CHAPTER – III
CHAPTER III

DIAGNOSTIC MODEL OF THE PROBLEM

3.1. DESIGNING OF THE PROBLEM

Diabetes mellitus is a set of disorders characterized by either an absolute or a relative deficiency of Insulin and/or Insulin resistance which results in abnormalities of carbohydrate, fat, protein metabolism expressed primarily as

- Hyperglycemia &
- Hypoglycemia

Failure of Insulin mediated transport of Glucose into cells results in loss of essential fluids and malfunctioning of major organs like Heat, kidney, eye etc.

3.1.1. DIABETES DEFINITION- IN DIAGNOSTICS

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose (blood sugar) resulting from defects in insulin secretion, insulin action, or both. Insulin is a hormone produced by the pancreas which allows glucose (sugar) to enter body cells and be converted into energy. Insulin is also needed to synthesize protein and store fats. In uncontrolled diabetes, glucose and lipids (fats) remain in the bloodstream and, with time, damage the body's vital organs and contribute to heart disease. Diabetes can be associated
with serious complications and premature death, but persons with early
diagnosis of diabetes can take measures to reduce the likelihood of such
occurrences.

Diabetes is classified into two main types: Type 1 (previously known as
insulin-dependent diabetes mellitus or "juvenile onset" diabetes), and Type 2
(previously known as non insulin-dependent diabetes mellitus or "adult onset"
diabetes). Type 1 diabetes accounts for 5 to 10 percent of diabetes cases.
Although this type of diabetes can occur at any age, it most often appears in the
childhood or teen years. In Type 1 diabetes, the pancreas produces little or no
insulin so that persons with Type 1 diabetes require daily injections of insulin
to live.

The most common type of diabetes is Type 2 diabetes which affects 90
to 95 percent of those with diabetes. In Type 2 diabetes, the pancreas usually
produces insulin, but for some reason like skin thickness etc, the body cannot
use the insulin effectively. In both Type 1 and Type 2 diabetes, if glucose level
is uncontrolled, the end result is an unhealthy excess level of glucose in the
blood stream. This creates incapacity in the body cells to make efficient use of
its main source of fuel. Over time, high levels of blood glucose damages
microvascular and macrovascular systems and lead to complications such as
blindness, amputations, heart disease and kidney failures.
3.1.2. PANCREAS - THE PRODUCTION HOUSE FOR INSULIN

The pancreas is an elongated organ, light tan or pinkish in color, that lies below the stomach, in a bend of the duodenum (the beginning portion of the small intestine). It is covered with a very thin connective tissue capsule that extends inward as septa (walls), partitioning the gland into lobules (small lobes). Functionally the pancreas is divided into two portions:

1. The Exocrine Pancreas

2. The Endocrine Pancreas

3.1.3. THE ROLE OF EXOCRINE PANCREAS

The bulk of the pancreas is composed of pancreatic exocrine cells fig [3.1] and their associated ducts. The exocrine cells secrete the digestive juices. Pancreatic exocrine cells are arranged in grape-like clusters called acini (singular acinus). The exocrine cells themselves are packed with secretory granules which contain digestive enzymes that are extruded into the lumen of the acinus.

Figure [3.1] Exocrine Portion of the Pancreas
The exocrine portion of the pancreas accounts for about 80% of the total glandular volume. It consists of at least two functional units:

1. acinar cells, which secrete primarily digestive enzymes;
2. centroacinar or ductal cells, which secrete fluids and electrolytes.

From there these secretions flow into larger and larger ducts, which eventually coalesce into the main pancreatic duct which drains directly into the duodenum. The exocrine functions are concerned with digestion.

Pancreatic secretion is regulated by several peptides that are released from the gastrointestinal tract. Some of these peptides, such as secretin and cholecystokinin (CCK), stimulate pancreatic secretions, whereas somatostatin and pancreatic polypeptide inhibit their release.

The pancreas secretes about 20 digestive enzymes and cofactors. Some enzymes are activated in the duodenum. These enzymes account for most of the intraluminal digestion of dietary proteins, triglycerides and carbohydrates. They are also important in the cleavage of certain vitamins (such as A and B12) from carrier molecules, thereby allowing them to be absorbed efficiently. Because pancreatic enzymes are secreted in great excess, maldigestion and serious nutritional deficiencies occur only when over 90% of the gland has been destroyed.
3.1.4. THE ROLE OF ENDOCRINE PANCREAS

Embedded within this exocrine tissue are roughly one million small clusters of cells called the Islets of Langerhans or simply the ‘islets’. The endocrine pancreas refers to these cells within the pancreas that synthesize and secrete hormones. The endocrine function consists primarily of the secretion of the two major hormones, insulin and glucagons. Humans have roughly one million islets fig [3.2].

Figure [3.2] Pancreatic Islets

Pancreatic islets house three major cell types, each of which produces a different endocrine product - hormone:

- Alpha cells (A cells) secrete the hormone glucagon. Glucagon is a catabolic hormone, that is, it mobilizes glucose, fatty acids and amino acids from stores into the blood.
- Beta cells (B cells) produce insulin and are the most abundant of the islet cells. Insulin is an anabolic hormone, that is, it increases the storage of glucose, fatty acids and amino acids in cells and tissues.
- Delta cells (D cells) secrete the hormone somatostatin, which is also produced by a number of other endocrine cells in the body. Somatostatin may regulate, locally, the secretion of the other pancreatic hormones; in brain (hypothalamus) and spinal cord it may act as a neurohormone and neurotransmitter.

Table [3.1] Type-1 and Type-2 Diabetes - the Differences

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously known as insulin-dependent diabetes mellitus (IDDM) or &quot;juvenile-onset&quot; diabetes. [27]</td>
<td>Previously known as noninsulin-dependent diabetes mellitus (NIDDM) or &quot;adult-onset&quot; diabetes.</td>
</tr>
<tr>
<td>Less common, accounts for 5 to 10 percent of diabetes cases.</td>
<td>The most common type of diabetes, accounts for 90 to 90 percent of diabetes cases.</td>
</tr>
<tr>
<td>Most commonly diagnosed in childhood or teen years.</td>
<td>Most commonly diagnosed in adults over the age of 40.</td>
</tr>
<tr>
<td>The pancreas produces little or no insulin so that person with Type 1 diabetes require daily injections of insulin to live.</td>
<td>The pancreas either produces an insufficient amount of insulin or the body cannot use the insulin effectively.</td>
</tr>
<tr>
<td>If untreated, the end result is death.</td>
<td>If untreated, the end result is serious complications which can lead to death.</td>
</tr>
</tbody>
</table>

For both Type 1 and Type 2 diabetes, if uncontrolled, the end result is an unhealthy buildup of glucose in the blood and an inability of the body to make efficient use of its main source of fuel. Over time, high levels of blood glucose damage microvascular and macrovascular systems and lead to complications such as blindness, amputations, heart disease and kidney disease.
Table [3.2] Complications / Co-Morbidity Rates

CENTRAL OHIO DIABETES

<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>CLINICAL SAMPLE</th>
<th>ASSOCIATION SAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision Problems</td>
<td>44 percent</td>
<td>54 percent</td>
</tr>
<tr>
<td>Numbness / Tingling in Fingers or Toes</td>
<td>50 percent</td>
<td>50 percent</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>54 percent</td>
<td>74 percent</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>24 percent</td>
<td>29 percent</td>
</tr>
<tr>
<td>Breathing</td>
<td>28 percent</td>
<td>36 percent</td>
</tr>
<tr>
<td>Dental Problems</td>
<td>17 percent</td>
<td>28 percent</td>
</tr>
</tbody>
</table>

Table [3.3] Diagnosis of Diabetes

- symptoms and plasma glucose ≥ 11.1 mmol/l
- fasting plasma glucose ≥ 7.0 mmol/l
- 75g OGTT 2 hour plasma glucose ≥ 11.1 mmol/l
  - Impaired glucose tolerance
    - fasting plasma glucose < 7.0 mmol/l and
    - 75g OGTT 2 hour plasma glucose 7.8 - 11.0 mmol/l
  - Impaired fasting glucose
    - fasting plasma glucose > 6.0 mmol/l and < 7.0 mmol/l
- Normal plasma glucose levels
  - fasting ≤ 6.0 mmol/l and 2h 75g OGTT < 7.8 mmol
Table [3.4] Classification of Diabetes Mellitus

| Type 1 | autoimmune destruction of insulin producing pancreatic beta islet cells  
UK prevalence 0.5% and rising. |
| Type 2 | insulin resistant condition with inadequate insulin secretion UK prevalence 4% (2% overt) and rising |
| Gestational diabetes | |
| Other types | pancreatic disease  
endocrine disease  
drug induced  
specific genetic disorders |
3.1.5. INSULIN
FROM PANCREATIC ISLET CELLS
SECRETION REQUIRES GLUCOSE ENTRY IN CELLS [28]
SECRETION TRIGGERED BY

- Hyperglycaemia
- vagal stimulation
- leucine / arginine
- free fatty acids & ketone bodies
- sulphonylurea drugs

**Figure [3.3] Secretion of Insulin**

SECRETION ENHANCED BY

- GIP
- glucagon like peptide
- vagal stimulation
- neuropeptide Y
- neuropeptide Y

SECRETION INHIBITED BY

- catecholamines
- neuropeptide Y
- omatostatin
- diazoxide
### Table [3.5] Differences Between Type 1 & Type 2 Diabetes

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>typical onset &lt; 30 years</td>
<td>typical onset &gt; 20 years</td>
</tr>
<tr>
<td>can start at any age</td>
<td>can start at any age</td>
</tr>
<tr>
<td>sudden onset</td>
<td>gradual onset</td>
</tr>
<tr>
<td>severe symptoms</td>
<td>may be no symptoms</td>
</tr>
<tr>
<td>recent weight loss</td>
<td>often no weight loss</td>
</tr>
<tr>
<td>usually thin</td>
<td>usually obese</td>
</tr>
<tr>
<td>spontaneous ketosis</td>
<td>not ketotic</td>
</tr>
<tr>
<td>absent C – peptide</td>
<td>detectable C-peptide</td>
</tr>
<tr>
<td>markers of autoimmunity</td>
<td>no autoimmune markers</td>
</tr>
</tbody>
</table>

### Figure [3.4] Symptoms of Diabetes due to Hyperglycaemia

- hyperglycaemia
  - swelling of lens → blurred vision
  - cerebral effects → lightheadedness malaise mental changes
3.1.6. CAUSES OF DIABETES

CAUSES OF TYPE 1 DIABETES [29]

- 30% identical twin concordance rate
- prevalence increasing currently 0.5%
- in Europe prevalence increases toward north pole
- onset in childhood increasing
- childhood diabetes more prevalent in rural areas

3.1.7. CAUSES OF TYPE 2 DIABETES

Underlying insulin resistance

- genetic (90% identical twin concordance)
- ethnicity (thrifty genotype hypothesis)
- obesity
- inactivity / low physical fitness
- intrauterine malnutrition (Barker hypothesis)
- smoking & drugs

Impaired insulin secretion

- genetic
- environmental

Insulin secretion worsens with time
3.1.8. TYPE 2 DIABETES MELLITUS

- usually insulin resistant with inadequate insulin production to maintain normal glucose levels
- onset (usually gradual) at any age, usually >20 years
- usually overweight or obese but not ketotic and often no symptoms at presentation
- higher rates in UK Asian and Afro-Caribbean people
- Worldwide very high prevalence in rural to urban migrant communities
### Table [3.6] Treatment of Diabetes [30]

<table>
<thead>
<tr>
<th>Type of Diabetes</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>diet, exercise &amp; insulin</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>diet, exercise, metformin or sulphonylurea alone, metformin and sulphonylurea, metformin, sulphonylurea &amp; thiazolidinedione, insulin, GDB, diet, insulin</td>
</tr>
</tbody>
</table>

### Table [3.7] Drugs to treat Hyperglycaemia [31]

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin and Insulin Analogues</td>
<td>lispro insulin, aspart insulin, insulin glargine</td>
</tr>
<tr>
<td>Insulin Secretagogues</td>
<td>Sulphonylurea: gliclazide, glibenclamide; non-sulphonylurea: repaglinide, nateglinide</td>
</tr>
<tr>
<td>Insulin Sensitizers</td>
<td>biguanide metformin, thiazolidinedione rosiglitazone, pioglitazone</td>
</tr>
<tr>
<td>Intestinal Absorption Inhibitors</td>
<td>acarbose, orlistat</td>
</tr>
</tbody>
</table>
3.2. ANALYSIS OF THE DISEASE
GENETICS OF DIABETES MELLITUS

3.2.1. MAJOR CAUSES FOR TYPE 2 DIABETES

Although researchers know from studying family histories, that a person can inherit a risk for type 2, [32] there are difficulties in identifying specific gene mutations that causes the disease. Some of the problems include:-

Number of genes: Many genes are involved in controlling our food intake and energy regulation. Sudden mutations in any one gene may not lead to diabetes but mutations in several genes may add up the risk to a higher level.

Environmental influence: A person’s lifestyle and domestic environment play a larger role in whether or not they develop type 2 diabetes. Stress, anxiety and tension must be avoided in day-to-day life. Two people may have the same gene mutations but may not be developing the disease.

Inherited Life style: Poor eating habits and lack of exercise inherited from familial habits which children picked up from their parents may even lead to genetic risk for diabetes. Obesity must be avoided by children and adults.

Despite these problems researches have found a few gene mutations that dominantly influence Diabetes risk in certain ethnic groups. One well studies gene is Beta 3-adrenergic receptor gene.

The Beta 3-adrenergic receptor gene makes a protein in fat cells that is involved in determining how much fuel the body burns when it is resting.
Linux mutation in this gene slows down how quickly a person burns fat increasing their tendencies to be obese. One specific mutation in this gene called TRP64ARG is almost four times more common in Pima Indians than in people of European descent and one and half times more common in African or American descent. Peoples with two copies of TRP64ARG mutation have slower metabolism than people without the mutation. Therefore they tend to be more obese and tend to develop diabetes. In addition, people with TRP64ARG mutation develop diabetes at an earlier age than type 2 diabetes without mutations. This mutation may not be present in all type 2 diabetes, but it appears to change the course of diabetes in those who carry it. The TRP64ARG mutation cause the Beta3 - adrenergic receptor gene to make a different protein sequence. The name is an abbreviation for the change in the protein causes by the mutation. The altered protein sequence has the amino acid Arginine (ARG) at the 64th position rather than the amino acid Tryphtophan (TRP). This switch in amino acid building blocks prevents the protein from working properly. The Beta-3 adrenergic receptor gene is not the only gene that regulates how we metabolize fat. Researches indicate that mutations in similar genes may also put a person at high risk for diabetes.

Genetic defects of β-cell function by characteristic genes

a) Chromosome 20 - HNF-4G or HNF-α (MODY 1)
b) Chromosome > - Glucokinase (MODY 2)
c) Chromosome 12 - HNF-1 α c (MODY 3)
d) Chromosome 13 - IDF-1 (MODY 4)
e) Chromosome 20 - HNF-1 β (MODY 5)
f) Mitochondrial DNA mutations
g) Others


3.2.3. MAJOR CAUSES FOR TYPE 1 DIABETES [33]
GENETIC CAUSES OF β CELL AUTOIMMUNITY AND DIABETES

As mentioned previously, the development of IDDM [34] is controlled by several genetic loci, of which the most significant contributor may be the Major Histo Compatibility complex region (MHC) located on chromosome six. Specifically, it has been found that the primary locus of susceptibility to IDDM includes the HLA-DR and HLA-DQ Table [3.9] to Table [3.11] genes, but new possible loci [35] for IDDM outside the HLA region are currently being identified. Studies involving the BB rat demonstrate that susceptibility to diabetes is strongly linked to genetic markers for the MHC and the inheritance of phenotypic markers like T lymphopenia. It is not yet known which of these markers associated with diabetes are important for development of β cell autoimmunity and which determine progress to full scale diabetes. Here three
out of fifteen loci linked to type 1 diabetes in NOD mice leads to autoimmunity [36] without the progression of diabetes. Researchers have been unable to identify a particular HLA genotype that is associated with the initiation of β cell autoimmunity in human beings. However, it has been determined that the HLA-DRβ1*0301/04, HLA-DQβ1*0201/0302 genotypes promotes autoimmunity [37] persistence and progression to the diseases state of diabetes. Although the DRβ1*0301/04, DQβ1*0201/0302 heterozygotes make up only 2% of the population, this genotype is found in 30-40% of IDDM patients. The genetic nature of diabetes continues to perplex scientists as both susceptibility and protection from IDDM, are associated with changes in the sequences of amino acids even within one locus. For example, the human HLA-DQβ1 gene, the genes *0302 and *0201 are found to be linked to progression of autoimmunity, while other gene such as *0602 inhibit progression from autoimmunity to diabetes.

In most non-diabetic persons, position 57 of the HLA-DQβ1 [38] chain contains an aspartic acid residue. However, Caucasians patients with IDDM show an increased likelihood of having valine, serine, or alanine at this position. In non-diabetic individuals with an aspartic acid residue at position 57, a salt bridge is able to form to an arginine residue in the adjacent alpha chain of the MHC class II molecule. In patients with IDDM, a substituted amino acid at position 57 to an uncharged residue such as alanine
disrupts the stability of the MHC class II molecule and interferes with the salt bridge formation Figure 3.5 to 3.7. Additionally, as discussed in the previous section, some research has found that slight variations in the genes for the Tap transporter protein, which are located within the region of the MHC class II molecule may play an integral role in causing an autoimmune reaction by CD8 T cells to self peptides on β cells. This knowledge gave way for scientists to determine the role of HLA and additional IDDM [39] candidate genes in the induction of autoimmunity and progression to diabetes.
3.3. FIGURES FOR MUTATIONS

HLA and additional IDDM candidate genes in the induction of autoimmunity and progression to diabetes.

**Fig [3.5]** Position 57 (shown in red) of the HLA-DQB chain (blue) plays an integral role in susceptibility to IDDM (Janeway et al., 1998).

**Fig [3.6]** An MHC class II molecule (from a non-diabetic individual) with an aspartic acid residue at position 57 is able to form a stable salt bridge (green) between an aspartic acid residue (red) and an arginine residue (pink) of the adjacent alpha chain (gray). An aspartic acid residue at this position is associated with resistance to IDDM (Janeway et al., 1998).

**Fig [3.7]** An MHC class II molecule from a type 1 diabetic has a substituted amino acid at position 57. This photo shows alanine (yellow) at position 57. The presence of alanine at this position disrupts the formation of the salt bridge and is associated with increased susceptibility to IDDM (Janeway et al., 1998).
3.4. CONCLUSIONS FROM DIAGNOSTIC MODEL

Diabetes mellitus is a killer disease facing the mankind characterized by absolute or relative deficiency of the hormone insulin from pancreas of human body. It creates higher level of glucose in bloodstream and urine. The elevated levels of glucose may damage major organs of the body's heart and kidney. In type 1 diabetes pancreas produce little or no insulin requiring daily injection of insulin to live. Type 2 diabetes have the product of insulin but transportation of the insulin to cells of the body is disrupted. Major causes of TYPE-1 diabetes are found to be number and types of genes (and their mutations), lifestyle, environmental hazards of an individual. The Beta3-adrenenergic receptor gene with its TRP64ARG mutation is a major cause of type-2 diabetes. In MHC class II molecules the substitution of alanine at position no 57 of amino acid sequence disrupts the formation of salt bridge formation and gives increased susceptibility to IDDM.
3.5. ANNEXURE

3.5.1. TABLES AND GRAPHS FOR CHAPTER 3 AND 4

Table [3.8] HLA - DQ and Type 1 Diabetes

Relative, Absolute § and Attributable Risk for S/S, S/P and P/P from the WHO DiaMond Molecular Epidemiology Project^.

<table>
<thead>
<tr>
<th>Population</th>
<th>Odds Ratio</th>
<th>Absolute Risks§</th>
<th>Population Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S/S</td>
<td>S/P</td>
<td>P/P</td>
</tr>
<tr>
<td>Caucasian^a</td>
<td>15.9*</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>African American^b</td>
<td>44.8*</td>
<td>7.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Asian^c</td>
<td>10.7*</td>
<td>3.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*p = < 0.0001, Test for trend
§Absolute risks are expressed as % through age 30

Caucasian^a: S = DQA1*0301-DQB1*0302, DQA1*0501-DQB1*0201,
DQA1*0301-DQB1*0201

African American^b: S = DQA1*0301-DQB1*0302, DQA1*0501-DQB1*0201,
DQA1*0301-DQB1*0201

Asian^c: S = DQA1*0301-DQB1*0401, DQA1*0301-DQB1*0303
Table [3.9] HLA - DQ and Type 1 Diabetes

Frequencies of DQB1 alleles among type 1 diabetic cases and unrelated non-diabetic controls from WHO Diamond Molecular Project\(^6\) and the 12\(^{th}\) International Histocompatibility Workshop and Conference\(^8\)

<table>
<thead>
<tr>
<th>DQB1 Alleles</th>
<th><strong>Caucasian</strong>&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>African American</strong>&lt;sup&gt;b&lt;/sup&gt;</th>
<th><strong>Asian</strong>&lt;sup&gt;c&lt;/sup&gt;</th>
<th><strong>12&lt;sup&gt;th&lt;/sup&gt; IHWC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=163)</td>
<td>Controls (n=192)</td>
<td>Cases (n=99)</td>
<td>Controls (n=152)</td>
</tr>
<tr>
<td>*0201</td>
<td>.30</td>
<td>.22</td>
<td>.46&lt;sup&gt;*&lt;/sup&gt;</td>
<td>.18</td>
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<tr>
<td>*0301</td>
<td>.10&lt;sup&gt;*&lt;/sup&gt;</td>
<td>.17</td>
<td>.09&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>.31&lt;sup&gt;*&lt;/sup&gt;</td>
<td>.09</td>
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<tr>
<td>*0303</td>
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<td>*0401</td>
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<tr>
<td>*0402</td>
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<tr>
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<tr>
<td>*0604</td>
<td>.06</td>
<td>.03</td>
<td>.02</td>
<td>.03</td>
</tr>
<tr>
<td>*0605</td>
<td>.01</td>
<td>.03</td>
<td>.01</td>
<td>.02</td>
</tr>
</tbody>
</table>

Caucasian<sup>a</sup> : Jefferson County, AL; Allegheny County, PA.
African American<sup>b</sup> : Jefferson County AL; Allegheny County, PA.
Asian<sup>c</sup> : Hokkaido, Japan; Seoul, Korea.
Non-Asp-57 alleles are italicized.
* p < 0.05 for cases versus controls (corrected for multiple comparisons).
Table [3.10] HLA - DQ and Type 1 Diabetes

Frequencies of DQA1 alleles among type 1 diabetic cases and unrelated non-diabetic controls from WHO DiaMond Molecular Project and the 12th International Histocompatibility Workshop and Conference.

<table>
<thead>
<tr>
<th>DQA1 Allele</th>
<th>Caucasian(^a)</th>
<th>African American(^b)</th>
<th>Asian(^c)</th>
<th>12(^{th}) IHWC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=163)</td>
<td>Controls (n=192)</td>
<td>Cases (n=99)</td>
<td>Controls (n=152)</td>
</tr>
<tr>
<td>*0101</td>
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</tr>
<tr>
<td>*0102</td>
<td>.09*</td>
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<td>*0301</td>
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<td>.16</td>
<td>.42*</td>
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<td>---</td>
<td>---</td>
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</tr>
</tbody>
</table>

Caucasian\(^a\) : Jefferson County, AL; Allegheny County, PA.
African American\(^b\) : Jefferson County AL; Allegheny County, PA.
Asian\(^c\) : Hokkaido, Japan; Seoul, Korea.
Arg-52 alleles are italicized.
* \( p < 0.05 \) for cases versus controls (corrected for multiple comparisons).
**Figure [3.8]**

![Risk Levels of DR &DQ Alleles](image)

**Significance of Graphical Representations**

**X Axis:** Type of Inherited Diabetes Allele

**Y Axis:** Percentage of risk upon inheriting the allele following the discussions of diagnostic and fuzzy – genetic model are shown as a chart.

**Significance of the Graphical Plot:**

- People with different levels of inherited diabetic allele can be cautioned of its extent of proneness to the disease.
- High risk genes if inherited caution can be taken.
Figure [3.9]

RISK LEVEL OF DR &DQ ALLELES

SIGNIFICANCE OF GRAPHICAL REPRESENTATIONS

X AXIS: TYPE OF INHERITED DIABETES ALLELE

Y AXIS: PERCENTAGE OF RISK UPON INHERITING THE ALLELE FOLLOWING THE DISCUSSIONS OF DIAGNOSTIC AND FUZZY-GENETIC MODEL ARE SHOWN AS A CHARTS.

SIGNIFICANCE OF THE GRAPHICAL PLOT:

- PEOPLE WITH DIFFERENT LEVELS OF INHERITED DIABETIC ALLELE CAN BE CAUTIONED OF ITS EXTENT OF PRONENESS TO THE DISEASE

- HIGH RISK GENES IF INHERITED CAUTION CAN BE TAKEN.
Figure [3.10] Risk levels of HLA-DR & DQ Alleles

SIGNIFICANCE OF GRAPHICAL REPRESENTATIONS

**X AXIS**: TYPE OF INHERITED DIABETES ALLELE

**Y AXIS**: PERCENTAGE OF RISK UPON INHERITING THE ALLELE FOLLOWING THE DISCUSSIONS OF DIAGNOSTIC AND FUZZY - GENETIC MODEL ARE SHOWN AS A CHARTS.

SIGNIFICANCE OF THE GRAPHICAL PLOT

- PEOPLE WITH DIFFERENT LEVELS OF INHERITED DIABETIC ALLELE CAN BE CAUTIONED OF ITS EXTENT OF PRONENESS TO THE DISEASE.

- UPON INHERITANCE LEVEL OF RISK CAN BE ANTICIPATED
3.6 TYPES OF GENE MUTATIONS

Figure [3.11] Missense Mutation [40]

In this example, the nucleotide adenine is replaced by cytosine in the genetic code, introducing an incorrect amino acid into the protein sequence [42].
TYPES OF GENE MUTATIONS [43]

Figure [3.13] Nonsense Mutation

In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein [44].

Figure [3.14] Intense Mutation

In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.

**Figure [3.16] Types of gene mutations**

A section of DNA is accidentally duplicated when a chromosome is copied.
Figure [3.17] Types of gene mutations

Frameshift mutation

A frameshift mutation changes the amino acid sequence from the site of the mutation.

Figure [3.18] Types of gene mutations

Repeat expansion mutation

In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid glutamine to the resulting protein.
In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid GLUTAMINE TO THE CHAIN. Changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders. Such disorders can cause the diseases like diabetes mellitus [45].