International Journal for Research in Applied Sciences and Biotechnology

ISSN: 2349-8889
Volume-8, Issue-2 (March 2021)

www.ijrasb.com

https://doi.org/10.31033/ijrasb.8.2.15

Review Article: Defective Genes Cause Disease

Istabraq A. Al-Husseiny
Tropical-Biological Research Unit, College of Science, University of Baghdad, IRAQ

Corresponding Author: sanbeter2015@yahoo.com

ABSTRACT

Variation in DNA, and genes to a lesser or greater extent, can play an important role in most diseases; that is because this variation in will reflect and affect the function of DNA, and genes (combined genes and DNA or separately). This can be affected by environment, life style, as well as the inheriting from parents and previous generations. All these factors can contribute in human diseases. There are different alterations in genes, like imbalance and inequality in chromosomes, disorder in gene (deficiency in gene, which could be complex or single disorder), and cancer. In the last decades, scientists were focus on medicine and genetics; they pay an extensive attention to reach better understanding about diseases and their causes, to serve patients in better way. This tendency and preparations were focused on genes and the changes that may occur, and the sequences of these changes on health. In this regard scientists studied the epigenetic diseases as well, and the application of genes in therapy. Implementation of these concepts in labs and clinics required full understanding of genetic alterations.

Keywords- genes, defective, mutation, disorder, disease**.**

I. INTRODUCTION

The body of human usually builds up and consists of millions of tiny cells; each of which has its own function and a certain role, such as smell, light sensation, oxygen absorbance and so on. In general, the cell has nuclei which has chromosome. Commonly, each cell in human has 23 pair of chromosomes (autosomes). Simply, the responsibility of chromosomes is to transfer the information of the genes from parents to their kids[(1-5)].

In human being, chromosomes are sorted in to 2 types, two chromosomes (allosomes), which are either Y and X. Typically female kid (child) take only X chromosomes from both parents, while male kid (child) take X from mother and Y from father. Every chromosome is built up from what is called DNA (Deoxyribonucleic Acid). The role of this DNA is to manage proteins production, when to produce them and where, and it has all the required information to achieve that. Commonly, proteins contain amino acid and build up from it as a main unit of its structure, and each molecule of proteins has a certain function that plays it in the body, organs, tissues and starting from the cells [(6-8)]. Genes are an exact length of DNA molecules by which it verifies the protein via amino acid molecules lengths. There are some types of proteins that are required and necessary for all types of cells, while other types are not needed by every cell. This selectivity is because of the protein structure, and precisely according to what is known as gene code, and in accordance to that, switching the sequence of genes (the code) will result in diverse in structure, and different function of the protein [(9-10)]. Mutation is gene with dysfunction (defective gene), this defect in gene is the main reason that accounted to cause diseases. This mutation in gene start from the sperm or the egg cells, and can inherited from parents. The illness and disease generally happened because of mutation in one or many genes [(12)].

In relation to that, and according to the level of defect in gene, the diseases can be classified into four main categories [(13-15)]

➢ ***Disorders due to mitochondria****:* These types of diseases are caused by defect in the DNA that exists in the mitochondria itself, and because mitochondria is responsible for providing energy to the cell itself, and to whole body; this genetic mutation and defect can have eventfully influence on muscles, brain, kidney, liver, eyes, pancreas, heart, as well as nerves.

➢ ***Disorders due to chromosomes:*** **T**hese types of diseases usually happened due to abnormal things in chromosomes, such as, duplication, alteration, missing. This abnormality known as syndrome (such as Down and mosaic Down), which will lead to physical distortions such as abnormality in physical appearance as well as heart problem, and disorder in thyroid.

➢ ***Disorder due to multi factors****:* These types of disorders can happen due to environment, surrounding, bad habits, cancer, diabetes, hypertension.

➢ ***Disorder due to defect in single gene****:* This kind of disorder occurs due to mutation in one gene, such diseases that resulted are dystrophy in muscles, cystic fibrosis, anemia, and much more.

So defective genes can cause or participate in a lot of communicable and infectious diseases such as cancer and tuberculosis.

II. DOWN SYNDROME (SIGNS AND SYMPTOMS)

Down syndrome has a certain hallmark that appears and shows on babies. On the other hand, each feature has certain look according to the type of the gene (genotype), which reflects on the looking of the child and has a diverse mark that can be noticed on every patient [(5,16)].

In general, there are common signs and symptoms, such as the following:

1. Small neck and undersized head (small).
2. The face look flat.
3. Sloping eyes and looks upward.
4. The positions of ears are not normal (lower), and look like flat.
5. Protrude and large tongue (abnormal tongue).
6. Muscles look weak and lack.
7. Extra weight (have obesity).
8. Joints are flexible.
9. Fingers are short, and the hands look like wider than normal one.
10. Disability in thinking and intellective brain (mental disorder).
11. Development delay.

III. MUTATION AND DEFECTIVE GENES

In general, the main causes of mutation are the changes that happened to the DNA accidently. According to geneticists, mutation is defined as transmissible alteration in the sequence of the DNA and cause changes in the code. These changes may cause damage to the proteins, and may propagate and spread from cells, to tissues, and organs, and eventually cause disease. The consequence of the mutation usually ends with a certain signs and implications on the whole body of the human being [17-21].

Variants may inherited from parents (father or mother), or may related to the diseases itself (pathogenic), and sometimes it is classified as unknown (because it is not related to parents nor to disease). However some variation occurred during duplication of DNA (during cell division). Also there are a mutations that happened due to environmental reasons such as exposure to chemicals, radiation, or biological viruses. Not all types of mutations are bad, some of them could be useful and beneficial and this can be refers to the creation of diverse genes. Besides, there are a lot of mutations that has no bad effect on health, these types of mutation are classified as " silent mutations" [22]. In this review article the researchers will focus on the harmful mutations that considered as a reason for diseases.

IV. MUTATIONS THAT ARE INHERITED

These are inherited with disorder in genes, such as anemia, cystic fibrosis, color blindness, phenylketonuria, and a lot more. These disorders are happened due to single gene mutation. The majority of these diseases were recessive, and that's mean, to be effective on the person and cause disorder to him, he must receive or inherited 2 copies at that time, this will caused mutation to gene and eventually leads to disorder, and that's why it is not good to marry relatives, because, this will increase the possibility of inheriting 2 copies of disordered genes (mutated with deficiency) [23].

It is good to know that patients having these genes with bad effect are died in most cases before they inherit the genes to their offspring. It was estimated that there are from five to ten very bad genes that may cause death, but they are exist in one copy only and this will not enable them to be noticeable, marked, and manifested. In general, cancer resulted from a sequence of disorder and mutations in only one single faulty cell which cause missing or damage a certain gene (precisely p53), this gene is responsible to produce a certain protein that prevent the mutated and damaged cell from growth, dividing and spreading, and eventually be become canerous [24-25].

Figure 1 represents a scheme of what does defective gene means.

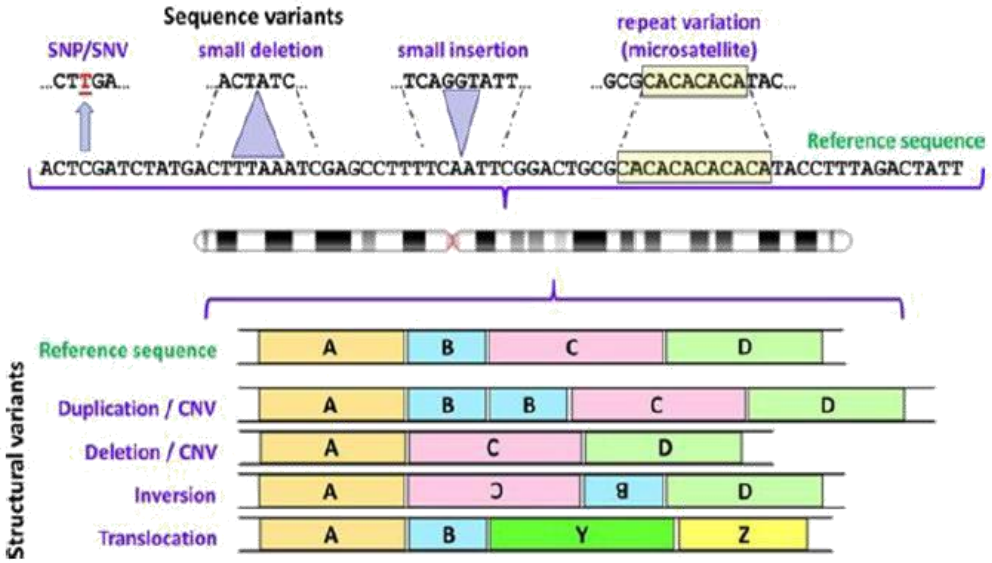

Figure 1: Deficiency in genes [22]

V. GENETIC DIVERSITY AMONG HEALTHY PEOPLE, AND POPULATIONS

Since there are no 2 persons looks like the same or identical (except twins), this indicates that the DNA in each one is different and diverse from others. this usually referred to the single nucleotide polymorphisms (SNPs). There are around 3,000,000 SNPs in the genome, and there are around 2 thousands alternates, which indicates unlimited sequence of the nucleotide. This variation is related to what is called CNVs (copy number variation) which mainly occurs in the coding of the DNA. Some of these variations that cause damages in the function of the gene are either predicted or known. Among them there are around eighty five variants that may affect the productivity of proteins and affect their functions, and it is well known now that these variations are the main reason of the most of the diseases that may appears in the individuals [22-24].

The variation peak will be much more between mixed populations, especially among populations that consist and build up from immigrants such as USA, Canada, or countries that has different ancestry, but only a very rare and specific genetic variation can be noticed among homogenous populations, and a number of these differences can be related to the environment which can cause some adaptations in genes such as, skin color, body shape, hair type, eye color, tooth [26-27]. The enormous variation in genotypes among human beings makes things very complicated to level that scientists become unable to distinguish variants that has association and relation with diseases and the benign variants. Furthermore there are some variations that have effect on the harshness (struggle and severity) towards diseases. This complication further increase the investigations to study the influences of genomic deficiency and their contribution in different diseases. Many scientific methods and procedures are used to determine if the deficiency referred to proteins, genes, or chromosomes and decide the effect of each one of them. This need a very good collaborations between clinics and laboratories. The researchers, and the scientists put a certain role and regulation to name the genes in human beings, this system called HUGO Gene Nomenclature Committee (HGNC), while the disorder genes (genes with variations) are named to different system called Human Genome Variation Society (HGVS) particularly the variation in DNA [22-26].

VI. COMPLEX DISORDERS

Monogenic disorder is related to the variation in one gene which has a very little impact, however there is different type of variation in gene which has multi effect called (multifactorial disorder), and best examples for this type of disorder are schizophrenia, diabetes, heart diseases, which appears as a result of several variations in genes in addition to the influence of the environment, this variation have different impact and may increases the risk of the disease [29-30]. Type 2 diabetes, which is very frequent around the world, is considered as a result of complex variations in several genes, the contribution of the environment on this disease is usually has relation with exercise, diet, in addition to habits (such as spending long time watching TV), and the style of life of patients. The effect of genetic disorder in type 2 diabetes is very little compared with type 1 diabetes which normally characterized due to the loss in production of insulin, which comes as a result of damage in the pancreas [31].

There many approaches to investigate if the type 2 diabetes is due to gene variation; it is by check a certain gene named loci (which is a certain gene in chromosome). An alternative approach is by checking the insulin receptors *PPARG*. To reach the defected gene it is necessary to investigate the loci as well (a certain gene in insulin receptors which is responsible for metabolism of glucose). Investigating PPARG and loci can occur if the diabetes due to deficiency in glucose receptors genes or due to glucose metabolism gene [22-32].

Figure 2 represent a scheme of type 2 diabetes (T2D) risks.

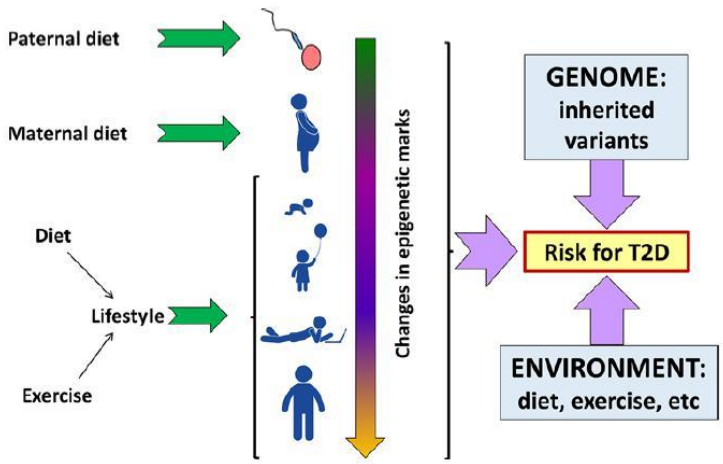

Figure 2: type 2 diabetes risks [22]

VII. MUTATIONS ASSOCIATED WITH CANCER

Cancer is a very common and well known disease. It is thought to affect quarter of world population. This prediction is due to abnormal increasing in the rates of diagnosed cancer cases all over the world, this is due to increasing in the size of population, as well as the longevity (prolonged existence of the human beings lives) [22-28]. There are a lot of cancer types and origins such as prostate, breast, colon, brain, bladder, and much more. Each kind demonstrate singular rate of mortality, and survivals. But all types of cancers shared the abnormal growth of cells which shows uncontrolled and wild propagation (proliferate) which end with a tumor. Two types of tumors, benign, by which cells shows limited growth, cells do not attack and damage the whole tissue, do not spread to other body parts, and cells can keep doing its function (or keep active in certain activities), but if the cells shows uncontrolled growth, spreading, it is called metastases, which end with death [10-14]. Figure 3 shows the number of mutation in different types of cancers. It is clear from this figure that some types of cancers combined with hundred thousand of mutations such as lung cancer and melanoma.

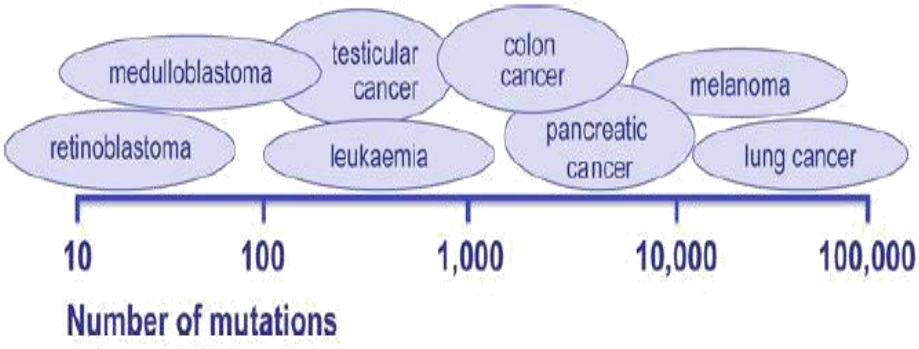

Figure 3: Types of cancers with their mutation numbers

In 2011, Hanahan & Weinberg [17] indicate that there are many factors that can contribute in the abnormal growth of cells, among these factors are:

- ❖ The uncontrolled growth of cells is due to inherent aptitude to divide.
- ❖ Cells don't respond to the growth inhibitors
- ❖ Cells promote a certain environment to keep growing.
- ❖ Cells developed their ability to spread and move to new and further tissues.
- ❖ Cells have ability to promote increase in blood to provide more nutrients and oxygen to enable them to keep growing.
- ❖ Cells are mutated.
- ❖ Resist death.

These changes in the cancer cells are mainly attributed to alterations in the genomes. The mutation normally increase the ability of chromosomes to have some changes (micro mutations); such as translocation, deletion, inversions, and duplicated.

VIII. CONCLUSIONS

- ➢ Disorder, defective genes cause diseases.
- ➢ There are different types of disorder in chromosomes and genes that cause disease, due to inheritance factor, among them are single/or multifactorial, and mitochondrial.
- ➢ Different types of cancer combined with different number of mutations, each type has certain number of mutation.

REFERENCES

[1] Torgerson T, Ochs H. Chapter 3 - Genetics of Primary Immune Deficiencies. Stiehm's Immune Deficiencies. 2014; 73-81. https://doi.org/10.1016/B978-0-12-405546-9.00003-0

[2] Levine F. Basic Genetic Principles. Fetal and Neonatal Physiology (Fifth Edition), 2017; 1: 1-13. https://doi.org/10.1016/B978-0-323-35214-7.00001-9

[3] Cole WG, Mäkitie O. Chapter 54 - Primary Disorders of Connective Tissue. Textbook of Pediatric Rheumatology (Seventh Edition). 2016: 706-719.e3. https://doi.org/10.1016/B978-0-323-24145-8.00054-5

[4] Bull, M. J., & the Committee on Genetics. (2011). Health supervision for children with Down syndrome. *Pediatrics*, 128, 393–406.

[5] Down syndrome. (2012). In A.D.A.M. Medical Encyclopedia. Retrieved June 11, 2012, from https://medlineplus.gov/ency/article/000997.htm

[6] Ulrich, D. A., Burghardt, A. R., Lloyd, M., Tiernan, C., & Hornyak, J. R. (2011) Physical activity benefits of learning to ride a two-wheel bicycle for children with Down syndrome: A randomized trial. *Physical Therapy*, 91, 1463–1477.

[7] https://genetics.thetech.org/about-genetics/mutations-and-disease

[8] https://my.clevelandclinic.org/health/diseases/15612-mitochondrial-diseases
[9] Martin, G. E., Klusek, J., Estigarribia, B., & Roberts, J. E. (2009). Language characteristics of individuals with Down syndrome. *Topics in Language Disorders*, *29*(2), 112–132.
[10] Malt, EA; Dahl, RC; Haugsand, TM; Ulvestad, IH; Emilsen, NM; Hansen, B; Cardenas, YE; Skøld, RO; Thorsen, AT; Davidsen, EM (Feb 5, 2013). "Health and disease in adults with Down syndrome". *Tidsskrift for den Norske Laegeforening: Tidsskrift for Praktisk Medicin, NY Raekke*. 133 (3): 290–94
[11] Sheets KB, Crissman BG, Feist CD, et al. (October 2011). "Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors". *J Genet Couns*. 20 (5): 432–41. doi:10.1007/s10897-011-9375-8. PMID 21618060
[12] Jackson M, Marks L, May GHW, Wilson JB. The genetic basis of disease. *Essays in Biochemistry* (2018) 62 643–723. https://doi.org/10.1042/EBC20170053
[13] Malt, EA; Dahl, RC; Haugsand, TM; Ulvestad, IH; Emilsen, NM; Hansen, B; Cardenas, YE; Skøld, RO; Thorsen, AT; Davidsen, EM (Feb 5, 2013). "Health and disease in adults with Down syndrome". *Tidsskrift for den Norske Laegeforening: Tidsskrift for Praktisk Medicin, NY Raekke*. 133 (3): 290–94.
[14] Sheets KB, Crissman BG, Feist CD, et al. (October 2011). "Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors". *J Genet Couns*. 20 (5): 432–41. doi:10.1007/s10897-011-9375-8. PMID 21618060
[15] Murphy, E. (2018) Forensic DNA typing. *Annu. Rev. Criminol.* 1, 497–515, https://doi.org/10.1146/annurev-criminol-032317-092127
[16] Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J. et al. (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 17, 405–424, https://doi.org/10.1038/gim.2015.30
[17] Hanahan, D. and Weinberg, R.A. (2011) Hallmarks of cancer: the next generation. *Cell* 144: 646–674, https://doi.org/10.1016/j.cell.2011.02.013
[18] Pereira, B. (2016) The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes. *Nat. Commun.* 7, 11479, https://doi.org/10.1038/ncomms11479.
[19] Chaturvedi S, Singh AK, Keshari AK, et al. Human Metabolic Enzymes Deficiency: A Genetic Mutation Based Approach. Scientifica. 2016; 2016: Article ID: 9828672. http://dx.doi.org/10.1155/2016/9828672
[20] Bonora, G. and Disteche, C.M. (2017) Structural aspects of the inactive X chromosome. *Phil. Trans. R. Soc. B Biol. Sci.* 372, 20160357, https://doi.org/10.1098/rstb.2016.0357
[21] Fiot, E., Zenaty, D., Boizeau, P., Haignere, J., Dos Santos, S. and Leger, J (2016) X-chromosome gene dosage as a determinant of impaired pre and postnatal growth and adult height in Turner syndrome. *Eur. J. Endocrinol.* 174, 281–288, https://doi.org/10.1530/EJE-15-1000.
[22] Jackson M, Marks L, May GHW, Wilson JB. The genetic basis of disease. Essays in Biochemistry (2018) 62 643–723. https://doi.org/10.1042/EBC20170053
[23] Stevant, I., Papaioannour, M.D. and Nef, S. (2018) A brief history of sex determination. Mol. Cell. Endocrinol., https://doi.org/10.1016/j.mce.2018.04.004
[24] Tanaka, S.S. and Nishinakamura, R. (2014) Regulation of male sex determination: genital ridge formation and Sry activation in mice. *Cell. Mol. Life Sci.* 71, 4781–4802, https://doi.org/10.1007/s00018-014-1703-3
[25] Martiniano, S. L., Sagel, S. D., & Zemanick, E. T. (2016). Cystic fibrosis: A model system for precision medicine. *Current Opinion in Pediatrics*, *28*(3), 312–317. https://doi.org/10.1097/MOP.0000000000000351
[26] Nopoulos, P.C. (2016) Huntington disease: a single-gene degenerative disorder of the striatum. *Dialogues Clin. Neurosci.* 18, 91–98.
[27] Ornitz, D.M. and Legeai-Mallet, L. (2017) Achondroplasia: development, pathogenesis, and therapy. *Dev. Dyn.* 246, 291–309, https://doi.org/10.1002/dvdy.24479
[28] Schmidt, B.Z., Haaf, J.B., Leal, T. and Noel, S. (2016) Cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis: current perspectives. *Clin. Pharmacol.* 8:, 127–140
[29] Garone C, Garcia-Diaz B, Emmanuele V, Lopez LC, Tadesse S, et al. 2014. Deoxypyrimidine monophosphate bypass therapy for thymidine kinase 2 deficiency. *EMBO Mol. Med.* 6:1016–27
[30] Ghezzi D, Baruffini E, Haack TB, Invernizzi F, Melchionda L, et al. 2012. Mutations of the mitochondrial-tRNA modifier *MTO1* cause hypertrophic cardiomyopathy and lactic acidosis. *Am. J. Hum. Genet.* 90:1079–87
[31] Ghezzi D, Saada A, D'Adamo P, Fernandez-Vizarra E, Gasparini P, et al. 2008. FASTKD2 nonsense mutation in an infantile mitochondrial encephalomyopathy associated with cytochrome c oxidase deficiency. *Am. J. Hum. Genet.* 83:415–23.
[32] Girardet A, Viart V, Plaza S, Daina G, De Rycke M, et al. 2016. The improvement of the best practice guidelines for preimplantation genetic diagnosis of cystic fibrosis: toward an international consensus. *Eur. J. Hum. Genet.* 24:469–78

