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Genetic Variations: Heroes or Villains

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Abstract

Gene pool of every organism has shown a wide occurrence of genetic variations. Variations have not only been associated with diseases like cancer, turner syndrome, sickle cell anaemia, cystic fibrosis etc., but some of them have even been proved to be beneficial in certain cases like for increasing bone density, lowering down cholesterol level, and for developing malaria resistance. Genetic variations or switches have also been explored for their significant role in evolution of human species. Monogenic diseases are the inherited disorders caused by the mutations in a single gene. Single Nucleotide Polymorphism, structural variants and genomic rearrangements are considered as some of the forms of genetic mutations. Genetic mutations are the fundamental cause of some monogenic disorders such as Schizophrenia, Alzheimer's disease, Hutchinson-Gilford Progeria syndrome (HGPS), Proteus syndrome and Congenital generalized hypertrichosis (CGH). However, some variants have even offered protection against a disease like blocking of HIV infection due to mutations in co-receptors needed for entry of infection into the cells. This review aims to provide insights into the role of variants present in the genes associated with the monogenic disorders in order to determine the underlying mechanism of the disease, which might further pave a way for the scientists to discover the therapeutic approaches for dealing with the same.

Keywords: Genetic variations; Schizophrenia; Alzheimer's disease; Hutchinson-gilford progeria syndrome (HGPS); Proteus syndrome; Congenital generalized hypertrichosis (CGH); HIV resistant

Introduction

Human genetics is one of the most fascinating studies that provide the better understanding towards human beings. The study of human genetics unveils the factors responsible for human diseases. In recent times, scientists have overcome the complexity of some rare genetic disorders. Several genes seem to be involved in genetic diseases. In order to correlate genotype with phenotype of genetic disorders, studies were carried out to determine nucleotide diversity among individuals [1]. Variation in the DNA sequence of a gene is one of the several factors held responsible for rare diseases and they arise due to the mutations. While mutation is defined by alteration in DNA sequence that changes the function of the gene, single nucleotide polymorphism (SNP) is the most common form of genetic variation that occurs 1 in 1000 base pairs in which nucleotide differs only at one position of the DNA sequence [2]. Till now, approx. 11 million SNPs have been reported in the human genome [3]. Out of these, around 60,000 are found to be present in coding and regulatory regions [4]. They may alter the structure or function of DNA by influencing the promoter activity or conformation of pre-mRNA. SNPs might play a direct or indirect role in genetic disorder. Another important class of genetic variation is structural variants that include insertion-deletion of the bases, block substitution, DNA sequence inversion and copy number variants. It is reported that approx. 20% of all genetic variants are accounting for structural variations in humans [1] and there are evidences of approx. 2.8 million insertions and deletions [3]. Changes that occur genetically can be described either as hereditary or somatic. Some cases involve variation in an egg or sperm cell but not in other cells, while some cases displayed the variation in the fertilized egg after the egg and sperm cells combine which results into growing of an embryo with mutation. Mutation in a single cell of an embryo which is under development results into a condition known as mosaicism (somatic mutation).

Genetic variants can be either polygenic or monogenic depending on the number of genes involved. Monogenic mutations include single gene causing diseases which are considered as rare and severe diseases. These kinds of diseases run in families and are not adversely affected by environmental factors. Till now, there are 85000 diseases such as Cystic fibrosis, Sickle-cell anaemia, Huntington's disease, Neurofibromatosis etc. that arise due to single-gene mutation [5]. But there are a few rare diseases caused by single-gene mutations having comparatively rare treatments. Furthermore, cost of these treatments seems to be immensely high which directly affects the patients and their families. A patient may suffer from a rare disease through different pathways such as autosomal recessive, imprinting disorders, X-linked recessive and autosomal dominant [6]. Some of these abnormalities are represented in Figure 1.

Historically, people suffering from rare diseases were treated as monsters or freaks but today, they are treated with all the respect and care. In this article, we are going to explore the genes responsible for few rare diseases such as Schizophrenia, Alzheimer's disease (AD), Hutchinson-Gilford Progeria syndrome (HGPS), Proteus syndrome; Congenital generalized hypertrichosis (CGH) which are considered weird and severe. Some genetic mutations are also responsible for preventing diseases such as HIV infection. Thus, it becomes very crucial to understand genetic variations in detail in order to determine the underlying disease mechanisms and potential therapeutic

strategies. The treatment of Mendelian disorders is considered difficult, as it focuses on the symptoms rather than the cure. It becomes very troublesome to restore protein activity due to genetic variation, as it results in the complete loss of gene function [7].

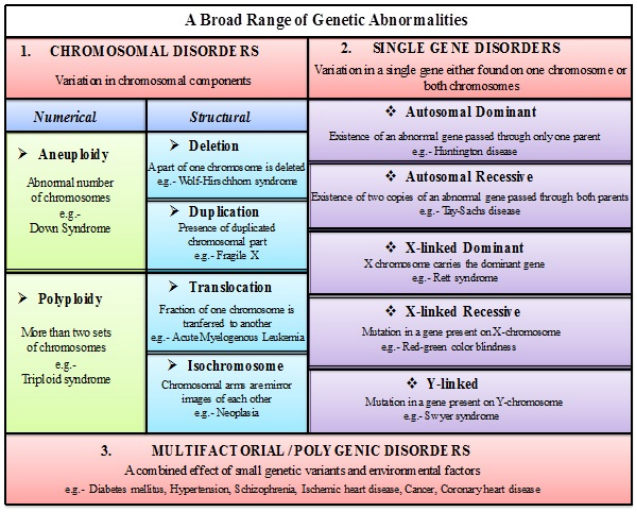

Figure 1: A broad range of rare diseases.

Genomic mutations can be of varied types such as point mutation which is described by a change in single base pair or mutation caused by deletion of a few base pairs which usually affects only one gene [8]. Point mutation can be further including subdivided missense mutation which substitute one amino acid for another in the protein, nonsense mutation which involves signalling of the cell by the altered DNA to stop constructing a protein. Another type of variations involves insertion or deletion of DNA bases resulting into altered gene function as in Figure 2.

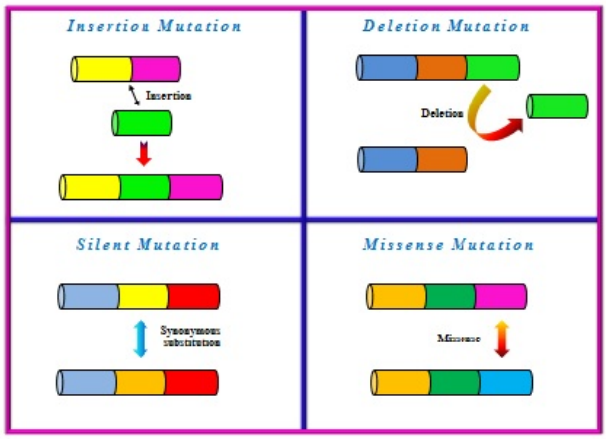

Figure 2: Examples of different types of mutations.

Several genes having different kinds of mutations along with their associated diseases have been summarized in Table 1. This review has an aim to discuss the contradictory aspects of various genetic variations, in which they may offer both constructive as well as destructive role in various biological processes.

S. No.	Gene	Associated Diseases	Ref.
Missense-SNP resulting in a codon that codes for different amino acid			
1	SLC12A3 (179C>T)	Gitelman's Syndrome	56
2	DUOX2 (1060C>T, 3616 G>A)	Congenital Hypothyroidism and goiter	57
Silent - Codes for similar amino acid (Synonymous substitution)			
3	mabA (609 G>A)	Isoniazid resistance on Mycobacterium tuberculosis, gonadal dysgenesis	58
4	MAP3K1 (1284G>A)	Gonadal dysgenesis	59
Nonsense - Premature Stop codon			
5	CFTR	Cystic-fibrosis	60
6	LGR4 (376C>T)	Electrolyte imbalance, late onset of menarche and reduced testosterone levels, increased risk of squamous cell carcinoma of the skin and biliary tract cancer.	61
Insertion - Addition of one or more base pairs in to DNA sequence			
7	NOD2	Crohn's disease	62, 63
8	SHANK3	Impaired synaptic transmission	64
9	APOA-I	high-density lipoprotein (HDL) deficiency	65
Deletion - Deletion of one or more base pairs from a DNA sequence			
10	pre-S2 region of hepatitis B virus (HBV)	hepatocellular carcinoma	66

11	TMEM38B	Osteogenesis imperfecta	67
Gene amplification - Duplication of a region of DNA sequence			
12	KRAS	Colorectal cancer	68
13	HER2	Gastric cancer	69
14	EGFR, MCL1	Breast cancer	70, 71
Loss of heterozygosity - Loss of one allele either by a deletion or a genetic recombination			
15		Lung cancer	72
16	Cohesin Rad21	Transcriptional Dysregulation in Gastrointestinal Tumors	73
Frameshift - Insertion or deletion of number of nucleotides in a DNA sequence which is not divisible by 3			
17	CALR (exon 9)	Thrombocytosis	74
18	CUBN (exon 53)	Imerslund-grasbeck syndrome	75
19	PHOX2B	Congenital central hypoventilation syndrome	76

Table 1: Summary of various genes having different mutations and their associated diseases.

Destructive genetic variations

Schizophrenia, Alzheimer's disease, Progeria syndrome, Proteus syndrome, all belong to the category of diseases caused by single nucleotide polymorphism (SNPs), whereas Hypertrichosis involves an interchromosomal insertion. Schizophrenia has been characterized by hallucinations, delusions, and abnormal behaviour. It is caused by mutation found in the promoter region of GRIN1 gene located on chromosome 9. It has been reported that when G1001C mutation occurs, then binding site for transcription factor NF-κB gets altered resulting in reduced gene expression that leads to schizophrenia [9]. On the other hand, Apolipoprotein E (APOE) gene located on chromosome 19 has a strong connection with Alzheimer's disease. There are three different isoforms (ε2, ε3 and ε4) of APOE gene which are studied well and evidences support that ε4 allele increase the risk of developing late-onset Alzheimer's disease, whereas ε3 is the most common among the general population. On the other hand, ε2 allele has been associated with a decreased risk [10]. ε4 allele differs from ε3 allele by a SNP at position +2985 (T/C). These changes alter the structure and function of APOE gene and regulate its ability to bind lipids, receptors and amyloid-β, whose instability in the brain causes neurodegeneration and dementia [11].

Aging in humans is the result of deterioration of cells, molecules or tissues leading to the process of becoming old. It occurs over a life span of nearly 60 years of age. It is one of the largest risk factors for most diseases. But if it occurs prematurely, then it becomes an important factor for scientists. There are diseases like Cockayne syndrome, Bloom syndrome, Werner syndrome, Hutchinson-Gilford Progeria syndrome (HGPS) associated with premature ageing. Progeroid syndromes are monogenic disorders in which multiple tissues and organs are affected and they show conditions associated with ageing [12,13]. In this article, the genetic changes that occur in HGPS syndrome have also been discussed. It was first reported by Hutchinson and Gilford in 1886 and 1897 respectively. HGPS is a rare genetic disorder marked by rapid ageing that begins in childhood [14]. Children that are affected by this disease look normal at birth but while in their infancy, they show signs of retarded growth, weight loss and change in skin colour when compared to normal children. Characteristic features such as protruding eyes, a thin nose with a beaked tip, thin lips, and slender limbs with prominent joints, baldness, and small jaw are developed in affected children. HGPS patients also have aged-looking skin, abnormality in their joints, nail dystrophy, and loss of subcutaneous fat. HGPS markedly increases the risk of heart attack at a young age which could be life-threatening, if condition worsens and it also decreases the life-span of children to an average of 13 years [15]. HGPS is caused by mutations in the LMNA gene encoding lamin A present at position 22 on the long arm (q) of chromosome 1. Laminopathies is a class of diseases that are caused by mutations in nuclear lamins, whereas progerin is a particular splicing form of lamin A that leads to the HGPS laminopathy [16]. C-terminal of prelamin A (precursor of lamin A) which contains CaaX motif experiences multistep posttranslational modifications as a result, Cysteine residue undergoes farnesylation leading to the cleavage of remaining 3 amino acids, i.e., aaX group [13]. Then methyl esterification of Cysteine residue takes place by isoprenylcysteine carboxyl methyltransferase (ICMT) after which this carboxymethylated precursor enters into the inner nuclear membrane, where the metalloproteinase, ZMPSTE24 cleaves additional 15 amino acids from the prelamin A to develop mature lamin A. But when a single base at position 1824 changes from C to T (C1824T) in the LMNA gene, an activation of enigmatic splice site within exon 11 takes place, which generates progerin, a protein lacking 50 amino acids. This protein doesn't comprise those 15 amino acids essential for second cleavage. The farnesylated progerin is considered as toxic to the cells [14].

Another rare genetic disorder is Proteus syndrome which was distinguished by the disproportion of the bones, skin, and other tissues. Patchy or asymmetric overgrowth of the affected tissues and organs, along with the liability to the development of tumors are characteristics of this disease [17]. It was originally outlined by Cohen and Hayden in 1979 [18]. People having Proteus syndrome may also have neurological disorders, such as intellectual defect, seizures and vision impairment. Long face, wide nostrils, open-mouth expression are distinctive features of affected people with neurological disability [19]. Happle proposed in 1987 that it is a genetic disorder resulted

from somatic mosaicism. Based on further reports, the hypothesis was confirmed that it is caused by a post zygotic mutation and does not recur in the family of the affected people but has been reported in discordant monozygotic twins [18]. This syndrome occurs due to mutation in the AKT1 gene encoding protein AKT1 kinase, present on chromosome 14 at position q32.32. This protein is found throughout the body, where it helps in managing signalling pathways, regulating cell growth and division and cell death. In order to carry out normal development and function of the nervous system, AKT1 kinase protein appears to be crucial. A nucleotide change at position 49 from G to A (Glu17Lys at amino acid level) in the AKT1 gene leads to mutated AKT1 gene [20]. As the cells continue to divide, the number of cells with mutated AKT1 gene and the number of unchanged AKT1 gene increases, this result in abnormal growth and division of cells. The developed baby is inherited with both types of cells and the parts of his body containing altered gene, experience overgrowth than other part which is a characteristic of Proteus syndrome.

Apart from diseases caused by single nucleotide change, there are some rare of the rarest genetic diseases that have been diagnosed lately. One of such disease is hypertrichosis which was distinguished by excessive and abnormal hair growth in any area of the body irrespective of sex, age or race and it also doesn't depend on androgens. There are several types of hypertrichosis based on different aspects such as generalized or localized depending on the distribution of the body hair. It is also categorized as congenital or acquired based on the age of the onset [21]. One such type is Congenital generalized hypertrichosis (CGH) described by Flores et al in 1984 which is also termed as 'werewolf syndrome' sometimes. It was thought to be the missing link between human and ape and describes a group of phenotypically and genetically heterogeneous rare conditions. The first location for hypertrichosis was mapped to chromosome Xq24-q27.1 by Figuera et al. and thus by analyzing a large Mexican family with X-linked CGH. Activity of genes might be disrupted by the complete loss or gain of gene sensitivity due to different genomic rearrangements [22]. For instance, microdeletions and micro duplications of a genomic region are commonly related to genomic disorders [23]. But interchromosomal insertion is another type of genomic rearrangement which occurs very rarely. In interchromosomal insertion, part of one chromosome intercalates into another chromosome and also termed as interchromosomal insertional translocation [24]. Recently, one Chinese and one Mexican family with history of CGH were investigated. It was found out that the Chinese family members suffering from CGH had an interchromosomal insertion of 125, 577 bp intragenic section of COL23A1 on chromosome 5 into region q27.1 of an X chromosome. That means 125, 577 bp of COL23A1 on chromosome 5 had broken off from its position and during DNA repair mechanism, it got inserted into chromosome X instead of getting attached to its usual position on chromosome 5, whereas in Mexican family, an interchromosomal insertion of 300, 036 bp genomic fragment on chromosome 4 into the same Xq27.1 site enclosing PRMT10 and TMEM184C. Remarkably, both of these insertions occurred within the short palindromic sequence and considered to be present near the SOX3 gene, which is a member of a gene family involved in hair growth. As a whole, palindromic sequence at the end of chromosome X was disrupted due to these unique insertions which increase the activity of SOX3 gene resulting into the disease [25].

Constructive genetic variations

Few of the genetic variation turn out to be a boon for individuals. This kind of genetic variation allows positive and advantageous environmental changes. Mutations in the CCR5 gene appeared to be the most recent example that contributes towards HIV resistance. Human Immunodeficiency Virus (HIV) is the most deadly infection that causes AIDS due to which around 25 million have died so far. 85% of all HIV infections are due to heterosexual transmission which is considered the supreme mode of transmission [26]. C-C chemokine receptor type 5 (CCR5) is a type of chemokines defined as small proteins having diverse functions that includes immune surveillance and immune cell recruitment. It was discovered in 1996 that CCR5 behaves as a co-receptor for entry of HIV into cells [27]. HIV targets only those cells which have receptors known as CD4 lying on the outside of cells. CD4 receptors are predominant part of body's immune system. Along with CD4, chemokine co-receptors, CCR5 and CXCR4 are also required for entry of HIV into the cell. During initial infection, the virus uses CCR5, whereas CXCR4 is employed during the progression of an infected individual towards AIDS [27,28]. CCR5 protein is encoded by the CCR5 gene in humans which is present at position 21 on the short arm of chromosome 3. Certain individuals are inherited with mutations in the CCR5 gene known as CCR5-Δ32, which might result into altered protein function or expression, which in turn, changes the chemokine binding or signalling site for HIV strain [29-31].

Deletion of 32 base pairs in the CCR5 gene is termed as CCR5-Δ32, allele of CCR5 that creates an untimely stop codon into the receptor locus which results into non-functional receptor [32]. Functional CCR5 receptors are not expressed on the cell surfaces in homozygous individuals having CCR5-Δ32 variant due to incomplete protein providing high level protection against HIV infection [33]. Studies revealed that heterozygous individuals carrying CCR5-Δ32 allele are infectable by HIV, but disease progression rate is slower in these people [34]. About 1% of Caucasian people are inherited with two copies of CCR5- Δ32 genes leading to virtual immunity to HIV infection. On the other hand, 20% of Caucasians carry only one copy of CCR5-Δ32 allele which gives some protection against infection, thus making the disease less severe on the occurrence of infection [35]. Other examples of constructive genetic variations include mutation in zinc transporter 8, due to which, it loses its function that protect obese patients from diabetes. Variations in PCSK9 protect individuals from heart disease and high lipid levels. Recently, a mutation in Jagged1 gene was found to prevent Duchenne muscular dystrophy in dogs, suggesting that the genetic variations may also behave as therapeutic targets for various diseases [7].

Role of penetrance in genetic variations

A specific genetic variant or genotype is expressed with different extents in each individual. People carrying a particular variant do not always experience the expression of that variant in the same way. It is just not true to say that a mutation present in all persons carrying it always leads to its regulation. A percentage of different people carrying a distinct mutation are defined as penetrance. A person developing clinical symptoms of the disease caused by a genetic variant leads to complete penetrance. On the other hand, when the symptoms have not been detected at the time of clinical examination or incomplete clinical detection, then it is known as pseudo-incomplete penetrance [36]. Severity of disease may vary among individuals carrying even a similar variant. Genetic variations, neurofibromatosis and holoprosencephaly

are few of the examples of disorders that exhibit phenotype diversity. It has already been reported that about 80 genes of a healthy person may extensively damage or become inactivated in its life time, but it does not always lead to a disease by damaging gene or protein or even one's health [37]. Onset of disease also varies with the genetic variation. For example, Familial Alzheimer's disease (FAD) develops at different stages of life depending upon the gene at which mutation is taking place. Alzheimer's disease type 1 which accounts for 10-15% FAD is caused by mutation of exon 16 and 17 of Amyloid Precursor Protein (APP) gene [38]. These mutations mostly belong to the category of missense or nonsense type. Alzheimer's disease type 1 generally develops between 40 or 50 of age. APOE ε4 allele might be associated with younger age of onset. Alzheimer's disease type 3 is caused by mutation of Presenilin1 (PSEN1) gene [39]. A deletion of 4555 base pairs of exon 9 was found to takes place in Finnish population that accounts for 30-70% of FAD. This type of mutation is rarely found in other populations. On the other hand, Alzheimer's disease type 4 is found to be caused by missense mutation of Presenilin2 (PSEN2) gene which accounts for less than 5% of FAD and onset range of disease lies between 40 and 75 of age [40,41].

Schizophrenia generally develops at the age of early adulthood or adolescence. Evidences show that a child of schizophrenic parent has about 10 times the risk of developing disease over a general population. Other studies report that males are more susceptible to the schizophrenia disorder than females. Migrants are at higher risk of developing disease than native born individuals. Similarly, people living in urban areas are more likely to get affected as compared to rural areas [42]. A copy number variant such as microdeletion at 22q11.2 was the first ever genetic variation described in schizophrenia which accounts for nearly 1-2% of the cases. It was found that this mutation involves the disruption of DGCR2 gene which may increase the risk of schizophrenia. Genes including Neurexin1 and ERBB4 disrupt due to duplications and deletions found in schizophrenia that was observed in 15% of sporadic cases, 5% of controls and 20% of cases of early-onsets [43]. Likewise, progeria syndrome can be divided into two categories- typical early onset progeria syndrome and atypical late onset progeria syndrome. As it's already discussed that early onset progeria is caused by mutation C1824T at exon 11 of the LMNA gene but the development of late onset progeria syndrome was found to be caused by mutation A899G in LMNA gene modulating the highly conserved residue found in the lamin family of proteins that includes cutaneous and cardiovascular disorders. The processing of lamin A does not get affected due to this variation [44]. Few of the patients suffering from Proteus Syndrome are also found to contain germ line PTEN variations. Nonsense variants such as C211X and R335X resulting into truncated protein which do not possess functionally vital C-terminal domain are found in proteus-like syndromes. Other variations observed at residues 35 and 111 belong to the missense type of variation [45]. Hypertrichosis can be classified into congenital or acquired, depending upon age of onset. Congenital hypertrichosis is very rare as compared to acquired hypertrichosis. Congenital hypertrichosis lanuginosa is caused by inverse mutation on the 8q chromosome, while autosomal dominant mutation in Xq24-q27.1 leads to Congenital Hypertrichosis Universalis [46].

Classification of genetic variation on the basis of pathogenicity

Pathogenesis of a particular disease is simply the biological mechanism involved in the progress of the disease. The bacterial pathogenesis generally follows invasiveness and toxigenesis mechanism [47]. Oxidative stress, fitful protein metabolism as well as fibrillar deposits by phosphorylated tau are the key factors for the Alzheimer's disease pathogenesis [48,49]. Various neurological disorders associated with C9orf72 mutations and their pathogenesis is very well reviewed by Chi and their coworkers [50]. Various studies have shown that serum miRNAs and blood serum of Alzheimer's disease patients can be used as biomarkers in diagnosis of AD [51,52]. It is also reported that the decline in the catalytic properties of γ-secretase might be able to facilitate the pathogenesis in sporadic and Familial AD [53].

Various reports suggest that one genetic variation can be related to different diseases. Concept of diseaseome describes a network showing connection between distinct genes and pathways with several diseases. Disorders such as multiple sclerosis, rheumatoid arthritis, and Crohn's disease are associated with different interleukin receptor genes and are believed to follow a common etiology. A common SNP present on chromosome 9p21 was found to associate with three vascular phenotypes. Pathogenicity is a common thread which needs a better understanding in order to gather information about interconnectivity of fundamental basis of several diseases [1]. Genetic variants are classified as pathogenic, probably pathogenic, variant of unknown significance, probably non-pathogenic and benign. In case of Lynch syndrome, pathogenic variants are identified by describing family histories of breast or ovarian cancer while benign variants are independent of family history [54]. Several genetic databases are available online that proved to be helpful in determining the type of genetic variant [55]. Classification on the basis of pathogenicity of genetic variants is still being explored quite extensively by using lot of computational and biological studies.

Future perspective

Since long, there was a perception related to genetic mutations that they are always associated with the development of certain disease, but with recent advances in the fields of genetics and molecular biology, this scenario has certainly changed. A variety of genetic mutations have now been explored for their association or the positive role in preventing an organism from certain diseases in specific circumstances. Scientists, clinicians, and geneticists are more interested in the recognition of genes involved in complex and rare disorders. Our understanding of genetic mutations causing various diseases like cancer, sickle cell anaemia, cystic fibrosis, color blindness etc. is quite significant for winning our battle against the same. With a substantial increase in the bioinformatics databases and computational approaches, mining of the genetic mutations throughout various genomes have certainly become faster. Knowledge for building up of relationships between the causes, roles and curative measures for altering genetic as well as somatic mutations is really essential for the formulation of any pharmaceutical drug for its treatment.

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