MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Genomics & Gene Therapy International Journal
ISSN: 2642-1194

Genomic Variant and Complex Disorders in Human

Chakravarty A[1]* and Chakravarty S[2]

[1]Institute of Genetic Engineering, India

[2]Institute of Genetic Medicine and Genomic Science, India

***Corresponding author:** Amit Chakravarty, Institute of Genetic Engineering, Badu, Kolkata, India, Tel: 9903850960, Email: ige.amit@gmail.com

Review Article

Volume 4 Issue 1

Received Date: June 09, 2020

Published Date: July 22, 2020

DOI: 10.23880/ggtij-16000115

Abstract

Genomic rearrangements are hot topics for research and debates due to their complex natures as well as significant health impact in either congenital or malignant disorders. In order to explain the mechanisms responsible for their generation, models have been proposed to the literature with the most well recognized of them the non-allelic homologous recombination (NAHR), micro homology-mediated break induced recombination and fork stalling and template switching, each associated with own limitations. In an attempt to address the limitations associated with the previous models, in the current study a new model is represented and substantiated by describing some of the most frequently observed recurrent rearrangements that have been reported to the literature.

Keywords: Genomic variants; DNA; Genome Reference Consortium; Pathogenic; Copy number variation

Abbreviations: GRC: Genome Reference Consortium; GWAS: Genome Wide Association Studies; SNP: Single Nucleotide Polymorphism; SV: Structural Variation; CNV: Copy Number Variation.

Background

With reference to current literature in Genetics, many well-known genetic diseases are not following mendelian inheritance pattern, they are known as multifactorial or complex trait are not caused by one specific gene or mutation. Their genotype represent multiple genes and environmental factors. So complex trait are so important they affect everybody. For example, complex disorders such as heart disease type II diabetes and obesity are the leading cause of death all over the world and also huge burden on the economy. Current understanding of these disorders have limitation and daunting task due to the complexity of the factors involved in individual genome In addition to these trait do not follow traditional principles and predictable pattern of inheritance causing to the need to approach modern methods of research.

Human Genome Variation

Understanding of our genome after Human Genome Project (DOE: USA) was over in the year 2003, made a revolution in modern biology or life science in understanding of our own genome. Now we know the difference between two individual genome are almost 99.9% identical in DNA level but 0.1 % difference are many of the things that make us unique! Now we know the people's genome differ from each other in genomic level (DNA level) these difference in your DNA help to determine what look (phenotype) like and what your risk might be for various diseases. Genome analysis (DNA sequencing) has shown that human genomes differ from one other in nucleotide level sometimes at single base and sometimes in chunks of thousands of bases. Even today researchers are still discovering new type variants (difference between two genome) within human genome. So human genome variation is more important because a very small set of these Variants are linked to difference in various trait: height, weight, skin colour, type of earwax and even with specific genetic disease.

Human Genome Project

It has made change in our understanding of human trait and how we to reach them – one example are eye color. We used to know that one dominant gene controlled brown or blue eyes and that blue eyed parents could not have brown eyed children. Now we know due to genomic variants the determine eye color. In fact at least ten genes each of which comes in several "flavours" contribute to eye color .So the combination of these gene variants in a person's genome that produces the wonderful range in human eye color (Human Genome Variation: NHGRI, USA) [1].

Hap Map Project

The first draft of DNA sequencing is over in the year 2003 and it was not understood the genetic language (code or sequence) of nucleotide sequence of first draft by the researcher involved in the same project. So Hap Map project was launched to understand the meaning of DNA nucleotide sequence and biology of the genetic code. It was applied to understand genetic variant affecting health and diseases along with interaction of drug and environment.

1000 Genome Project (1K GP)

The same project was launched in January 2008, was an International Research effort to make catalogue of Human Genetic Variation in World population. Scientists planned to sequence the genomes of at least thousand genomes of anonymous participants from number of different ethnic group using advanced genetic technology. The Project (Pilot phase) was over in the year 2010 which was published in journal Nature. After three years in 2015, two papers was published in Nature and reported many variants, restricted to closely related groups, were identified and eight structural-variation classes were analysed (Figure 1) [2].

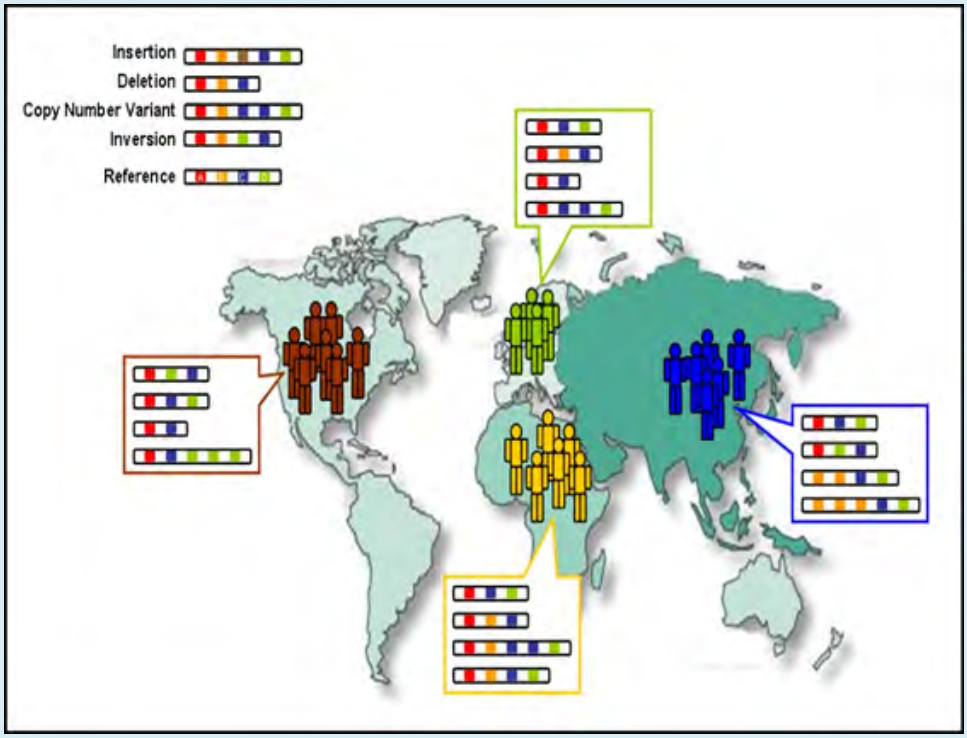

Figure 1: Changes in the number and order of genes (A-D) create genetic diversity within and between populations [2].

Human Genetic Variation Assessment

Genetic variation among human (individual) observed in DNA level in many scales from gross alteration in human karyotype to Single Nucleotide changes in above 1000 genome project reports (Nature: 2015) . The same chromosomal abnormalities observed in 1 in 160 live human birth The Nucleotide diversity (DNA level) differ between two individual was estimated (year 2004) to be 0.1 to 0.4% base pairs and later in year 2015 , the 1000 genome project which sequenced one thousand individuals and reported typical individual genome differ to 0.6% of total number of base pairs. Nearly all (>99.9%) of these sites are small

differences, either single nucleotide polymorphisms or brief insertions or deletions (indels) in the genetic sequence, but structural variations account for a greater number of base-pairs than the SNPs and indels. As of 2017, the Single Nucleotide Polymorphism Database (dbSNP), which lists SNP and other variants, listed 324 million variants found in sequenced human genomes (Figure 2).

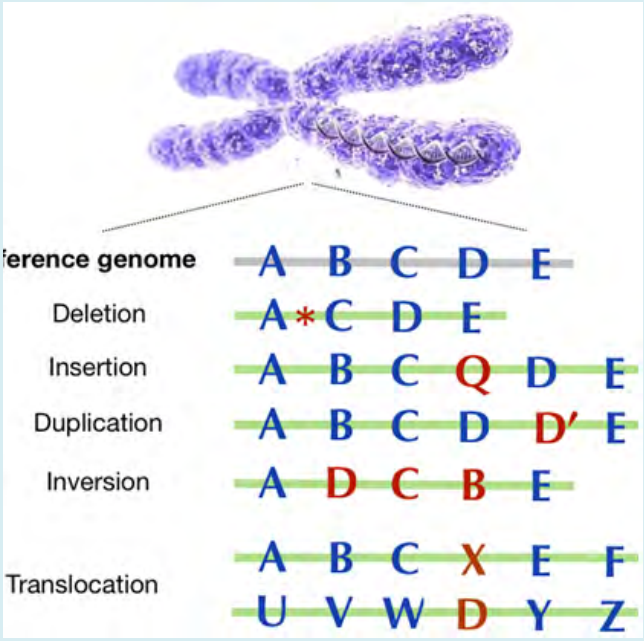

Figure 2: Genomic variation definitions [3].

Single-Nucleotide Polymorphism (SNP)

A nucleotide sequence consist of four nucleotide (known symbol is A,T,G,C) and usually these letters make sentences (known as genetic code) instruct living cell in our body to work .So in Single Nucleotide Polymorphism (SNP) make a change in genetic code i.e. make a substation of a single nucleotide that occurs at a specific position in the genome, which is very common up to 0.5% variation among normal population has shown in 1000 genome project(year;(Nature 2015) For example, at a specific base position in the human genome, the C nucleotide may appear in most individuals, but in a minority of individuals, the position is occupied by an A. This means that there is a SNP at this specific position, and the two possible nucleotide variations C or A are said to be the alleles for this specific position SNPs pinpoint differences in our susceptibility to a wide range of diseases (e.g. sickle-cell anaemia, β-thalassemia and cystic fibrosis result from SNPs). The severity of illness and the way the body responds to treatments are also manifestations of genetic variations. For example, a single-base mutation in the APOE (apolipoprotein E) gene is associated with a lower risk for Alzheimer's disease (Figures 3-5).

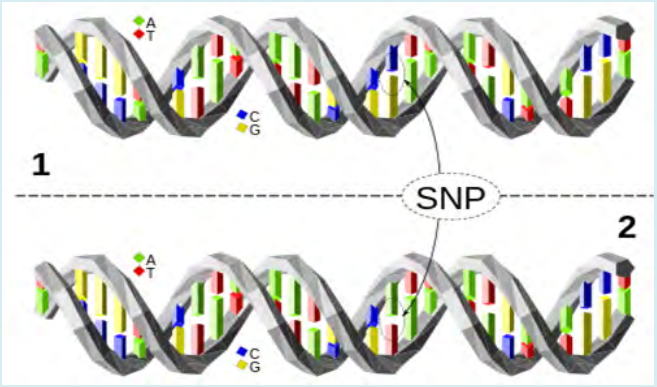

Figure 3: The upper DNA molecule differs from the lower DNA molecule at a single base-pair location (a C/A polymorphism) [4].

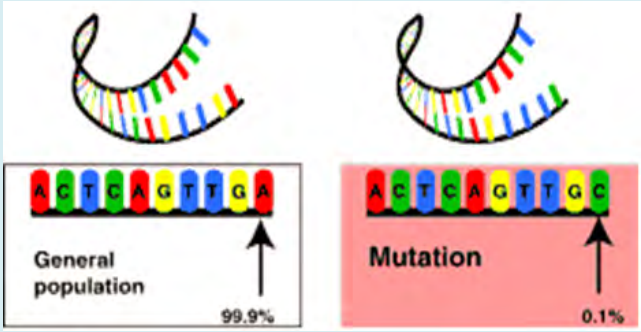

Figure 4: Genome variation due to Mutation [5].

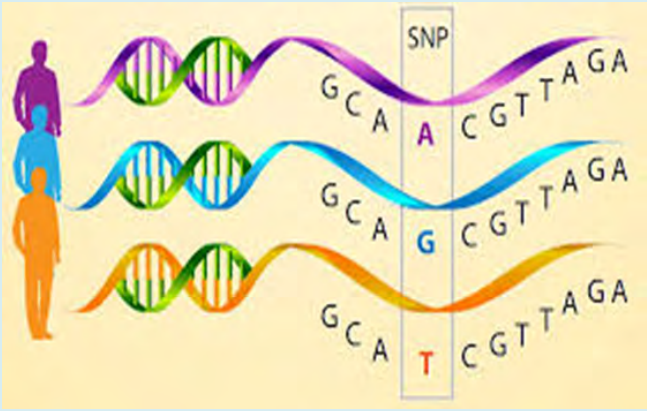

Figure 5: SNP Genotype.

Structural Variation (CNV/SV)

With reference to 1000 genome project reports (Nature;

2015), observed SVs in normal human DNA sequence are Copy Number variation (CNV), Deletions, Inhersions and duplications are much more common than SNPs diversity This observation was confirmed in 2007 studies of diploid genomes of two famous Geneticist: Craig Venter and James D. Watson (their DNA sequence was donated for research) and published in Human Genome Project and Celera Genomics respectively. So according to 1000 genome project, a typical human has 2,100 to 2,500 structural variations, which include approximately 1,000 large deletions, 160 copy-number variants, 915 Alu insertions, 128 L1 insertions, 51 SVA insertions, 4 NUMTs, and 10 inversions (Nature: 2007) (Figure 6).

Figure 6: 2007 scientific breakthrough of the year.

Copy Number Variation (CNV)

Large number of human genome sequence studies has shown CNVs a phenomenon in which section of the genome is repeated and the number of repeats in the genome varies between individual. (Nature: 2015). So it is defined that CNV is type of structural variation specifically, it is a type of duplication or deletion event that affects a considerable number of base pairs (may be Exon / Intron) So genome studies has shown, approximately two-thirds of the entire human genome may be composed of repeats and 4.8–9.5% of the human genome can be classified as Copy Number Variation (Nature: 2015). In mammals, these CNVs play an important role in making different variant (phenotype) in population as well as disease phenotype. However large population studies have demonstrated that there are two main groups of repeats (CNVs) observed they are short repeats and long repeats in human genome and have definite effect on phenotype (? Disease or Variant) (Figures 7 & 8).

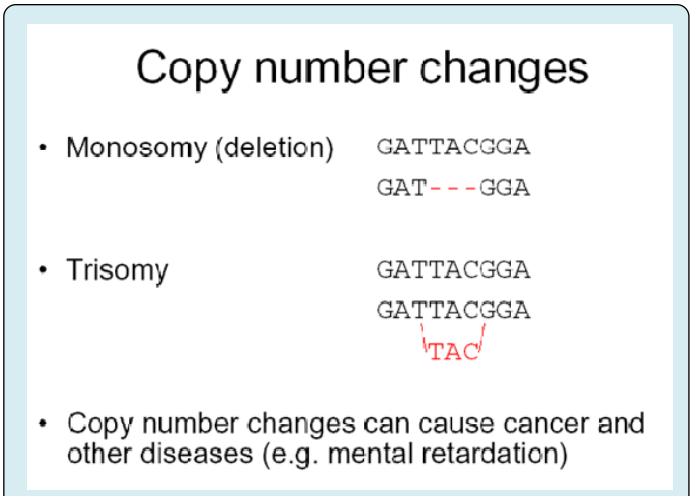

Figure 7: Copy number changes.

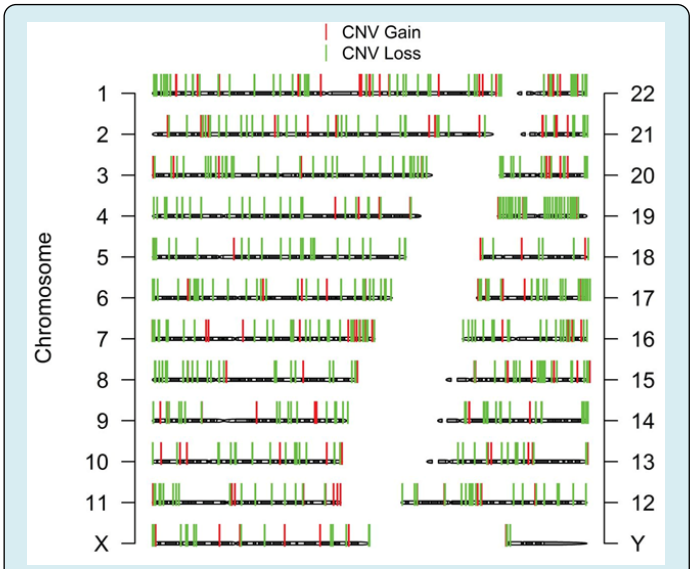

Figure 8: Genome-wide aCGH analysis reveals copy number variation (CNV) in the SSc population. Significant SSc-associated CNV identified by aCGH array were noted in the human genome. Red bars represents high copy number in SSc, while green bars represent low copy number in SSc. aCGH: array comparative genomic hybridization; SSc: systemic sclerosis [6].

Recognised Genomic Diseases in Human

Case Presentation

Diabetes Type-1: Current medical literature has define that in Diabetes type-1 patient have severe insulin deficient due to malfunction of beta-cells of pancreas as a result high blood sugar level in patient blood caused Diabetes.

Clinical Phenotype: In type 1 diabetes patient usually have high blood sugar (hyperglycaemia) due to abnormal function of bets-cells in pancreases as a result body (tissues/cells) unable to use glucose for making energy and in the long-run patient get hypoglycaemia (low sugar in brain) and leads to coma in untreated patient.

Type 1 Diabetes could occur at any age (onset), usually in many patient it is observed in early adulthood or in adolescence. Patient high blood sugar could cause symptoms of the disorder may include frequent urination (polyuria) excessive thirst (polydipsia), fatigue, blurred vision and weight loss. Uncontrolled type 1 diabetes can lead to a life-threatening complication called diabetic ketoacidosis. Without insulin, cells cannot take in glucose (Figure 9).

The retina, which is the light-sensitive tissue at the back of the eye can be damaged (diabetic retinopathy), leading to vision loss and eventual blindness. Kidney damage (diabetic nephropathy) may also occur and can lead to kidney failure and end-stage renal disease (ESRD). Pain, tingling, and loss of normal sensation (diabetic neuropathy) often occur, especially in the feet. Impaired circulation and absence of the normal sensations that prompt reaction to injury can result in permanent damage to the feet; in severe cases, the damage can lead to amputation. People with type 1 diabetes are also at increased risk of heart attacks, strokes, and problems with urinary and sexual function [7].

Figure 9: Main symptoms of Diabetes [8].

Frequency: Type 1 diabetes occurs in 10 to 20 per 100,000 people per year in the United States. By age 18, approximately 1 in 300 people in the United States develop type 1 diabetes. The disorder occurs with similar frequencies in Europe, the United Kingdom, Canada, and New Zealand. Type 1 diabetes occurs much less frequently in Asia and South America, with reported incidences as low as 1 in 1 million per year. For unknown reasons, during the past 20 years the worldwide incidence of type 1 diabetes has been increasing by 2 to 5 percent each year. Type 1 diabetes accounts for 5 to 10 percent of cases of diabetes worldwide. Most people with diabetes have type 2 diabetes in which the body continues to produce insulin but becomes less able to use it.

Genotype: The causes of type 1 diabetes are unknown, although several risk factors have been identified. The risk of developing type 1 diabetes is increased by certain variants (mutation) of the HLA-DQA1, HLA-DQB1, and HLA-DRB1 genes. These genes provide instructions for making proteins that play a critical role in the immune system. The HLA-DQA1, HLA-DQB1, and HLA-DRB1 genes belong to a family of genes called the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria. Type 1 diabetes is generally considered to be an autoimmune disorder. Autoimmune disorders occur when the immune system attacks the body's own tissues and organs. For unknown reasons, in people with type 1 diabetes the immune system damages the insulin-producing beta cells in the pancreas. Damage to these cells impairs insulin production and leads to the signs and symptoms of type 1 diabetes.

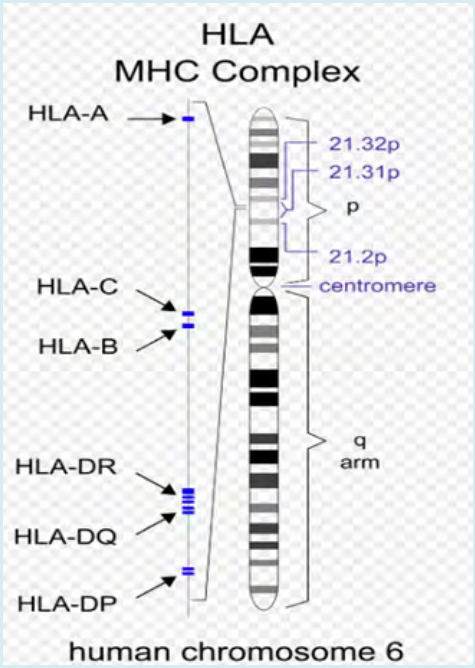

Figure 10: HLA genotype in diabetes type I.

HLA genes, including HLA-DQA1, HLA-DQB1, and HLA-DRB1, have many variations, and individuals have a certain combination of these variations, called a haplotype. Certain HLA haplotypes are associated with a higher risk of developing type 1 diabetes, with particular combinations of HLA-DQA1, HLA-DQB1, and HLA-DRB1 gene variations resulting in the highest risk. Other HLA variations appear to be protective against the disease. Additional contributors, such as environmental factors and variations in other genes, are also thought to influence the development of this complex disorder (Figure 10).

Genetic Testing and Diagnosis: Is Type 1 diabetes genetically inherited?

Family History: Since type 1 diabetes involves an inherited susceptibility to developing the disease, if a family member has (or had) type 1, you are at a higher risk. If both parents have (or had) type 1, the likelihood of their child developing type 1 is higher than if just one parent has (or had) diabetes (Figure 11).

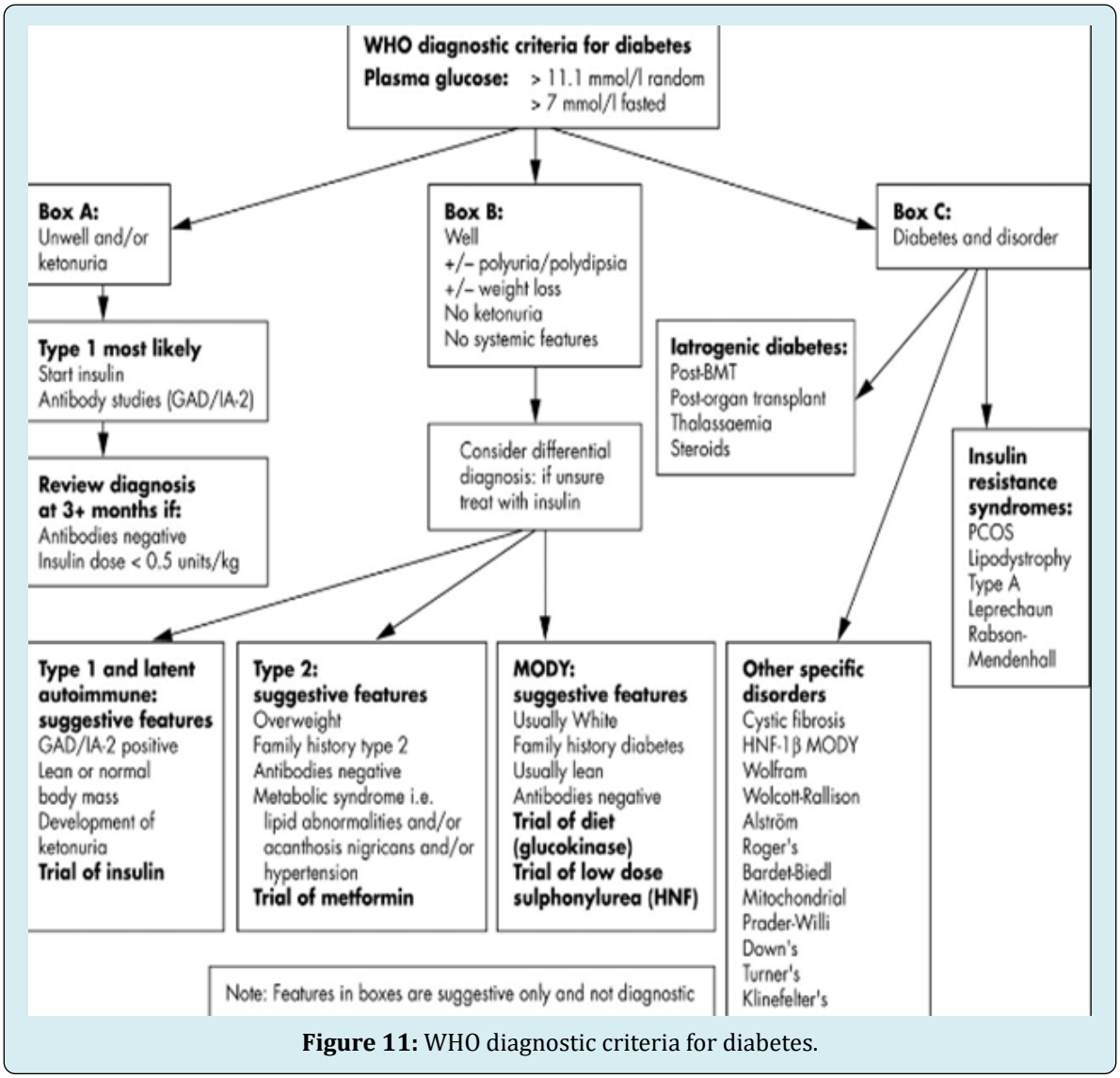

Figure 11: WHO diagnostic criteria for diabetes.

Genetic Counselling: A predisposition to develop type 1 diabetes is passed through generations in families, but the inheritance pattern is unknown. In general, if you are a man with type 1 diabetes, the odds of your child developing diabetes are 1 in 17.If you are a woman with type 1 diabetes and your child was born before you were 25, your child's risk is 1 in 25; if your child was born after you turned 25, your child's risk is 1 in 100.Your child's risk is doubled if you developed diabetes before age 11. If both you and your partner have type 1 diabetes, the risk is between 1 in 10 and 1 in 4.

Researchers are learning how to predict a person's odds of getting diabetes. For example, most whites with type 1 diabetes have genes called HLA-DR3 or HLA-DR4. If you and your child are white and share these genes, your child's risk is higher. (Suspect genes in other ethnic groups are less well studied. The HLA-DR7 gene may put African Americans at risk, and the HLA-DR9 gene may put Japanese at risk).

Diabetes Type-2

Diabetes Type 2 patient usually have high blood sugar (hyperglycaemia) levels in bloodstream unable to utilize by cells or tissues without insulin response (low levels or absent insulin) make system hypoglycaemic (low glucose) resulted coma in untreated patient.

Clinical Phenotype: In normal physiological condition, insulin produced by pancreas that helps to regulate blood sugar levels and balanced by feedback system makes our body energy system normal. Diabetes Type 2 patient have typical featured is hyperglycaemia (high blood sugar) and low levels of insulin make body to stops using enough glucose resulted diabetes condition (hypoglycaemia).

In large number of patient with type 2 diabetes first have insulin resistance, a condition in which the body's cells insulin less efficiently than normal, as insulin resistance develops, more and more insulin is needed to keep blood sugar levels in normal range. Over time, the beta cells response reduced leading to insulin shortage that prevents the body from reducing blood sugar levels (hypoglycaemic condition) effectively. Diabetes Type 2 can occur at any age, but it most commonly observed onset at middle age or later. Most common signs and symptoms are include frequent urination (polyuria), excessive thirst (polydipsia), fatigue, blurred vision, tingling or loss of feeling in the hands and feet (diabetic neuropathy), sores that do not heal well, and weight loss.

Frequency: Diabetes Type 2 is most commonly observed accounting 90 to 95% of all cases. In 2015, in USA more than 23 million people had diagnosed as diabetes type 2 and in additional 7 million people likely had undiagnosed diabetes. And it is seventh leading cause of death in USA. It is observed in World Population, diabetes type 2 is rapidly increasing due to increase inactive (sedentary) lifestyle, obesity and other risk factors, the frequency of this disease has more than quadrupled in the past 35 yrs.

Americans and Alaska Natives. It also has a higher prevalence among people of African American or Hispanic ancestry than those of non-Hispanic white or Asian ancestry. Geographically, diabetes is most prevalent in the southern and Appalachian regions of the United States.

Genotype: Genetic variation likely to act together with life style and obesity to influence an individual's overall risk of getting type 2 diabetes Large population studies has shown that at least 150 DNA variation that are associated with risk of developing type 2 diabetes and each person has some variations that increase risk and others that reduce risk To date only two genes, calpain 10 (CAPN10) and hepatocyte nuclear factor 4 alpha (HNF4A), have been identified by 1000 genome studies (Nature: 2015).

Most of the Genetic variations associated with type 2 diabetes are thought to act by subtly changing the amount, timing and location of the gene activity (expression) and the release and processing of insulin, and cells' sensitivity to the effects of insulin. Gestational Diabetes usually occurs during pregnancy. Currently literature has shown that risks factors predispose to type 2 diabetes are-Lifestyle factors including smoking, a poor diet, and physical inactivity also increase the risk of type 2 diabetes (Figure 12).

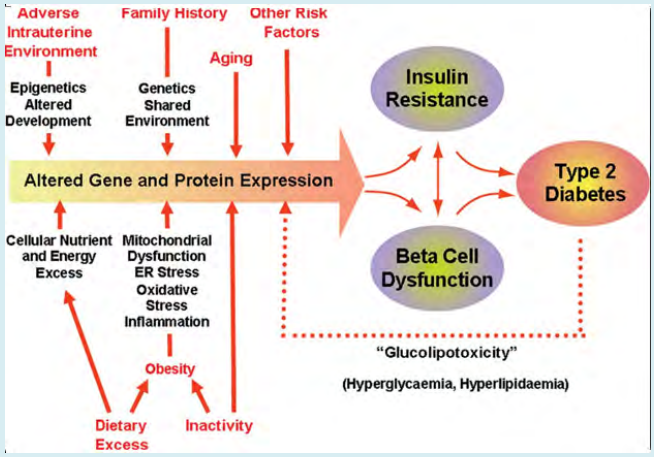

Figure 12: Altered Gene and Protein Expression [9].

Genetic Testing and Diagnosis: New genetic risk test for Type 1 Dr Oram and colleagues have developed a test which looks for 30 genetic changes in a person's DNA. If a person score is high, they are more likely to have Type 1 diabetes. If the score is low, they are more likely to have Type 2 diabetes

Diabetes susceptibility genetic testing, analysis of 9 types of common diabetes mellitus, 116 mutations of the 206 mutations. It can be used to evaluate the risk assessment of diabetes mellitus and determine the genetic background of the pathogenesis of diabetes (Table 1) [10].

Type of Diabetes	Detection of Susceptibility Genes
Type II diabetes	TMEM163、VEGFA、INS、AGT、IGF2BP2
Type I diabetes	INS、TNF、HNF1A、ERBB3、CLEC16A
Gestational diabetes	TCF7L2、PNPLA3、SLC30A8、RBP4、CDKN2A
Diabetic retinopathy	VEGFA、ICAM1、NOS3、VEGF、SOD
Diabetic nephropathy	ACE、ADIPOQ、MTHFR、ACE、SERPINEL
Diabetic foot	TNFRSF11B
Diabetes pyruvic acid disease	HNF1A PAX4
pre-diabetes	ATF6
Wolfram syndrome	WFS1

Table 1: Diabetes susceptibility genetic testing.

Genetic Counselling: Type 2 diabetes has several causes: genetics and lifestyle are the most important ones. A combination of these factors can cause insulin resistance, when your body doesn't use insulin as well as it should. Insulin resistance is the most common cause of type 2 diabetes. Type 2 diabetes can be hereditary.

a) Does Type 2 diabetes skip a generation?

b) Type 2 Diabetes: Your Child's Risk. Type 2 diabetes runs in families. In part, this tendency is due to children learning bad habits eating a poor diet, not exercising from their parents. But there is also a genetic basis.

The risk of developing type 2 diabetes increases with the number of affected family members. The increased risk is likely due in part to shared genetic factors, but it is also related to lifestyle influences (such as eating and exercise habits) that are shared by members of a family.

References

1. (2020) Human Genome Project FAQ. National Human Genome Research Institute (NIH).
2. 1000 Genomes Project.
3. (2015) We combine computational and genomic techniques to explore genome biology and the genetic basis of traits. Quinlan lab.
4. Single-Nucleotide polymorphism.
5. (2003) Genome Variations. Genome News Network.
6. Shicheng G, Li Y, Wang Y, Chu H, Chen Y, et al. (2016) Copy Number Variation of HLA-DQA1 and APOBEC3A/3B Contribute to the Susceptibility of Systemic Sclerosis in the Chinese Han Population. The journal of Rheumatology 43(5): 880-886.
7. (2013) Type 1 diabetes. Genetics Home Reference.
8. Type 1 diabetes.
9. Jin W, Mary Elizabeth P (2009) Genetic determinants and molecular pathways in the pathogenesis of Type 2 diabetes. Clinical science 116(2): 99-111.
10. Diabetes Susceptibility Genetic Test. Ardent Biomed Hong kong.