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Pharmacogenomics for Obesity Associated Diabetes: A Review

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Abstract:
This review aims at exploring new pharmacogenomics for obesity associated diabetes. The recent advances in pharmacogenomic therapy lead to the gene discovery of various diseases. In this regard we summaries the various genes which are supposed to be involved in occurrence of obesity associated diabetes. Such genes include Interlukin 6 , Insulin receptor substrate - 2, Protein Tyrosine Phosphatase 1B, Adiponectin Gene, Islet Amyloid Polypeptide, Ectonucleotide Pyrophosphatase/phosphodiesterase 1 gene, Uncoupling protein, Resistin, Lamins A and C, Leptin Receptor Gene etc. These genes are considered to be responsible for the pathophysiology of obesity associated diabetes and can be used as targeted therapy, paves the way for development of new pharmacogenomic therapy. To list a few, PPAR γ agonists, PPAR γ and RXR agonists, PPAR γ and PPARδ agonists, direct modulators of metabolism, PPAR α & PPAR γ agonists, canabinoid-1 antagonist, ciliary neurotropic factors and selective β-3 adrenergic agonists are the pharmacogenomic therapies used in current practice towards the additional advantages. To conclude, pharmacogenomic therapy will provide an added advantage over the currently available conventional therapies and this study will be helpful for future studies towards inventions in pharmacogenomic therapies for obesity associated diabetes.
Keywords: Diabetes, genes involved in obesity associated diabetes, obesity, pharmacogenomic therapy.

Introduction:

With the completion of the Human Genome Project and advances in technologies for genomic analysis, the new genomic discoveries were emerged out. Genomic intervention affecting disease susceptibility is providing the basis for new drug therapies to improve the management of disease or its prevention [1, 2]. Using individual genetic make up, pharmacogenomic therapies overcomes traditional methods by development and tailoring of drugs for maximization of benefit and minimization of harm [3, 4]. Recent discoveries have unveiled the roles of genomic variants that demonstrate variable efficacy or adverse effect and explained specific alleles in the metabolizing enzyme [5, 6, 7].

The movement within pharmaceutical companies to integrate pharmacogenomics into drug development programs has been gaining momentum. A survey of recent investigational new drugs and new drug applications was carried out by the Food and Drug Administration (FDA) to determine the extent to which pharmacogenomics was being used in clinical practices. The survey identified a small, but growing proportion of applications where pharmacogenomic tests were reported [8]. There are many disorders which have roots embedded in the pharmacogenomics and gene based approach is needed to give the basic and symptomatic relief. Among these obesity, diabetes, hypertension, hyperbilirubinemia, prothrombic state, proinflammatory state etc. are of prominent concern. It will be need of hour to develop new treatment for these disastrous diseases. Obesity and diabetes are in the midst of rapidly growing diseases all over the world as there is remarkable increase in their incidence across the globe [9]. As the technology for introducing new genes into cells has been improving, the disease targets for gene therapy have expanded beyond traditional genetic diseases to chronic diseases such as diabetes. Type 2 diabetes mellitus (T2DM) is a complex metabolic disease in which multiple genetic effects; and metabolic and environmental factors contribute to pathogenesis [10]. Obesity, insulin

resistance and diabetes mellitus share a chronic, low-grade inflammatory component as reflected by increased expression of proinflammatory cytokines such as TNF-α and IL-6 [11, 12]. A positive association between overweight and obesity and risk of type 2 diabetes has been established repeatedly in many cross-sectional and prospective studies. It was shown that the risk conferred by obesity for developing diabetes was higher by over 40 times in obese women compared to those who remained slim [13]. There is a strong association of body weight with insulin resistance, higher BMI is associated with hyperinsulinaemia and insulin resistance. Insulin resistance is one of the major etiological factors for diabetes and the risk association of obesity with diabetes is greatly mediated through insulin resistance [14]. Increased risk posed by intra-abdominal fat for diabetes and other metabolic diseases could be related to higher fat cell number in the abdominal adipose tissue, higher blood flow, increased receptors for cortisol and testosterone and greater catecholamine induced lipolysis when compared with the subcutaneous adipose tissue [15]. Hyperinsulinaemia and insulin resistance are closely associated with central adiposity. Visceral fat increases the risk of diabetes and hyperlipidaemia by favoring insulin resistance [16]. Prevalence of diabetes ranges between 1.2 % and 15.1 % all over the world [17]. The prevalence of diabetes worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [18]. After all beta cells are destroyed by insulitis, the inflammatory process declines, the islets become atrophic and most immunologic markers disappear.

Obesity increases the risk of type 2 diabetes, cardiovascular disease, cancer, and premature death [19]. More than 1.1 billion people are estimated to be overweight of which around 320 million are calculated to be obese. The International Obesity Task Force (IOTF) estimates that up to 1.7 billion people may be exposed to weight-related health risks. More than 2.5 million deaths each year are attributed to higher BMI, a figure that is expected to double by 2030 [17]. Incidence rate of about 300 million adults worldwide are obese [17]. Physiological factor involved in obesity is Liver-derived IGF-I (insulin growth factor), it is important for carbohydrate and lipid metabolism also for, regulation of GH secretion at the pituitary level. Pharmacological factor involved in obesity and diabetes is lipoprotein lipase (LL), having a central role in the metabolism of both triglyceride-rich particles and high density lipoproteins. LL is determinant of serum triglyceride and HDL concentrations. In insulin deficiency, the enzyme activity in adipose tissue and muscle tissue is low but increases upon insulin therapy. In type 2 diabetic patients, the average enzyme activity in adipose tissue and post heparin plasma is normal or subnormal [20]. The Polyol pathway has long been associated with diabetic retinopathy. Glucose is converted to sorbitol with the help of the enzyme aldose reductase. Aldose reductase inhibitors can prevent changes induced by diabetes [21].

Pharmacogenomics of Diabetes:

Pharmagenomics plays vital role at every step in drug development process because its primary benefit is the potential to reduce ADRs and increases drug response [22].

Pharmacogenomics involves the various genes with the potential of inducing the physiological changes in the host and thereby may induce the disorder. Following are the genes involved in diabetes and its allied symptoms.

1. MCP1 (Monocyte Chemo attractant Protein-1)

MCP-1, a potent chemo-attractant of monocytes/macrophages participates in metabolic activities that involve regulation of adipose tissue functions, inhibition of insulin-stimulated glucose uptake into adipocytes [23] and accumulation of macrophages in adipose tissue in obese humans [24]. In obesity, monocyte chemo attractant protein-1 (MCP-1), a key chemokine in the process of macrophage accumulation is over expressed in adipose tissue. MCP-1 is an insulin-responsive gene that continues to respond to exogenous insulin in insulin-resistant adipocytes. There is increasing evidence that MCP-1 and presence of the MCP-1 G–2518 allele was associated with decreased plasma MCP-1, a decreased prevalence of insulin resistance and diabetes [25].

2. GNAS1 (α subunit of Gs (Gsα))

The α subunit of Gs (Gsα) is encoded by the GNAS1 gene, located on chromosome 20q13.11 [26]. Albright's hereditary osteodystrophy (AHO) is disorder in which imprinted genes are involved in the dysregulation of body weight and insulin level [27]. The AHO phenotypes are linked with GNAS1 (Gsα) loss of function which includes frame-shift, nonsense and splice junction mutations, missense mutations and imprinting defects [28].

3. GLUT1 (Glucose Transporter 1)

GLUT1 was the first glucose transporter to be characterized [29]. It is widely distributed in fetal tissues and located at glomerular mesangial cells [30]. In adult it is expressed at highest levels in erythrocytes and also in the endothelial cells of barrier tissues such as the blood-brain barrier. Glut1 is a major receptor for take-up of vitamin C as well as glucose, especially in non vitamin C producing mammals as part of an adaptation to compensate by participating in a Vitamin C recycling process [31]. Mutations in the GLUT1 gene are responsible for GLUT1 deficiency or De Vivo disease, which is a rare autosomal dominant disorder [32]. The association between diabetic nephropathy (DN) and the XbaI polymorphism in the GLUT1 gene has been investigated in several case-control studies. It has been postulated that XbaI polymorphism in the glucose GLUT1 gene is involved in the development of diabetic nephropathy in patients with types 1 and 2 diabetes mellitus [33, 34]. It facilitates glucose transporters in glomerular mesangial cells [35].

4. LGALS2 (Galectin 2)

This gene is located at chromosome 14 (Location 14q21-q) on Lymphotoxin-α [36] and associated with lower fasting insulin and glucose levels [37] as well as with myocardial infarction [36]. Lymphotoxin-alpha in coronary event pathogenesis and in metabolic syndrome traits has also implicated LGALS2. Lower fasting insulin and glucose levels were associated with LGALS2. LGALS2 rs7291467 was not associated with BMI (Body Mass Index), triglyceride levels, HDL-c or blood pressure [38].

5. CAPN 10 (Calpain-10)

CAPN 10 is located at chromosome 2q37 of tissues such as the pancreas, heart, brain, liver, skeletal muscle and kidney [39]. It influences glucose uptake in skeletal muscle and adipocytes as well as glucose-induced insulin secretion in pancreatic β cells [40]. The allele combination of CAPN10 (SNP-43, -19, and -63) is reported to be associated with increased risk of T2DM in many populations [41, 42]. The 112/121 diplotype of CAPN10 is associated with increase in the risk of T2DM [39].

6. CTLA-4 (Cytotoxic T-Lymphocyte-Associated protein 4)

This gene is a member of the immunoglobulin super family and encodes a protein which transmits an inhibitory signal to T cells located at Chromosome 2

(Location: 2q33) on T cells [43]. The protein contains a V domain, a transmembrane domain and a cytoplasmic tail. Polymorphism of CTLA-4 gene i.e. A/G (A to G substitution) was associated with the occurrence of type 1B diabetes and type 1B diabetics with a GG (G to G substitution) genotype were associated with more severe cell dysfunction than their type 1A counterparts. CTLA-4 is considered the most likely candidate gene for IDDM and other autoimmune disorders because of its important role in the T-cell proliferative response [44]. Also, involved in maintaining peripheral T-cell tolerance and thus protects against autoimmunity and severe β-cell dysfunction [43].

7. TCF7L2 (Transcription Factor 7-like 2)

TCF7L2 located at Chromosome 10 (Location: 10q25.3) on pancreatic beta cells [44], encoding an enteroendocrine transcription factor involved in glucose homeostasis which have role in the Wnt signaling pathway [45]. A strong association between susceptibility to type 2 diabetes and transcription factor 7-like 2 (TCF7L2). The TCL7L2 gene product is a high mobility group (HMG) box-containing transcription factor implicated in blood glucose homeostasis. The study of Yi et al (2005) suggested that TCL7L2 acts through regulation of proglucagon through repression of the proglucagon gene in enteroendocrine cells via the Wnt signaling pathway [44].

8. E23K (Glutamate (E) with Lysine (K) 23 gene)

E23K are located at pancreatic β- and α-cells and its polymorphism is linked with increased susceptibility to type-2 diabetes, weight gain and obesity [46, 47]. The subtle nature of alterations in K-ATP channel activity induced by E23K highlights the importance of detailed probing of channel properties including both macroscopic and single channel activity, when examining ion channel mutations [48]. It is involved in optimizing skeletal muscle contractility during exercise through increasing blood flow and potentiating force development via increased extracellular K+ levels [49]. Also, associated with alterations in glucose homeostasis [50, 51].

9. IL4R (Interleukin 4 receptor)

IL4R is located at chromosome 16 (Location: 16p12.1-p11) of lymphocytes, encodes the alpha chain of the interleukin-4 receptor, a type I transmembrane protein that can bind interleukin 4 and interleukin 13 to regulate IgE production [52]. Haplotypic association of IL4R has also been reported in type 1 diabetes and multiple sclerosis, study shows no association of IL4R with type 1 diabetes [53]. IL4R genes are also involved in asthma, primary Sjogren 's syndrome, penicillin allergy and atopic dermatitis [54, 55]. The IL4R gene can promote differentiation of Th2 (T cells) cells through binding with IL-4 [56].

10. GCKR (Glucokinase Regulatory Protein)

GCKR is located at chromosome 2p23.2–3 of pancreatic β-cell [57]. The relationship between GK and diabetes mellitus has been demonstrated by the identification of specific rare mutations in GCK [58]. Decrease in serum insulin release among GCKR rs780094 carriers may lead to a secondary increase in serum triacylglycerol due to increased hepatic fatty acid oxidation. GCK–30GA polymorphism influencing GK production increase hyperglycaemia by enriching the threshold for glucose-stimulated insulin releases [59]. The glucokinase regulatory protein is also involved in triacylglycerol regulation , modestly decreased plasma glucose levels, increased insulin sensitivity as estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) and lower risk of type 2 diabetes [60].

Table 1: Pharmacogenomics of diabetes

Genes	***Characteristics***	***References***
MCP1	These proteins are significantly correlated with plasma MCP-1 levels and the prevalence of insulin resistance and Type 2 diabetes.	25
GNAS1	Short stature, brachydactyly, ectopic ossifications, often associated with pseudo hypoparathyroidism, and elevated parathyroid hormone levels (PHPIa).	27, 28
GLUT1	It was shown either to be a risk factor or neutral or even protective for the development of the disease to diabetic nephropathy	29,30
LGALS2	Influence on glucose-insulin regulation	38
CAPN10	Associated with the risk of type 2 diabetes mellitus (T2DM) in Mexican- Americans and Northern Europeans whereas these variations are not associated with T2DM in other populations	41, 42
CTLA-4	Suggested to be associated with type 1 diabetes in human populations.	44
TCF7L2	Gene contributes to the risk of type 2 diabetes. The population-attributable risk from this factor in the Dutch type 2 diabetes population is 10%.	45
E23K	Plays a role in the etiology of type-2 diabetes in a significant percentage of the Caucasian population.	48
IL4R	No association between type 1 diabetes and the six nsSNPs	53
GCKR	To increase glucokinase regulatory protein activity, to induce improved glycaemic regulation at the expense of hypertriacylglycerolaemia	63
IAPP	60% deficit in cells due to increased cell apoptosis cause increase in insulin resistance.	65

Improved glycaemic regulation at the expense of hypertriacylglycerolaemia and other abnormalities in energy metabolism has been demonstrated in mice and rat liver overproducing either GK or GKRP [61].

11. IAPP (Islet Amyloid Polypeptide)

Islet or insulinoma, amyloid polypeptide (IAPP or amylin) is commonly found in pancreatic islets of diabetes mellitus type II patient at Chromosome 12 (Location: 12p12.3-p12.1) [62]. There appears to be at least three distinct receptor complexes that bind with high affinity to amylin. All three complexes contain the calcitonin receptor at the core, plus one of three receptor activity-modifying proteins, RAMP1, RAMP2, or

RAMP3 [63]. IAPP is capable of forming amyloid fibrils in vitro. Within the fibrillization reaction, the early prefibrillar structures are extremely toxic to beta-cell and insuloma cell cultures [64]. Islet amyloid in T2D is composed of extracellular fibrils of islet amyloid polypeptide 1 (IAPP1), a 37-amino acid protein that is co-expressed and co-secreted with insulin by β-cells [65]. Rodent IAPP is not amyloidogenic, thus commonly used rodent models of diabetes do not summarize islet pathology in humans [66]. Human IAPP-induced β -cell apoptosis appears to prevent recovery of β -cell mass as replicating β-cells have increased vulnerability to IAPP induced apoptosis [67]. Genes for diabetes are shown in table 1.

Pharmacogenomics of Obesity:

Pharmacogenomics involves various genes with the potential of inducing the physiological changes in the host and thereby may induce the disorder. Following are the genes involved in obesity and its allied symptoms.

1. WNT10B (Wingless-type 10B)

WNT10B genes are located at Preadipocytes and stromovascular cells [68]. These are implicated in the regulation of murine adipogenesis in vitro and in vivo. It has been shown that WNT signaling maintains preadipocytes in an undifferentiated state by inhibition of binding protein α (CEBPA) and peroxisome proliferators activated receptor γ (PPAR γ) [69, 70]. Disruption of WNT signaling results in spontaneous adipogenesis, WNT10B under the control of the fat-specific Fabp4 promoter display a 50% reduction in total body fat without lipodystrophic diabetes and resist high-fat diet-induced obesity [68].

2. FTO (Fat mass and Obesity associated gene)

The fat mass and obesity associated gene region on chromosome 16q12 has recently been found to contribute to the risk of obesity. Single nucleotide polymorphism (SNP) rs9939609 in the fat mass and obesity associated gene was originally found to be associated with type 2 diabetes [71].

3. INSIG2 (Insulin-induced Gene 2)

The protein encoded by this gene is highly similar to the protein product encoded by gene INSIG1. INSIG2 is located at chromosome 2 (Location: 118.56 - 118.58) at liver cell receptors. Recent genome-wide association studies have shown that rs7566605 in the upstream region of the INSIG2 gene is associated with obesity [72, 73]. Associations between rs7566605 and obesity phenotype have been observed in many Caucasian subjects [74]. Rs7566605 in the upstream region of the INSIG2 gene may influence the risk of severe obesity [75]. INSIG2 genes are down regulated by insulin in the liver and involved in fatty acid synthesis, affects lipid metabolism. INSIG2 also mediates feedback control of cholesterol synthesis [76].

4. MC4R (Melanocortin 4 receptor)

The MC4R genes are associated with obesity, located on chromosome 18 (Location: 18q22) on Hypothalamus [77]. MC4R mutant alleles have shown late onset obesity with increased food intake in rodents [78]. Mutations in MC4R contribute to hyperphagia and hyperinsulinemia in obese individuals ,also in binge-eating disorders [79].

5. POMC (Pro-opiomelanocortin)

POMC located at chromosome 2 (Location: 2p23) in Quantitative trait loci (QTL) encodes a polypeptide hormone precursor that undergoes extensive, tissue-specific, post-translational processing via cleavage by subtilisin-like enzymes known as prohormone convertases [80, 81]. QTL have been identified for obesity-related traits which encompasses the POMC gene [82]. Mutations in this gene associated with early onset obesity, adrenal insufficiency and red hair pigmentation.

Table 2: Pharmacogenomics of obesity

Genes	Characteristics	Reference
WNT10B	Candidate gene for human obesity	69, 70
FTO	To contribute to the risk of obesity	71
INSIG2	Associated with the obesity phenotype in many Caucasian populations.	75
MC4R	Melanocortin-4 Receptor Gene Variant I103 Is Negatively Associated with Obesity	77, 78
POMC	Associated with obesity, particularly because a loss of POMC function results in obesity.	82
UBE3A	Also, associated with Short stature, small hands and feet, hypogonadism, mild-moderate mental retardation, temper tantrums, obsessive - compulsive behavior.	135
COH1	No progressive mental and motor retardation, typical dysmorphic features, progressive retinochoroidal dystrophy, myopia, granulocytopenia	86, 87
PHF6	It regulates cholesterol absorption in the body	85

An amino acid missense substitution in the POMC gene, R236G, produces an aberrant fusion protein that can interfere with signaling through MC4R .The binding of aberrant fusion protein to MC4R receptor acts as an agonist, reducing the normal antagonist effect of alpha-Melanocortin stimulating harmone (α-MSH) [83].

6. UBE3A (Ubiquitin ligase E3A)

UBE3A encodes an E3 ubiquitin ligase involved in the ubiquitinylation pathway of protein degradation and its expression is imprinted with maternal expression, only in cerebellar and hippocampal neurons and obesity [84]. UBE3A gene turbulence on maternal allele chromosome 15q11-q13 is Angelman syndrome (AS) with no phenotype on paternal inheritance of mutations [85].

7. COH1 (Cohen syndrome gene)

The COH locus is at chromosome 8q22 and mutations in the COH1 gene were found to cause the syndrome [86]. The Cohen syndrome (COH) is a rare disorder characterized by obesity, mental retardation, hypotonia, joint laxity, neutropenia, microcephaly, myopia or pigmentary retinopathy, characteristic facial appearance consisting of downslanting palpebral fissures, high nasal bridge, short philtrum, high narrow palate, prominent central incisors, and open mouth. Obesity is usually truncal, idiopathic, and does not represent a ubiquitous feature of the syndrome [87].

8. PHF6 (Plant Homeodomain-like Finger 6)

This gene is a member of the plant homeodomain like finger (PHF) family. It encodes a protein with two PHD-type zinc finger domains, indicating a potential role in transcriptional regulation that localizes to the nucleolus. The Borjeson-Forssman-Lehmann syndrome (BFLS) is a rare X-linked recessive disorder characterized by obesity, severe mental retardation, epileptic seizures, gynecomastia, hypogonadism, short stature and large thick ears [85]. Recently, missense and truncation mutations have been identified in BFLS in the PHF6 gene that encodes a putative plant homeodomain– like zinc-finger polypeptide of unknown function that is localized to the

nucleolus [88]. Genes for obesity are shown in table 2.

Genes Involved in Obesity Associated Diabetes:

Following are the genes involved in obesity associated diabetes and its allied symptoms.

1. IRS-2 (Insulin receptor substrate - 2)

Insulin receptor substrate (IRS-2) located at β cells in pancreas plays an important role in insulin signaling and its disruption in mice results in diabetes [89]. Diabetes could be attributed largely to hepatic insulin resistance and lack of β cell compensation [90]. IRS-2 signaling promotes regeneration of adult β cells and central control of nutrient homeostasis, which can prevent obesity and diabetes in mice [91]. IRS-2 gene disruption results in leptin resistance, causing an obesity, diabetes and fatty liver [92].

2. PTPN1B (Protein Tyrosine Phosphatase 1B)

PTPN1B protein sequence located at chromosome 20 (Location: 20q13.1-q13) in human cells. The protein encoded by this gene is the founding member of the protein tyrosine phosphatase (PTP) family, which was isolated and identified based on its enzymatic activity and amino acid [93]. PTPs catalyze the hydrolysis of the phosphate monoesters specifically on tyrosine residues. Members of the PTP family share a highly conserved catalytic motif, which is essential for the catalytic activity. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, fat synthesis, differentiation, mitotic cycle and oncogenic transformation. The gene for Protein tyrosine phosphatase 1B (PTPN1) investigated as a positional candidate gene for the linkage to type 2 diabetes [94]. This PTP has been shown to act as a negative regulator of insulin signaling by dephosphorylating the phosphotryosine residues of insulin receptor kinase [95].

3. ADIPOQ (Adiponectin Gene)

This gene is expressed in adipose tissue exclusively at Chromosome 3 (Location: 3q27) of peripheral and sympathetic nervous System [96]. The 'A' allele seemed to enhance the ADIPOQ promoter activity and increased transcriptional activity [97]. It encodes a protein with similarity to collagens X and VIII and complement factor C1q. The encoded protein circulates in the plasma and is involved with metabolic and hormonal processes. ADIPOQ spans 16 kb and contains three exons. Variants in ADIPOQ have been inconsistently associated with adiponectin levels or diabetes [98]. This gene is major risk factors for type 2 diabetes and insulin resistance [99].

4. IL6 (Interleukin-6)

IL6 is an immunoregulatory cytokine located at Chromosome 7 (Location: 7p21) in adipose tissue, skeletal muscle and hypothalamus [100]. It activates a cell surface signaling assembly composed of IL6 and the shared signaling receptor gp130 (IL6ST) [101]. Interleukin encoding gene IL6 exerts crucial effects not only in inflammation and infection but also within the nervous and endocrine systems [102]. The lack of circulating IL-6 was associated with obesity, low energy expenditure. The recently described C-174G promoter polymorphism of the IL-6 gene has been found to influence transcriptional regulation [103, 104] and plasma IL-6 levels in patients with systemic-onset juvenile chronic arthritis and primary Sjogren's syndrome [105]. In humans, IL-6 has been shown to increase heart rate and nor epinephrine levels [106] and to stimulate the sympathetic nervous system [107, 108].

5. LEPR (Leptin Receptor Gene)

LEPR located at Cytokine receptors of tissue and pancreatic beta cells [109]. Polymorphisms of the leptin receptor gene (LEPR) might contribute to obesity or

obesity-related diseases [110]. Leptin (LEP) is a well known anti-obesity hormone that regulates body weight through its effects on food intake and energy expenditure [111]. The study addressed the relationship between leptin receptor gene variations and type 2 diabetes mellitus [112]. Leptin and its receptor are known to play a role in glucose metabolism. For instance, leptin exerts insulin and glucose lowering effects by enhancing peripheral insulin sensitivity and glucose uptake [113].

6. LMNA (Lamins A and C)

The LMNA consists of a two-dimensional matrix of proteins located next to the inner nuclear membrane on Chromosome 1 (Location: 1q21.2-q21) on Adipocytes [114, 115]. Identification of a common single nucleotide polymorphism (SNP) in exon 10 of LMNA, namely a silent C3T substitution at T 1908, was associated with variation in obesity-related indexes. As LMNA 1908T allele being associated with increased anthropometric measurements [116] the LMNA 1908T allele dominantly influenced BMI (Body Mass Index), waist, hip, thigh in non-diabetes and diabetes, implicating the abnormality of alternative splicing of the LMNA/C which affects the adiposity [117]. LMNA mutation leads to failure of differentiation of fibroblast [118]. LMNA 1908 C/T polymorphism was closely related to adiposity, dyslipidemia and insulin resistance phenotypes of the metabolism syndrome [119]. Mutations in the LMNA gene associated with several diseases including muscular dystrophy, familial partial lipodystrophy, limb girdle muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth disease, and Hutchinson-Gilford progeria syndrome. A truncated version of lamin A commonly known as progerin causes Hutchinson-Gilford progeria syndrome [120, 121].

7. PPAR γ (Peroxisome Proliferator-activated Receptor Gamma)

This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors located at Chromosome 3 (Location: 3p25) expressed in adipocytes, hematopoietic cells and later also in spleen, liver, testis, skeletal muscle, and brain [122, 123]. PPAR- γ has been identified as a nuclear receptor for thiazolidenediones, which are compounds with insulin-sensitizing properties in several tissues including skeletal muscle [124]. Peroxisome proliferator-activated receptor-gamma (PPARGγ) involved in obesity-related phenotypes [125]. PPARγ has been shown to inhibit the expression of the aromatase gene, a key enzyme in estrogen biosynthesis [126]. PPARγ plays a key role in adipogenesis and lipogenesis and treatment with PPARγ-agonists alters plasma lipid profiles [127, 128]. Peroxisome proliferator-activated receptor-gamma (PPARγ) is a transcription factor that plays a key role in activation of adipocyte differentiation and is an important modulator of gene expression in a number of specialized cell types, including adipocytes [122].

8 RETN (Resistin)

The gene encoding resistin (RETN) is located at Chromosome 8 (Location: 8 A1; 8 0.3) encodes the adipokine resistin [129]. Several single nucleotide polymorphisms (SNPs) have been associated with resistin levels [130,131]. Associations between RETN and body mass index (BMI) or other measures of adiposity have shown very inconsistent results [132]. Polymorphisms in RETN also have been associated with indices of insulin resistance in some reports [133]. RETN, rs10401670 is associated with both resistin levels and fasting glucose [134].

9. UCP (Uncoupling protein)

UCP genes are located at chromosome11 (Location: 11q13) on skeletal muscle, members of the larger family of

Table 3: Pharmacogenomics of obesity associated diabetes

Genes	Characteristics	Reference
IRS-2	Interacts with obesity to affect beta cell function	89
PTPN1	SNPs within PTPN1 are unlikely to have a major role in the aetiology of type 2 diabetes or obesity in Pima Indians.	94
ADIPOQ	Variants in ADIPOQ have been inconsistently associated with adiponectin levels or diabetes	96, 97
IL6	IL-6 gene influences energy expenditure and insulin sensitivity	101, 102
LEPR	LEPR gene could be a risk factor associated with T2DM. Mutation of the leptin receptor gene (LEPR) leads to a rare obese syndrome	112, 113
LMNA	LMNA variants are associated with type 2 diabetes and quantitative metabolic traits. Genetic variation in LMNA is an important determinant of obesity-related quantitative traits.	116, 117
PPARγ	Abnormalities of PPAR-γ may be involved in skeletal muscle insulin resistance of obesity and type II diabetes. PPARγ gene has a gender-specific effect and contributes to the susceptibility to obesity in this population.	124, 125
RETN	Associations of RETN with plasma resistin levels, type 2 diabetes and related metabolic traits	130
UCP	UCP2 haplotype may protect against insulin resistance in the obese population group.	136, 137
ENPP1	ENPP1 inhibits insulin-induced conformational changes of the insulin receptor, thereby affecting its activation and downstream signalling	139

mitochondrial anion carrier proteins (MACP). UCPs separate oxidative phosphorylation from ATP synthesis with energy dissipated as heat, also referred to as the mitochondrial proton leak. UCPs facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons [135]. Adenovirus-mediated over expression of UCP1 and UCP3 in vitro prevents neurons from glucose-induced degeneration by preventing mitochondrial hyper polarization [136]. Polymorphisms in UCP2 and UCP3 genes shows enhanced transcriptional activity and increased mRNA levels. By providing higher expression of genes, prevent or reduce the hyperglycemia-induced depolarization of the inner mitochondrial membrane of neurons, normally seen in states of chronic diabetes [137, 138].

10. ENPP1 (Ectonucleotide Pyrophosphatase/phosphodiesterase 1 gene)

The ENPP1 is located at chromosome 6q16-q27 on insulin receptor. The association between the ENPP1, three-allele risk haplotype and childhood obesity was recently confirmed.. ENPP1 directly inhibits insulin-induced conformational changes of the insulin receptor, thereby affecting its activation and downstream signaling [139].

Genes for obesity associated diabetes are shown in table 3.

Pharmacogenomic Therapies for Diabetes :

1. PPARγ agonists

PPARγ is a member of the nuclear receptor superfamily of ligand-dependent transcription factors that regulates adipocyte differentiation and glucose homeostasis [140, 141]. Natural and synthetic PPARγ ligands have also shown to exert anti-inflammatory effects in models of atherosclerosis, inflammatory bowel disease and allergic encephalomyelitis established route to improve insulin sensitivity in type 2 diabetes, as illustrated by the thiazolidinediones in present clinical use, namely rosiglitazone and pioglitazone [142]. Stimulation of PPARγ causes transcription of certain insulin-sensitive genes such as lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid–binding protein (aP2), fatty acyl-CoA synthase, malic enzyme, glucokinase, phosphoenolpyruvate carboxykinase, and glucose transporter isoform- 4 (Glut-4) [143]. PPARγ enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism [144]. Leptin gene expression is shown regulated by PPARγ and the decrease in circulating leptin concentrations after PPARγ activation seem to be associated with an increase in food intake, which provides substrates, subsequently to be stored in the adipocytes. TNFα exerts an antiadipogenic action in part by the down-regulation of the expression of adipogenic factors including PPARγ [145, 146]. Activation of PPARγ stimulates adipogenesis and blocks the inhibitory effects of TNFα on insulin signaling as well as the TNFα-induced glycerol and non-esterified fatty acid release [147]. Stimulation of PPARγ with thiazolidinediones in 3T3- L1 adipocytes or in diabetic rodents lead to increased c- Cbl-associating protein (CAP) expression and increased insulin-stimulated c-Cbl phosphorylation that correlates well with increased insulin sensitivity both in vitro and in vivo [148].

2. RXR and PPAR γ agonists

RXR (retinoid X receptor) exists as a heterodimer with the Peroxisome proliferator-activated receptor- γ and co activation of RXR and PPAR γ has been reported to cause an additive or synergistic improvement of insulin action in skeletal muscle compared with stimulation of PPAR γ alone [149]. Stimulating RXR alone may be ineffective or produce variable effects such as reduced food intake, reduced body weight gain, increased expression of uncoupling proteins and increased expression of the p85a subunit of PI3K [150, 151].

3. PPARδ and PPAR γ agonists

Several established PPARδ agonists are known to bind PPAR γ with low affinity and enhanced stimulation of PPAR γ is associated with a greater lipid lowering effect. Hence, dual agonists of PPARδ and PPARγ are now seen as an opportunity to achieve both glucose and lipid-lowering effects. Stimulation of PPAR δ (e.g. by fibrates) is an established mechanism to lower circulating lipid concentrations (e.g. Bezafibrate) [152].

4. Other insulin action enhancers

Direct stimulation of insulin receptor tyrosine kinase activity has recently been reported using metabolite (LY783281) from a Pseudo massaria fungus and a synthetic molecule (TLK16998) (e.g. Metformin, Tfroglitazone) [153].

5. Direct modulators of metabolism

A selection of substances that directly stimulate glucose uptake and metabolism or suppress gluconeogenesis, aminoimidazole carbox-amide ribonucleotide (AICAR), a ribofuranoside activator of AMP-activated protein kinase, is interesting because it inhibits (by inhibiting fructose-1, 6-

bisphosphatase) hepatic gluconeogenesis and increases the expression of Glut-4 and hexokinase in muscle e.g. Lysophosphatidylcholine (LPC), lysophosphatidylserine (LPS), lysophosphatidic acid (LPA), and urocortin (UCN) [154].

6. PPAR α & PPAR γ agonist

Nonthiazolidinedione dual PPARα and PPARγ agonists led to the discovery of ragaglitazar (DRF 2725, NNC 61-0029), a phenoxazine analogue of phenyl propanoic acid having dual (PPARα and PPAR γ) agonist property [155]. Efficacy of ragaglitazar with comparison of PPARγ activator rosiglitazone, PPARα activator fenofibrate enhances and dual activator KRP-297.

Pharmacogenomic Therapies for Obesity :

1. Ciliary Neurotropic Factors

Genetically engineered CNF (Regeneron) injected subcutaneously in obese patients, produced dose-related weight loss in shorter trials and last-observation-carried-forward mean weight loss for placebo treatment at 1 year [156]. The endocannabinoid system interacts with several neuropeptides that modulate hunger and satiety signals, with the net result being stimulation of appetite [157].

2. Canabinoid-1 antagonist

One of its actions is to increase Acrp30 mRNA expression. Acrp30 is an adipose tissue-derived plasma protein that induces free fatty acid oxidation, decreases hyperglycemia and hyperinsulinemia and reduction of body weight e.g. rimonabant, surinabant, otenabant [158].

3. Selective β -3- Adrenergic Agonist

A selective β-3- adrenergic agonist, increased energy expenditure 8% and lipolysis, as assessed by increased plasma glycerol and free fatty acid concentrations after a single 1000-mg dose without apparent cardiovascular adverse effects [159]. Chronic activation of the β3-adrenoceptor (β3-AR), which is predominantly expressed in white and brown adipose tissue by selective agonists, exerts both anti-obesity and anti-diabetic effects in rodent models of obesity [160, 161]. The improvement in glucose homeostasis induced by β3-AR agonists appears to be a consequence of increased insulin sensitivity in peripheral tissues rather than stimulation of insulin secretion by the pancreas [162]. Obese rats treated with β3-AR agonists demonstrated an improvement of insulin sensitivity in brown and white adipose tissue as well as in skeletal muscle [163, 164].

Clinical Implications of Pharmacogenomic Therapies:

Use of genetic tools has been beneficial in increasing our understanding of the diseases. The reviewed pharmacogenomic therapies are offering good therapeutic potential. However, the genes traced for obesity and same for diabetes may be targeted for the newer pharmacogenomic therapies. The technology is advancing so that such endeavors are becoming practical and cost efficient. The understanding and identification of genetic influences in obesity associated diabetes will impact on the development of public health initiatives to reduce and prevent obesity associated diabetes. The data explored in this review provides targets for future development of therapies for obesity associated diabetes.

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