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Genetic Mutations and Major Human Disorders: A Review

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Abstract

Mutations are genetic sequence changes, and they are the principal cause of organism diversity. These changes occur at many different levels and can have far-reaching different consequences. These alterations occur due to genetic or epigenetic factors. These changes possibly cause phenotypic change in human which develop a disorder or evolution. Notably, our genetics can repair undesirable mutations during replication in most of the time. The types of mutations will be reviewed and discussed in this report.

Keywords: Human genome, DNA mutations, diseases.

1. Introduction

A mutation is a change in the nucleotide sequence of a short region of a genome [1] (**Figure 1**). Mutation, (a term coined by Hugo de Yeries in 1900, a rediscover of Mendels principles) is both the process by which a gene or chromosome changes, structurally and the end result of that process [2].

Although most mutations are harmful, significant numbers are thought to be "silent" and do not appear to affect the individual. A mutation may even be beneficial on rare occasions, and may tend to spread rapidly through a population; deleterious changes tend to die along with the organism that harbors them [3].

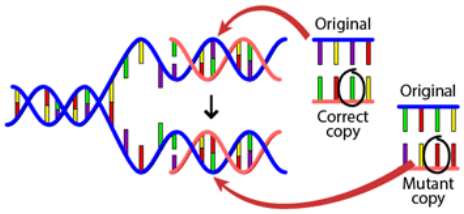

Figure 1: mutation [4]

Mutations are usually notable in multicellular organisms only when they occur in the cells of the germline (**Figure 2**), so that the change is passed on to all the cells of the offspring of the organism. Damage to the DNA of a somatic cell, on the other hand, seldom affects the cell, unless the mutation leads to a malignant transformation [5].

However, if the mutation occurs in a gene, it can alter the product of the gene and cause an observable change in the organism (phenotype shift). An organism that displays the usual phenotype for that species is called "a wild-type" and "a mutant" is called an organism whose phenotype has been altered by mutation [6, 7]. The natural rate at which a gene changes is usually very small but can be increased by environmental factors (mutagens), including ionizing radiation and mutagenic radiation [8].

In general, rates of spontaneous mutation vary between one in 10^4 and one in 10^8 gene per generation. Humans inherit 3 x 10^9 base pairs of DNA from each parent, in humans and other mammals, mutations occur at the rate of about 1 in every 50 million (5 x 10^7) nucleotides added to the chain. The males contribute more mutations than females, and that children of older fathers experience more genetic defects than those of young fathers, but aneuploidy is more likely to occur in eggs than in sperms [9, 10]

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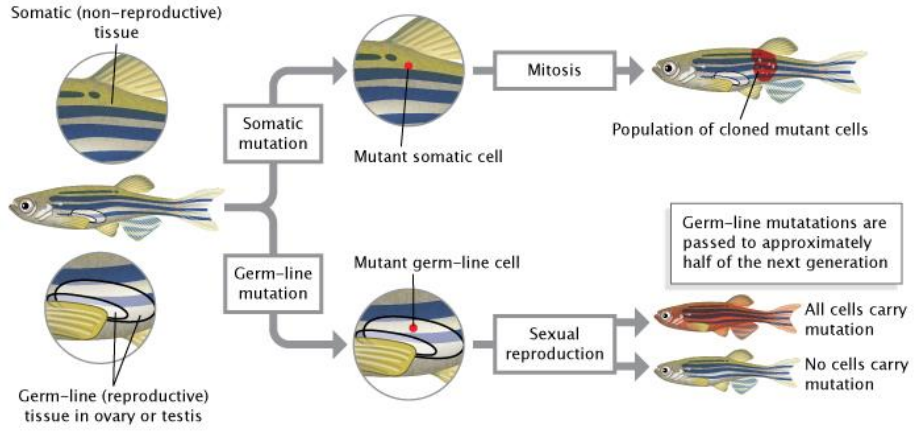

Figure 2: Mutations can occur in germ-line cells or somatic cells.

- Germ-line mutations occur in reproductive cells (sperm or eggs) and are passed to an organism's offspring during sexual reproduction.
- Somatic mutations occur in non-reproductive cells; they are passed to daughter cells during mitosis but not to offspring during sexual reproduction.

2. Types of Mutations

Changes in the DNA sequence can also occur at the chromosome level, in which large chromosome segments are changed. In this case, chromosome fragments can be deleted, duplicated, inverted, translocated to various chromosomes, or otherwise rearranged, resulting in changes such as modification of the gene dosage, the complete absence of genes, or gene sequence alterations. The type of variation that occurs when whole areas of chromosomes are duplicated or lost, called copy number variation (CNV), has particularly significant implications for human disease and evolution. Table 1 lists mutation types and provides examples of the various diseases associated with each.

Table 1: Types of DNA Mutations and Their Impact

Class of Mutation	Type of Mutation	Description	Human Disease(s) Linked to This Mutation
Point mutation (Figure 3)	Substitution	One base is incorrectly added during replication and replaces the pair in the corresponding position on the complementary strand	Sickle-cell anemia
	Insertion	One or more extra nucleotides are inserted into replicating DNA, often resulting in a frameshift	One form of beta-thalassemia
	Deletion	One or more nucleotides is "skipped" during replication or otherwise excised, often resulting in a frameshift	Cystic fibrosis
Chromosomal mutation (Figure 4)	Inversion	One region of a chromosome is flipped and reinserted	Opitz-Kaveggia syndrome
	Deletion	A region of a chromosome is lost, resulting in the absence of all the genes in that area	Cri du chat syndrome
	Duplication	A region of a chromosome is repeated, resulting in an increase in dosage from the genes in that region	Some cancers
	Translocation	A region from one chromosome is aberrantly attached to another chromosome	One form of leukemia
Copy number variation (Figure	Gene amplification	The number of tandem copies of a locus is increased	Some breast cancers
	Expanding trinucleotide repeat	The normal number of repeated trinucleotide sequences is expanded	Fragile X syndrome, Huntington's disease

Mutations alter the way a gene is read through either the insertion or the deletion of a single base. In these so-called frameshift mutations, entire proteins are altered as a result of the deletion or insertion. This occurs because nucleotides are read by ribosomes in groups of three, called codons. To better understand this concept, consider the following sentence composed entirely of three-letter words, which provides an analogy for a series of three-letter codons:

THE BIG BAD FLY HAD ONE RED EYE AND ONE BLU EYE.

Now, it is known that a mutation eliminates the first G. As a result, the rest of the sentence is read incorrectly:

THE BIB ADF LYH ADO NER EDE YEA NDO NEB LUE YE.

The same will happen in a protein. For example, a protein might have the following coding sequence: AUG AAA CUU CGC AGG AUG AUG AUG

A codon translation table (Figure 3) can be used to determine that this mRNA sequence would encode the following stretch of protein: Met-Lys-Leu-Arg-Arg-Met-Met-Met considering that a mutation removes the fourth nucleotide resulting a code, separated into triplet codons, would read as follows: AUG AAC UUC GCA GGA UGA UGA UG. This would encode the following stretch of protein: Met-Asn-Phe-Ala-Gly-STOP-STOP. Each of the STOP codons tells the ribosome to terminate protein synthesis at that point. Thus, the mutant protein is entirely different due to the deletion, and it's shorter due to the premature stop codon [11, 12].

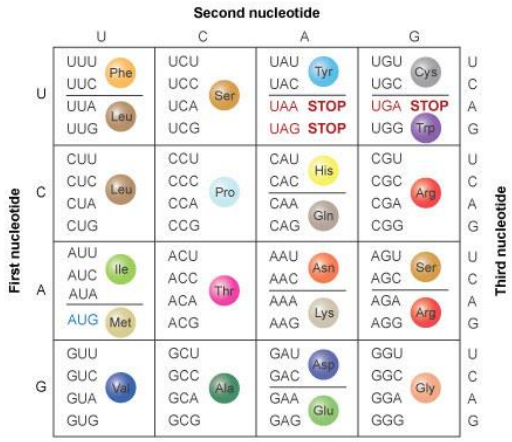

Figure 3: The amino acids specified by each mRNA codon. Multiple codons can code for the same amino acid.

Figure 4: Point mutation

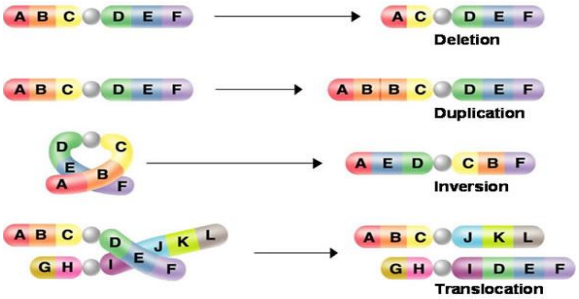

Figure 4: Chromosomal mutation

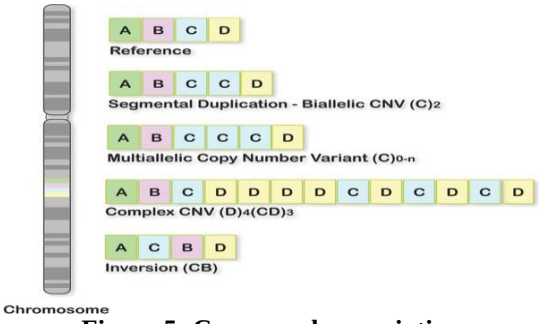

Figure 5: Copy number variation

3. Causes and Mechanisms of Mutation

a) Errors in DNA replication.
b) Errors in DNA repair.
c) Environmental mutagen causes DNA damage that is not repaired correctly.
d) Transposons and insertion sequences (a mobile DNA elements that can move from one location in the chromosome to another; the element may "jump" into a gene thereby mutating it).
e) External Causes: Mutagenic agents that damage DNA such as chemical mutagens, physical mutagens or biological mutagens.

4. Mutations and the Environment

DNA interacts with the environment and this interaction can often be harmful to genetic material. For example, the DNA is in danger any time because of outside ultraviolet (UV) light from the Sun which triggers mutations in the skin cells. One type of mutation produced by UV involves the hydrolysis of a cytosine base to a hydrate form, causing the base to mis-pair with adenine during the next round of replication and eventually being replaced by thymine. Indeed, researchers have found that this UV-induced C-to-T fingerprint-type mutation occurs at an extremely high rate in genes associated with basal cell carcinoma, a form of skin cancer. UV light can also

cause covalent bonds to form between adjacent pyrimidine bases on a DNA strand, which results in the formation of pyrimidine dimers. Repair machinery exists to cope with these mutations, but it is somewhat prone to error, which means that some dimers go unrepaired. Furthermore, some people have an inherited genetic disorder called *xeroderma pigmentosum* (XP), which involves mutations in the genes that code for the proteins involved in repairing UV-light damage. In people with XP, exposure to UV light triggers a high frequency of mutations in skin cells, which in turn results in a high occurrence of skin cancer. As a result, such individuals are unable to go outdoors during daylight hours. In addition to ultraviolet light, organisms are exposed to more energetic ionizing radiation in the form of cosmic rays, gamma rays, and X-rays. Ionizing radiation induces double-stranded breaks in DNA, and the resulting repair can likewise introduce mutations if carried out imperfectly. Unlike UV light, however, these forms of radiation penetrate tissue well, so they can cause mutations anywhere in the body [13].

5. Mutagens Resulting From Cooking Of Foods

a. Benzo[a]pyrene and Other Polynuclear Aromatic Hydrocarbons

Almost 20 years ago Lijinsky and Shubik (1964) and Seppilli and Sforzolini (1963) [14]reported that beef grilled over a gas or charcoal fire contained a variety of polycyclic aromatic hydrocarbons (PAH's).

Benzo[a]pyrene was found in charcoal-broiled steak in levels up to 8 µg/kg [14]. The source of the PAH's resulting from charcoal broiling was the smoke generated when pyrolyzed fat dripped from the meat onto the hot coals. Thus, meat with the highest fat content acquired the highest levels of these chemicals. When meat was cooked in a manner that prevented exposure to the smoke generated by the dripping fat, this source of contamination was either reduced or eliminated [15-18]. PAH's have also been found in a variety of smoked foods and in roasted coffee. Vegetables can easily become contaminated by PAH's from air, soil, or water; fish and shellfish can assimilate such chemicals from their marine environments. However, unless vegetables or seafood are obtained from highly contaminated environments, the major source of PAH will probably be the smoking or cooking of food [19].

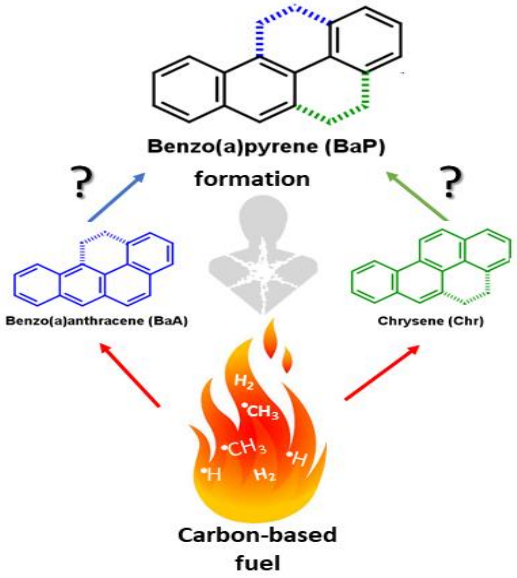

Figure 6: Benzo[a]pyrene[20]

b. Mutagens from Pyrolyzed Proteins and Amino Acids

Studies have been conducted to examine the mutagenicity of smoke condensates from various substances. Smoke obtained from pyrolyzed proteins, such as lysozyme and histone, was found to be highly mutagenic to S. typhimurium, whereas smoke condensates from pyrolyzed DNA, RNA, starch, or vegetable oil were only slightly mutagenic [21]. Pyrolysis of tryptophan resulted in more mutagenic activity than did any other common amino acid, but almost all of the amino acids tested yielded some mutagenic activity when pyrolyzed [21, 22].

Purification of the mutagenic products resulting from pyrolysis of tryptophan resulted in the isolation of two previously unknown amino-γ-carbolines that are potent mutagens: 3-amino-l,4,-dimethyl-5H-pyrido-[4,3-b]indole (referred to as Trp-P-1, for “Tryptophan Pyrolysate 1”) and 3-amino-1-methyl-5H-pyrido[4, 3-b]indole (Trp-P-2).

The mutagenic activity resulting from pyrolysis of L-glutamic acid was shown to be due to the formation of 2-amino-6-methyldipyrido-[1, 2-a:3'2'-d]imidazole (Glu-P-1) and 2-aminodipyrido[1, 2-a:3',2'-d]-imidazole (Glu-P-2) [23]. The structural similarity between these products of glutamic acid pyrolysate and Trp-P-1 and Trp-P-2 [24-26] (Figure 7).

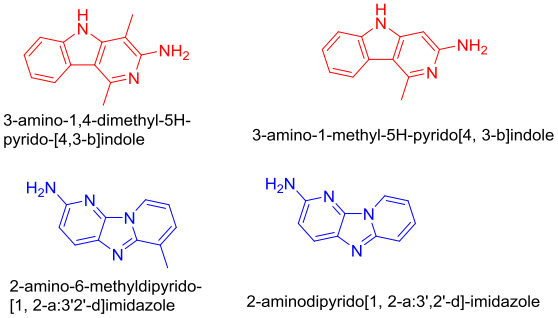

Figure 7: mutagenic activity resulting from pyrolysis of amino acids

c. Mutations Caused by Chemicals

Chemical agents

a) Reactive oxygen species (ROS) These may be superoxide, hydroxyl radicals and hydrogen peroxide, and large number of these highly reactive species which are generated by normal cellular processes.
b) Deaminating agents, such as nitrous acid which can cause transition mutations by converting cytosine to uracil.
c) Polycyclic aromatic hydrocarbon (PAH), when activated to diol-epoxides can bind to DNA and form adducts.[27]
d) Nitrosamines are an important group of mutagens found in tobacco, and may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives. Other alkylating agents include mustard gas and vinyl chloride.
e) Alkaloid from plants, such as those from Vinca species, may be converted by metabolic processes into the active mutagen or carcinogen.
f) Benzene, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

Chemical mutagens are standard tools for mutagenesis in a variety of organisms, and they are a primary means of creating mutations in phenotype-based screens in most genetic systems. Although varied in the experimental design, all whole animal screens involve the generation of lines harboring mutated chromosomes followed by the examination of the resulting phenotypes in the heterozygous or homozygous state. In contrast, gene-based screens rely on the identification of lines that carry mutations in specific genes, prior to any phenotypic examination. The ability to perform gene-based screens has been made possible by recent technological advances in the high-throughput detection of subtle mutations [28].

Oxidizing agents, commonly known as free radicals, are substances that can chemically modify nucleotides in ways that alter their base-pairing capacities. For instance, dioxin intercalates between base pairs, disrupting the integrity of the DNA helix and predisposing that site to insertions or deletions. Mutations such as these that are fairly specific to particular mutagens are called signature mutations [27]

When chemical mutagens or radiation damage DNA during G1, DNA replication is postponed until the damage is repaired. The key molecular species that operates this checkpoint is a protein called p53. p53 is a transcription factor that induces the expression of DNA-repair genes. It also acts indirectly to inhibit the activity of the cyclin–CDK complex that normally drives the cell from G1 to S. Mutations in p53 interfere with its checkpoint function, leading to chromosomal rearrangements and gene amplification (from two copies to hundreds). These rearrangements predispose to cancer. Furthermore, in the presence of p53, irreparably damaged cells commit suicide via apoptosis. In the absence of p53, damaged cells may proliferate, thereby being another predisposing factor toward malignancy [29, 30]. Exposure to mutagens occurs from natural chemicals in our diet, from synthetic chemicals (such as industrial chemicals, pesticides, hair dyes, cosmetics, and drugs), and from complex mixtures (such as cigarette smoke and contaminants in air and water)[31, 32].

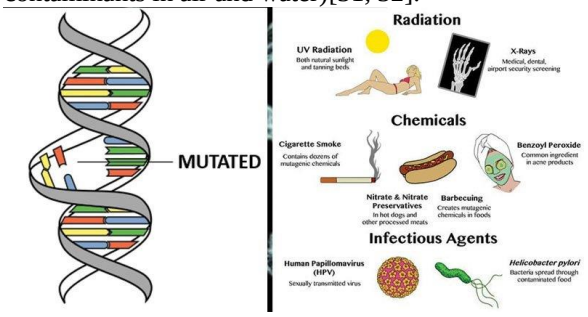

Figure 8: Mutations Caused by Chemicals [31]

d. Induced mutagenesis

Induced mutagenesis has played an important role in the development of superior crop varieties by generating greater genetic diversity in existing varieties. It is particularly important for the genetic improvement of vegetatively propagated crops where cross-breeding is not possible or is time-consuming [33]. Induced mutagenesis offers the possibility of introducing desired attributes that have either been lost during evolution or are not present in nature. Another major advantage is the ability to isolate mutants with multiple traits as well as mutant alleles with varying degrees of trait modification. The resultant mutant varieties can be readily commercialized without the regulatory requirements applied to transgenic crops, though the limitation remains that mutagenesis can only be used to manipulate already existing genes, usually by suppressing/deleting their function [34].

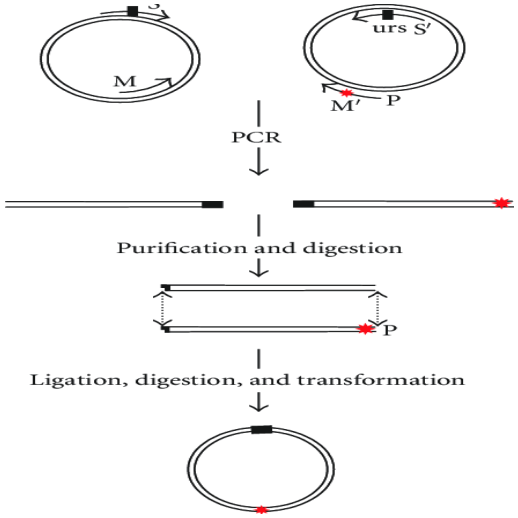

Figure 9: Mutagenesis [35]

As indicated earlier, the Joint FAO/IAEA Division has made irradiation technology more widely available to developing countries through extensive research and development as well as training and capacity development activities [36]. Almost 3000 improved crop varieties in about 170 species have been developed through induced mutation and released in an estimated 100 countries generating economic benefits for farmers. For example, three improved varieties of rice produced a total net profit of USD 348 million for farmers in Viet Nam in 2007 alone, while in Peru, the introduction of nine superior barley varieties has resulted in 50% increased harvests translating to roughly USD 9 million a year [36, 37].

The most commonly used chemical mutagens are alkylating agents such as ethylmethane sulfonate and N-methyl-N-nitrosourea that induce point mutations in DNA. Since point mutations are less detrimental than large chromosomal rearrangements, this method has a higher frequency of achieving a saturated mutant population [38]. However, point mutations are often recessive, and therefore, the second or later generations of mutagenized tissues must be screened to identify homozygous recessive mutations. Chemical mutation-derived varieties have been obtained and commercially released for numerous staple species including rice, wheat, maize, soybean, and barley. A recent approach that combines classical mutagenesis with high-throughput identification of mutations is TILLING (targeting induced local lesions IN genomes). DNA from a collection of mutagenized plants is pooled, subjected to PCR amplification, and screened for mutations by detecting mismatches in duplexes with non-mutagenized DNA sequences [39]. TILLING is particularly advantageous as mutations can be detected in pools of small plantlets without the need to screen adult plants for an observable phenotype. It is also amenable to automation, making it especially conducive for crop species that have large and complex polyploid genomes. However, TILLING requires prior DNA sequence information and is a labor-intensive technique. Further, the availability of a mutagenized population is a prerequisite for TILLING, and the development of such populations is expensive and time-consuming for many species.

TILLING platforms and associated large mutagenized populations, valuable resources for screening for traits of interest, have been created for several crops including rice, maize, durum wheat, barley, and tomato, rapeseed, and pea [40].

e. Human Diseases Caused by Spontaneous Mutations

Many common human diseases are due to mutations in single genes, which are often devastating in their effects. For example, sickle-cell anemia, which affects 1 in 500 people of African descent, is caused by a single missense mutation in the β-globin gene codon 6; as a result of this mutation, glutamic acid in the normal protein at position 6 is converted into valine in the mutant protein, figure 10. Spontaneous mutation in somatic cells (i.e., non-germline body cells) also is an important mechanism in certain human diseases, including retinoblastoma, which is associated with retinal tumors in children. The hereditary form of retinoblastoma, for example, results from a germ-line mutation in *Rb* allele, The *Rb* protein has been shown to play a critical role in controlling cell division [41].

Figure 10: Sickle-cell anemia is characterized by deformed red blood cells.[42]

6. Most common genetic disorders by Mutation

a. Angelman syndrome

AS is a genetic disorder mainly affecting the nervous system. Symptoms include a small head and a specific facial appearance, severe intellectual disability,

developmental disability, limited to no functional speech, balance and movement problems, seizures, and sleep problems. Children usually have a happy personality and have a particular interest in water. The symptoms generally become noticeable by one year of age [43].

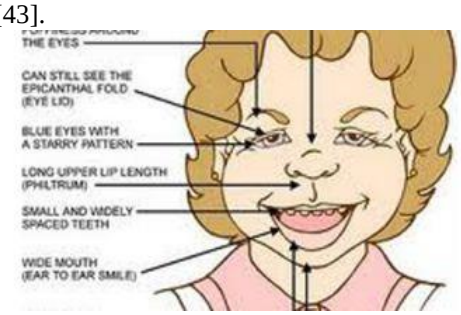

Figure 11: Angelman syndrome[44]

Angelman syndrome is due to a lack of function of part of chromosome 15 inherited from a person's mother. Most of the time, it is due to a deletion or mutation of the UBE3A gene on that chromosome. Occasionally, it is due to inheriting two copies of chromosome 15 from a person's father and none from their mother. As the father's versions are inactivated by a process known as genomic imprinting, no functional version of the gene remains. Angelman syndrome is typically due to a new mutation rather than one inherited from a person's parents. Diagnosis is based on symptoms and possibly genetic testing [43, 45]. No cure is available and is by general support in nature. Anti-seizure medications are used in those with seizures. Physical therapy and bracing may help with walking. Those affected have a nearly normal life expectancy [45].

AS affects 1 in 12,000 to 20,000 people. Males and females are affected with equal frequency. It is named after British pediatrician Harry Angelman, who first described the syndrome in 1965. An older term, "happy puppet syndrome", is generally considered pejorative. Prader–Willi syndrome is a separate condition, caused by a similar loss of the father's chromosome 15 [46, 47].

b. Canavan disease

Canavan disease is an autosomal recessive degenerative disorder that causes progressive damage to nerve cells in the brain, and is one of the most common degenerative cerebral diseases of infancy. It is caused by a deficiency of the enzyme aminoacylase 2, and is one of a group of genetic diseases referred to as leuko-dystrophies. It is characterized by degeneration of myelin in the phospholipid layer insulating the axon of a neuron and is associated with a gene located on human chromosome 17. Symptoms of the most common (and most serious) form of Canavan disease typically appear in early infancy usually between the first three to six months of age. Canavan disease then progresses rapidly from that stage, with typical cases involving intellectual disability, loss of previously acquired motor skills, feeding difficulties, abnormal muscle tone (i.e., initial floppiness - hypotonia - that may eventually translate into spasticity), poor head control, and megalocephaly (abnormally enlarged head). Paralysis, blindness, or seizures may also occur [48]. There exists a much less common variant of Canavan disease which is generally much less serious, and involves later onset of symptoms, which are often mild and nonspecific enough to go unrecognized as manifestations of Canavan's disease. This variant does not seem to have any effect on lifespan, and is typically limited to minor cases of speech and motor skill development delay [49, 50].

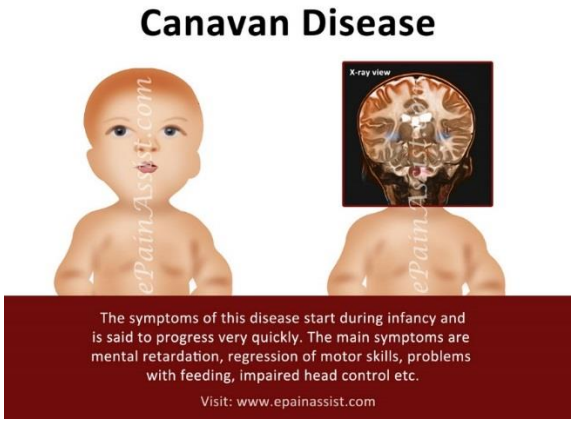

Figure 12: Canavan disease

Canavan disease is inherited in an autosomal recessive fashion. When both parents are carriers, the chance of having an affected child is 25%. Genetic counseling and genetic testing are recommended for families with two parental carriers. Canavan disease is caused by a defective ASPA gene which is responsible for the production of the enzyme aspartoacylase. Decreased aspartoacylase activity prevents the normal breakdown of N-acetyl aspartate, wherein the accumulation of N-acetylaspartate, or lack of its further metabolism interferes with growth of the myelin sheath of the nerve fibers of the brain. The myelin sheath is the fatty covering that surrounds nerve cells and acts as an insulator, allowing for efficient transmission of nerve impulses [50].

c. Charcot–Marie–Tooth disease

CMT is a hereditary motor and sensory neuropathy of the peripheral nervous system characterized by progressive loss of muscle tissue and touch sensation across various parts of the body. This disease is the most commonly inherited neurological disorder affecting about one in 2,500 people. Currently, there are no curative treatments for this disorder, with care focused on maintaining function. CMT was previously classified as a subtype of muscular dystrophy (Krajewski et al., 2000).

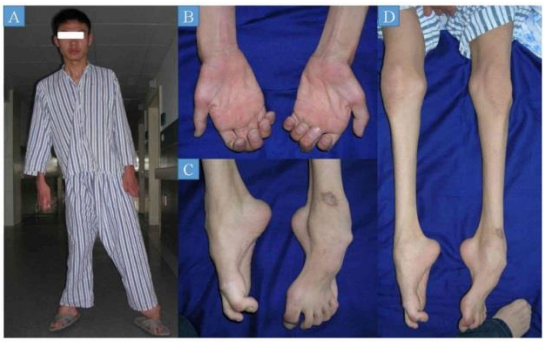

Figure 13: CMT features[51]

Symptoms of CMT usually begin in early childhood or early adulthood, but can begin later. Some people do not experience symptoms until their early 30s or 40s. Usually, the initial symptom is foot drop early in the course of the disease. This can also cause hammer toe, where the toes are always curled. Wasting of muscle tissue of the lower parts of the legs may give rise to a "stork leg" appearance. Weakness in the hands and forearms occurs in many people as the disease progresses. Loss of touch sensation in the feet, ankles, and legs, as well as in the hands, wrists, and arms occurs with various types of the disease. Early- and late-onset forms occur with 'on and off' painful spasmodic muscular contractions that can be disabling when the disease activates. High-arched feet (pes cavus) or flat-arched feet (pes planus) are classically associated with the disorder.Sensory and proprioceptive nerves in the hands and feet are often damaged, while unmyelinated pain nerves are left intact. Overuse of an affected hand or limb can activate symptoms including numbness, spasm, and painful cramping [52].

The most common cause of CMT (70–80% of the cases) is the duplication of a large region on the short arm of chromosome 17 that includes the gene PMP22. Some mutations affect the gene MFN2, on chromosome 1, which codes for a mitochondrial protein. Mutated MFN2 causes the mitochondria to form large clusters, or clots, which are unable to travel down the axon towards the synapses. This prevents the synapses from functioning [53].

d. Cri du chat syndrome

Cri du chat syndrome is a rare genetic disorder due to a partial chromosome deletion on chromosome 5 Its name is a French term ("cat-cry" or "call of the cat") referring to the characteristic cat-like cry of affected children. It was first described by Jérôme Lejeune in 1963. The condition affects an estimated 1 in 50,000 live births across all ethnicities and is more common in females by a 4:3 ratio [54, 55].

Figure 13: Cri du chat syndrome[54]

Cri du chat syndrome is due to a partial deletion of the short arm of chromosome number 5, also called "5p monosomy" or "partial monosomy." Approximately 90% of cases result from a sporadic, or randomly occurring, de novo deletion. The remaining 10–15% are due to unequal segregation of a parental balanced translocation where the 5p monosomy is often accompanied by a trisomic portion of the genome. These individuals may have more severe disease than those with isolated monosomy of 5p. A recent study suggests this may not be the case where a trisomy of chromosome 4q is involved[56, 57].

Most cases involve total loss of the most distant 10–20% of the material on the short arm. Fewer than 10% of cases have other rare cytogenetic aberrations (e.g., interstitial deletions, mosaicisms, rings and de novo translocations). The deleted chromosome 5 is paternal in origin in about 80% of de novo cases. Loss of a small region in band 5p15.2 (cri du chat critical region) correlates with all the clinical features of the syndrome with the exception of the catlike cry, which maps to band 5p15.3 (catlike critical region). The results suggest that 2 noncontiguous critical regions contain genes involved in this condition's cause. Two genes in these regions, Semaphorine F (SEMA5A) and delta catenin (CTNND2), are potentially involved in cerebral development. The deletion of the telomerase reverse transcriptase (hTERT) gene localized in 5p15.33 may contribute to the phenotypic changes in cri du chat syndrome as well[57].

e. Down syndrome

Down's syndrome, also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is usually associated with physical growth delays, mild to moderate intellectual disability, and characteristic facial features. The average IQ of a young adult with Down syndrome is 50, equivalent to the mental ability of an 8- or 9-year-old child, but this can vary widely [58-60]. There is no cure for Down syndrome. Education and proper care have been shown to improve quality of life. Some children with Down

syndrome are educated in typical school classes, while others require more specialized education [61, 62].

Figure 14: Down syndrome

Down syndrome is one of the most common chromosome abnormalities in humans [60]. It occurs in about 1 in 1,000 babies born each year [58]. It is named after British doctor John Langdon Down, who fully described the syndrome in 1866. Some aspects of the condition were described earlier by French psychiatrist Jean-Étienne Dominique Esquirol in 1838 and French physician Édouard Séguin in 1844. The genetic cause of Down syndrome was discovered in 1959[63, 64].

f. Haemochromatosis

Hereditary haemochromatosis is a genetic disorder characterized by excessive intestinal absorption of dietary iron, resulting in a pathological increase in total body iron stores. Humans, like most animals, have no means to excrete excess iron [65, 66].

Excess iron accumulates in tissues and organs, disrupting their normal function. The most susceptible organs include the liver, adrenal glands, heart, skin, gonads, joints, and the pancreas; patients can present with cirrhosis, polyarthropathy, adrenal insufficiency, heart failure, or diabetes [67].

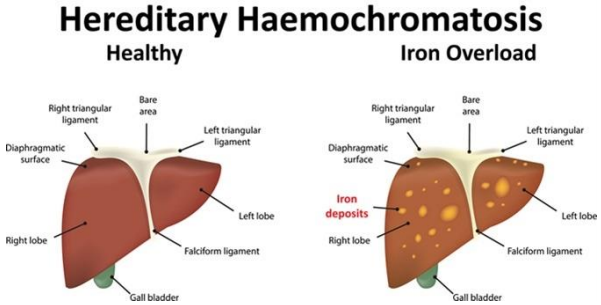

Figure 15: hereditary haemochromatosis

One of the better-characterized genes responsible for hereditary haemochromatosis is HFE on chromosome 6 which codes for a protein that participates in the regulation of iron absorption. The HFE gene has three common mutations, C282Y, H63D and S65C.[67]The C282Y allele is a transition point mutation from guanine to adenine at nucleotide 845 in HFE, resulting in a missense mutation that replaces the cysteine residue at position 282 with a tyrosine amino acid.[67, 68].

Mutations of the HFE gene account for 90% of the cases of nontransfusional iron overload. This gene is closely linked to the HLA-A3 locus. Each patient with the susceptible genotype accumulates iron at different rates depending on iron intake, the exact nature of the mutation, and the presence of other insults to the liver, such as alcohol and viral disease. As such, the degree to which the liver and other organs are affected is highly variable and is dependent on these factors and co-morbidities, as well as age [69].

g. Turner syndrome

TS, also known 45,X, or 45,X0, is a genetic condition in which a female is partly or completely missing an X chromosome. Signs and symptoms vary among those affected. Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most people with TS have normal intelligence. Many have troubles with spatial visualization that may be needed for mathematics. Vision and hearing problems occur more often [70].

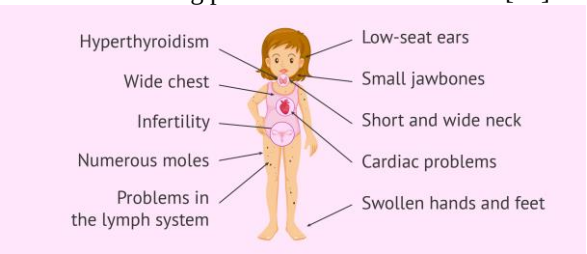

Figure 16: Turner syndrome[70]

Turner syndrome is not usually inherited; rather, it occurs during formation of the reproductive cells in a parent or in early cell division during development.Turner syndrome is due to a chromosomal abnormality in which all or part of one of the X chromosomes is missing or altered. While most people have 46 chromosomes, people with TS usually have 45. The chromosomal abnormality may be present in just some cells in which case it is known as TS with mosaicism. In these cases, the symptoms are usually fewer and possibly none occur at all. Diagnosis is based on physical signs and genetic testing [70]. Turner syndrome occurs in between one in 2,000 and one in 5,000 females at birth. Henry Turner first described the condition in 1938. In 1964, it was determined to be due to a chromosomal abnormality [71].

Turner syndrome is caused by the absence of one complete or partial copy of the X chromosome in some or all the cells. The abnormal cells may have only one

X (monosomy) (45,X) or they may be affected by one of several types of partial monosomy like a deletion of the short p arm of one X chromosome (46,X,del(Xp)) or the presence of an isochromosome with two q arms (46,X,i(Xq)). Turner syndrome has distinct features due to the lack of pseudoautosomal regions, which are typically spared from X-inactivation. In mosaic individuals, cells with X monosomy (45,X) may occur along with cells that are normal (46,XX), cells that have partial monosomies, or cells that have a Y chromosome (46,XY). The presence of mosaicism is estimated to be relatively common in affected individuals (67–90%)[72].

h. Klinefelter syndrome

KS, also known as 47,XXY is the set of symptoms that result from two or more X chromosomes in males. The primary features are infertility and small poorly functioning testicles. Intelligence is usually normal; however, reading difficulties and problems with speech are more common. Symptoms are typically more severe if three or more X chromosomes are present (48,XXXY syndrome or 49,XXXXY syndrome).[73]

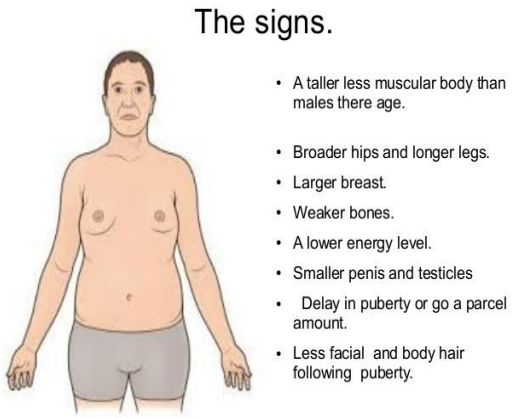

Figure 17: Klinefelter syndrome[74]

i. Marfan syndrome

MFS is a genetic disorder that affects the connective tissue. Those with the condition tend to be tall and thin, with long arms, legs, fingers, and toes. The severity of the symptoms of MFS is variable. MFS is caused by a mutation in FBN1, one of the genes that makes fibrillin, which results in abnormal connective tissue. It is an autosomal dominant disorder. About 75% of the time, the condition is inherited from a parent with the condition, while 25% of the time it is a new mutation. MFS It is named after French pediatrician Antoine Marfan, who first described it in 1896 [75, 76]. This spontaneous mutations occur in about one in 20,000 births. Marfan syndrome is also an example of dominant negative mutation and haplo-insufficiency[77, 78].

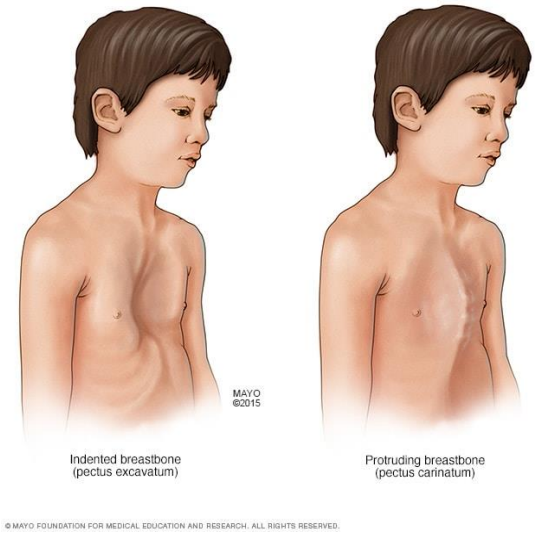

Figure 18: Marfan syndrome

j. Fragile X syndrome

Fragile X syndrome (FXS) is a genetic disorder in FMR1 region of X-chromosome in which the IQ of individuals decreases sharply mostly with more severe effects on females despite a more prevalent in males. The expansion of CGG triplet and repeats causes this disorder. The methylation of this region causes deficiency of FMRP protein in neuronal cells leading to inhibition of connections. Autism and seizure are among disabilities of these patients [79-81].

Figure 19: Fragile X syndrome (FXS)[80]

k. *Huntington's disease*

HD is a rare, adult-onset, autosomal dominant, progressive neurodegenerative disease. Also known as Huntington's chorea, is mostly an inherited disorder that results in the death of brain cells. The earliest symptoms are often subtle problems with mood or mental abilities. A general lack of coordination and an unsteady gait often follow. As the disease advances, uncoordinated, jerky body movements become more apparent. Physical abilities gradually worsen until coordinated movement becomes difficult and the person is unable to talk. Mental abilities generally decline into dementia. The specific symptoms vary somewhat between people. Symptoms usually begin between 30 and 50 years of age but can start at any age. The disease may develop earlier in life in each successive generation. About eight percent of cases start before the age of 20 years, and are known as juvenile HD, akinetic-rigid, or Westphal variant HD, they typically present with symptoms more like Parkinson's disease [82-84].

HD is typically inherited, although up to 10% of cases are due to a new mutation. When inherited, the disease is caused by an autosomal dominant mutation in either of an individual's two copies of a gene called huntingtin. This means a child of an affected person typically has a 50% chance of inheriting the disease. The huntingtin gene provides the genetic information for huntingtin protein (Htt). Expansion of CAG repeats of cytosine-adenine-guanine (known as a trinucleotide repeat expansion) in the gene coding for the huntingtin protein results in an abnormal protein, which gradually damages cells in the brain through mechanisms that are not yet fully understood. Diagnosis is by genetic testing, which can be carried out at any time, regardless of whether or not symptoms are present. The first likely description of the disease was in 1841 by American physician Charles Oscar Waters. The condition was described in further detail in 1872 by American physician George Huntington[85]. The genetic basis was discovered in 1993 by an international collaborative effort led by the Hereditary Disease Foundation [86].

Figure 20: ***Huntington's disease[86]***

All humans have two copies of the huntingtin gene (HTT), which codes for the huntingtin protein. The gene is also called HD and IT15, which stands for 'interesting transcript 15'. Part of this gene is a repeated section called a trinucleotide repeat expansion, which varies in length between individuals and may change length between generations. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant huntingtin protein (mHTT). The differing functions of these proteins are the cause of pathological changes which in turn cause the disease symptoms. The Huntington's disease mutation is genetically dominant and almost fully penetrant: mutation of either of a person's HTT alleles causes the disease. It is not inherited according to sex, but by the length of the repeated section of the gene and hence its severity can be influenced by the sex of the affected parent[87].

HD is one of several trinucleotide repeat disorders which are caused by the length of a repeated section of a gene exceeding a normal range. The HTT gene is located on the short arm of chromosome 4 at 4p16.3. HTT contains a sequence of three DNA bases—cytosine-adenine-guanine (CAG)—repeated multiple times (i.e. ... CAGCAGCAG ...), known as a trinucleotide repeat. CAG is the 3-letter genetic code (codon) for the amino acid glutamine, so a series of them results in the production of a chain of glutamine known as a polyglutamine tract (or polyQ tract), and the repeated part of the gene, the PolyQ region [88].

l. Phenylketonuria

PKU is an inborn error of metabolism that results in decreased metabolism of the amino acid phenylalanine. Phenylketonuria is a genetic disorder inherited from a person's parents. It is due to mutations in the PAH gene, which results in low levels of the enzyme phenylalanine hydroxylase. This results in the buildup of dietary phenylalanine to potentially toxic levels. It is autosomal recessive, meaning that both copies of the gene must be mutated for the condition to develop. There are two main types, classic PKU and variant PKU, depending on whether any enzyme function remains. Those with one copy of a mutated gene typically do not have symptoms (Al Hafid and Christodoulou, 2015). Phenylketonuria affects about 1 in 12,000 babies. Males and females are affected equally. The disease was discovered in 1934 by Ivar Asbjørn Følling, with the importance of diet determined in 1953[89-91].

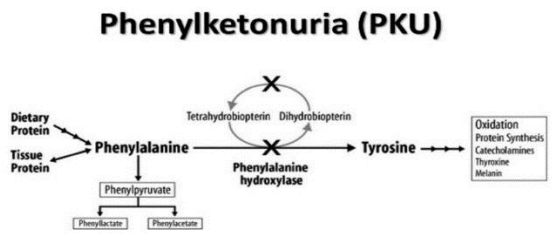

Figure 21

PKU is characterized by homozygous or compound heterozygous mutations in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it nonfunctional. This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine (Tyr). When PAH activity is reduced, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which can be detected in the urine [92]. The PAH gene is located on chromosome 12 in the bands 12q22-q24.2[93].

m. DiGeorge syndrome

DiGeorge syndrome, also known as 22q11.2 deletion syndrome is typically due to the deletion of 30 to 40 genes in the middle of chromosome 22 at a location known as 22q11.2. About 90% of cases occur due to a new mutation during early development, while 10% are inherited from a person's parents. It is autosomal dominant, meaning that only one affected chromosome is needed for the condition to occur. DiGeorge syndrome occurs in about 1 in 4,000 people. The syndrome was first described in 1968 by American physician Angelo DiGeorge. In late 1981, the underlying genetics were determined [94, 95].

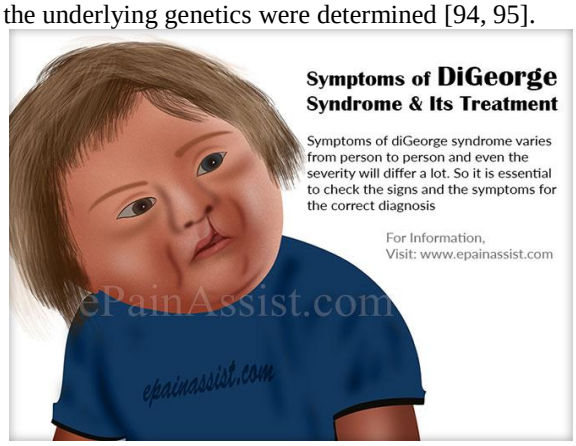

Figure 22: DiGeorge syndrome

DiGeorge syndrome is caused by a heterozygous deletion of part of the long arm (q) of chromosome 22, region 1, band 1, sub-band 2 (22q11.2). Approximately 80-90% of patients have a deletion of 3 Mb and 8% have a deletion of 1.5Mb. The number of genes affected by the deletion has been cited as approximately 30 to 50. Very rarely, patients with somewhat similar clinical features may have deletions on the short arm of chromosome 10[96-99].

n. Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a boys' disorder mainly in age of four and develops in one in 3,500 to 6,000 cases at birth. One-third of cases occur following mutation in the X-chromosome locus Xp21. This disorder has also no treatment and physical activity is needed. The dystrophin protein connects the actin to the basal lamina[100, 101].

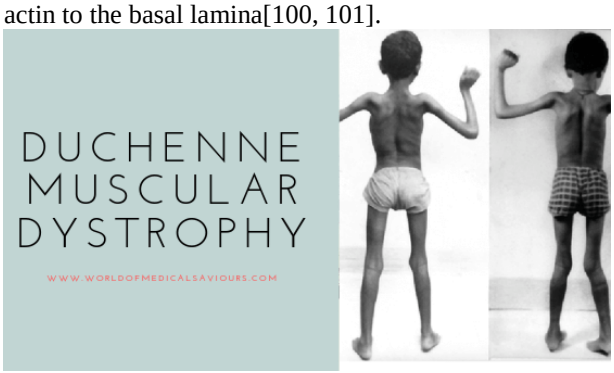

Figure 23

o. Color blindness

Color blindness (color vision deficiency) is the decreased ability to see color or differences in color. It can impair such tasks as selecting ripe fruit, choosing clothing, and reading traffic lights.

The most common cause of color blindness is an inherited problem in the development of one or more of the three sets of the eyes' cone cells, which sense color. Among humans, males are more likely to be color blind than females, because the genes responsible for the most common forms of color blindness are on the X chromosome. Females have two X chromosomes, so a defect in one is typically compensated for by the other. Non-color-blind females can carry genes for color blindness and pass them on to their children. Males only have one X chromosome and therefore always express the genetic disorder if they have the recessive gene. Color blindness can also result from physical or chemical damage to the eye, the optic nerve, or parts of the brain.Diagnosis is typically with the Ishihara color test; other methods include genetic testing [102]. Color blindness is typically an inherited genetic disorder. It is most commonly inherited from mutations on the X chromosome. Two of the most common inherited forms of color blindness are protanomaly (and, more rarely, protanopia—the two together often known as

"protans") and deuteranomaly (or, more rarely, deuteranopia—the two together often referred to as "deutans"). Both "protans" and "deutans" (of which the deutans are by far the most common) are known as "red–green color-blind").[103]

7. Selected mutations

In 2009, researchers at the Broad Institute in Boston, led by geneticist David Altshuler, started recruiting elderly, overweight individuals who, by all accounts, ought to have type 2 diabetes but didn't. The scientists weren't looking for genetic mutations that cause diabetes but rather hoping to find mutations that prevent it. The group reported in Nature Genetics that people who have particular mutations in a gene called SLC30A8 (Solute carrier family 30, member 8) are 65% less likely to get diabetes, even when they have risk factors like obesity [104, 105].

Similarly protective mutations—that disable a gene but create a benefit rather than a problem—have been discovered somewhat accidentally in the past. One percent of Northern Europeans, for instance, are now known to carry a mutation in a gene called CCR-5 that renders a cellular receptor defective and confers total immunity from HIV infection [106].

And there's evidence of more lucky mutations lurking in human genomes, in the form of people who seem to defy the odds—the long-lived smokers, or the individuals who remain unscathed in the midst of an infectious disease outbreak. Especially intriguing are those who carry gene mutations that are known to cause disease yet who show no signs of illness (Levine and Crimmins, 2016; Williams, 2016).

The effect of mutations on the phenotype of viruses

In the case of viruses, mutations may lead to different phenotypic changes. Mutations which affect the third base in a code word may be completely silent and have no influence on virus replication. This is the case if the mutation hits a triplet which codes for an amino acid for which there are several code words varying only in the third base. In other cases the mutation may lead to the protein containing a different amino acid in a single position, a phenomen which does not necessarily imply that the configuration or the stability of the protein is changed. Thus in this case also the mutation may be phenotypically silent. If the mutation has changed an amino acid in a structurally important part of the protein, normal functions may be lost. The mutation may as a consequence have a lethal effect. However, in occasional cases the modified protein configuration will lead to the protein remaining stable and retaining its function at lower temperatures, but developing a configurational change at higher temperatures which leads to it being readily broken down by cellular proteases. In these rare cases a temperature-sensitive (ts) mutant has been established. Such ts mutations frequently affect single bases and usually have a substitution character. When a deletion or an addition of a nucleotide base has occurred, the mutant that arises is often lethal since usually the reading frame becomes incorrect.

Certain mutations lead to a code word for an amino acid possibly being changed to a code word that signals a termination in the translation mechanism. Code words for such nonsense mutations as expressed in mRNA are UAG, UAA and UGA. If the mutation leads to the appearance of a termination codon, the protein which is synthesized will be smaller than normal. However, mRNA which contains such altered sequences can be expressed to its normal length in cell-free translation systems if a special form of tRNA, suppressor-tRNA, is added. This tRNA can introduce an amino acid at the place of the nonsense codon. Suppression mutations have been of great help in the identification of genes in bacteria and phages, since certain bacteria have a suppressor-tRNA which can compensate for the nonsense mutations. By comparing the protein synthesis in suppressor-negative and suppressor-positive cells it has been possible to identify directly the modified gene product.

Concerning animal cells, it has not as yet been possible to isolate cell lines which contain suppressor-tRNA and suppressor mutants therefore have to be analysed using in vitro translation systems. Both in the case of adenovirus and herpesvirus genes, it has been possible to demonstrate suppressor mutants by this technique. In vitro translation of mRNA from these mutants can synthesize a normal protein in the presence of suppressor-tRNA from yeast. Thus the protein altered by the mutation can be identified directly. Temperature-sensitive mutants and suppressor mutants are called conditional lethal mutants because the mutations are lethal only under certain conditions. All cell-dependent mutants referred to as host-range mutants belong also in the category of conditional lethal mutants. These virus mutants can replicate normally in certain cells but not in other cells. They frequently show a normal phenotype in a cell which is transformed by a DNA fragment containing the gene which is influenced by the mutation. This occurs via complementation between the virus and the cellular genome or via recombination between the two genomes. These kind of mutants have primarily been used to map the early genes in transforming animal DNA viruses, such as polyoma viruses and adenoviruses. Since the transformed cells contain the part of the virus-genome which is needed for transformation, a virus which has been mutated in this gene cannot induce productive infection in normal cells but may do so in transformed permissive cells. A prerequisite for the usefulness of this technique is that the genes which are required for transformation are also needed for a productive replication of virus. For

adenoviruses and polyoma viruses it has been shown that the early transforming genes exert control over the formation of early gene products. On the other hand it appears that the transforming genes, oncogenes, which occur in retroviruses are not required for replication of these viruses. In contrast, a presence of helper viruses is needed for replication of defective leukaemia viruses which are responsible for transformation [107].

Viruses have core sets of essential genes that are always required for genome replication. Examples include capsid proteins and polymerases. Other genes, sometimes called nonessential, are dispensable, and may be lost, under certain specific some conditions (for example, during replication in cultured cells) [108]

The extremely high mutation rates of viruses are not matched by any other organism in the kingdom of life. The high mutation rates of viruses, coupled with short generation times and large population sizes, allow viruses to rapidly evolve and adapt to the host environment. This has important implications for the pathogenesis of viral infections.

Virus mutations create genetic diversity, which is subject to the opposing actions of selection and random genetic drift, both of which are directly affected by the size of the virus population. When the population size is large, selection will be predominant and random drift less common. This means that deleterious alleles will be efficiently removed from the population, while adaptive alleles will have an opportunity to take over the population. However, when the population size is small, random effects may obscure the effects of selection. Under these conditions, slightly deleterious alleles may rise to an unexpectedly high frequency in the population, and adaptive alleles may be lost by chance.

High mutation rates create many viral variants. During an infection with human immunodeficiency virus (HIV), all genotypes that are one mutation away from the infecting genotype will be created every day. The rich cloud of mutants, often termed a “quasispecies,” has the potential to encode viruses with elevated resistance to a drug, or the ability to evade neutralizing antibodies created by the host. As a corollary, this complicates efforts to design effective vaccines, as evolution can greatly increase the number of virus serotypes that circulate in human populations. Furthermore, the unique ability of viruses to change allows them to cross species barriers, resulting in zoonotic infections.

Virus evolution is further characterized by additional layers of complexity. One unique characteristic of viruses is their MOI, which is the ratio between the number of viruses and the infecting cells. MOI has several consequences for evolution that are discussed in a later section, and these are subject to the constantly changing size of the virus population. The typical view of viral evolution is that viruses create huge population sizes within the infected host. However, this huge population size is punctuated by frequent bottlenecks during host-to-host transmission, and population structure within an infected host, where different organs and tissues may support different independently replicating populations. These differences in population size will affect both the selection-drift balance mentioned above, and the MOI of different virus subpopulations. In the rest of this chapter, we discuss the different factors affecting the virus population, and how these factors intertwine to shape virus evolution [109].

The cellular environment can impact virus mutation rates and frequency. For example, dNTP pool imbalances can affect retrovirus mutation rates, and it has been suggested that differences in substitution rates between RNA viruses is a consequence of differences in virus RNA synthesis rates in different cell types. In addition to these effects, there are also cellular factors that can result in increased mutation in RNA viruses. Adenosine-to-inosine modification by enzymes called adenosine deaminase acting on RNA (ADAR) is the most common form of RNA base modification that occurs in mammals. A-to-I conversion has important consequences in the coding potential of substrate RNAs, as inosine is decoded as a G by polymerases during template copying. The A-to-I conversion in a dsRNA duplex also has consequences to stability of RNA secondary structures, as the A:I pairing is less stable than a canonical A:U pair. This can have important consequences for RNAs that depend on their structure rather than sequence for their function. ADAR modification of cellular double-stranded RNA was shown to prevent its recognition by the cytoplasmic sensor of nonself RNAs that would otherwise lead to chronic activation of innate immune pathways. There is also evidence that ADAR can modify viral RNAs. Sequence analysis of RNA virus genomes has revealed that they preferentially accumulate A-to-G transitions, which are characteristic hallmarks of ADAR activity. Measles virus is a negative-stranded RNA virus, responsible for an acute disease predominantly in infants, but in rare instances associated with a fatal latent infection of the CNS known as subacute sclerosing panencephalitis (SSPE). Analysis of measles virus genomes from SSPE victims has revealed abundant A-to-G transitions, suggesting a role for ADAR in establishment of SSPE. Consistent with an antiviral role for ADAR, measles virus infection of ADAR knock-out cell lines displayed increased cellular pathology, and similar findings were reported for other RNA viruses, implicating ADAR as

a cellular restriction factor for a wide range of negative-stranded RNA viruses. Direct evidence of ADAR modification of a viral RNA genome comes from studies of hepatitis delta virus (HDV). HDV is the smallest of the RNA viruses and encodes just two proteins, HDAg-L and HDAg-S, both of which are essential for virus viability. HDAg-L and HDAg-S share the same amino terminal open reading frame, but HDAg-L possesses a carboxyl terminal extension that is accessed when the stop codon at the end of the HDAg-S ORF is bypassed. Early during infection only the truncated HDAg-S is expressed, but then at later times expression of HDAg-L increases due to the site-specific modification of the stop codon by ADAR. This editing event is highly specific and is promoted by the highly secondary structured HDV RNA genome. This action by ADAR is clearly proviral, in that without the activity of ADAR, no infectious HDV particles would form.

Another family of cellular factors that can modify the sequence of viral genomes is the APOBEC family of enzymes. These comprise an extensive arm of the innate immune system. They are responsible for the modification by deamination of cytosine residues to uracil, which is an activity largely performed on single-stranded DNA substrates, leading to the phenomenon of hypermutation. APOBEC activity can affect the retroviruses. HIV infection is blocked by APOBEC, unless it expresses the viral infectivity factor (Vif). The mechanism for this blockade relies on the packaging of multiple APOBEC family members within HIV virions, which can act on the HIV genome once it has been copied by reverse transcriptase into a complementary DNA. The effect of APOBEC activity can be the modification of up to 10% of susceptible cytosine residues, resulting in a drop in infectivity of up to 100-fold[110].

The remarkable capacity of some viruses to adapt to new hosts and environments is highly dependent on their ability to generate de novo diversity in a short period of time. Rates of spontaneous mutation vary amply among viruses. RNA viruses mutate faster than DNA viruses, single-stranded viruses mutate faster than double-strand virus, and genome size appears to correlate negatively with mutation rate. Viral mutation rates are modulated at different levels, including polymerase fidelity, sequence context, template secondary structure, cellular microenvironment, replication mechanisms, proofreading, and access to post-replicative repair. Additionally, massive numbers of mutations can be introduced by some virus-encoded diversity-generating elements, as well as by host-encoded cytidine/adenine deaminases. viral genetic diversity is determined by multiple virus- and host-dependent processes, and that viral mutation rates can evolve in response to specific selective pressures[111].

Emergence of Henipaviruses

Phylogenetic analyses show that Nipah and Hendra viruses are old viruses, which suggests that their emergence in the 1990s was due to ecologic factors rather than virus mutations. Ecologic change that drew flying foxes closer to horses, pigs, and humans was probably the largest contributor to the emergence of Hendra and Nipah viruses. Deforestation has caused flying foxes (genus Pteropus; suborder Megachiroptera) to move into suburban and urban areas to use the trees in these regions for roosting. Climate change is likely to be causing an expansion of the geographic areas that are suitable for the bat host species of henipaviruses [112, 113].

Conclusion

Thanks to our DNA repair system, almost all abnormal DNA mutations are repaired by it. By adopting a healthy lifestyle we can save our DNA from the harmful effect of mutagens. For example, use sun scream while coming out in sunlight. Eat healthy food and stay away from unnecessary radiation. Mutagens are harmful, but not always. Some mutations are also beneficial to us, however, those are rare. In fact, different phenotypes for our survival are originated due to different mutations but those are not originated from the mutagens, possibly.

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