MAJOR PROJECT

NutriGene: An online resource for personalized nutrition

A Major Project dissertation submitted in partial fulfilment of the requirement for the degree of

Master of Technology
In
Bioinformatics

submitted by

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CERTIFICATE

This is to certify that the M. Tech. dissertation entitled **"NutriGene: An online resource for personalized nutrition"**, submitted by **NAVNEET KAUR SONI (DTU/13/M.TECH/361)** in partial fulfilment of the requirement for the award of the degree of Master of Technology, Delhi Technological University (Formerly Delhi College of Engineering, University of Delhi), is an authentic record of the candidate's own work carried out by him under my guidance.

The information and data enclosed in this dissertation is original and has not been submitted elsewhere for honouring of any other degree.

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DECLARATION

I, Navneet Kaur Soni hereby declare that the project entitled "**NutriGene: An online resource for personalized nutrition**" is a record of the original work that is done under the guidance of Dr. Yasha Hasija, Assistant Professor, Department of Biotechnology, Delhi Technological University, Delhi-110042. This report is submitted for the fulfilment of the Major-II. The Introduction, methodology and results that are embodied in this report have not been submitted to any other University or Institution for the award of any degree or diploma.

Date: Name:

Place: Signature:

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2K13/BIO/11

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LIST OF ABBREVIATIONS

SNP: Single Nucleotide Polymorphism

NCBI: National Centre of Biotechnology Information

CVDs: Cardiovascular Disorders

PPARG: Peroxisome Proliferator-Activated Receptor Gamma

APOE: Apolipoprotein E

APOA1: Apolipoprotein A1

PLIN1: Perilipin

HDL-C: High Density Lipoprotein Cholesterol

LDL-C: Low Density Lipoprotein Cholesterol

TC: Total Cholesterol

APOB: Apolipoprotein B

BMI: Body Mass Index

IHD: Ischemic Heart Disease

PKU: Phenylketonuria

MTHFR: Methylenetetrahydrofolate Reductase.

OMIM: Online Mendelian Inheritance in Man

HGNC: HUGO Gene Nomenclature Committee

HGVS: Human Genome Variation Society

rsID: Reference SNP cluster ID

HTML: HyperText Markup Language

OR: Odds-Ratio

LEP: Leptin

LEPR: Leptin Receptor

TNFA: Tumor Necrosis Factor A

GIT: Gastrointestinal Tract

NutriGene: An Online Resource for Personalized Nutrition

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1. ABSTRACT

Introduction: NutriGene is a manually curated database which is aimed at providing a freely accessible interactive databank of the interactions of human SNPs and disorders affected by nutrition along with supporting evidence in the form of already published studies. By doing so, NutriGene hopes to facilitate a freely available user-friendly platform that can show the significance of associations between human variations and dietary factors.

Method: A comprehensive literature search was completed to retrieve all available evidences in the literature documenting association of the host genetic variability with nutrition. For the literature review, we explored NCBI-PubMed using the keywords, such as 'nutritional genomics', 'nutritional science', 'nutrigenomics', 'nutrition genomics', 'nutrigenetics', and 'gene-diet interactions'. Data for each of the associated polymorphism was manually scrutinized and then documented when no discrepancy was observed in the entries.

Result & Discussion: The database comprehensively includes genetic variants across all major populations and ethnicities. This information can be used for associative studies to uncover the role of genetic variants in a particular population that make them more susceptible to any chronic disorder on the basis of their diet. Mining the database for biologically meaningful information keeping these points in mind is likely to reveal unknown facts about the underlying causes of gene-diet interactions.

Conclusion: In a nutshell, disease prevention and health optimizing measures could be achieved with the presence of such databank systems that can provide the information at least on already completed and proven studies which were conducted on a given set of population groups to figure out appropriate gene-diet interactions.

Database URL: http://genomeinformatics.dtu.ac.in/nutrigene/

2. INTRODUCTION

Nutrition and the environment are the major factors that affect the health of an individual. Different population groups could experience different health consequences in spite of the fact that they are consuming similar diets owing to their different environment or lifestyles. Thus, this important concern has been on the awareness of healthcare experts in the medical community. Studies in the area of nutrition have increased the understanding of how to maintain health of individuals following different dietary patterns (Mariman *et al*., 2006). Traditional nutritional research has significantly contributed to modern biomedicine and has helped prolonged the longevity whereas presently, the nutritional science is more focussed on preventing development of disorders as well as supporting the repair processes mandatory for curing the diseases completely by delving into underlying molecular mechanisms of health-nutrition inter-relationship (Norheim *et al*., 2012). So, in order to improve diet and health of entire population, efficient study designs and novel and advanced techniques are required to have a proper understanding between diet and gene relationship.

It has long been suspected that genetics plays a significant role in evaluating how an individual responds to intake of nutrition. With such concept in mind a science called "Nutrigenomics" came into picture that could answer how the interaction between genes and diet (bioactive food) positively or negatively influence an individual's health (Ferguson *et al*., 2009).

The discovery of such interactions will play an important role in prescribing customized diets as per each individual's genotype in a similar way as "Personalized Medicine" tends to provide targeted therapy. Since one-size-fits-all paradigm has lost its validity, now the nutritionists would be able to provide dietary recommendations depending upon the population environment .i.e., diet, behavioural patterns, heredity, physical activity etc. (Mutch *et al*., 2005).

The selective use of genome-protective nutrients in individuals with specific gene variants could potentially result in improved resistance towards these major chronic diseases (Fig 1). But we need to start taking foods and diets in terms of their content of genome-protective nutrients (Ommen *et al*., 2002). For instance, Folate is among the nutrients that is critical for genomic stability. Folate intake of more than 200 µg/day is needed for chromosomal stability. But it was seen in many cases that moderate folate deficiency within the physiological range is the cause of as much DNA damage in cultured lymphocytes as 10 times the annual allowed limit of exposure to X rays and other forms of low linear energy transfer ionizing radiation for the general population (Muller *et al*., 2003 and Emed, Personalised Nutrition).

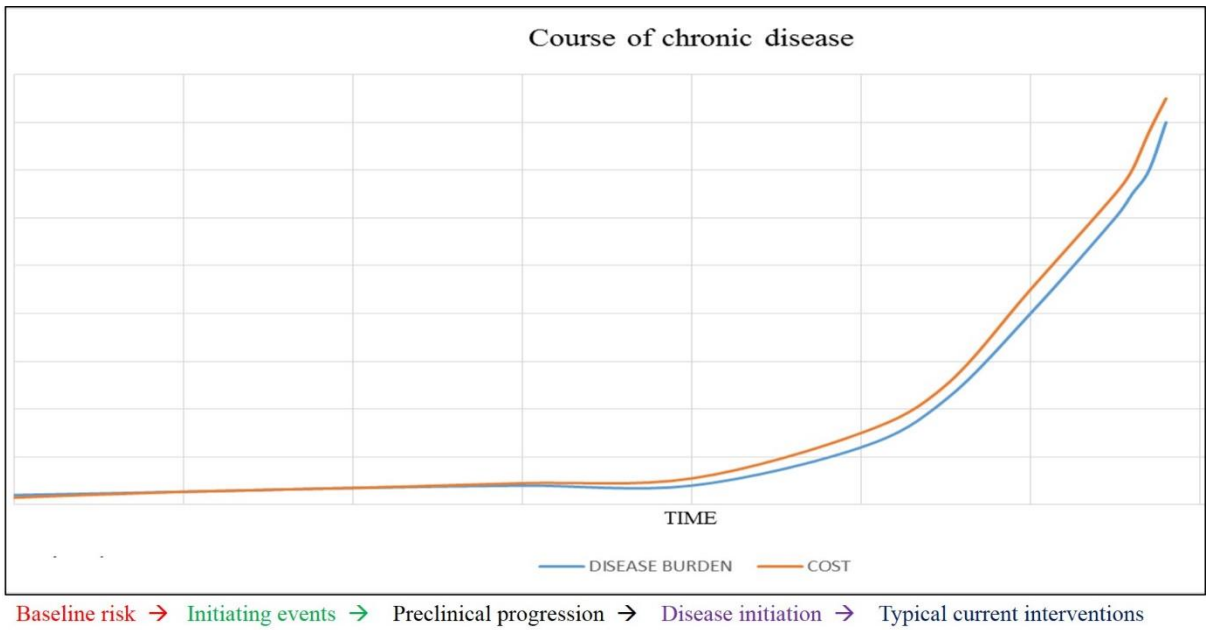


Fig 1: Curve for the course of chronic diseases over cost and disease burden.

Thousands of SNPs are likely to affect nutritional status of human beings so it will not be possible for dieticians to make an exhausted recommendations. Also, determining the SNP–diet and SNP–nutrient interactions that form the basis of chronic disorders is challenging due to the complexities inherent in studying genotypes and in assessing dietary and nutrient intakes (Fig 2) (Sales *et al*., 2014). However, overall the human genome project and SNP databases along with the rapid development of tools suitable for investigating the polymorphisms and the kind of study being considered may provide a means to initiate the development of an integrative database which can tell about the genes influenced by different kind of diet and the disease risks associated directly in human subjects (Mariman *et al*., 2006). Also, Nutrigenetics, a branch of nutritional genomics, with its retrospective analysis, can allow nutritionists and physicians to provide personalized health and diet recommendations (German, 2005). For practicing personalized nutrition, not only the researchers had to discover more SNPs that influence nutritional status, but also a developed and extensive database can provide information related to dietary effects based on each individual's genetic composition (Lead *et al*., 2006). Till date no such comprehensive database exists. The NutriGene Database could unravel the studies already published on diet-gene interactions along with other notable factors such as lifestyle, ethnicity of population, gender that influence such interactions. To our knowledge we have only included studies that have a significant interaction .i.e., p-value (<0.05) and odds-ratio.

Therefore, it is being hoped that in upcoming era people will be able to obtain tailored nutrition recommendations as per their genetic constitution to prevent chronic diseases and complex disorders such as CVDs and diabetes.

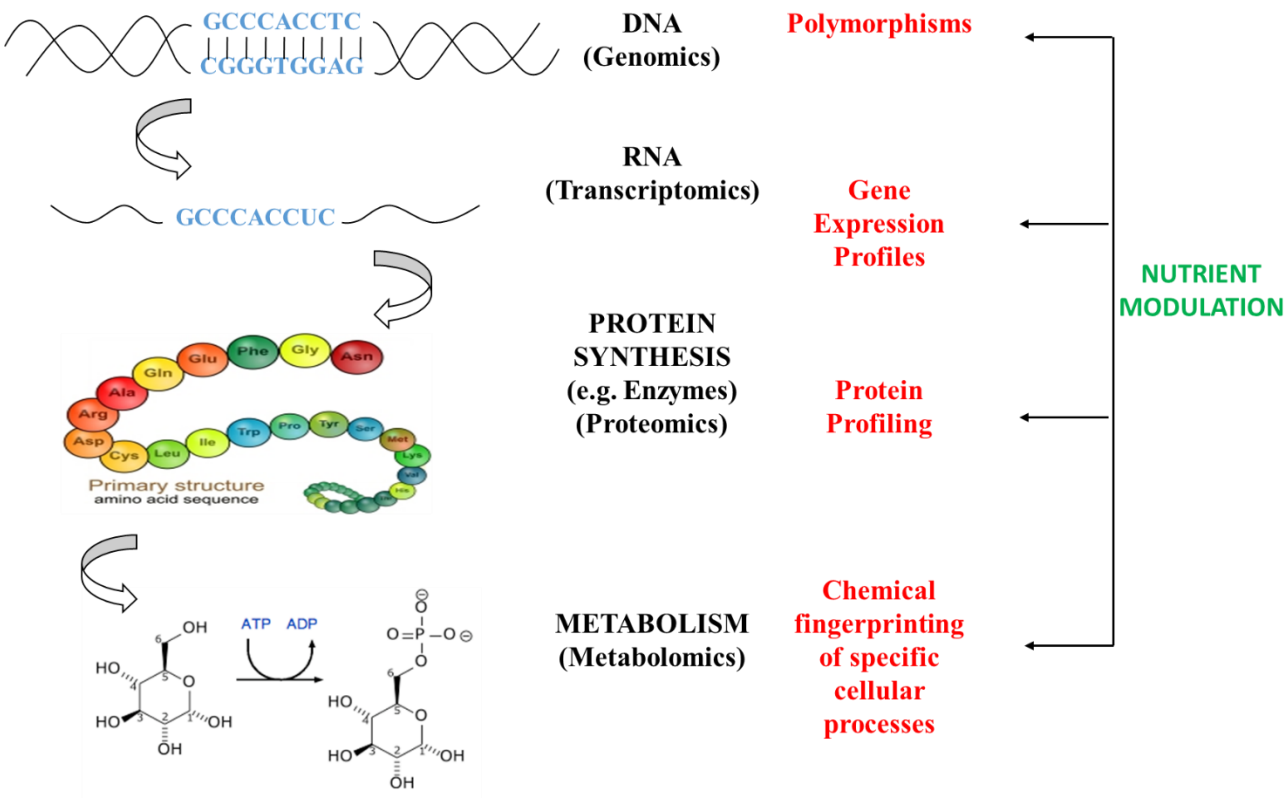


Fig 2: Association of Nutrition & Healthy Genomics, Proteomics, and Metabolomics

3.REVIEW OF LITERATURE

The term "Nutrition" can be defined as an act or process of nourishing or being nourished. Food empowers one's life and fuels all bodily processes that enables a person to work, think and breathe. A healthy diet provides our body the nutrients it needs to perform physical activities, maintain wellness, and fight against diseases. In short, what we eat and absorb is fundamental to our health. Food also acts as medicine to maintain health, as well as prevent and treat diseases. However studies from past decade have proven that nutrients can influence gene expression directly by inducing epigenetic modifications or function as ligands for nuclear receptors. However, nutrients also act as building blocks or can be converted into bioactive products or coenzymes in chemical reactions or inhibit oxidation of other molecules or serve as energy sources (essential amino acids, vitamins, fatty acids, antioxidants respectively). Components of a particular diet (bioactive compound) may alter the expression of genes by either increasing their potential or suppressing them. Studies performed with vitamins A, D and fatty acids have indicated that they can trigger direct signals in activating nuclear receptors and inducing gene transcription (Sales *et al*., 2014). When dietary fat reaches the adipose cell, it activates the nuclear receptor peroxisome proliferator activated receptor gamma (PPARG), which migrates to the nucleus and binds to the promoter of fatty acid binding protein, thereby transcriptionally activating or deactivating further series of events (Muller *et al*., 2003). The occurrence of such phenomena in the regulation of key molecules is associated with several disorders such as obesity, inflammation, cancer, etc.

In the recent post-genomic era, the knowledge of genomic layout of organisms communicates a detailed molecular and systematic understanding of all the life's processes. The 0.1% variability in human genome is the main cause of difference in weight, height, eye colour, skin pigmentation etc. This slight variation in genome also determines ones' nutritional requirements .i.e., taste preference, appetite and the risk of developing certain chronic diseases. Single nucleotide polymorphisms accounts for most of such genetic variations that can even change the encoded protein. It has been shown that certain genes and their variants can be regulated by nutrients from the diet and these molecular variations may have beneficial effects to the health of an individual (Carlson *et al*., 2004 and Hirschhorn *et al*., 2005).

Thus, nutritional genomics on the lines of functional genomics is deciphering this knowledge for guiding the future of human health and malfunctions. The advent of both the modern sciences has led to the understanding that not only certain nutrients are essential, but also that specific quantities of each are necessary for achieving optimal health, which can lead to such concepts as dietary recommendations, nutritive requirements, and the realization that diet can directly or indirectly contribute to disease onset. That is why, it's being said that human development is clearly defined by both environmental influences (e.g., diet, lifestyle, physical activity, etc.) and heredity, which indicate that both aspects must be considered if an individual aims to optimize health (Mariman *et al*., 2006). But till date experimental studies often consider one factor, i.e., either genes or environment is being analysed but the combined effects are not

being studied. The advent of modern technologies can now efficiently resolved this issue by allowing both factors to be considered hand in hand, as demonstrated by current advances in our understanding of health and disease (Mutch *et al*., 2005).

An insight into the era of nutritional sciences has brought up new dimensions of studying such effects named as 'Nutrigenomics' and 'Nutrigenetics' which may inculcate better understanding into the influence of genetic polymorphisms on nutrient metabolism and nutrient-related disorders (Ommen *et al*., 2002).

3.1 Nutrigenomics

Nutrigenomics is the study of how genes and nutrients interact at the molecular level. A decade ago, the Human Genome Project, identified all the genes in human DNA and determined the sequence of the 3 billion chemical base pairs that make up human DNA was completed. This project has opened the opportunities to examine the relationship among an individual's genetic makeup, dietary intake, and health outcomes. Nutrigenomics combines molecular biology, genetics and nutrition to reveal how gene expression can be regulated through specific nutrients/bioactive compounds.

Moreover, it is the application of high-throughput genomics tool in nutritional sciences which are lying at the interface between the nutritional environment and genetic process. It aims to impart a molecular level understanding of how common dietary nutrition affects health by altering the expression or structure of an individual's genetic makeup (Kwak *et al*., 2006). The environmental factors (i.e., dietary habits, smoking, alcohol consumption) along with gender also adds to the complexity of studying diet-related disorders which increases difficulty for researchers and nutrition to maintain the balance between health and diseases (Ordovas, 2007). Although men and women share most genetic information, they have dramatically different disease susceptibilities that go well beyond the expected gender-specific diseases (i.e., cervical or prostate cancer) (Rossouw *et al*., 2002). Sex influences susceptibility to nearly all common diseases that affect both men and women, including atherosclerosis and diabetes and their preceding risk factors (e.g., hyperlipidemia, insulin resistance, and obesity). These are all known to be highly complex and multifactorial in their origin, not only involving genetic factors but also a myriad of environmental and behavioural factors that interact with the genetic component, which itself is highly polygenic (Ordovas *et al*., 2005a; Ordovas *et al*., 2005b; Ordovas *et al*., 2004). A few examples that provide strong support for the concept of high-level interactions involving genes, gender, and environment are Apolipoprotein E, Apolipoprotein A1, Perilipin, Fat Mass and Obesity associated genes.

For instance, Apolipoprotein E (APOE) is associated with chylomicrons, very-low-density lipoproteins, and high-density lipoproteins (HDLs), and serves as a ligand for the low-density lipoprotein (LDL) receptor and the LDL receptor-related protein (Beisiegel *et al*., 1989). The most commonly studied genetic variation at the APOE locus results from 3 common alleles in the population: E4, E3 and E2 (Singh *et al*., 2006). Population studies have shown that plasma

total cholesterol (TC), LDL cholesterol (LDL-C), and apolipoprotein B (APOB) concentrations are highest in individuals carrying the E4 allele, intermediate in those with the E3 allele, and lowest in those with the E2 allele (Eichner *et al*., 2002; Ordovas *et al*., 1987). Based on a large body of evidence, it has been estimated that these APOE alleles may account for up to 7% of the variation in TC and LDL-C concentrations in the general population, with this effect being substantially greater in women than in men (Ordovas *et al*., 1987; Lahoz *et al*., 2001). Variation at the APOE locus is associated with an individual's cardiovascular disease (CVD) risk. The Framingham Heart Study showed gene-gender interaction for CVD which showed the presence of the E2 or E4 allele in men was associated with significantly greater CVD risk. Whereas the E4 allele was also associated with increased CVD prevalence in women, the E2 allele was found to be protective, unlike its presence in men (Lahoz *et al*., 2001) and the Copenhagen City Heart Study also proves such interactions for Ischemic Heart Disease (IHD) by postulating that the presence of the E2E3 genotype was protective in women (9% lower relative risk of IHD) compared with E3E3,whereas in men, E3E4 and E4E4 were associated with increased risk (8% and 2%, respectively) (Frikke-Schmidt *et al*., 2004). Another report from the Framingham Offspring Study investigated the interaction between alcohol consumption and LDL-C concentration (Corella *et al*., 2001). In this study, men who reported themselves to be non-drinkers did not show the traditional association between the APOE alleles and LDL-C concentrations (E2<<E3<E4). Conversely, in those classified as drinkers, the E4 allele was associated with significantly elevated LDL-C concentrations, resulting in a significant APOE-drinking-LDL-C interaction after adjusting for age, body mass index (BMI), smoking, and diet. However, no such interaction was observed in women, those who reported drinking alcohol generally had lower LDL-C concentrations independent of APOE genotype. Another behavioural factor that has been receiving increased and well-deserved attention relates to physical activity. The first study that confirms such interaction in more detail was by Bernstein *et al*, who investigated this interaction in a population-based cross-sectional survey that included 1708 men and women aged 35 to 74 years (Bernstein *et al*., 2002). Similar to those described for alcohol consumption, smoking, and BMI, the findings were gender dependent. For men, increased physical activity had a greater protective effect in E4 carriers compared with E3 homozygotes and E2 carriers in terms of increases in HDL-C concentrations and decreases in triglyceride concentrations. In women, the protective effect of exercise on E4 carriers was limited to HDL-C, and it was significant only for the difference versus carriers of the E2 allele. There also appears to be a significant interaction between exercise training and APOE genotype (Hagberg *et al*., 1999). Overall, the data suggest significant interactions between the APOE gene and behavioural factors. However, the fact that several of these factors have the potential to interact and that they may be distributed differently among populations may result in one of the factors (i.e., drinking alcohol, intake of any regular medication, smoking, physical activity) having more weight in some populations than in others.

The potential of such field and its role in health management is very extensive. In order to accomplish such study, nutrition should no longer be viewed as a matter of epidemiological study which aims at identify relationship between diet and chronic disorders in genetically uncharacterized population. In fact emphasis has to be laid on complex cell and molecular biology coupled with biochemistry and genetics of the study sample (Mutch *et al*., 2005). For

example, studies aimed at elucidating the molecular and mechanistic overview of metabolic disorders and related diseases have used classical biomarkers, such as leptin, adiponectin, or triglycerides. But the ability to further identify novel mechanisms of action and/or and biomarkers that can pinpoint health status with accuracy is diminished because only accepted and validated studies are examined until now. Nutrigenomics seems to resolve such concerns by determining unexplored and unanticipated studies (Mooser *et al*., 2003).

3.2 Nutrigenetics

Nutrigenetics has been defined as "an integrated framework that examines genetics and associated polymorphisms concurrently with diet-related diseases" and may lead to a better understanding of how genetic variations on the interaction between diet and disease or on nutrient requirements (McCann *et al*., 2010). This field of study seems to be most promising in order to elucidate poorly understood associations of diet and disease prevention.

But recent studies have shown that particular dietary compounds may or may not modulate the phenotypic effect of genetic variant. A traditional example of gene X diet interactions is the dietary treatment of Phenylketonuria (PKU). PKU is an inherited monogenic disorder that enhances the level of an amino acid called phenylalanine (Phe) in the blood. It is caused by a mutation in the gene that encodes the hepatic enzyme phenylalanine hydroxylase. This enzymes converts phenylalanine to tyrosine and absence of which may cause accumulation of phenylalanine in the body. Thus, leading to intellectual instability and other serious health issues. However, infants with PKU are prescribed phenylalanine-free diet, which prevents the neurotoxic effects of high blood levels of phenylalanine (Phenylketonuria, Wikipedia).

The principles of nutrigenetics follow naturally from those of pharmacogenetics as illustrated in Figure 3.

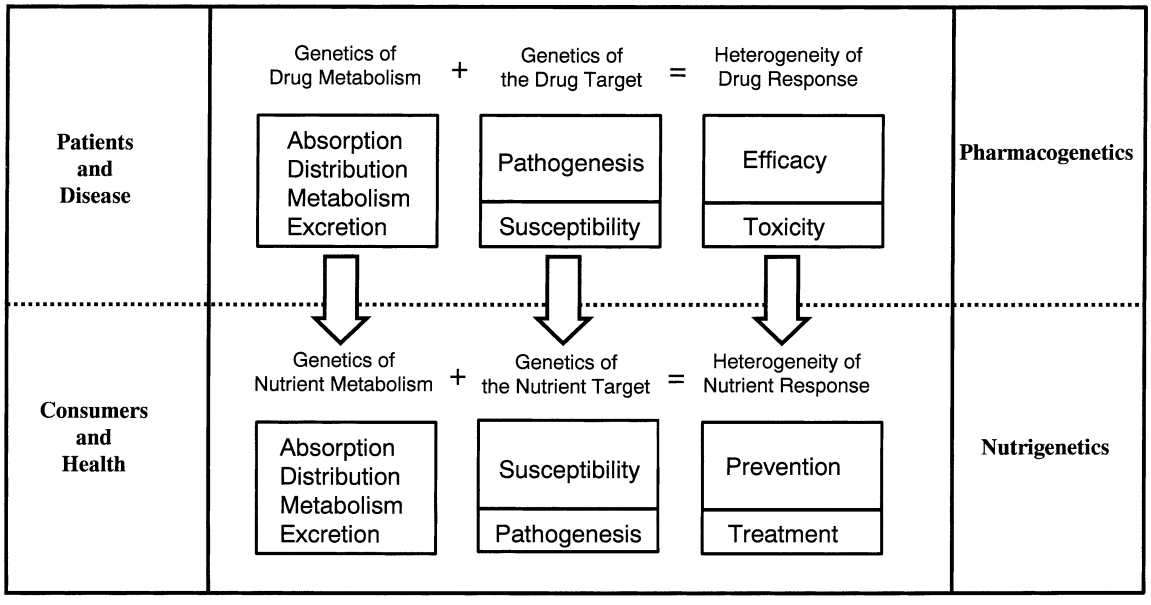


Fig 3: Pharmacogenetics to nutrigenetics.

Several studies indicate that diet has an important influence on the risk of developing certain diseases in which predisposition has a role. One interesting example of such complicated interaction between genetics, diet and disease comes from a study of the occurrence of hepatocellular carcinoma in Sudan; there was a stronger relationship between the risk of developing the disease and the consumption of peanut butter contaminated with aflatoxins in Sudanese population with the glutathione S-transferase M1 null genotype than there was in those lacking this genotype (Orner *et al*., 2001).

Patients can be genotyped for particular genetic variations, made aware of their chronic disease risk and deficiencies in diet, and given strategies to drastically reduce their risks. An extensive progress in research studies has already been made in recent years to understand the mechanisms and cause of non-transmissible chronic diseases with the focus on curing disease rather than prevention. But the system by which nutrition is significantly modulating these diseases are still unexplored because of lack of appropriate tool or any platform where all multifactorial disorders are enlisted according to number of studies conducted upon them, sample number of each study, type/ethnicity of population, etc. (Ommen *et al*., 2002). Molecular epidemiological studies need to be more focussed for identifying specific polymorphisms that are linked to alter risk of disease or sensitivity to diet (Muller *et al*., 2003).

The concept of nutrigenetics shouldn't be misunderstood with the term nutrigenomics as it refers to the impact of inherited traits on the response to a specific dietary pattern or food supplements on a specific health outcome whereas nutrigenetics aims to provide understanding on how the genetic constitution of an individual coordinates with the response to dietary pattern (Fig 4). Nutrigenetics is coined from the notion that it is the foundation of personalized nutrition. Population-based dietary recommendations are helpful, but they are not appropriate for all individuals since people respond differently to diets, like the concept of "one size doesn't fit all". Similar to the theory of pharmacogenetics that seeks to tailor drugs as per the genetic environment of the patient on the basis of variations in the genes of xenobiotic metabolism coupled with genetic variations in the drug target, nutrigenetics offers personalized nutrition to the genetic constitution of an individual on the basis of knowledge of polymorphisms in the genes of nutrient metabolism and genetic variations in nutrient targets (Fig 3). Although the implementation of this type of personalized diet is still in its infancy. However, if the use of genotypes in the dietary prevention of disease is to be established, the field of molecular nutrition must first be successful in identifying the mechanism driving the connection between diet and phenotype according to specific genetic variations.

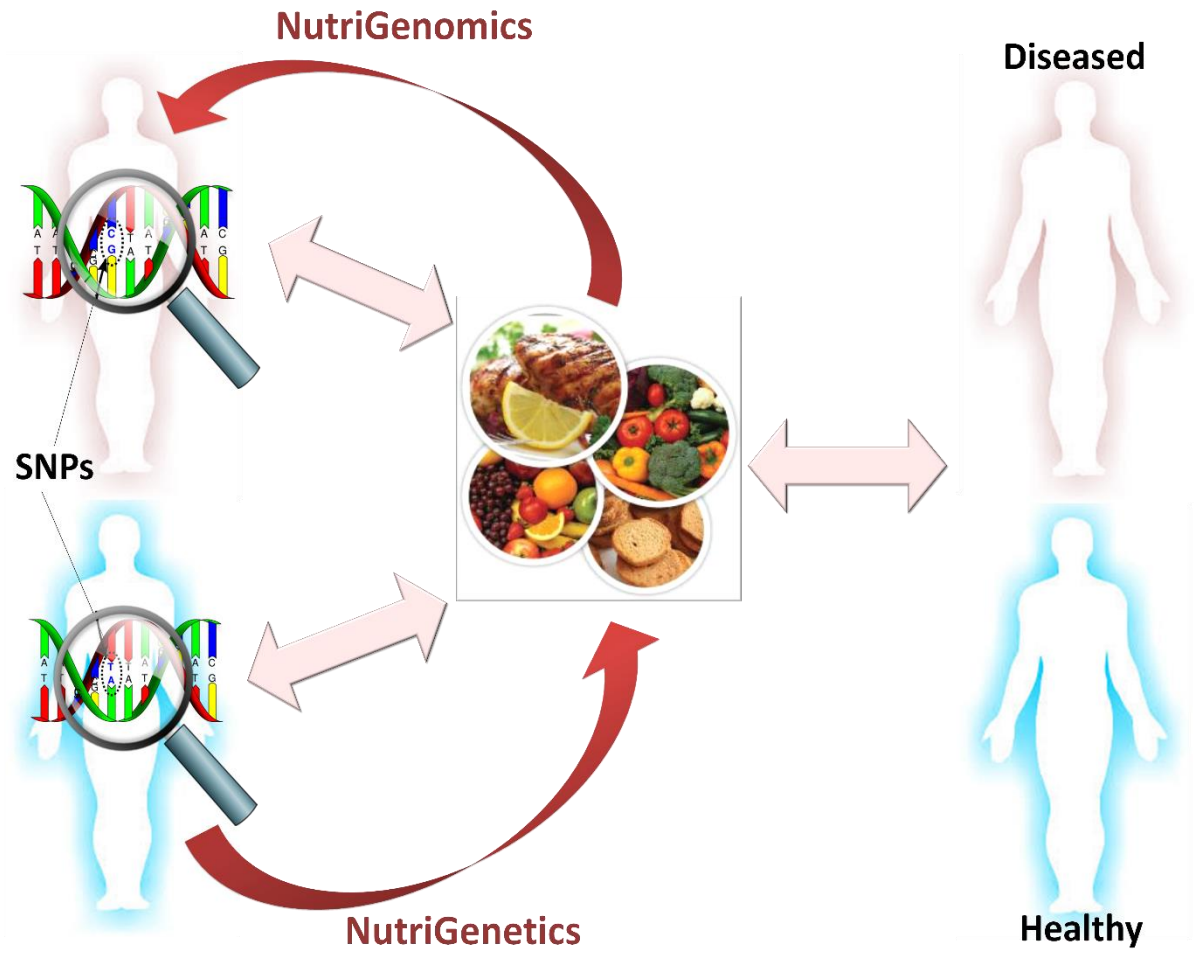


Fig 4: Diet-Gene interaction has given rise to – Nutrigenomics and Nutrigenetics

3.3 Role of polymorphisms in Disease & Nutrition relationship

Nutritional studies are focussed upon SNPs, the DNA sequence variations that account for most of the human genetic variations. A SNP is a variation of a single nucleotide of a gene, in the segment of DNA that encodes for a protein. SNPs may either have no consequence (synonymous) or a significant effect (non-synonymous) on the function of the gene product and can change the structure, function, or amount of the protein that is made (Fig 5).

In rare cases, a SNP may cause a disease, such as sickle cell anaemia or phenylketonuria. SNPs affect health by increasing or decreasing chronic disease risk. Studies have shown that more than 10 million SNPs in the human genome exist; each individual has his or her own pattern of SNPs. And some of these SNPs will influence a person's nutritional status, although it's vague that how many polymorphisms are contributing.

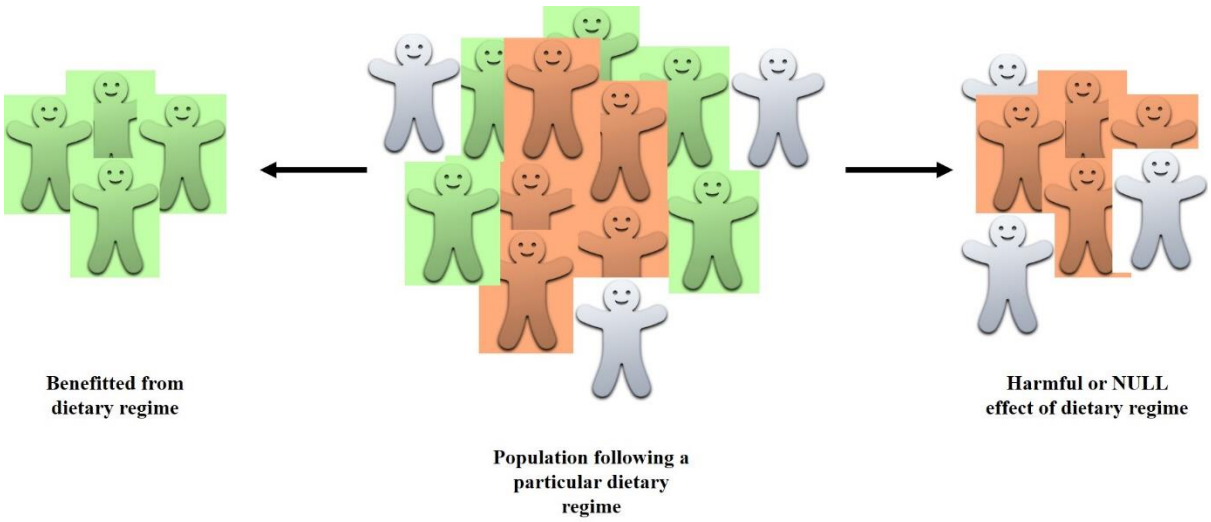


Fig 5: Effect of Polymorphisms - Distinguishing individuals who may or may not get benefitted by particular recommended dietary regime.

The genetic variability of a person affects a person's nutritional status because micro/macronutrients as well as certain bioactive food components can act as ligands for transcription factors or can alter signal transduction pathways and chromatin structure, thus overall influencing gene expression (Mead, 2007).

In fact an individual's nutrient requirements, taste & appetite, energy utilization, metabolism and risk of developing chronic disease in response to di*et al*l such factors are dependent on the genetic sequence of each individual. For example, a diet-SNP interaction involves the common C677T polymorphism of MTHFR gene. This variant slows down the enzyme activity of MTHFR which results in reduced efficiency to metabolize folic acid so as to convert homocysteine to methionine and then to s-adenosyl methionine which is required for methylation of cytosine in DNA resulting in control of gene expression. On the other hand, this variant may also enhance the form of folate that can be utilized to make thymidine and prevents incorporation of mutagenic uracil in DNA that is why in a low-folate environment homozygous carriers of C677T polymorphism is more prone to develop defects but could be more protective against certain cancers (van der Put *et al*., 1995 and van der Put *et al*., 1998).

The field of nutrigenetics can be useful for bifurcating the most susceptible groups or can most benefit from intake of specific food components and allow for better estimation of risk among different groups of population (Mc Cann *et al*., 2010).

4. METHODOLOGY

The NutriGene Database aims to integrate the experimental and observational studies on diet and gene interactions into single user-friendly accessible database. An exhaustive literature search was performed to retrieve all available evidences documenting association of the nutrition with host genetic variability. For the literature review, PubMed was hunted using the keywords, such as 'nutritional genomics', 'nutritional science', 'nutrigenomics', 'nutrition genomics', 'nutrigenetics', and 'gene-diet interactions'. Related research articles were downloaded and studied thoroughly. Data for associated polymorphisms was manually curated. Gene names were mapped and standardized according to the Human Gene Nomenclature Committee (HGNC). Only SNPs related to each disease which reached statistical significance i.e. p-value < 0.05 are included from the literature and already existing public databases such as dbSNP, SNPedia, OMIM, and PubMed. The significance of genetic variation in physiological response to particular nutrients has already been described. However, it has been observed that there are several genetic variations that influence the risk in chronic disorders such as Diabetes, CVDs, Metabolic Syndrome, etc. Thus SNP analysis could provide an influential molecular tool for investigating the importance of nutrition in human health optimization and disease prevention (Mutch *et al*., 2005).

Genetic variants were mapped and standardized to confirm to the recommendations of the HGVS nomenclature version 2.0 by accessing Mutalyzer 2.0 (Dunnen *et al*., 2000). The Mutalyzer 2.0 (Wildeman *et al*., 2007) was used to further validate the entries. The dbSNP as well as Ensembl was used for scrutinizing the IDs of the variant data. The obtained HGVS values from Mutalyzer 2.0 were further evaluated using dbSNP and Ensembl. For the cases where the dbSNP rsIDs were not available, the genomic variant and location were uploaded directly from the literature followed by comparison with the databases using Mutalyzer (Fig 6). Also the ethnic and geographical variation in chronic disease onset is a contributing factor. Therefore, ethnicity of population and where the study was being conducted was also noted for each genetic variant. The set of each entry was manually scrutinized and then finalized when no discrepancy was observed in the entries.

4.1 Structure and features of the Database

The NutriGene database has a browsable interface which was created using HTML. Information for each mutation was compiled and made available through the searchable and interactive web interface. The database was built considering data interoperability and recommendations for curation of data using the guidelines provided by HUGO Gene Nomenclature Committee (HGNC) (Gray *et al*., 2013). For each mutation, information is stored at the molecular level, such as genotype change as per HGVS nomenclature, predicted amino acid change if known, type of mutation, study design, sample size, associated disease and unique PubMed ID along with significant scores such as p-value and odds ratio (OR).

Fig 6: NutriGene Database – Methodology in brief.

4.2 Interface Development

For the determining each polymorphism that is related to dietary habits of population, easily accessible web interface was developed. For creating presentation layer of NutriGene, XHTML and CSS were used along with Apache/2.4.4 (Win 32) Open SSL/0.9.8y PHP/5.4.19 as web server. The database server version 5.5.32 MySQL community server (GPL) was used for backhand data handling. The database, NutriGene is hosted at http://www.genomeinformatics.dce.edu/nutrigene

4.3 Data access and exchange

In NutriGene, the query can be searched in an interactive manner through a web-based interface using a variety of identifiers including its HGNC gene name, rsID or PubMed ID. The total

number of 19 attributes was enlisted for each of the diet-gene interaction (Table 1). Information including the HGVS nomenclature for the variants, the rsID, type of mutation of the variant and its genomic location as described in the primary literature have been included in the database. Moreover, a brief summary is also included of each study being conducted on a particular population with respect to its corresponding PubMed ID.

4.3.1 Attributes

The database includes 19 attributes in order to provide a quick overview of the study conducted in past. The attributes include are mentioned in the table 1.

Table 1: List of Attributes of NutriGene.

Attributes	**Explanation**
Dietary Factor	A nutrient or bioactive compound present in diet or whose intake is supplemented or it is in behavioural pattern.
Gene Associated	Name of the gene (HGNC Gene Symbol) which is associated (involved) with the Diet-Gene Study.
rsID	The SNP (Single Nucleotide Polymorphism) associated with the dietary factor The rs number is an accession number used by researchers and databases to refer to specific SNPs. It stands for Reference SNP cluster ID.
PMID	It connects each individual study to PubMed record(s) of publications cited at the time of research.
HGVS Nomenclature	Gives the genomic position as well as variation in standard format.
Genotype Variant (amino acid change)	Nucleotide change and amino acid change, if given.
Functionality Type	Type of SNPs .i.e., functional category of the SNP (coding-synonymous, coding-non synonymous, intron, etc.)
Sample Number in study	Number of individuals considered in the Study Design.
Study Design	It defines the hypothesis to be tested amongst samples. This includes a precise definition of the exposure(s) and outcome(s) under study
Magnitude	A given locus in a population gene pool represented by a particular allele
Summary of Study and Outcomes	A brief overview of the study was being conducted in populations and their results.
Associated Disease	Standard Nomenclature for Diseases as per MeSH.
p-value	When you perform a hypothesis test in statistics, a *p*-value helps you determine the significance of your results.
Odds Ratio[CI]	An odds ratio (OR) represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. The odds ratio can also be used to determine whether a particular exposure is a risk factor for a particular outcome, and to compare

	the magnitude of various risk factors for that outcome. The confidence interval for an Odds Ratio has the same general formula as the Confidence Interval for a population mean or population proportion. The difference is that the confidence interval for the Odds Ratio is calculated on the natural log (LN) scale and then converted back to the original scale.
Ethnicity/Type of Population	The ethnic group representing the population like Caucasians, Dutch, Germans, Sindhi etc.
Origin of Population	Specify the population related to your keywords
Summary in brief	Brief summary of the variant in one sentence.
Genotype effect • Major homozygous • Minor homozygous • Heterozygous	Effect of each kind of allele, major or minor.

4.4 Current State of Database

After extracting information from the research literatures, total 409 entries are manually curated as of till July, 2015. A total of 178 unique genes and 196 unique variants were obtained as associated diet-gene interactions or nutritional polymorphisms. More importantly, the number of research articles referenced in NutriGene has grown to more than 500, which have provided a broad perspective of different kind of study designs. It makes NutriGene as an ideal and reliable repository for accessing the existing studies on nutrient-gene interactions.

5. RESULT

The home page (Fig 7) of interactive web-interface of the NutriGene provides a brief introduction about the database. Query can be made using Gene Symbol as an identifier or dbSNP rsID (Fig 8). On querying database, the user can select attributes (Fig 9) on this database which allows them to view only the desired information without cluttering the screen with data which is of no interest to the user. Selected fields will appear in tabular format (Fig 10) and for each entry a 'view more' tab is present which gives a complete overview/outlay of the study being conducted (Fig 11a & 11b) in corresponding PubMed ID.

The fields such as HGNC Gene Symbol, dbSNP RSID, PubMed ID are hyperlinked and will redirect user to the respective webpages of HUGO HGNC, NCBI-dbSNP, and NCBI-PubMed respectively.

196 unique variants along with their reference SNP ID were obtained from over several studies. After completing data collection from public rsources and already published studies, it was concluded that there were such genotypic polymorphisms which were getting affected by more than one dietary factor thereby causing same or different diseases. For example, IL6 with polymorphism -174G>C is moved with various kinds of diets such as low-calorie diets, mediterranean diets etc.(Table 2). Moreover, amongst such populations metabolic syndrome was the most prevalent disorder followed by cardiological disorders. Cancers such as prostate cancer, breast cancer were also observed to get affected by dietary pattern followed by an individual (Fig 12).

Table 2: List of Single Nucleotide Polymorphisms Affected By Multiple Dietary Factors

S.No.	HGNC Gene Name	Genotype	rsID	Dietary Factors
1.	GPX1	C/T (Pro198Leu)	rs1050450	Selenium (Karunasinghe *et al*., 2012), Smoking (Hansen *et al*., 2008)
2.	ADIPOQ	G/T	rs1501299	MUFA (Ntalla *et al*., 2009) , Low-fat diet (Razquin *et al*., 2009)
3.	CD36	G/A	rs1761667	Fish Oil (Madden *et al*., 2007), Carbohydrates (Delgado-Lista *et al*., 2013)
4.	FABP2	G/A (Ala54Thr)	rs1799883	Hypocaloric Diet (Luis *et al*., 2008), Low-fat diet (Weiss *et al*., 2007)

5.	TNFA	G/A	rs1800629	Dietary Fat (Fontaine-Bisson *et al*., 2007), Carbohydrates (Delgado-Lista *et al*., 2013)
6.	IL6	G/C	rs1800795	High-fat diet (Shen *et al*., 2008), Zinc intake (Kanoni *et al*., 2010), Low-calorie diet (Goyenechea *et al*., 2006)
7.	IRS1	C/T	rs2943641	25-hydroxy Vitamin D (Zheng *et al*., 2014), Saturated Fats (Zheng *et al*., 2013)
8.	APOE	E2/E3/E4 alleles	rs429358 and rs7412	Black tea (Loktionov *et al*., 1998), Alcohol (Corella *et al*., 2001), Low Calorie (Nieminen *et al*., 2007)
9.	PON1	A/G (Q192R)	rs662	Oleic acid intake (Tomas *et al*., 2001), Lycopene (Mackinnon *et al*., 2010)
10.	APOA5	T/C/G	rs662799	Dietary Fat (Corella et al., 2007 and Mattei et al., 2009), Vitamin A (Moreno et al., 2006), Fenofibrate (Quiang Lai et al., 2007)
11.	CETP	C/T	rs708272	Dietary fat (Li et al., 2007), Alcohol (Jensen et al., 2008, Zhou et al., 2008 and Mehlig et al., 2014)

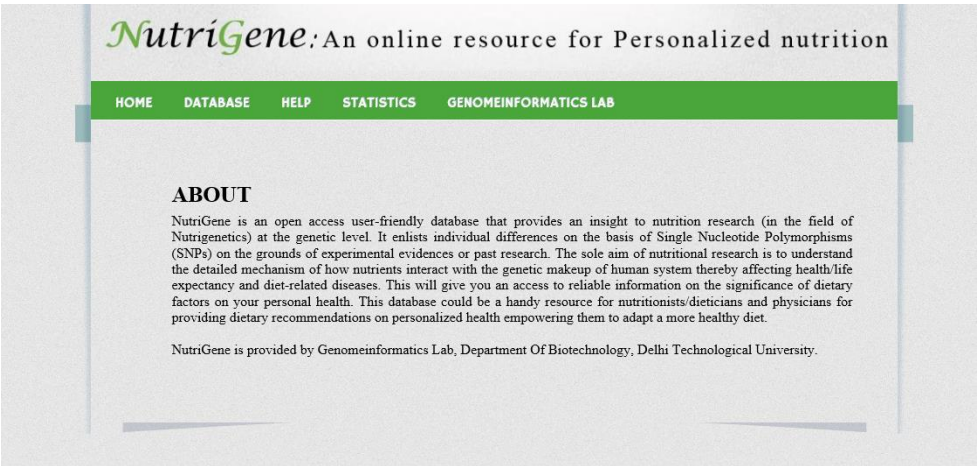


Fig 7: Homepage of NutriGene.

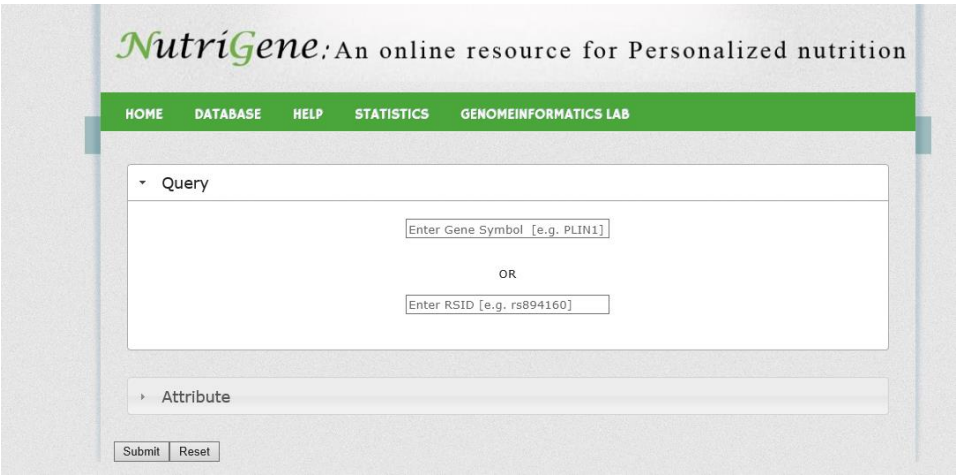


Fig 8: Query Page

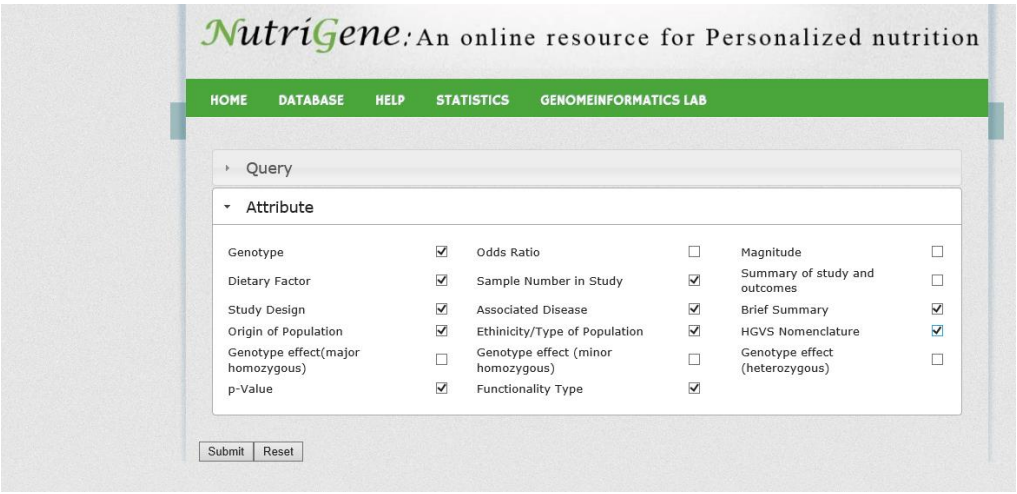
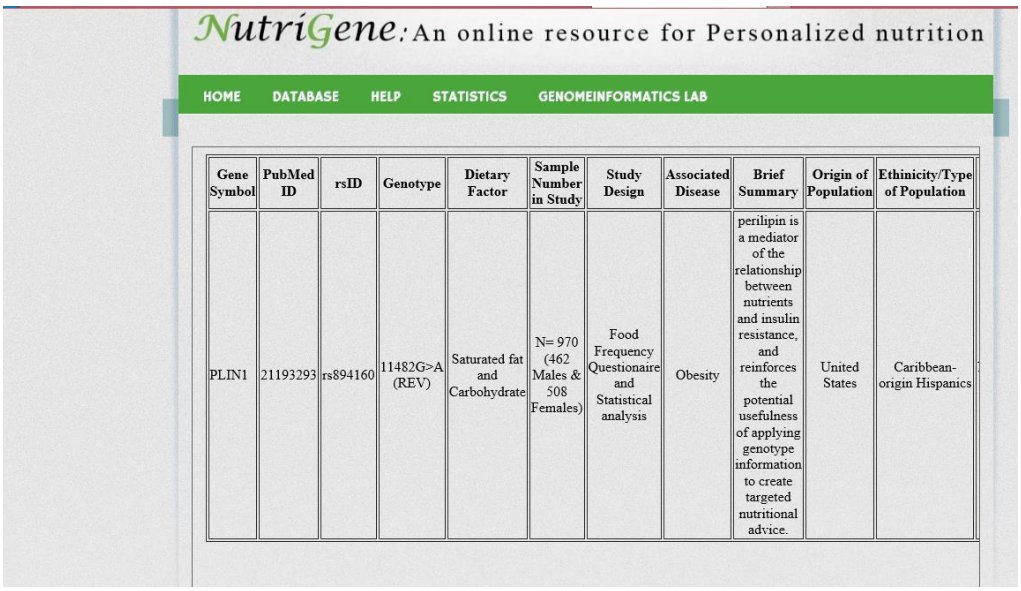


Fig 9: Attributes Selected.



Gene Symbol	PubMed ID	rsID	Genotype	Dietary Factor	Sample Number in Study	Study Design	Associated Disease	Brief Summary	Origin of Population	Ethinicity/Type of Population
PLIN1	21193293	rs894160	11482G>A (REV)	Saturated fat and Carbohydrate	N= 970 (462 Males & 508 Females)	Food Frequency Questionaire and Statistical analysis	Obesity	perilipin is a mediator of the relationship between nutrients and insulin resistance, and reinforces the potential usefulness of applying genotype information to create targeted nutritional advice.	United States	Caribbean-origin Hispanics

Fig 10: Result Page

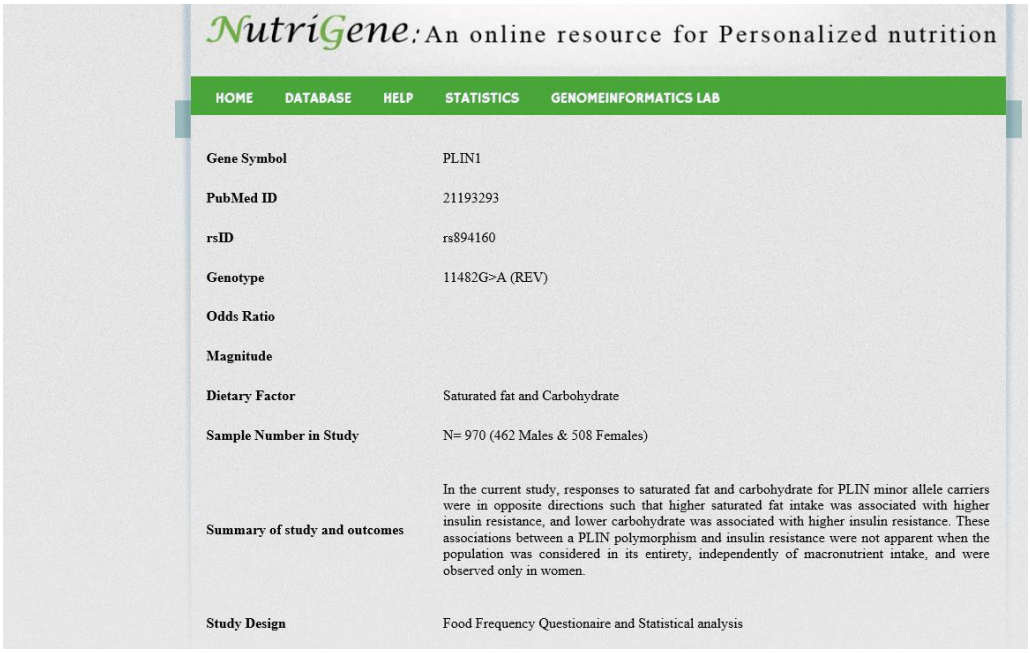
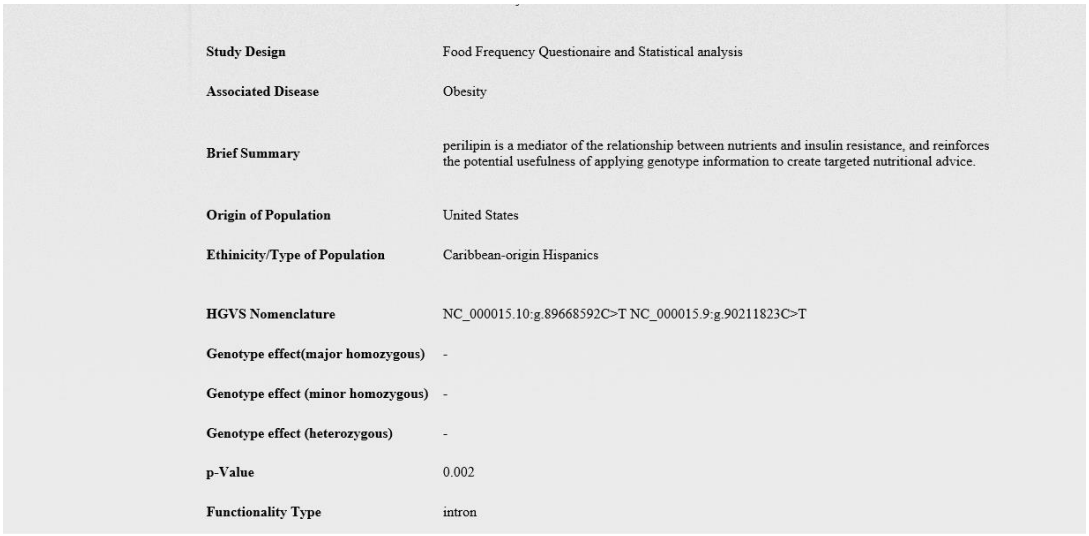


Fig 11: Detailed Result



Study Design	Food Frequency Questionaire and Statistical analysis
Associated Disease	Obesity
Brief Summary	perilipin is a mediator of the relationship between nutrients and insulin resistance, and reinforces the potential usefulness of applying genotype information to create targeted nutritional advice.
Origin of Population	United States
Ethinicity/Type of Population	Caribbean-origin Hispanics
HGVS Nomenclature	NC_000015.10:g.89668592C>T NC_000015.9:g.90211823C>T
Genotype effect(major homozygous)	-
Genotype effect (minor homozygous)	-
Genotype effect (heterozygous)	-
p-Value	0.002
Functionality Type	intron

Fig 12: Detailed Result

6. DISCUSSION

The new era of nutritional science is moving towards practicing personalized nutrition due to two governing factors: one, the successful completion of Human Genome Project and second is, easy to access knowledge about health and adequate nutrition via clinical data. Since, the chronic disorders emerging globally are due to multifactorial interactions of an individual's genotype, their behavioural pattern, ethnicity/origin of population and lifestyle (Hill *et al*., 2004). The modern concern for healthcare experts is the concern of continuous effect of increasing chronic non-communicable diseases on the developing world. Obesity is one such disorder in which both genomic and nutritional genomic approaches are essentially required. Application of such approaches has led to the discovery of a protein called Leptin (a hormone produced by fat cells), and its receptors (Allison *et al*. 2001). It plays an important role in regulating the amount of calories we eat and burn, as well as the amount of fat we carry in our bodies. Mutations in the genes, LEP 2548G>A and LEPR Q223R encoding them have been proved to be associated with obesity in most of the population (Trayhurn *et al*., 2003). The *LEP* 2548G >A variant may influence the *LEP* gene expression and the leptin secretion by adipose tissue. The Q223R polymorphism is located in the extracellular region of the *LEPR* within the first cytokine domain (C domain), which represents a leptin binding site. It has been previously suggested that this single amino acid changed from neutral to positive, could affect the functionality of the receptor, and alter its signalling capacity (Boumaiza *et al*., 2012). The current prevalence of obesity is linked to several factors such as lack of physical activity, westernized-diet, heredity etc. (World Health Organization, 2002). The control over the body weight and mass is dependent on the intake of nutrients, energy utilization and fat metabolism which are affected by susceptible genes that in turn influence appetite or food preferences of a human being (Martinez, 2000). However, the reasons for high rate of obesity are still partially explained. It appears that genetic variants get triggered with the presence of fat-dense foods and westernized lifestyle.

Due to various technological advancements in the field of Nutritional Sciences, an enormous set of novel data and knowledge pertaining to SNP-diet interactions, population-based case-control and cohort studies has been generated. Streamlining such data and its analysis in order to ensure better quality and comparability of the data obtained at diverse sites is one of the major concern.

Thus, the NutriGene Database aims to address such issues up to some extent. We have shared and integrated multiple published studies into a complete user-friendly web interface which is made freely available at http://genomeinformatics.dtu.ac.in/nutrigene/. On querying database, the user can select attributes on this database which allows them to view only the desired information without cluttering the screen with data which is of no interest to the user. NutriGene contains information related to the genes, such as chromosome, type of SNP, reference and mutant nucleotide and amino acid change if given, ethnicity which describes the ethnic group on which the study was carried out, geographical location in which the study was conducted. The p-value assigned to the disease- SNP association (Only those SNPs were included whose p-value is less than or equal to 0.05) and the odds ratio of the disease - SNP

association were also included. Furthermore, the genomic location of SNP on gene such as exon, intron, intergenic and untranslated region was also included in this database. It was observed that same genetic variant of a gene gets affected by multiple dietary factors and may or may not lead to the cause of onset of multiple diseases. For example, Tumor Necrosis Factor A (TNFA) with polymorphism G/A gets affected by dietary fats as well as carbohydrates (Table 2).

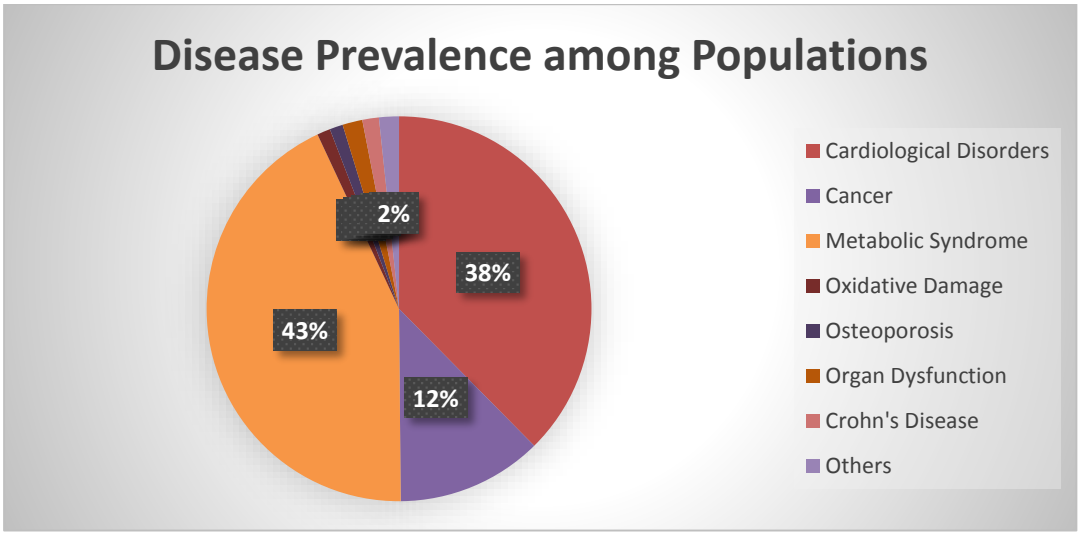


Fig 12: Disease Prevalence among Populations.

In a nutshell, disease preventive and health optimizing measures could be achieved with the presence of such databank systems that can provide the information at least on already completed and proven studies which were conducted on a given set of population groups to figure out appropriate gene-diet interactions.

7. FUTURE PERSPECTIVE

The diet has long been considered as a complex mixture of natural substances that serves as building blocks to develop and sustain organisms on earth. A healthy diet constitutes several bioactive compounds and are shown to be potent signalling molecules, nutritional hormones or ligands for nuclear receptors. The benefits that a population may get from the application of this new era of scientific discipline are many such as knowledge about the genes and their molecular pathways along with their specific role in the pathogenesis will bring forth novel strategies for prevention of many disease processes. Therefore, in the pre-symptomatic phase, expression profiles of biomarkers as well as the knowledge on their molecular pathogenesis, will be useful for designing and applying functional foods which are also termed as 'nutraceuticals'. Such functional foods can only be helpful for optimizing health or preventing disease, whereas remedies are intended to cure the disease (Greef *et al*., 2004).

Moreover, risk-conferring genes for a certain trait needs to be determined for e.g. by comparing biopsy material between patients and matched controls to reveal up-regulated and down-regulated genes. Such genes and their holistic expression profile can be used as biomarkers for different diseases which can be applied into diagnostic protocols for determining the right moment for disease-stage-specific nutritional therapy. Similar comparative studies are also indicative of the progressive and the successful treatment by dietary factors.

Eventually, accessing such online resources will provide the knowledge of associative studies to uncover the role of nutrient related genetic variants in various populations that make them more susceptible for the risk of any disease. Presently (June, 2015), NutriGene constitutes 445 population-based studies that were conducted and contains genetic variants across a majority of populations and ethnicities.

This combined knowledge will influence more physicians to indulge in the genetic profiling of each individual, thereby evaluating risk for acquiring nutrition-related disorders. On the basis of this, the personal-risk profile of a patient can be generated and then a 'personalized diet' could be advised by which the onset of a disorder could be prevented or at least delayed. Although such contributions are the long-term efforts to be applied in this field but they could answer nutritional queries few years down the lane.

8. CONCLUSION

Nutrition is a complex entity because majority of essential nutrients, chemical compounds with or without known biological functions altogether helps in maintaining homeostasis. The physiological effects of nutrients depends up on numerous processes such as digestion and absorption in gut, transportation in the blood, metabolism occurring in different cells, and excretion via GIT and kidneys. Multiple gene products are involved in different pathways of these processes. Moreover, different physiological states like exercising, fasting, gender, menstrual cycle, pregnancy and age group again adds to variability in individual's response. Also the genetic and epigenetic variations potentially alter the host's physiological response to diet.

NutriGene Database explores the relations between diet and health for different ages, ethnic groups, gender and physiological conditions. This could help in identifying SNPs which will enhance the understanding of an individual response to a specific nutrient. The database comprehensively includes genetic variants across all major populations and ethnicities. This information can be used for associative studies to uncover the role of genetic variants in a particular population that make them more susceptible to any chronic disorder based on their dietary patterns.

NutriGene can be accessed through http://genomeinformatics.dce.edu/nutrigene/.

Mining the database for biologically meaningful information keeping these points in mind is likely to reveal unknown facts about the underlying causes of gene-diet interactions. This knowledge may eventually be helpful in understanding genetic variants affected with the nutrition intake.

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