cystic fibrosis, sickle cell anemia (Figure 1B).

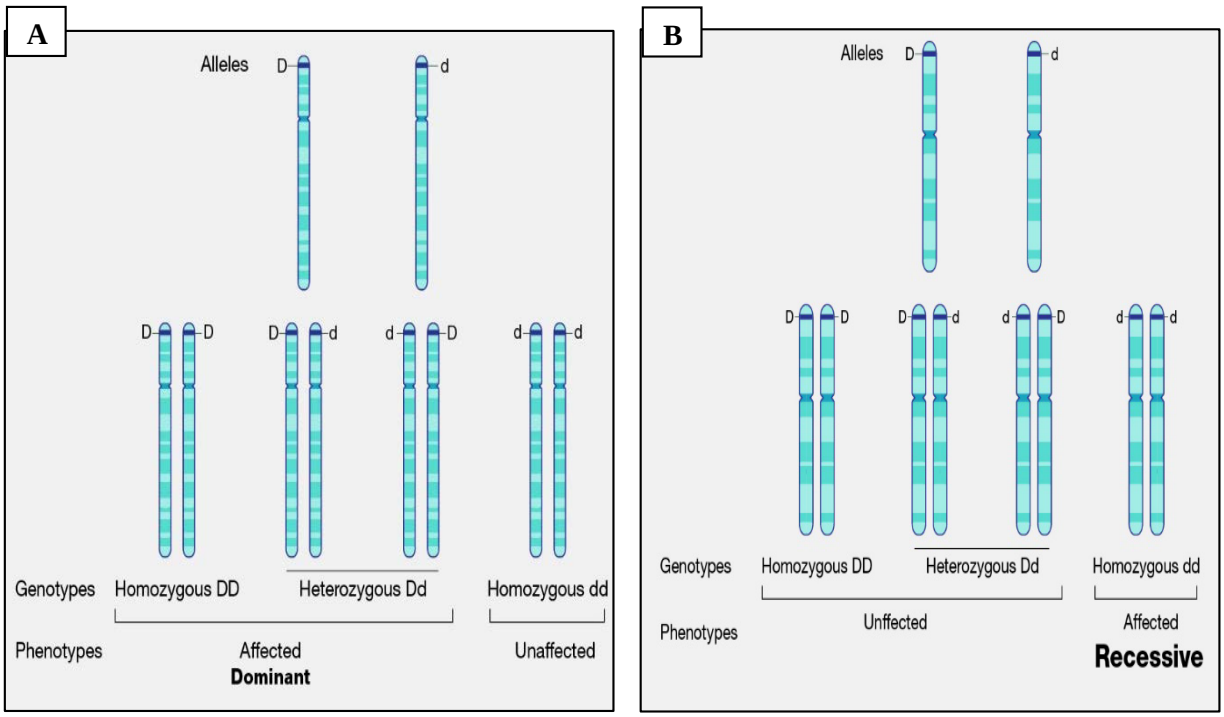

Figure 1: Autosomal Dominant Disorder Allele Inheritance pattern (A) and Autosomal Recessive Disorder Allele Inheritance pattern (B).

In this blog our focus would be on autosomal dominant disorders and autosomal recessive disorders that can be cured with gene therapy approach. Gene therapy has faced numerous obstacles and took extensive period of time for reaching up to the clinic from research lab. However, continuous and rapid advancement in the molecular biology and genomics field set the stage to develop gene therapies for a range of inherited disorders. Because of the certain limitation of the application of drug and surgical treatment, some of the cardiovascular disease also needed gene therapy approach. Though huge progress has been observed in the treatment of autosomal recessive disorders by delivering the normal exogenous genes that can restore the proper biological function of the affected or mutated gene. However, similar outcome cannot be expected in case of autosomal dominant disorder as precise differentiation is required between diseases/mutated allele from that of healthy/unaffected allele.

Novel technologies such as siRNA (small interfering ribonucleic acid), shRNAs (short hairpin RNAs), ASO (antisense oligonucleotide), TALENs (Transcription Activator-Like Effector Nucleases), ZFNs (Zinc Finger Nucleases) and CRISPR (Clustered Regulatory Interspaced Short Palindromic Repeats) based strategies have surfaced as solution to overcome the shortcomings of current therapies for autosomal dominant disorders.

Recently, CRISPR/Cas9 mediated gene-editing technology such as base and prime editors have emerged as potential therapeutic tool for the treatment of such diseases because of its efficiency, versatility and sustained effects.

Drug Products manufactured by Bio-pharmaceutical companies for Genetic Disorders

Depending on the demand of the situation, bio-pharmaceutical companies have also come forward and hugely contributed in the research and development of the personalized therapeutics as well as general RNA therapeutics. List of some of the approved therapies for autosomal genetic disorders including both recessive and dominant is provided Table 1.

Product Name	Generic Name	Disease	Type of Genetic Disorder	Innovator Company
Kynamro	Mipomersen sodium	Homozygous familial hypercholesterolemia	Form of Autosomal Dominant Disorder	Ionis Pharmaceuticals
Leqvio	Inclisiran	Heterozygous familial hypercholesterolemia	Autosomal Dominant Disorder	Alnylam

Waylivra	Volanesorsen	Familial hyperchylomicronemia syndrome	Autosomal Recessive Disorder	Ionis Pharmaceuticals
Zynteglo	Betibeglogene autotemcel	Transfusion-dependent beta thalassemia	Autosomal Recessive Disorder	Bluebird Bio
Glybera	Alipogene tiparvovec	Lipoprotein Lipase Deficiency (LPLD)	Autosomal Recessive Disorder	Amsterdam Molecular Therapeutics (AMT)
Spinraza	Nusinersen	Spinal Muscular Atrophy	Autosomal Recessive Disorder	Ionis Pharmaceuticals
Onpattro	Patisiran	Amyloidosis, transthyretin-related hereditary	Autosomal Dominant Disorder	Alnylam

Further, gene therapies for certain autosomal recessive disorders like sickle cell anemia, cystic fibrosis along with some autosomal dominant disorders are presently in the pipeline. As per "Gene Therapy Market (2nd Edition), 2018-2030" published by Root Analysis, approximately 300 products are under different stages of development such as preclinical or clinical trial and with constant effort of commercializing the gene therapies in a profitable way, global market for gene therapy has been expanded paving the way for future research and development for treating formerly untreatable genetic disorders by understanding the molecular mechanism involved in such diseases.

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