NUTRIGENOMICS: DELIVERING CARE AND PERSONALIZED LIFESTYLE CENTRED AROUND YOU

PRECISION MEDICINE
www.e-precisionmed.com/pmj

ISSN 2456-2254

ARTICLE

HIGHLIGHTS

Nutrigenomics is an emerging science which highlights the complex interaction between nutrient - gene which is crucial with relevance to risk reduction of several disease conditions. Our report details the expanse of risk markers assessed in our Indian cohort along with related modifiable environmental factors. This report is one of the first to document a comprehensive genomics guided disease management outlook which forms the basis of preventive healthcare.

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ABSTRACT

The arena of “precision medicine” has become the biggest gift by genomics to the field of clinical medicine. The continuous efforts in studying the nuclear material and its role in controlling every pathophysiological aspect have led to the birth of “Nutrigenomics”. Though numerous studies have identified and reported on the interaction between “genes and diet”; the ability of this “personalized nutrition” concept to provide pointers for risk reduction of numerous disease conditions has made it quite popular among Nutritionist and Dieticians world over. Our report in this aspect aims to provide a consolidated review connecting different nutrigenetic aspects with major disease conditions from an Indian population study perspective. Such reports become the need of the hour to enable shatter generic myths surrounding dietary and lifestyle do's and don'ts in relation to disease conditions and risk reductions of the same.

KEY WORDS *Indians; nutrigenetics; cardiovascular disease; type 2 diabetes; obesity*

Received 12 June 2017; **Revised** 20 June 2017; **Accepted** 21 June 2017; **Published** 8 July 2016

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ISSN: 2456-2254
PRECISION MEDICINE

INTRODUCTION

Nutrigenomics first described in the year 2001 by Peregrin, is deemed to be a relatively new science that highlights the intricate relationship between dietary factors and the control these can exert on our genes culminating into different rates of metabolic reactions [1]. This science has identified the ability to alter this gene-nutrient interaction by identifying certain critical genetic markers which can be utilized as keys to unlock the mechanism of interaction and also decipher the nodes to achieve development of an optimal health status.

The influence of nutrition on gene has been an ancient ideology, wherein the concept of using certain food materials and plants as medicine had been developed and set into practice. The science behind this relationship however came to be extensively studied post the successful completion of the Human Genome Project (HGP). Nutrigenomics in order to explain the concept of the gene-diet interaction at the molecular level takes into account different aspects of science like biochemistry, physiology, genomics, nutrition, etc [2]. Though the pathogenesis of many disease conditions were known clinically, after the sequence of human genome was made available, the reverse working to establish a molecular level association and identifying modifiable nutrition and lifestyle factors became a possibility giving birth to "Nutrigenetics". Akin to "personalized drug therapy", the feasibility for prescribing a personalized dietary and lifestyle regimen taking into account the genotype of the individual for different genetic markers which have been shown to significantly impact the phenotype ensures the possibility to cut the risk of onset or slow down the progression of multiple disease conditions.

Every disease condition has two influencing factor; Genes and Environment, and the percentage contributed by each towards predisposition varies from one condition to other. For eg: in case of neurological disorders, contribution by genetic markers weigh over environmental factors, while for many lifestyle disorders the contribution may be equal or vice-versa as well. Also, every dietary factor has multiple nutritional components which may exhibit a different interaction and hence consolidated analysis of multiple markers in many genes becomes a necessity to draw an appropriate conclusion. With more than one million people having their whole genome or exome sequenced till date, this huge data analysis was made a possibility only through support from multiple bioinformatics tools developed over a period of time, which bear the ability to precisely annotate genetic information generated by multiple wet-lab platforms like microarray, next-generation sequencing, etc.

Though research in this field is a continuous ongoing process, many metabolic and lifestyle conditions like obesity, cardiovascular diseases, diabetes, etc. have been well studied in different population groups and their associated nutrigenetics factors have also been well-elucidated. For eg; The "A" allele of the marker rs9939609 in the *FTO* gene or the "fat gene" as popularly known, has been associated with increased risk for obesity as well as type 2 diabetes. Interaction studies have also identified this marker to influence benefit of lifestyle intervention against risk of obesity as well as intake of mediterranean diet against risk of type 2 diabetes [3,4]. Another classic example which can be cited in this regards is the relationship between intake of omega-3 fatty acids towards risk reduction of cardiovascular disease influenced by the genetic marker rs4783961 in the CETP (cholesterylester transfer protein) gene [5].

High-density lipoprotein (HDL) cholesterol is known as good cholesterol, because high levels of of the same has been proven to protect against heart disease, while low levels increases the risk of same. The role of HDL is transporting excess cholesterol away from the arteries and back to the liver, where it is passed from the body. HDL cholesterol can be measured with a simple blood test. Q192R genetic variant in *PON1* gene has been shown to raise HDL cholesterol concentrations under consumption of food rich in oleic acid. Canola oil, sunflower oil, olive oil, and almonds are best food sources of oleic acid. Individuals with AG/GG genotype of PON1 gene are recommended to increase the consumption of oleic acid rich diet to reduce likelihood of heart disease [6]. An oleic acid-rich diet has been postulated to prove beneficial among individuals who carry one or more PON1–192R alleles, which was seen in 50% of our population, to achieve favorable antioxidant status similar to that observed in PON1 QQ homozygous subjects.

Genomics in cancer research as well as oncologic therapeutic implication determination has been used for years now, with many of these tests being approved even by the US FDA. However, apart from cancer, which still continues to plague the entire world with its complicated heterogeneity, there are many other non-communicable ailments which pose threat to the overall global health and are at the realm of being declared as epidemics in certain parts of the world. These include diabetes, cardiovascular conditions, obesity, etc. Non-communicable ailments have been documented to have caused about 60% deaths world over in the year 2005, and the rise in total death due to the same has been postulated to be increased by over 17% in the next ten years. By the year 2020, these have been predicted to cause over 80% of global disease burden [7]. Though the role of pharmacogenetic intervention has been extended to even these growing segment of ailments, the role of genomics in risk prediction as well as providing insights on risk

ISSN: 2456-2254
PRECISION MEDICINE

reduction modalities definitely adds up to highlighting the true potential of this field which deciphers molecular signatures.

Landscape of nutrigenetics recommendations

The field of nutrigenetics as rightfully stated, has and is continuously being developed to suite and address the detrimental gene and environment interaction which arise due to the changing dietary landscape. Modern age humans have also been postulated to consume more carbohydrates in comparison to their ancestors and thus end up ingesting high levels of omega-6 fatty acids in place of the healthy omega-3. Omega-6 fatty acids are inflammatory in nature and thus fuel many conditions like metabolic disorders, cardiovascular diseases, and many such conditions which have risen to the levels of chronic health crisis today globally [8]. Though, the field is evolving on technical as well as interpretational grounds, its pivotal role in the field of biomedicine has risen to levels wherein it cannot remain underplayed.

Personalized nutrigenetics recommendations, generally are analyzed and reported in sync with definite disease conditions to ensure a better level of understanding is achieved among clients who opt for this test. Connecting high risk conditions with pertinent nutrition and lifestyle recommendations compatible with the genetic makeup of an individual ensures actionable risk reducing modalities become available. In this review, we highlight a few disease conditions which continue to pose a major healthcare threat and discuss the role of genomics in assessing risk from a lifetime and preventive health care perspective and the corresponding nutrigenetic recommendations drawn. This analysis from the Indian perspective has been designed to communicate the spectrum of actionable compatible nutrition available and the benefit that can be derived out of such tests.

Type 2 Diabetes

This “sweet killer” condition continues to be the top ranking metabolic disorder world over and pertaining to the Indian scenario, this adverse condition has been identified to have grown to epidemic proportions. Scientific studies have identified India to harbor the maximum burden of diabetes affected and has come to be termed as the diabetes capital of the world. Futuristic predictions have thrown up a number of 79.4 million to be likely affected by the year 2030 [9]. Though a metabolic disorder clinically, apart from bearing risk factors attached to lifestyle and other environmental factors, genetic factors have also detected to bear a 27% contribution towards development of this condition. Many genes have been implicated towards the etiology of this condition, and few prominent ones with well-established mechanism and higher odds of risk have been routinely detected and evaluated. The summary of such genetic markers detected in our analysis pertaining to risk of type 2 diabetes have been highlighted in Table 1.

Markers	Genotype frequency (%)			P-value model of significance
rs9300039	AA = 4.3 (14)	AC = 25.3 (83)	CC = 70.4 (231)	AA Vs AC + CC
rs4402960	GG = 33.2 (109)	GT = 47.0 (154)	TT = 19.8 (65)	GG Vs GT + TT
rs7754840	CC = 10.4 (34)	CG = 37.5 (123)	GG = 52.1(171)	GG Vs GC + CC
rs8050136	AA = 6.4 (21)	AC = 43.9 (144)	CC = 49.7 (163)	CC Vs AC + AA
rs13266634	CC = 57.2 (187)	CT = 31.8 (104)	TT = 11.0 (36)	TT Vs CT + CC
rs7923837	AA = 25.5 (81)	AG = 46.8 (149)	GG = 27.7 (88)	AA Vs AG + GG
rs7903146	CC = 48.5 (159)	CT = 43.0 (141)	TT = 8.5 (28)	CC Vs CT + TT
rs9465871	CC = 31.1 (102)	CT = 51.2 (168)	TT = 17.7 (58)	TT Vs CT + CC
rs9939609	AA = 14.0 (46)	AT = 48.8 (160)	TT = 37.2 (122)	TT Vs AT + AA
rs13266634	CC = 52.4 (176)	CT = 33.3 (112)	TT = 14.3 (48)	TT Vs CT + CC

Table 1. Summary of high risk and significant markers (p </= 0.05) for type 2 diabetes reported frequently in our analysis.

All the above markers, bear well established connect with risk for this condition and have a good amount of scientific data backing. The mechanism for predisposition vary from fueling impairment in insulin sensitivity, glucose metabolism, insulin secretion to enhancing rate of hepatic glucose production, etc. Thus considering such markers for calculating risk odds in comparison to average population risk exhibits a true risk standing.

Apart from identifying many of the high risk disease markers for type 2 diabetes in our population, the report becomes significant and actionable from a preventive care perspective only when compatible diet and lifestyle modifications are reported. One of the risk markers listed above which

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PRECISION MEDICINE

have been associated with the etiology of this condition have also been detected to bear a significant interaction with diet for significant risk reduction. The transcription factor 7 like 2 (TCF7L2) gene variant, rs7903146 has been associated with impact of dietary fiber intake on risk reduction, which has been discussed in detail in later section of this article.

List of dietary and lifestyle factors associated with significant risk reduction for this condition have been highlighted in Table 2.

Markers	Genotype frequency (%)			P-value model of significance	Interaction factor
rs9939609	AA = 14.0 (46)	AT = 48.8 (160)	TT = 37.2 (122)	TT Vs AA + AT	Mediterranean diet
rs17782313	CC = 40.2 (132)	CT = 48.2 (158)	TT = 11.6 (38)	TT Vs CT + CC	
rs7903146	CC = 48.5 (159)	CT = 43.0 (141)	TT = 8.5 (28)	TT Vs CC + CT	Dietary fiber and whole grains
rs1800588	CC = 52.3 (171)	CT = 39.1 (128)	TT = 8.6 (28)	TT Vs CC + CT	Exercise

Table 2. Summary of actionable recommendations associated with risk reduction for type 2 diabetes.

Mediterranean diet has been widely studied in relation to its ability to modulate the effect of obesity-related genes like FTO (Fat mass and obesity-associated) and MC4R (Melanocortin 4), through epigenetic mechanisms. Though FTO and MC4R genes have been widely studied in association with diabetes, neither has been associated with type 2 diabetes. However, their role in dietary interactions; especially with mediterranean diet in relation to modulating risk of this condition has been established [10]. Studies in rats, have identified both the genes to be highly expressed in the hypothalamus, thus postulating a probable role in central regulation of energy balance and appetite [11]. A traditional mediterranean diet pattern includes low intake of whole-fat dairy products and red and processed meat along with an increase in intake of vegetables, fruits, legumes, fish, nuts and olive oil which are well-known to reduce incidence of this sweet killer condition. It also suggests moderate intake of fish and wine [12]. Folate, which is a key constituent present in rich quantities in this diet pattern, also ensures DNA methylation dysregulation is avoided, which is also the key epigenetic episode in type 2 diabetes. Methylation is also involved in regulation of both the genes; FTO and MC4R respectively [13-15]. The key markers as highlighted in Table 2, have been well studied in this relation, wherein carriers of variant alleles of both the markers exhibited higher risk for the condition when adherence to mediterranean diet was low. Also, when adherence was increased, this association disappeared [10]. This relation apart from holding a good significance in its published form, also has been detected to be of significance in our analysis from the actionable recommendation perspective.

Whole-grains and dietary fibers have been traditionally considered to be very beneficial because of their inverse association with diabetes risk. Whole-grains have high fiber content which delays gastric emptying, inhibits alpha-amylase and thus leads to reduced glucose absorption and subsequent low postprandial insulin secretion demand. However, this beneficial effect has been postulated to be affected by genetic variations in the beta-cells of the pancreas. The relation between intake of whole grains, risk of type 2 diabetes and variations in TCF7L2 (Transcription factor 7 like 2) gene has been popularly evaluated. Variations in TCF7L2 have been associated with impaired insulin sensitivity as the “T” allele of the rs7903146 bears the strongest evidence. Studies have identified the “T” allele carriers to exhibit no benefit of whole-grain consumption on risk for type 2 diabetes, while the carriers of the CC genotype have been shown to benefit from the protective effect of the same [16]. This is a very good example that highlights the role of nutrigenomics in understanding the exact benefit which can be reaped out of a particular dietary model. Though studies have highlighted the allele C vs T model, in our analysis, the CC + CT Vs TT have been detected to be of significance pertaining to this recommendation.

Regular physical activity and exercise have been generically associated with maintaining overall good health and studies have documented their ability to reduce risk towards development of insulin resistance as well as coronary heart disease. Exercise has been shown to affect peripheral glucose utilization as well as lipid-lipoprotein profile. The LIPC (hepatic lipase) gene has been widely studied in this respect to assess relationship between exercise and improvement in insulin sensitivity, levels of postheparin hepatic lipase and postheparin LPL activities. The LIPC -514C>T has been associated with postheparin LPL activity. Studies have identified the TT homozygotes to have a 25% higher LPL activity after

ISSN: 2456-2254
PRECISION MEDICINE

exercise, compared to CC and this variation has been accounted to contribute towards 7-8% of the variation in hepatic lipase activity. The TT genotype carriers have also been detected to bear an increased susceptibility towards coronary heart diseases, even among moderately physically active subjects. Thus screening for the "T" allele carriers of this variation have been postulated to be of significance in identifying individuals with need for individualized therapeutic strategies to reduce risk for heart as well as metabolic conditions [17]. Even in our analysis the TT vs CT + CC has been detected to be of significance in this regards.

Neurological conditions

Neurological disorders include a wide spectrum of conditions which affect the central nervous system and these include psychiatric as well as neurological disorders. Identifying and studying the pathogenesis in detail continues to pose a lot of clinical and technical hurdles as these conditions affect multiple aspects like behavior, thinking process, cognitive abilities, etc. Also, accessing and studying the live part of the brain poses a lot of difficulties for translational research and understanding [18]. Technical advancements in genomics have aided in a great way to investigate biomarkers which are involved in pathogenesis of the condition as well as those involved in nutrient, diet and lifestyle interaction. In this review, we present a detailed description a neurodegenerative condition; Alzheimer's disease and a manic depressive state; bipolar disorder.

An irreversible, progressive brain disorder; Alzheimer's, is characterized by the development of amyloid plaques that ultimately leads to death of nerve cells. It could be early- as well as late-onset and genetic factors have been documented to play a key role in both. The early-onset condition generally affects between the ages of 30 - 60 years and variations have been noted in chromosomes 1, 14 and 21. On the other side, the late-onset type becomes apparent only in the mid-60s and later and the APOE variations in chromosome 19 have been documented to play a key role. Emerging studies have also linked epigenetic mechanisms to the onset of this condition [19]. The heritability of this condition has been documented to be 79% and the lifetime risk has been detected to be higher in females at 17.2% in comparison with males at 9.1%.

Bipolar disorder or manic depression as called is a complex heritable condition characterized by recurrent episodes of mania and depression. Numerous studies have attempted to underpin the exact causative factors and familial studies along with whole genome analysis have detected a few major risk conferring loci albeit showing great heterogeneity. Classified as a complex genetic trait, many susceptibility loci at chromosomes 6, 13, 15, 16, 18, etc. has been reported [20]. The heritability of this condition has been estimated to be 70%, while the lifetime risk has been detected to be 5.2%. Few genetic markers detected in our routine analysis and included for risk estimation have been highlighted in Table 3.

Markers	Genotype frequency (%)			P-value model of significance
rs2075650	AA = 75.6 (238)	AG = 18.4 (58)	GG = 6.0 (19)	AA Vs AG + GG
rs11754661	AA = 2.6 (7)	AG = 11.8 (32)	GG = 85.6 (232)	GG Vs AG + AA
rs6859	AA = 6.6 (21)	AG = 39.3 (125)	GG = 54.1 (172)	GG Vs AG + AA
rs7561528	AA = 9.9 (32)	AG = 16.6 (54)	GG = 73.5 (239)	GG Vs AG +AA
rs6656401	AA = 3.5 (9)	AG = 20.1 (52)	GG = 76.4 (198)	GG Vs AG + AA
rs17125944	CC = 4.6 (11)	CT = 25.3 (61)	TT = 70.1 (169)	TT Vs CT + CC
rs1476679	CC = 11.0 (31)	CT = 33.3 (94)	TT = 55.7 (157)	CC Vs CT + TT
rs1064395	AA = 2.9 (9)	AG = 25.8 (81)	GG = 71.3 (224)	GG Vs AA + AG
rs7250872	CC = 32.9 (92)	CT = 39.3 (110)	TT = 27.8 (78)	TT Vs CT + CC
rs10994336	CC = 64.1 (202)	CT = 30.8 (97)	TT = 5.1 (16)	CC Vs CT + TT
rs10134944	CC = 75.2 (121)	CT = 24.2 (39)	TT = 0.6 (1)	CC Vs CT + TT
rs1006737	AA = 6.9 (18)	AG = 36.3 (94)	GG = 56.8 (147)	AA Vs AG + GG
rs3761218	CC = 9.3 (30)	CT = 62.2 (201)	TT = 28.5 (92)	CC Vs CT + TT
rs11622475	CC = 33.4 (98)	CT = 52.0 (153)	TT = 14.6 (43)	TT Vs CT + CC
rs1012053	AA = 52.7 (168)	AC = 39.8 (127)	CC = 7.5 (24)	AA Vs AC + CC

Table 3. Summary of high risk markers detected significant (p </= 0.05) in our analysis for Alzheimer's as well as Bipolar disorder.

ISSN: 2456-2254
PRECISION MEDICINE

All the mentioned high risk markers have been identified to bear a definite mechanism of action, thus contributing towards the pathogenesis of this condition. Though genetic factors bear a major contribution towards the pathogenesis over environmental aspects, few modifiable factors have been studied and associated with risk reduction for this condition. Such association markers for Alzheimer's and Bipolar disorder assessed in our cases have been highlighted in Table 4.

Markers	Genotype frequency (%)			P-value model of significance	Interaction factor
rs6265	AA = 5.1 (13)	AG = 35.7 (91)	GG = 59.2 (151)	AA Vs AG + GG	Physical activity
rs1801133	CC = 57.3 (188)	CT = 29.9 (98)	TT = 12.8 (42)	CC Vs CT + TT	Folate
rs1801131	AA = 39.3 (119)	AC = 45.9 (139)	CC = 14.8 (45)	AA Vs AC + CC	Folate
rs4654748	CC = 31.3 (98)	CT = 42.2 (132)	TT = 26.5 (83)	TT Vs CT + CC	Vitamin B6
rs602662	AA = 12.5 (28)	AG = 38.6 (86)	GG = 48.9 (109)	AA Vs AG + GG	Vitamin B12
rs1121980	CC = 9.2 (30)	CT = 51.4 (168)	TT = 39.4 (129)	CC Vs CT + TT	Exercise
rs8050136	AA = 6.4 (21)	AC = 43.9 (144)	CC = 49.7 (163)	AA Vs AC + CC	Endurance training

Table 4. Summary of actionable recommendations associated with risk reduction for Alzheimer's and Bipolar disorder.

Physical activity (PA) continues to be a well-studied interaction factor for risk reduction of many disease conditions and few studies have also highlighted its association with Alzheimer's with a probable mechanism of interaction. High body mass index (BMI) has been associated with decline in cognitive function and regular PA has been known to reduce central obesity, leading to reduction in BMI. The benefits of PA on brain have been postulated to be mediated through the increase in production of the insulin-like growth factor (IGF1) and brain derived neurotrophic factor (BDNF). BDNF is associated with learning and memory as well as handles hippocampal function, depression and anxiety. PA has been documented to upregulate both IGF1 and BDNF function. The effect of PA on expression of BDNF has been documented to be modulated by a genetic variant rs6265 in the same. This variant has also been associated with increased risk of Alzheimer's. Studies have identified carriers of the Val allele to derive better benefits of PA with respect to BDNF levels in comparison to Met carriers [21].

Folate, vitamins B6 and B12 have been regarded to be extremely crucial for neuronal function, wherein deficiency in these have been linked with neurodevelopmental disorders, psychiatric issues as well as dementia. The MTHFR variant C677T has been associated with many neurological conditions like schizophrenia, depression, bipolar disorder, dementia, etc. as the "T" allele has been documented to be less efficient in controlling plasma homocysteine levels. Studies have identified folate supplementation to improve many of the behavioral indices and thus variant allele carriers of MTHFR are recommended to optimize folate intake [22]. Also, low levels of vitamin B6 has been associated with risk of bipolar disorder and a particular genetic variant in the neuroblastoma breakpoint family, member 3 gene (NBPF3), located upstream of the tissue nonspecific alkaline phosphatase (ALPL). Studies have identified the "C" allele of a variant in NBPF3 to be associated with low levels of vitamin B6 and hence carriers of the same are recommended to optimize intake. Another variant in the fucosyltransferase 2 gene (FUT2) has been associated with leading to lower levels of vitamin B12 and hence carriers of the risk allele again are recommended to optimize intake of the same [23].

As per reports published in the Archives of Neurology, metabolic disorders have been detected to share risk factors which have been postulated to increase risk of Alzheimer's as well as other forms of dementia [24]. Obesity as a trait has been detected to arise as a result of a complex interplay between genes and environment and variations in the fat mass and obesity-associated gene (FTO) have been popularly associated with affecting BMI. The environmental factor of PA and exercise has been widely studied with FTO variants, wherein the probability to attenuate the risk has been associated with PA. The risk allele "T" of one such FTO variant has been associated with BMI and waist circumference, the effect of which has been detected to be attenuated with regular PA [25]. Another FTO variant has also been associated with body fat response to exercise. The "A" allele of the rs8050136 has been associated with promoting obesity because of resistance to exercise-induced reduction in total adiposity. The CC genotype carriers were detected to exhibit greater percentage loss in body fat in response to endurance training than AA homozygotes [26]. Our analysis has revealed, the AA vs AC + CC model to be of significance, indicating the

ISSN: 2456-2254
PRECISION MEDICINE

heterozygous genotype also exhibits benefit of endurance training with regards to percentage loss in body fat.

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death worldwide, responsible for over 17.5 million deaths annually [27]. It is believed that more than 50% of the Indian population will have heart ailments in the next 15 years, and also the age-of-onset has been detected to be almost a decade early than counterparts in developed countries [28, 29]. With the majority of the population belonging to the productive age group, the total loss in money and productive years for the country tends to be enormous [28]. Thus a strategy involving prevention of CVDs long before their onset works up to be cost-effective than providing interventions at a later stage when the disease is well established [30].

Current evidence suggests that CVD is a complex of genetic phenotypes, influenced by both environmental and genetic factors. Heritability estimates for cardiovascular disease are ~40–50% [31]. Genetic susceptibility plays a key role in CVD, particularly when clinical end points strike early in life. Several genes have been implicated towards the pathogenesis of this condition. Key genes with well established mechanism and higher odds of risk have been routinely screened. Coronary Artery disease (CAD), sudden cardiac arrest, myocardial infarction and stroke are the major manifestations of CVD. The summary of such genetic markers detected in our analysis leading to risk of cardiovascular disease have been highlighted in Table 5.

Markers	Genotype frequency (%)			P-value model of significance
rs10757274	AA = 10 (30)	AG = 49 (158)	GG = 41 (133)	AA Vs AG + GG
rs1412444	CC = 21 (68)	CT= 45 (141)	TT = 34 (110)	CC Vs CT + TT
rs17228212	CC = 10 (32)	CT = 22 (68)	TT = 68 (212)	CC Vs CT + TT
rs17465637	AA = 12 (38)	AC = 35 (110)	CC = 53 (168)	AA Vs AC + CC
rs17672135	CC = 6 (18)	CT = 38 (121)	TT = 56 (183)	TT Vs TC + CC
rs2259816	CC = 13 (42)	CT = 59 (193)	TT = 28 (91)	TT Vs TC + CC
rs2943634	AA = 14 (42)	AC = 41 (131)	CC= 45 (143)	AA Vs AC + CC
rs3869109	AA = 31 (102)	AG = 48 (158)	GG = 21 (68)	AA Vs AG + GG
rs4773144	AA = 38 (123)	AG = 52 (168)	GG = 10 (34)	AA Vs AG + GG
rs501120	AA = 44 (142)	AG = 47 (154)	GG = 9 (28)	AA Vs AG + GG
rs599839	AA = 56 (183)	AG = 37 (122)	GG = 7 (22)	AA Vs AG + GG
rs646776	AA = 56 (183)	AG = 38 (123)	GG = 6 (19)	AA Vs AG + GG
rs688034	CC = 67 (217)	CT = 26 (82)	TT = 7 (24)	TT Vs TC + CC
rs6922269	AA =8 (27)	AG = 45 (148)	GG = 47 (152)	AA Vs AG + GG
rs8055236	GG = 63 (206)	GT = 26 (85)	TT = 11 (37)	TT Vs TG + GG
rs9818870	CC = 61 (201)	CT = 27 (88)	TT = 12 (39)	TT Vs TC + CC

Table 5. Summary of frequently reported highly risk (p </= 0.05) genetic markers for CVD.

Numerous scientific studies have reported a well established association with the above markers and risk for this condition. The mechanism for predisposition vary from plasma measures of lipids; endothelial dysfunction; immune and inflammatory response of the artery; vascular smooth muscle cell (VSMC) proliferation; lipid absorption by macrophage and VSMCs, and the formation of foam cells; platelet activation and thrombosis. Thus genotyping for above markers provide more accurate information about the phenotype and the prognosis that could not be known from lipid levels alone. It can also help identification of more silent cases in the population, further decreasing the incidence of premature cardiovascular disease.

It should be borne in mind that diet has traditionally been considered as one of the main risk factors in the etiology of CVD, a significant percentage of the increase of the incidence of these diseases being attributed to the harmful changes toward less healthy diets that has taken place in recent decades in different geographical areas. List of dietary and lifestyle factors associated with significant risk reduction for CVDs have been highlighted in Table 6.

Coronary heart disease is a result of plaque formation in your coronary arteries. Cigarette smoking is a known potent risk for coronary heart disease. Mutagens such as polycyclic aromatic

ISSN: 2456-2254
PRECISION MEDICINE

hydrocarbons (PAHs) and aromatic amines in tobacco smoke cause atherosclerotic plaque formation. Scientific studies report that the GG genotype of a rs1048943 variant conferred decreased risk for heart disease among individuals who were never involved in tobacco exposure as well as consumption [32]. Even in our analysis the GG vs AG + AA has been detected to be of significance in this regards [Table 6].

Markers	Genotype frequency (%)			P-value model of significance	Interaction factor
rs1048943	AA = 70 (229)	AG = 26 (86)	GG = 4 (13)	GG Vs AG + AA	Smoking
rs2605100	AA = 3 (9)	AG = 28 (90)	GG = 70 (228)	AA Vs AG + GG	Lifestyle intervention
rs183130	CC = 63 (206)	CT = 30 (98)	TT = 7 (24)	CC Vs TC + TT	Omega-3 fatty acids
rs1801133	CC = 57 (188)	CT = 30 (98)	TT = 13 (42)	CC Vs TC + TT	Mediterranean diet
rs1801260	AA = 37 (121)	AG =49 (159)	GG = 14 (47)	AA Vs AG + GG	Mediterranean diet and weight loss
rs1137101	AA =24 (72)	AG = 47(141)	GG = 29 (86)	AA Vs AG + GG	Saturated fats
rs4977574	AA = 34 (110)	AG = 45 (141)	GG = 21 (68)	AA Vs AG + GG	Prudent diet
rs662	AA = 32 (103)	AG = 54 (174)	GG = 14 (48)	AA Vs AG + GG	Tomato juice
rs5051	AA = 39 (126)	GA = 47 (152)	GG = 14 (44)	GG Vs AG + AA	Salt intake and hypertension

Table 6. Summary of actionable recommendations associated with risk reduction for CVD.

Obesity is becoming a global epidemic in both children and adults. It is associated with numerous comorbidities such as CVD, type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing. In fact, obesity is an independent risk factor for CVD, and CVD risks have also been documented in obese children. The LYPLAL1 (lysophospholipase like 1) gene has been associated with obesity and is highly expressed in the adipose tissues [33]. Obesity is a highly heritable factor and many modifiable dietary as well as lifestyle interventions have been shown to bear a positive effect against this condition. Effect of variations in the LYPLAL1 (rs2605100) gene on weight loss due to lifestyle intervention; ~150 min of physical activity/week has been studied. Our analysis has revealed, the AA vs AG + GG model to be of significance [Table 6], indicating individuals carrying the " G" allele showed a greater short-term weight loss advantage due to this lifestyle intervention.

Omega-3 fatty acids have been documented to lower triglyceride (TG) levels. Many studies have shown that the higher level of triglycerides, can increase risk of heart disease. Omega-3 fatty acids lower the levels by reducing the amount of hepatic TG secretion and by enhancing the rate of TG clearance from circulation. The active ingredients of omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are responsible for the triglyceride lowering. CETP facilitates the bidirectional transfer of cholesteryl esters and TG between high-density lipoprotein (HDL) cholesterol and very-low-density lipoprotein (VLDL). Dietary intervention studies have analyzed the effect of omega-3 fatty acids, dyslipidemia and a variant in the CETP gene. The T allele carriers of CETP (rs 183130), has been associated with lower total cholesterol (TC), lower low-density lipoprotein cholesterol (LDL-C) or higher high-density lipoprotein cholesterol (HDL-C) concentrations [34]. The protective effect against dyslipidemia was also detected to be increased on adherence to dietary omega-3 fatty acids. Dyslipidemia is a strong risk factor for coronary heart disease. In our analysis the CC Vs TC + TT has been detected to be of significance in similar regards [Table 6].

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme for folate metabolism. It catalyzes the irreversible conversion of one form of folate 5, 10-methylentetrahydrofolate (5, 10-MTHF) to another form 5-methyltetrahydrofolate (5-MTHF). This conversion is required to make homocysteine to methionine. Variations of the MTHFR gene (rs1801133) are associated with reduced enzyme activity and increased risk for hyperhomocysteinemia. Increase in plasma total homocysteine (tHcy) is associated with the increase in risk of coronary heart disease as it results in the increase of serum

ISSN: 2456-2254
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cholesterol concentrations. According to scientific studies mediterranean diet has cardioprotective effect [35]. These studies suggest that higher consumption of mediterranean diet reduces total homocysteine concentrations among individuals with T allele within MTHFR gene. Methionine restriction is recommended in individuals with CT/TT genotype of MTHFR gene to reduce homocysteine accumulation and limit the effects of reduced MTHFR activity. Reduced enzyme activity associated with these variants can be compensated by increasing carotenoids, folic acid, and fiber intake, all of which are abundant in the mediterranean diet. Our analysis showed, the CC Vs TC + TT model to be of significance [Table 6].

The Circadian Locomotor Output Cycles Kaput (CLOCK) gene is involved in controlling the circadian rhythm and also influences response of diet on weight loss. A study on 500 subjects who followed a 28 week reduced calorie-mediterranean diet, the "G" allele carriers were detected to have lost less weight in comparison to the AA genotype [36]. The "G" allele of a particular variant in the CLOCK gene (rs1801260) has been identified to not bear a positive effect on weight loss on inclusion of a reduced calorie-mediterranean diet as the allele carriers showed higher ghrelin levels, and have a tendency to sleep less which leads to increased BMI as opposed to carriers of the "A" allele. Even in our analysis the AA vs AG + GG has been detected to be of significance in this regards [Table 6].

There is a long-standing association between elevated triglyceride levels and cardiovascular disease. Studies have identified, that among individuals carrying the A/G and G/G genotypes of the rs1137101 polymorphism in the leptin receptor (LEPR) gene with a higher intake of saturated fatty acids, have 2.4 times higher risk of hypertriglyceridemia than those with a lower intake of saturated fatty acids. Leptin is postulated to be a prominent endocrine hormone synthesized by the adipocytes which acts on various parts of the hypothalamus and brainstem which modulates appetite and energy expenditure. The presence of leptin is important to ensure efficiency of lipid metabolism [37]. The "G" allele of a particular genetic variant of the leptin gene and higher intake of saturated fat have been found to cause defect in leptin signaling and thereby increasing the risk of cardiovascular disease.

Many studies report high consumption of transfats and high glycemic carbohydrates, and low consumption of fruits, vegetables, fish, nuts, and whole grains, to be associated with CVD. Changes in dietary pattern can modify CVD risk. Genetic variations which alter the expression of cyclin-dependent kinase inhibitors (CDKN2B-AS) are associated with CVD [38]. Research studies report the combination of a low prudent diet and presence of the risk allele (G) to be associated with increase in risk for CVD, as it increases expression of CDKN2B-AS which in turn increases the expression of genes encoding the cyclin-dependent kinase inhibitors, preventing cell proliferation. Importantly, studies suggest that the deleterious effect of genetic variations on CHD might be mitigated by consuming prudent diet. Prudent diet includes fresh fruits, berries, vegetables, fish, nuts, and whole grains. Even in our analysis the AA Vs AG + GG has been detected to be of significance in this regards [Table 6].

Tomatoes help prevent and manage heart disease because of their niacin, potassium, folate, and vitamin B6 content. Tomatoes improve homocysteine levels, a chemical in the body that directly damages heart health. Lycopene (important content in tomato) also improves cardiovascular health. Studies have shown that diets containing tomatoes can reduce cardiovascular risk by nearly 30%. Tomato juice intake reduced lipid peroxidation in healthy volunteers carrying the AG/GG variations of the PON1-192 gene and could thus contribute to cardiovascular disease risk reduction in these individuals [39]. In our analysis, the AA Vs AG + GG model was found to be of significance [Table 6].

Hypertension stresses your body's blood vessels, causing them to clog or weaken thereby leading to CVD. Studies show that people carrying variant AGT gene (rs5051) are salt-sensitive, meaning they keep more sodium in the blood than non-carriers do. High sodium levels increase blood volume, leading to increased blood pressure. Therefore, carriers of this AGT variant have a higher risk for hypertension [40]. Genetic studies have shown that variant carriers (AA or AG) can reduce risk for hypertension more effectively with a low-sodium diet, whereas, non-carriers (GG) are salt-insensitive and low-sodium diets do not lower risk.

CONCLUSIONS

Our report is one of the first few attempts to highlight the power of genomics testing with relevance to risk assessment of a number of disease conditions, along with identifying actionable recommendations to ensure risk reductions. Each of the markers considered for every aspect of analysis, has been scientifically proven to bear an association and is being considered world over for calculating such estimates. The significance of such a report from the Indian perspective is to understand the standpoint of relevance in this population and to also highlight the benefit a simple genomics test can present with regards to devising prevention plans. Though such risk estimations are only predictive in nature, it can go a long way in assessing and connecting risk of conditions with existing family history as well as symptoms. This report envisions itself to be a starting point, from wherein the power of personalized genomics in preventive

ISSN: 2456-2254
PRECISION MEDICINE

health care can attain its true level of significance in the Indian healthcare system.

CONFLICT OF INTEREST

The author declares no competing interests.

ACKNOWLEDGEMENT

None.

FINANCIAL DISCLOSURE

None.

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