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Association of the rs7903146 and rs12255372 Polymorphisms of the TCF7L2 Gene with Type 2 Diabetes Risk: A Meta-Analysis

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Dedication

This work is dedicated to:

To my mother, Arbia who cared deeply about my education even when her worries stressed me out I finally made it.

To my father, Brahim who pretended not to notice but secretly cheered me on every step of the way this is for you too.

To my siblings, Houda, Abduallah, Hadjer, Hana, Hala who helped me study throughout my entire education from primary school to university thank you.

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To my niece Ranim and nephews Racime and Iyad may you achieve even greater heights in life.

And finally, to myself for never giving up.

Abbreviations list

ABCC8/KCNJ11	ATP Binding Cassette subfamily C member 8/Potassium inwardly-rectifying Channel subfamily J member 1.
AKT2	Ak strain transforming Serine/Threonine Kinase 2.
ALMS	Alström syndrome.
ALMS1	Alström syndrome protein 1.
AVP	Arginine Vasopressin.
BCL2	B-cell Leukemia/Lymphoma 2 protein.
BMI	Body Mass Index.
CAPN10	Calpain 10.
CCND2	Cyclin D2.
CDKAL1	CDK5 Regulatory Associated Protein 1 Like 1.
CDKN2A/B	Cyclin Dependent Kinase Inhibitor 2A/2B.
CI	Confidence Interval.
CRARF	Catenin-Regulated Activation and Repression Function.
CRISPR-Cas9	Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9.
CtBP	C-terminal Binding Proteins.
CTNNB1	β-catenin.
DI	Diabetes Insipidus.
FAM19A2	Family With Sequence Similarity 19 (chemokine (C-C motif)-like) Member A2.
FPG	Fasting Plasma Glucose.
FTO	Fat Mass and Obesity-Associated Gene.
G6PC2	Glucose-6-Phosphatase Catalytic subunit 2.
GC	GlucoCorticoids
GCK	Glucokinase.
GCT	Glucose Challenge Test.
GDM	Gestational Diabetes Mellitus.
GLP-1	Glucagon-Like Peptide-1.
GLUT4	Glucose Transporter Type 4.
GWAS	Genome-Wide Association Studies.

HbA1C	Hemoglobin A1C.
HHEX	Hematopoietically Expressed Homeobox.
HMGA2	High Mobility Group AT-Hook 2.
HNF1A/4A	Hepatocyte Nuclear Factor 1A/4A.
HNF1B	Hepatocyte Nuclear Factor 1B.
HWE	Hardy-Weinberg Equilibrium.
IDF	International Diabetes Federation.
IESCs	Intestinal Epithelial Stem Cells.
IGF2BP2	Insulin like Growth Factor 2 mRNA Binding Protein 2.
IGT	Impaired Glucose Tolerance.
INS	Insulin.
IRS1 & IRS2	Insulin Receptor Substrate -1/ -2.
LADA	Latent Autoimmune Diabetes in Adults.
LPS	Lipopolysaccharide.
MAPK/ERK	Mitogen-Activated Protein Kinases/Extracellular Signal-Regulated Kinases.
MC4R	Melanocortin 4 Receptor.
MODY	Maturity-Onset Diabetes of the Young.
MTNR1B	Melatonin Receptor 1B.
mTORC1	Mammalian Target of Rapamycin Complex 1.
ND	Neonatal diabetes.
NM	Not Mentioned.
NOTCH2-ADAM 30	Notch Receptor 2-A Disintegrin And Metalloproteinase 30.
OGTT	The Oral Glucose Tolerance Test.
OR	Odds Ratio.
OSA	Obstructive Sleep Apnoea.
PAM	Peptidylglycine Alpha-Amidating Monooxygenase.
PDX1	Pancreatic and Duodenal homeobox 1.
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha.
PP	Pancreatic Polypeptide cells.
PPARG	Peroxisome Proliferator Activated Receptor Gamma.
PPARGC1A	PPARG Coactivator 1 Alpha.
RAPGEF1 & TP53	Rap Guanine Nucleotide Exchange Factor 1/ Tumor Protein p53.

SLC30A8	Solute Carrier Family 30 Member 8.
SMA	Superior Mesenteric Artery.
T1DM	Type 1 Diabetes Mellitus.
T2DM	Type 2 Diabetes Mellitus.
TBC1D30	TBC1 Domain Family Member 30.
Tcf motif	T-Cell Factor/Lymphoid Enhancer-Binding Factor Motif.
TCF7L2	Transcription Factor 7 Like 2.
TLE4	Transducin-like enhancer of split-1/2/3/4.
VUS	Variants of Uncertain Significance.
WFS1	Wolfram syndrome 1.
WHO	World Health Organization.
Wnt	Wingless-type MMTV integration site family.
χ^2	chi-square.

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Introduction

Introduction

Before the discovery of insulin, many individuals with diabetes died either from severe hyperglycemia or from starvation caused by extreme dietary restrictions. It was not until 1921, when Banting and Best successfully isolated insulin, that mortality rates began to decline significantly (Vecchio et al., 2018). Despite this groundbreaking advancement and subsequent medical progress, diabetes remains one of the top 10 leading causes of death worldwide to this day (WHO, 2024).

The term *diabetes mellitus* has two etymological roots: *diabetes* derives from the Greek word meaning "siphon" or "pass through" while *mellitus* comes from Latin, meaning "sweet"(Sapra & Bhandari, 2023). It refers to a group of metabolic disorders characterized primarily by chronic hyperglycemia (Schleicher et al., 2022). Several types of diabetes have been identified, with the three most common types being: Type 1 diabetes (T1D), an autoimmune disease (Katsarou et al., 2017); Type 2 diabetes (T2D), the focus of this study, influenced heavily by environmental factors (DeFronzo et al., 2015); and gestational diabetes (GDM), which develops during pregnancy (Alfadhli, 2015).

The global burden of T2D has driven extensive research into its risk factors to aid in prevention. These risk factors are generally classified into two broad categories: environmental factors, primarily obesity and diet (Wu et al., 2014) and genetic factors, including specific gene variants and epigenetic modifications (Ali, 2013; Mannar et al., 2023).

One of the most well-established genetic risk factors for T2D is the TCF7L2 (Transcription Factor 7-Like 2) gene. It encodes a protein involved in the Wnt signaling pathway and functions as a transcription factor (Proteinatlas, 2003). More than 2,000 variants have been identified in TCF7L2 (Uniprot, 2025), including intronic variants such as rs7903146 and rs12255372, which are the focus of this study (Ensembl, 2024).

Numerous case-control studies have examined the association between these TCF7L2 polymorphisms and T2D. While some studies report a significant association (Komala et al., 2019), others do not (Pourahmadi et al., 2015). To address these inconsistencies, we conducted a meta-analysis, a robust statistical method for synthesizing findings from multiple studies, to evaluate the overall strength of the association between the rs7903146 and rs12255372 variants and susceptibility to T2D.

Accordingly, we set the following objectives:

• Conduct an updated literature review on T2D (anatomy, epidemiology, pathophysiology, risk factors, genetic factors, screening, and treatment) and on the TCF7L2 gene (protein function, polymorphisms, and its association with T2D risk).

• Perform a genetic meta-analysis to obtain a robust and precise estimate of the association between TCF7L2 rs7903146 and rs12255372 polymorphisms and T2D susceptibility.

Bibliographical part

Chapter 1:

Overview of the Pancreas

1. Anatomy of the Pancreas

The pancreas is a long, flat, lobulated, yellowish gland situated diagonally along the posterior abdominal wall. It is a retroperitoneal organ enclosed by a thin capsule. It has four parts: head, neck, body, and tail. The head **i**s the larger section nestled within the C-shaped curve of the duodenum. The bile duct travels along its rear surface or into its substance. Whereas the neck is a small part that connects the head and body. The body extends across the aorta and the L2 vertebra. The front surface is covered in peritoneum, whereas the posterior surface is in touch with the aorta, superior mesenteric artery (SMA), left suprarenal gland, left kidney, and renal arteries. The tail is located anterior to the left kidney and is closely associated with the splenic hilum and the left colic flexure. The major pancreatic duct meets the bile duct to produce the hepatopancreatic ampulla, which opens into the duodenum and is controlled by the Oddi sphincter to regulate bile and pancreatic juice flow (Figure 1)(Mahadevan, 2019; Talathi et al., 2023).

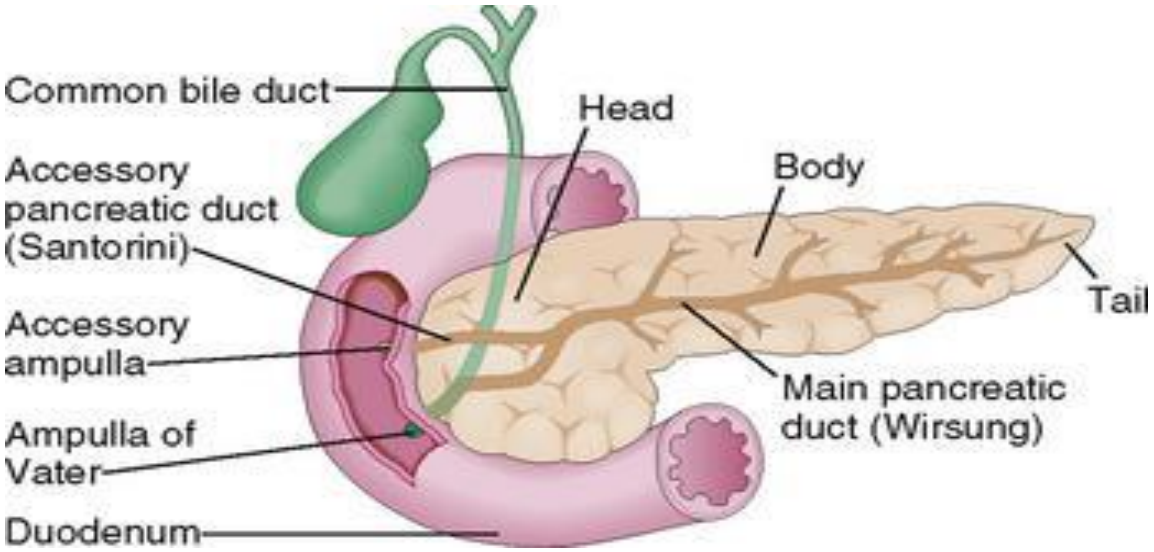

Figure 1: Anatomy of the pancreas(Themes, 2016).

1.1. The Exocrine Pancreas

The exocrine pancreas accounts for 96-99% of total volume and is composed of lobules made up of acini (Figure 2), which produce digesting catalysts into a ductal system that empties into the major pancreatic duct (Wirsung duct). This duct joins with the common bile duct at the ampulla of Vater, releasing into the duodenum, whereas some individuals have an auxiliary pancreatic duct called the duct of Santorini (Figure 1) (Dolenšek et al., 2015).

1.2. The Endocrine Pancreas

The Langerhans islets are distributed evenly throughout the pancreas. β-cells Predominantly located throughout the islets, comprising approximately 60% of the total islet cells. While α-cells make up around 30% of the cells and are interspersed with β-cells. δ-cells make up 10% of islet cells and are distributed throughout the islets. PP (Pancreatic polypeptide cells) cells are mostly located in the head of the pancreas. And finally ε cells are found in small quantities, mostly in the foetal pancreas, but persists in low concentrations in adulthood (Figure 2) (Da Silva Xavier, 2018).

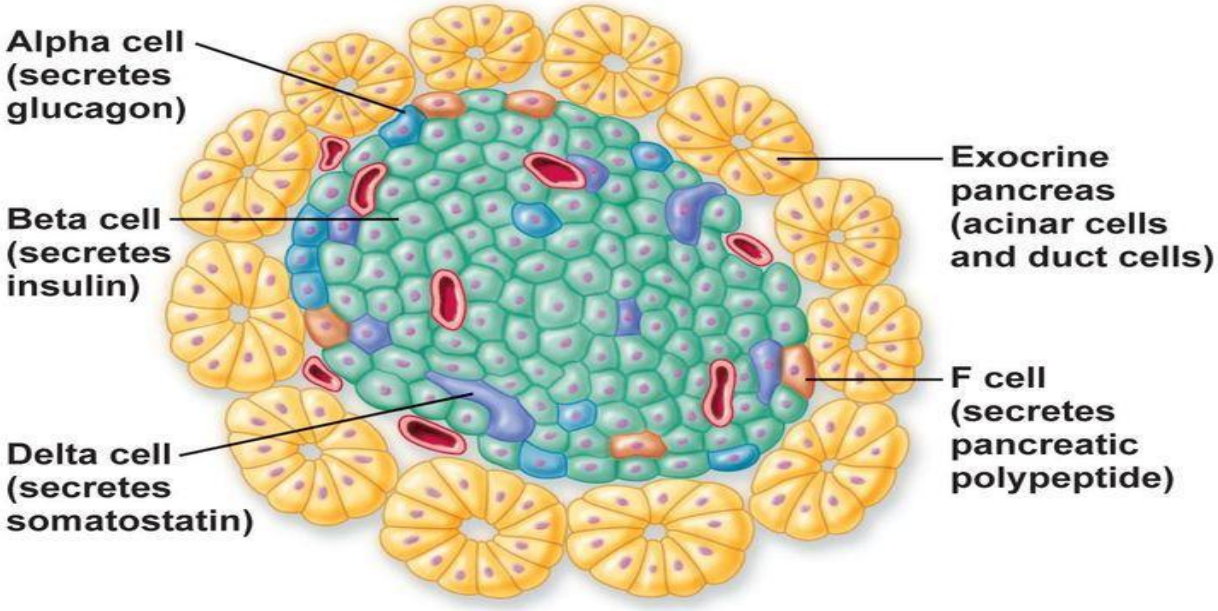

Figure 2: Cell Composition of the pancreas(Ramos, 2018).

2. Functions of the Pancreas

The pancreas has two functions exocrine and endocrine

2.1. The Exocrine Pancreas

The exocrine function of the pancreas is the generation and release of digestive enzymes inside alkaline pancreatic juice, which assists in the breakdown of food in the intestines. Specialised acinar cells release enzymes such as trypsin, chymotrypsin, carboxypeptidase, and elastase for peptide digestion; lipase, phospholipase, and esterase for lipid digestion; amylase and lactase for carbohydrate breakdown, and ribonuclease and deoxyribonuclease for breaking down nucleic acids. These enzymes are discharged into the duodenum via the pancreatic ducts, together with mucus

generated by goblet cells, and their production is controlled by food intake and neurohormonal systems, resulting in the emission of 1-4 litres of pancreatic juice every day (Karpińska & Czauderna, 2022).

2.2. The Endocrine Pancreas

The endocrine pancreas controls blood sugar and metabolism by secreting hormones from the islets of Langerhans. α-cells release glucagon to increase blood sugar while β-cells produce insulin to decrease it. Somatostatin, released by δ-cells, modulates insulin and glucagon levels. PP-cells and ε-cells generate pancreatic polypeptide and ghrelin, which affect digestion and appetite (Gittes, 2009).

3. The Role of Insulin

Insulin's primary physiological role is considered to be preserving glucose homeostasis, despite this insulin has many other roles (Table 1) (Wilcox , 2005 ; Unluhizarci et al., 2021).

Table 1: Roles of Insulin

Roles	Description
Glucose Homeostasis and Carbohydrate Metabolism	Insulin stimulates glucose absorption through GLUT4 (Glucose Transporter Type 4) transporters, enhances glycogen production, and inhibits the degradation of glycogen. It promotes glycolysis while suppressing gluconeogenesis, which aids in energy storage and utilisation.
Lipid Metabolism	Insulin promotes fatty acid and triglyceride production (lipogenesis) while preventing fat oxidation and breakdown (lipolysis). It also stimulates cholesterol production and modulates the phospholipid metabolism.
Protein Synthesis	Insulin stimulates mRNA transcription and translation, improving the synthesis of important metabolic enzymes and proteins in numerous tissues by activating pathways such as mTORC1 (Mammalian Target of Rapamycin Complex 1)
Cell Growth and Differentiation	Activates pathways such as MAPK/ERK(Mitogen-Activated Protein Kinases/Extracellular Signal-Regulated Kinases) , which promote cell proliferation and differentiation. While also promoting tissue development and repair through DNA and RNA production.

Chapter 2:

Type 2 Diabetes

1. Definition of Diabetes and Prediabetes

Diabetes mellitus is a typical word for a heterogeneous metabolic disorder with the principle symptoms being in a chronic hyperglycemia, it arises from either a reduced insulin secretion or diversed grade of insulin resistance or both (Petersmann et al., 2018 ; Schleicher et al., 2022).

Prediabetes refers to increased risk of acquiring type 2 diabetes. It is characterised by the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (Yip et al., 2017).

2. Types of Diabetes

2.1. Type 1 Diabetes Mellitus (T1DM)

T1DM is a chronic autoimmune condition in which T lymphocytes attack pancreatic β-cells, resulting in insulin insufficiency, hyperglycemia, and ketosis. It often appears during childhood but can happen at any age. Diagnosis is based on autoantibody detection, and treatment involves lifetime insulin administration, with modern alternatives such as insulin pumps (Katsarou et al., 2017; Syed, 2022).

2.2. Type 2 Diabetes Mellitus (T2DM)

T2DM is mainly caused by obesity, habits, and metabolic syndrome, causing insulin resistance, decreased secretion of insulin, and several metabolic conditions affected by environmental and genetic factors. T2DM raises the risk of significant microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular) problems. To maintain control of blood sugar and enhance quality of life, treatment should include antidiabetic drugs, lifestyle modifications, and innovative treatments (DeFronzo et al., 2015; Ahmad et al., 2022)

2.3. Gestational Diabetes Mellitus (GDM)

GDM is a frequent pregnancy condition characterised by hyperglycemia, which raises the risk for undesirable maternal and newborn consequences. Overweight, older maternal age, prior GDM, and a family heritage of diabetes are all risk factors. The oral glucose tolerance test (OGTT) or glucose challenge test (GCT) is commonly used to make the diagnosis, however there is no universal consensus. Treatment begins with a healthy diet and physical activity, with insulin or oral hypoglycemic medications administered as needed. While

therapy improves pregnancy outcomes, GDM increases the risk of metabolic diseases in the mother as well as the child, highlighting the importance of long-term care and protective plans (Alfadhli, 2015 ; McIntyre et al., 2019).

2.4. Other Types of Diabetes

Although type 1, type 2, and gestational diabetes are the three most prevalent diabetes diagnoses, other kinds of diabetes are as crucial. About 1.5-2% of individuals live with odd types of diabetes, which can be classified into nine groups (IDF, 2023).

2.4.1. Alström Syndrome: Alström syndrome (ALMS) is an infrequent monogenic condition resulting from alterations in the ALMS1 (Alström syndrome protein 1) gene that results in multisystem failure. Early-onset insulin resistance and T2DM are significant features, as they are frequently linked with obesity and metabolic problems. The ALMS1 protein, which is connected to primary cilia, is involved in cellular signalling and metabolic control (Dassie et al., 2021).

2.4.2. Diabetes insipidus: Diabetes insipidus (DI) is characterised by insufficient arginine vasopressin (AVP) activity, which results in excessive urine. There are two types of DI, Central DI is caused by a lack of AVP as a result of pituitary gland or hypothalamic injury and nephrogenic DI is induced by AVP resistance in the kidneys, which can be caused by genetic mutations, renal illness, or certain drugs. A water deprivation test or copeptin measurement are used to diagnose the condition, and therapy is determined on the underlying cause (Christ-Crain et al., 2019).

2.4.3. LADA (Latent Autoimmune Diabetes in Adults): Latent autoimmune diabetes in adults (LADA) is a slow-progressing type 1 diabetes that doesn't need insulin. It is identified based on age onset, the existence of islet autoantibodies, and insulin autonomy at diagnosis, separating it from type 2 diabetes, which doesn't need insulin at all, and classic type 1 diabetes, which does (Fourlanos et al., 2005).

2.4.4. MODY (Maturity-Onset Diabetes of the Young): Maturity-onset diabetes of the young (MODY) is a monogenic, autosomal dominant sort of diabetes that develops below the age of 25 and is frequently misidentified as type 1 or type 2. There are many types of MODY each has a responsible mutation, alterations in GCK (Glucokinase) (MODY 2) result in moderate, persistent hyperglycemia, whereas HNF1A/4A (Hepatocyte Nuclear Factor 1A/4A) (MODY 3/1) causes progressive β-cell failure that requires sulfonylureas or insulin. HNF1B (Hepatocyte Nuclear Factor 1B) (MODY 5) is associated with pancreatic and renal problems. An accurate genetic evaluation is essential for appropriate therapy and early discovery in

asymptomatic families (Anık et al., 2015).

2.4.5.Neonatal diabetes: Neonatal diabetes (ND) is a rare hereditary condition that causes severe high blood sugar levels before the age of six months as a result of decreased insulin production. This condition is caused by pancreatic deformity or β-cell malfunction, and is frequently associated with 6q24 abnormalities or mutations in ABCC8/KCNJ11 (ATP Binding Cassette subfamily C member 8/Potassium inwardly-rectifying Channel subfamily J member 11) genes that alter potassium channels. While some individuals require lifelong insulin, 90% of those with ABCC8/KCNJ11 mutations or 6q24 abnormalities can switch to sulfonylureas treatment (Beltrand et al., 2020).

2.4.6. Wolfram Syndrome: Wolfram syndrome is a rare inherited disease marked by juvenile-onset diabetes mellitus, diabetes insipidus, optic atrophy, hearing loss, and neurodegeneration. It has a poor prognosis, with lots of patients suffering from severe neurological degeneration and early death. Although there is no cure, regular surveillance and supportive care can enhance quality of life (Urano, 2016).

2.4.7. Secondary diabetes: Secondary diabetes arises thanks to additional health issues or drugs, such as cystic fibrosis, pancreatitis or corticosteroid usage (IDF, 2023).

2.4.8. Steroid-induced diabetes: Steroid-induced diabetes may occur in certain individuals who use steroids and is more prevalent in individuals at a greater risk of type 2 diabetes (IDF, 2023).

2.4.9. Type 3c diabetes: Type 3c diabetes defines a potential connection within Alzheimer's illness and insulin resistance, implying that Alzheimer’s may represent a form of diabetes. However, this kind of diabetes is not officially recognised (IDF, 2023).

3. Pathophysiology of Type 2 Diabetes

Under physiological circumstances, insulin secretion and insulin action are highly regulated to maintain blood glucose levels within a stable concentration. In T2D, this regulation is disrupted due to an impaired feedback mechanism between the two processes. The reduced feedback loop is caused either by β-cell dysfunction or insulin resistance. The body's capacity to regulate glucose is diminished due to the pancreas's inability to produce enough insulin, leading to high blood sugar as cells fail to absorb glucose. Meanwhile, insulin resistance occurs when cells especially in muscle and liver become less sensitive to insulin, resulting in decreased glucose absorption and increased glucose production by the liver, further contributing to hyperglycemia (Figure 3) (Ozougwu, 2013 ; Galicia-Garcia et al., 2020).

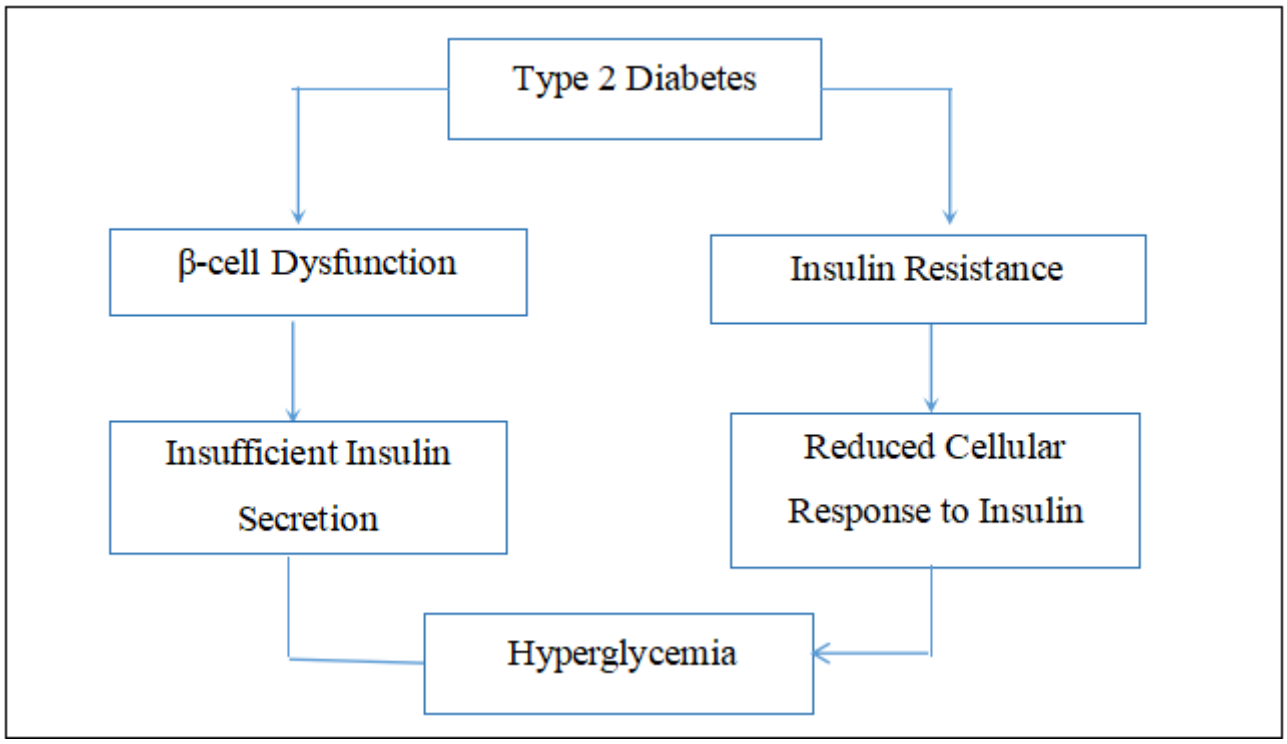

Figure 3: Pathophysiology of Type 2 Diabetes

4. Epidemiology

In 2024, approximately 589 million people worldwide had diabetes, and this number is expected to rise to 853 million by 2050. Additionally, 635 million people had impaired glucose tolerance (IGT). In Algeria, around 4.8 million people were diagnosed with diabetes in 2024, while 1.8 million had impaired glucose tolerance. By 2050, these numbers are projected to increase to 7.9 million and 2.8 million, respectively (Figure 4) (IDF, 2025). In 2024, diabetes was responsible for one death every nine seconds, totaling approximately 3.4 million deaths worldwide. In Algeria, around 20,000 people died due to diabetes in the same year (IDF, 2025).

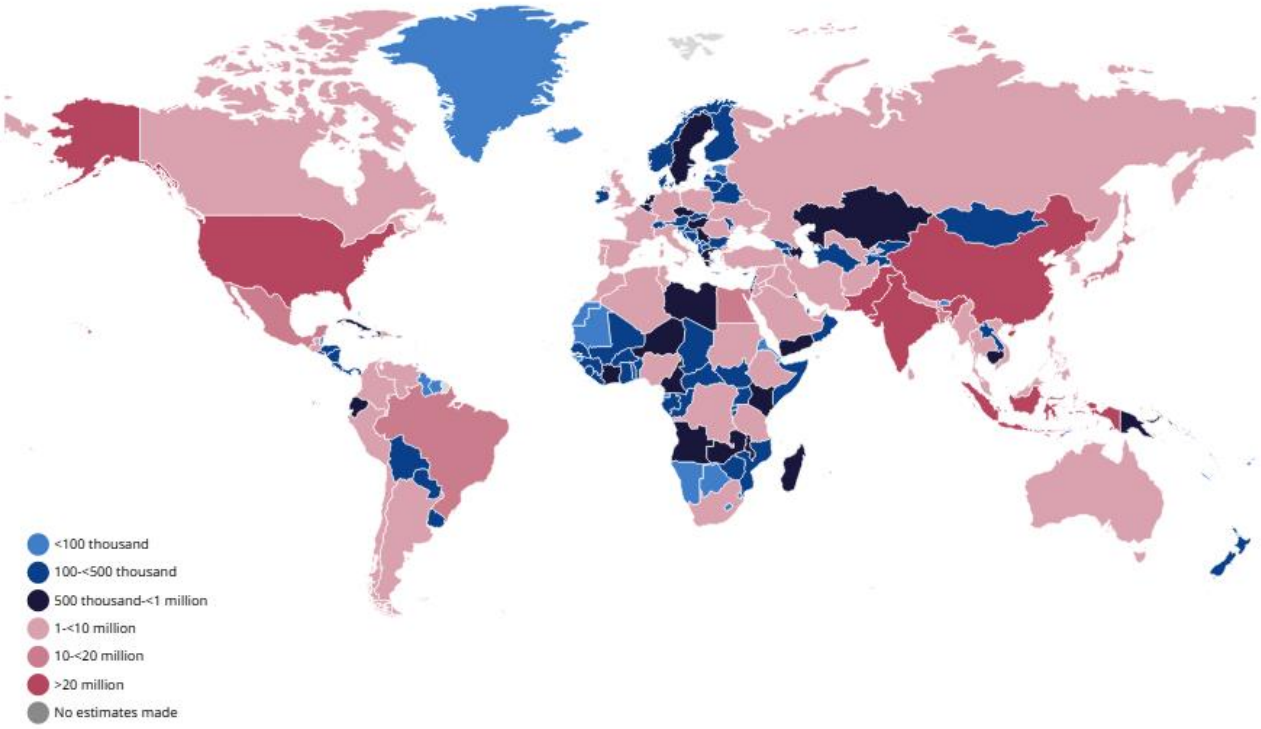

Figure 4: Epidemiology of Diabetes(IDF, 2025).

5. Risk Factors

T2D has many risk factors, including genetic and environmental factors whereas the genetic factors will be discussed in the third chapter, we will develop the environmental factors downbelow.

5.1. Hypertension: Hypertension significantly enhances the chance of getting type 2 diabetes. According to research, those with hypertension are around 2.5 times likely to acquire diabetes than those with normal blood pressure. Furthermore, the high frequency of hypertension among diabetics indicates that these two chronic illnesses commonly coexist and worsen one another. Certain antihypertensive medications may also affect diabetes risk. Hypertensive patients treated with β-blockers have a 28% higher risk of developing diabetes compared to untreated individuals (Sowers et al., 2001).

5.2. Family History: Having a family history of diabetes is a substantial risk factor, and it is often included in screening methods to identify susceptible or undiagnosed individuals. Diabetes has extended asymptomatic period, thus early diagnosis of impaired glucose metabolism (prediabetes) might help postpone or avoid the illness and its effects (Valdez, 2009).

5.3. Smoking: Smoking has long been recognised as a risk factor for a variety of ailments, including tumours and cardiovascular disease. Many studies have also found that smoking has

an unfavourable influence on diabetes. Smoking raises the likelihood of developing diabetes and worsens its consequences, both micro and macrovascular. Although smoking has been linked to insulin resistance the underlying processes affecting diabetes mellitus remain unclear (Chang, 2012).

5.4. Obesity and Diet: Obesity is the leading cause of T2DM, accounting for over 90% of cases. Diet has an important impact on T2DM risk. A low-fiber, high-glycemic diet is linked to increased susceptibility; processed meat intake and sweetened beverages with sugar enhance the risk due to their effect on BMI (Body Mass Index) (Wu et al., 2014).

5.5. Stress: Stress can be acute or chronic. While both types can cause a variety of side effects, chronic stress is more dangerous because of the long-term negative consequences on health. The most common hormonal responses to stress are glucocorticoids (GC) and catecholamines. Although these hormones rarely cause immediate damage during acute stress, sustained exposure can impair glucose homeostasis. Over time, this imbalance may cause persistent hyperglycemia, which can lead to insulin resistance and type 2 diabetes(Sharma et al., 2022).

5.6. Vitamins: According to research, vitamin D may help manage glucose and insulin levels. Low levels of vitamin D, particularly in winter, have been associated with worsened diabetes. It acts by activating certain receptors, regulating calcium levels, and decreasing inflammation. Vitamin K has two forms: K1 and K2. K1 may increase insulin sensitivity because it promotes glucose homeostasis, but K2 is required for bone health. Some research shows that vitamin K2 may help diabetics retain bone strength (Wu et al., 2014).

5.7. Sleep quantity/quality: The amount and quality of sleep are impacted by a variety of factors, including job schedules, lifestyle choices, and health status. Poor sleep is associated with intolerance to glucose and a higher risk of type 2 diabetes. Obstructive sleep apnoea (OSA) worsens this risk by generating hypoxia and inflammation, both of which contribute to insulin resistance (Ismail et al., 2021).

5.8. Serum uric acid: Serum uric acid, a typical consequence of purine synthesis, has been linked to insulin resistance and type 2 diabetes. Elevated blood uric acid levels result in nitric oxide-mediated blood flow, which impairs glucose absorption in muscles, increases oxidative stress, and increases inflammation, lowering adiponectin levels. These variables together raise blood glucose levels, causing beta-cell malfunction and eventually cell death (Ismail et al., 2021).

6. Symptoms

Many people with type 2 diabetes do not show any symptoms. Classic signs include polyuria (increased urination), polydipsia (increased thirst), polyphagia (uncontrollable appetite), weight loss, a lack of energy and exhaustion, fungal and bacterial infections, and slow wound healing. Some patients additionally complain of numbness or tingling in their hands or feet, or of cloudy eyesight (Khardori, 2022 ; Goyal et al., 2023). Persistent exposure to hyperglycemia impacts the blood vessels, ultimately causing diabetic nephropathy, retinopathy and neuropathy with a significant effect on the quality life span and longevity. Sexual dysfunction is an often-overlooked microvascular consequence of type 2 diabetes (Faselis et al., 2020).

T2DM produces a wide range of macrovascular problems involving many pathogenetic mechanisms, including hyperglycemia and insulin resistance. Macrovascular problems include coronary heart disease, cardiomyopathy, arrhythmias, sudden death, cerebrovascular disease, and peripheral artery disease. Cardiovascular disease is the leading cause of mortality among diabetes individuals (Viigimaa et al., 2019).

7. Prevention and Screening

Randomized clinical trials conducted to determine ways to prevent type 2 diabetes (T2D) have concluded that weight loss is a crucial factor in prevention. Engaging in a healthy diet and regular exercise significantly reduces the risk of developing the disease. Additionally, weight reduction surgery (bariatric surgery) has shown positive results in preventing T2D. Studies on diabetes drugs, such as metformin and acarbose, indicate that taking these drugs before developing diabetes may also help in prevention (Steyn et al., 2004 ; Crandall et al., 2008).

Screening for a disease is regarded as suitable if it fits certain requirements, such as illness severity, awareness of its inherent history, detectability in the preclinical stage, and the affordability of a reliable and acceptable screening test. Type 2 diabetes mellitus (T2DM) fits these requirements, leading to recommended screening for abnormal blood glucose levels in adults aged ≥45 years and high-risk persons who are overweight/obese, have a family history of diabetes, or are from racial/ethnic minorities (Olokoba, 2012 ; DeFronzo et al., 2015).

8. Diagnostic

Diabetes can be detected either through the hemoglobin A1C (HbA1C) guidelines or through plasma glucose levels (Olokoba, 2012 ; Goyal et al., 2023)

8.1. Fasting plasma glucose (FPG)

Following an overnight fast of 8 hours, a blood sample is collected. A fasting plasma glucose (FPG) level more than 126 mg/dL (7.0 mm/L) is indicative of the diagnosis

8.2. Two-hour oral glucose tolerance test (OGTT)

The plasma glucose level is tested before and two hours after consuming 75 gm of glucose. Diabetes is diagnosed when the plasma glucose (PG) level in a two-hour sample exceeds 200 mg/dL (11.1 mmol/L).

8.3. Glycated Hemoglobin (Hb) A1C

This test provides an average of blood glucose levels over the past two to three months. Patients with a Hb A1C level more than 6.5% (48 mmol/mol) are diagnosed with Diabetes. Hb A1C is a quick, standardized test with minimal variance owing to pre-analytical factors.

9. Treatment

9.1. Standard Treatment

Diabetes treatment includes lifestyle changes and maintaining a balanced diet that contains all essential nutrients. Regular exercise, including aerobic and resistance training, plays a key role in improving insulin sensitivity and enhancing cellular function. These lifestyle modifications help manage diabetes effectively and reduce the risk of complications (Pfeiffer & Klein, 2014).

Medication (Table 2) is a key component of diabetes treatment, alongside lifestyle changes. Medications help regulate blood sugar levels, improve insulin function, and prevent complications (Marín-Peñalver et al., 2016).

Table 2: Standard Treatment for Diabetes

Medication	Role
Metformin	The first line for treatment of T2DM. It Lower lipopolysaccharide (LPS) levels in the bloodstream and liver.

Sulfonylureas and meglitinides	Increasing insulin secretion
Alpha-glucosidase inhibitors	Delayed glucose absorption and digestion, which results in a decrease in postprandial hyperglycemia.
Thiazolidinediones	Increase insulin sensitivity
Dipeptidyl peptidase-4 inhibitors	Increase insulin secretion and inhibit glucagon
Sodium glucose co-transporter-2 inhibitor	Inhibit renal reabsorption of glucose, increase its excretion and reduce hyperglycemia
RA-GLP 1 (Glucagon-Like Peptide-1 Receptor Agonists)	Stimulates insulin release
Insulin	insulin analogue

9.2. Gene and Cell Therapy

Even though gene therapy primarily focuses on type 1 diabetes (T1D), the strong genetic background of type 2 diabetes (T2D) has allowed researchers to develop methods that target genes associated with genetic predisposition to T2D. The use of CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9) has shown promising results in animal studies, but it has not yet been tested in humans. Theoretically, targeting these genes could be a potential treatment for T2D. However, the wide range of genetic polymorphisms makes it more challenging to develop a universal genetic therapy (Yue et al., 2019 ; Khan, 2019).

Stem cell therapy has shown promising results in treating diabetes symptoms, such as lowering blood glucose levels, and reducing its macrovascular and microvascular risks. In 2021, endoderm stem cells were used to treat a Chinese patient with type 2 diabetes (T2D). The patient achieved insulin independence 11 weeks after the transplant, and oral medication was discontinued one year later. The patient successfully restored pancreatic function and is now living insulin-free (Wu et al., 2024 ; Bterrani et al., 2025).

Chapter 3:

Genetics of T2D and TCF7L2 gene

1. Heritability of Type 2 Diabetes

T2D has a significant hereditary component, with heritability estimates ranging from 20% to 80% based on community, family, and twin studies. The lifetime risk of developing T2D is approximately 40% for individuals with one affected parent, which rises to 70% if both parents are affected. This highlights familial linkage. First-degree relatives are around three times more likely to acquire T2D than those without a family history, and this risk increases to six times when both parents are afflicted. Twin studies highlight the genetic contribution, with a concordance rate of around 70% in monozygotic twins versus 20%-30% in dizygotic twins. The probandwise concordance percentage for monozygotic twins ranges from 34% to 100% meaning that if one twin has T2D the other has a chance from 34% to 100% of having T2D also. However, the degree of family risk changes with age at the beginning, reflecting a combination of genetic predisposition and environmental influences (Ali, 2013 ; Prasad & Groop, 2015).

2. Key Genes Associated with Type 2 Diabetes

T2D is a complicated metabolic condition that is affected by both hereditary and environmental factors. Throughout the years, researchers have found multiple genes associated with T2D risk through various genetic investigations. These include linkage studies, which follow disease inheritance patterns in families; candidate gene studies, which focus on genes hypothesized to to contribute to disease pathogenesis, and genome-wide association studies (GWAS), which scan the whole genome for genetic changes associated with T2D (Table 3) (Ali, 2013 ; Laakso & Fernandes Silva, 2022).

Table 3: Genetic Risk Factors

The Genes	Their Role
Genes Involved in Insulin Secretion and Beta-Cell Function	
KCNJ11 (Potassium inwardly-rectifying Channel subfamily J member 11)	Controls insulin secretion in beta cells by activating ATP-sensitive potassium channels.
TCF7L2 (Transcription Factor 7 Like 2)	The most significantly related T2D risk gene; influences beta-cell activity and insulin production.
HNF1A (Hepatic Nuclear Factor 1 Alpha)	Regulates beta cell growth and insulin secretion.
HNF1B (Hepatocyte Nuclear	Regulates pancreatic beta-cell activity.

Factor-1 Beta)	
HNF4A (Hepatic Nuclear Factor 4 Alpha)	Plays an important role in liver metabolism and beta cell control.
PAM (Peptidylglycine Alpha-Amidating Monooxygenase)	Involved in proinsulin processing.
TBC1D30 (TBC1 Domain Family Member 30)	Associated with insulin secretion.
WFS1 (Wolfram syndrome 1)	Encodes Wolframin, a protein required for beta-cell function and survival.
CDKAL1 (CDK5 Regulatory Associated Protein 1 Like 1)	Regulates beta cell activity and insulin processing.
IGF2BP2 (Insulin like Growth Factor 2 mRNA Binding Protein 2)	Regulates insulin-like growth factor 2 (IGF2) translation, which affects beta cell activity.
CDKN2A/B (Cyclin Dependent Kinase Inhibitor 2A/2B)	Regulates beta cell survival and insulin secretion.
NOTCH2-ADAM 30 (Notch Receptor 2-A Disintegrin And Metalloproteinase 30)	Might play a role in beta cell function.
Genes Related to Insulin Sensitivity and Glucose Uptake	
PPARG (Peroxisome Proliferator Activated Receptor Gamma)	Modulates fat metabolism and insulin sensitivity; it is a thiazolidinedione target.
AKT2 (Ak strain transforming Serine/Threonine Kinase 2)	Regulates insulin signalling and glucose metabolism; mutations are connected to insulin resistance.
IRS1 & IRS2 (Insulin receptor substrate -1/ -2)	Important for insulin signal transduction.
BCL2 (B-cell leukemia/lymphoma 2 protein)	Identified as an insulin sensitivity locus.
FAM19A2 (Family With Sequence Similarity 19 (chemokine (C-C motif)-like)	Associated with insulin sensitivity.

Member A2)	
HHEX (Hematopoietically Expressed Homeobox)	A transcription factor involved in Wnt signalling
Genes Associated with Glucose Homeostasis and Metabolism	
MTNR1B (Melatonin Receptor 1B)	Regulates fasting glucose levels and insulin secretion.
G6PC2 (Glucose-6-Phosphatase Catalytic subunit 2)	Regulates fasting glucose levels.
CAPN10 (Calpain 10)	The first gene found by linkage analysis; it is involved in glucose metabolism.
Genes Involved in Cell Cycle and Pancreatic Development	
CCND2 (Cyclin D2)	Regulates beta cell growth and pancreatic function.
HMGA2 (High Mobility Group AT-Hook 2)	May be involved in the development of pancreatic beta cells.
Genes Associated with Obesity and T2D Risk.	
FTO (Fat Mass and Obesity-Associated Gene)	Strongly related to obesity.
MC4R (Melanocortin 4 Receptor)	Influences appetite control and obesity.
Other Genes with Possible Roles in T2D	
KCNQ1 (Potassium Voltage-Gated Channel Subfamily Q Member 1)	Potassium channel gene, probably implicated in insulin production.
RAPGEF1 & TP53 (Rap Guanine Nucleotide Exchange Factor 1/ Tumor Protein p53)	Identified in candidate gene research but not reliably replicated.
Gene with Multiple Roles	
SLC30A8 (Solute Carrier Family 30 Member 8)	Zinc transporter in beta cells that is required for insulin granule storage and secretion (Involved in Insulin Secretion and Beta-Cell Function). Regulates glucose-stimulated insulin secretion (Glucose Homeostasis and Metabolism).

3. Epigenetics and Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is distinguished by insulin resistance in adipose tissue, skeletal muscle, and the liver, as well as reduced insulin production from pancreatic islets. While hereditary variables are important, epigenetic alterations such as DNA methylation regulate critical genes (PDX1 Pancreatic and Duodenal homeobox 1, INS insulin, TCF7L2) and modulate connections with environmental factors such as nutrition, obesity, and aging. Advanced sequencing technologies have found epigenetic markers that can predict T2DM risk, comorbidities, and treatment outcomes, demonstrating their promise in precision medicine. However, further study is required to identify cause and create epigenetic therapeutics (Ling & Rönn, 2019 ; Ling et al., 2022)

Epigenetic alterations, such as DNA methylation, histone modifications, and miRNA control, are important in Type 2 Diabetes Mellitus (T2DM) because they influence insulin resistance and insulin secretion. Poor maternal nutrition or gestational diabetes affect fetal epigenetics, predisposing children to T2DM through DNA methylation changes in IGF2. Insulin resistance is caused by DNA methylation abnormalities in PPARG, KCNQ1, IRS1, and PGC-1α (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha), which reduce insulin sensitivity in skeletal muscle, liver, and adipose tissue. Furthermore, increased DNA methylation in PPARGC1A (PPARG Coactivator 1 Alpha), INS, and PDX1 lowers insulin production, and histone changes, together with miRNA dysregulation, alter beta-cell function and insulin signalling pathways, causing T2DM development (Yang et al., 2022 ; Mannar et al., 2023).

4. The Gene Studied

4.1. TCF7L2 Gene

Transcription factor 7-like 2 (TCF7L2) gene is situated on chromosome 10q25.2-q25.3. The TCF7L2 gene produces a transcription factor with an N-terminal beta-catenin-binding domain, a Groucho-interacting domain, a conserved C-terminal CRARF domain (Catenin-Regulated Activation and Repression Function), and a CtBP (C-terminal Binding Proteins)-binding site. The pancreas has the highest expression, followed by the colon, brain, small intestine, monocytes, and lung, and it has tissue-specific splice variants that modulate its role in Wnt (wingless-type MMTV integration site family) signalling (OMIM, 2019).

4.2. TCF7L2 Variants

Over 2000 variants have been described in the TCF7L2 gene, and OMIM has categorized them into four groups based on their clinical significance: pathogenic or likely pathogenic, likely benign or benign, variants of uncertain significance (VUS), and those with predicted consequences. Among them the polymorphisms studied rs7903146 (C>T) and rs12255372 (G>T) are classified as likely pathogenic due to their strong association with type 2 diabetes, primarily through their effects on alternative splicing and pancreatic beta-cell function (Uniport, 2025).

The rs7903146 (C>T) variant is an intronic polymorphism on chromosome 10 forward strand. It has three alleles (C/G/T), with T being the ancestral allele. This variation is co-located with HGMD-PUBLIC CS065626 variant and has been classed as potentially pathogenic, with significant links to type 2 diabetes due to its role in TCF7L2 alternative splicing and pancreatic beta-cell activity (Ensembl, 2024).

The rs12255372 (G>A/T) intronic variation is found on the forward strand of chromosome 10. It has three alleles (G/A/T), with G being the ancestral allele. This polymorphism is co-located with HGMD-PUBLIC CS065627 and has been linked to type 2 diabetes, breast cancer, and aggressive prostate cancer in several investigations (Ensembl, 2024).

4.3. TCF7L2 Protein

TCF7L2 Engages in the Wnt signalling pathway and controls MYC expression by binding to its promoter on a sequence-specific basis. In the absence of CTNNB1 (β-catenin), it acts as a repressor, but when it is present, it acts as an activator. When CTNNB1 is present, transcription is activated from promoters containing multiple copies of the Tcf motif (T-Cell Factor/Lymphoid Enhancer-Binding Factor Motif) 5'-CCTTTGATC-3'. TLE1, TLE2, TLE3, and TLE4 (Transducin-like enhancer of split-1/2/3/4) inhibit transactivation induced by TCF7L2/TCF4 and CTNNB1. Expression of dominant-negative mutants causes cell cycle arrest in G1. Required for the maintenance of the small intestine's epithelial stem-cell compartment (proteinatlas, 2003).

The Wnt/β-catenin-TCF7L2 signalling system regulates intestinal epithelial stem cells (IESCs) in the small intestine. These cells maintain the gut lining and develop into specialised cell types, such as enteroendocrine cells. ESCs emit glucagon-like peptide-1 (GLP-1), an intestinal hormone that regulates blood glucose levels by increasing insulin production from

pancreatic β-cells, suppressing glucagon release, and slowing stomach emptying (Grant et al., 2006 ; Sato & Clevers, 2013).

4.4. The Function of The TCF7L2 in Diabetes

TCF7L2 is the most significant genetic risk factor for type 2 diabetes (T2D), according to genome-wide association studies. Variants like rs7903146 have been related to reduced insulin secretion, which predominantly impacts β-cell function. TCF7L2 modulates insulin secretion through affecting exocytotic proteins and the distribution of voltage-gated Ca^{2+} channels, which are necessary for granule fusion and insulin release. Despite the hypothesis that decreasing TCF7L2 production would contribute to T2D, investigations have found higher TCF7L2 mRNA levels in diabetic islets, indicating a complicated regulatory function. The gene is part of the Wnt/β-catenin signalling system, which affects several physiological activities, including glucose metabolism (Gloyn et al., 2009 ; del Bosque-Plata et al., 2021).

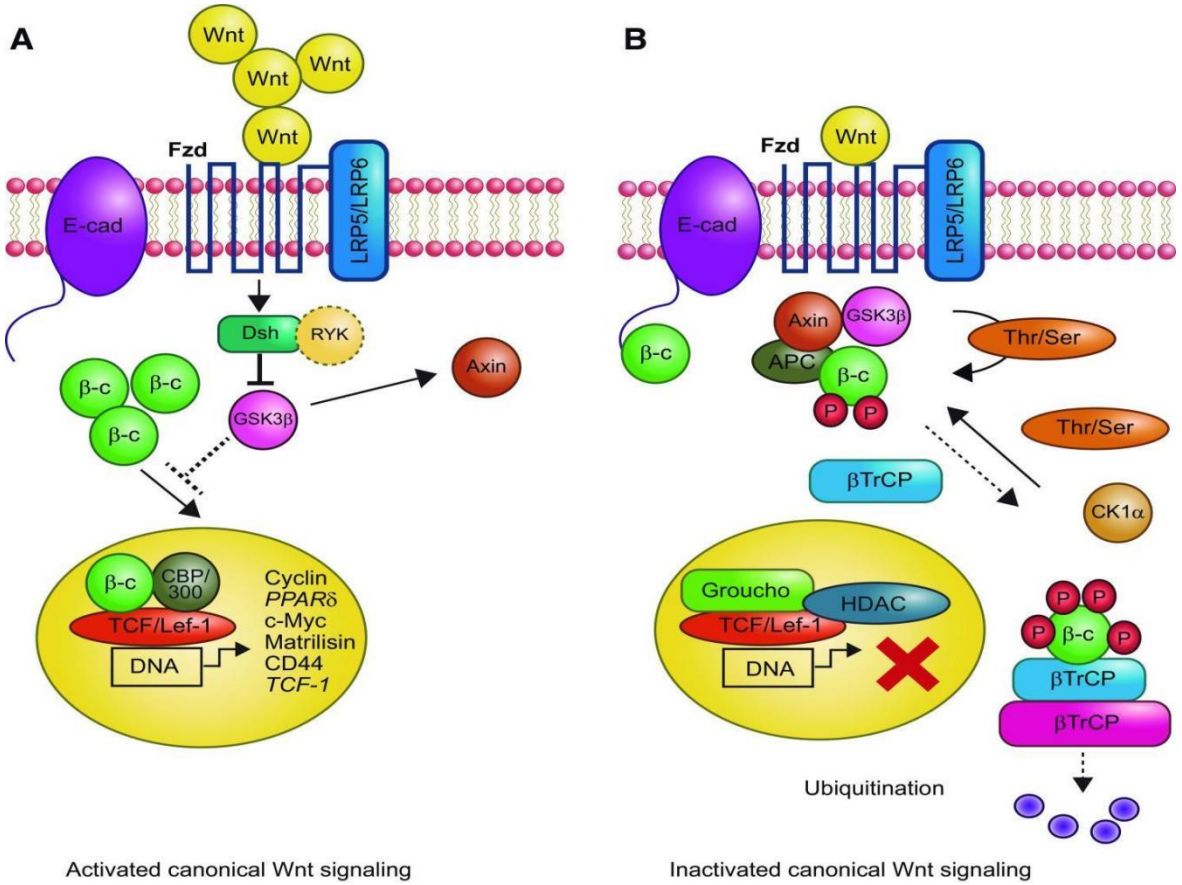

Figure 5: Canonical Wnt signaling pathway(del Bosque-Plata et al., 2021).

A: Activated Wnt pathway. β-c, β-catenin; CK1α, casein kinase Iα; Fzd, Frizzled receptor; GSK3β, glycogen synthase kinase 3β; Lef-1, lymphoid enhancer factor-1; LRP5/LRP6, low-density lipoprotein–related receptors 5 and 6; β-TrCP, β-transducin repeat–containing protein; TCF, T-cell factor (TCF7, TCF7L1, TCF7L2). **B:** Inactivated Wnt pathway

Practical part

Material and methods

1. Principle of Meta-Analysis

Meta-analysis is a set of statistical methods that enables the quantitative analysis of results from multiple studies that address a research topic in the most comprehensive way. When applied appropriately, it provides a more objective evaluation than traditional narrative reviews. Furthermore, meta-analysis aids in the extraction of relevant findings from published research by improving statistical power due to the higher number of subjects examined. It also helps to understand the differences in outcomes between studies. Before data may be merged quantitatively, certain conditions must be followed to ensure that the combined effect estimation is not corrupted, resulting in incorrect findings.

The most frequent biases include:

- **Publication bias:** occurs when statistically insignificant findings are less likely to be published.
- **Selection bias:** occurs when study selection criteria are not adequately met.
- **Detection bias:** occurs when studies are conducted incompletely or inadequately.
- **Estimation bias:** occurs when not all completed research is reported or included.

Approaches for doing a meta-analysis:

- Clearly define the research objective.
- Determine the inclusion and exclusion criteria for studies.
- Identify and select relevant literature and articles.
- Evaluate the presence of bias in research (selection, data extraction, etc.) and reject those with clearly biased findings.
- Perform statistical analysis to estimate the effect size.
- Test for homogeneity between studies.
- Assess the robustness of the results through sensitivity analysis.

2. Methodology

2.1. Research Strategy

Our study consists of a meta-analysis. The studies were gathered from electronic databases such as PubMed and Google Scholar. We chose findings from a variety of research investigating the relationship between the TCF7L2 gene's rs7903146 and rs12255372 variants and the risk of type 2 diabetes. Keywords used included TCF7L2 gene, Type 2 Diabetes, polymorphism, rs7903146, and rs12255372.

2.2. Selection Criteria

The criteria used to select studies from the PubMed and Google Scholar databases were as follows:

2.2.1. Inclusion Criteria:

- Studies analyzing the association between TCF7L2 gene polymorphisms (rs7903146 and rs12255372) and Type 2 Diabetes (T2D).
- Case-control studies with genotyping results for patients (cases) and healthy individuals (controls).
- Studies reporting genotypic and allelic frequencies to estimate the Odds Ratio (OR), Confidence Interval (CI), and *p*-value.

2.2.2. Exclusion Criteria:

- Studies analyzing other TCF7L2 polymorphisms.
- Studies on the therapeutic response of TCF7L2 in T2D.
- Studies with genotypic distribution violating Hardy-Weinberg Equilibrium (HWE).
- Studies with insufficient data for meta-analysis.
- Studies published before 2014 or after 2024.

2.3. Data Extraction

For each research, we extract:

- First author name, publication year, country, and ethnicity.
- Number of cases and controls.
- Genotypic and allelic frequencies of rs7903146 and rs12255372. If not reported, calculate using the study's raw data.

3. Statistical Analysis

Strength association between the rs7903146 and rs12255372 polymorphism in the TCF7L2 gene and Type 2 Diabetes was statistically calculated by the Odds Ratio (OR), 95% Confidence Interval (CI), and p-value. Comparisons were made for the rs7903146 and the rs12255372 variants (Table 4).

Odds Ratio (OR), 95% Confidence Interval (CI), and *p*-value were calculated using https://www.medcalc.org/calc/odds_ratio.php while for khi^2

https://www.standarddeviationcalculator.io/chi-square-calculator was used. For HWE we used https://www.sebc.me/bioblog/labs/hwe-calculator , and for estimating funnel and forest plot utilized https://metaanalysisonline.com/ .

Table 4: Comparison model of polymorphism effect.

	rs7903146	rs12255372
Allelic model	C vs T	G vs T
Homozygotic model	CC vs. TT	GG vs. TT
Heterozygotic model	CC vs. CT	GG vs. GT
Dominant model	CC vs. CT+TT	GG vs. GT+TT
Recessive model	CC+CT vs. TT	GG+GT vs. TT

3.1. Calculation of the Odds Ratio (OR)

The Odds Ratio (OR) assesses the relationship between an exposure and its result. It is used to establish if a certain exposure is a risk factor for a given outcome and to compare several risk factors. OR denotes the likelihood that a result happens given exposure, as opposed to the chance that the outcome occurs in the absence of exposure. OR is often utilized in case-control, cross-sectional, and cohort studies (Szumilas, 2010).

Table 5: Method to calculating the OR

Criterion	**Cases**	**Controls**
Exposed (criterion present)	a	B
Non-exposed (criterion absent)	c	D

Formula:

OR= (a/c)/(b/d)= (a*d)/(b*c)

Where:

a = cases with risk allele

b = controls with risk allele

c = cases without risk allele

d = controls without risk allele

Interpretation:

OR = 1: Exposure occurs equally in both groups (no effect).

OR > 1: Exposure is associated with a higher probability of the outcome.

OR < 1: Exposure is associated with a lower probability of the outcome.

3.2. Confidence Interval (CI)

The 95% Confidence Interval (CI) is used to estimate the precision of the OR. A small CI indicates high precision. A large CI indicates low precision.

It can be calculated using two methods: the Woolf method and the Miettinen method.

Woolf's method (logit method):

$$\textbf{CI (OR)=}\ (e)LN(OR)\pm 1.96(1/A+1/B+1/C+1/D)1/2$$

3.3. *p*-Value

p-values were interpreted in the context of study heterogeneity and risk of type I error due to multiple comparisons.

***p* > 0.05:** No significant association (could indicate heterogeneity in studies).

***p* < 0.05:** Statistically significant association (suggests the mutated allele likely plays a role in disease development).

3.4. Hardy-Weinberg Equilibrium (HWE)

HWE represents the genotypic frequency equilibrium of two alleles (dominant: p, recessive: q) at a genetic locus where mating occurs randomly, and the mutation rate is constant. With the condition: p+q=1

Formula:

$$HWE=p^2+2pq+q^2$$

Results and discussion

1. Characteristics of the included studies

In total, we reviewed 2,882 studies focusing on the association between the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene and T2D. Of these, 155 publications met the inclusion criteria. Among them, 52 articles were excluded from the analysis set due to limited access, 42 articles had incomplete data, and 1 article was retracted, leaving us with 60 articles included in our meta-analysis (Figure 6).

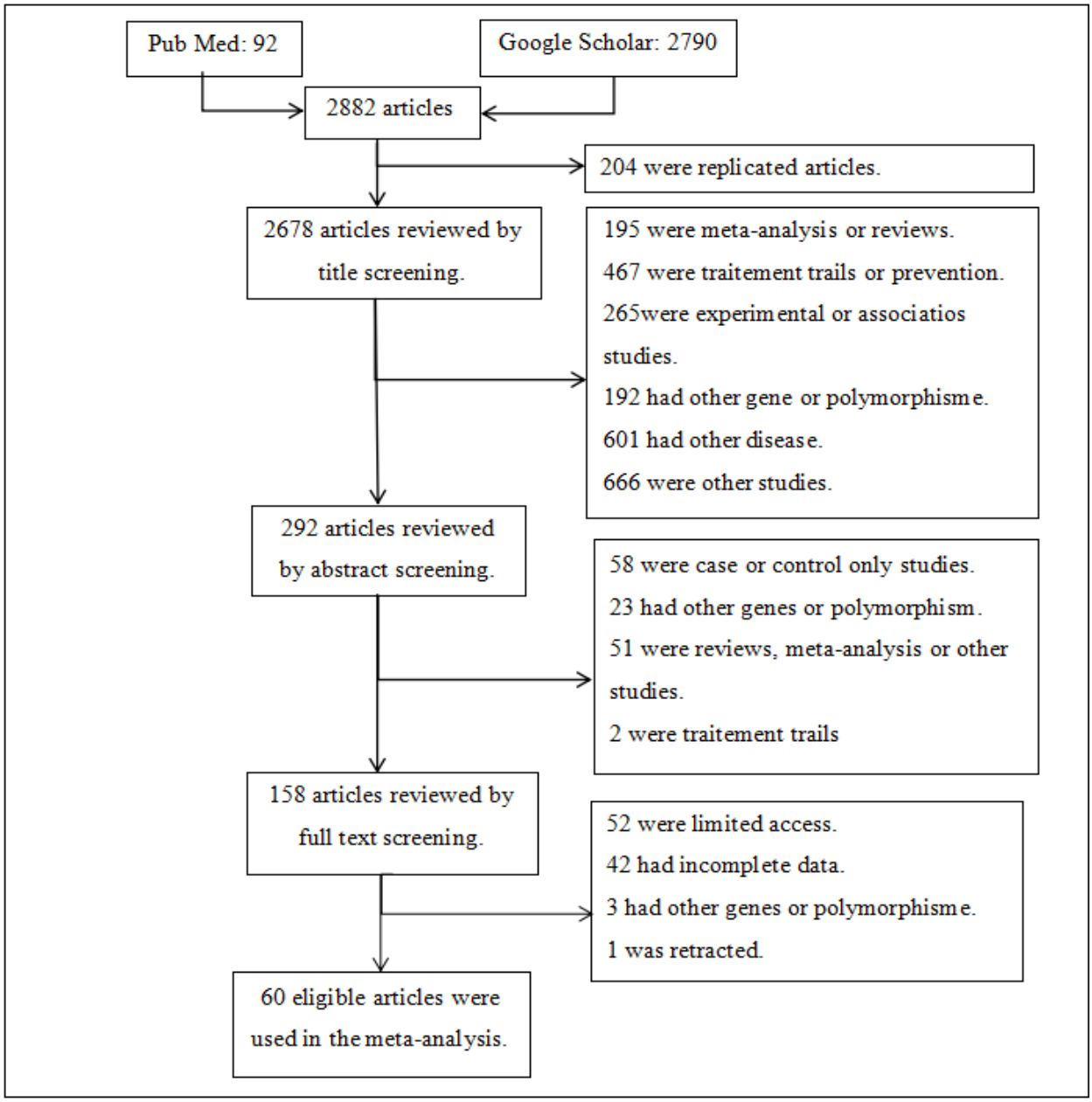

Figure 6: Summary of published studies indexed in PubMed and Google Scholar on the impact of the rs7903146 and re12255372 polymorphisms of the TCF7L2 gene

The main characteristics of the selected studies are presented in the table below (Table 6). Among the included studies, 27 focused on Asian populations, 14 on Arab populations, 6 on Persian populations, 6 on Hispanic populations, 4 on African populations, and 3 on Caucasian populations. The studies were conducted in the following countries: India, China, Turkey, Thailand, Kazakhstan, Indonesia, Pakistan, Myanmar, Azerbaijan, Algeria, Iran, Iraq, Egypt, Palestine, the United Arab Emirates, Morocco, Kuwait, Brazil, Argentina, Venezuela, Cuba, South Africa, Cameroon, Niger, Ghana, Romania, Poland, and the United Kingdom (England, Wales, and Scotland). These studies were published between 2014 and 2024. Finally, the total population for this meta-analysis consisted of 39,591 cases and 463,251 controls.

Table 6: Characteristics of the selected studies

AUTHOR/ YEAR	Country	Ethnicity	Patient (case)	Control	1*	2*	HWE*		Average age	
							1	2	Patient (case)	Control
(Ouhaibi-Djellouli et al., 2014)	Algeria	Arab	76	644	+	-	1	/	52.0 ± 9.5	42.8 ± 9.6
(Assmann et al.,2014)	Brazil	Hispanic	953	535	+	-	1	/	59.3 ± 10.7	44.0 ± 7.8
(Rafati et al., 2015)	Iran	Persian	127	71	-	+	/	1	**NM***	
(Khan, 2015)	India	Asian	250	250	+	-	1	/	57.19± 8.22	53.93 ±6.32
(Rezazadeh et al., 2015)	Iran	Persian	101	101	+	+	1	1	55.51± 7.35	54.66± 8.64
(Siewert et al., 2015)	Argentina	Hispanic	108	88	+	+	1	1	59.12 ± 8.41	55.45 ± 12.16
(Kaftan, 2015)	Iraq	Arab	100	80	+	-	1	/	53.57± 9.71	55.66± 9.13
(Yao et al., 2015)	China	Asian	877	871	-	+	/	1	51.14 ± 9.66	50.34 ± 9.70
(Pourahmadi et al., 2015)	Iran	Persian	200	200	+	+	1	1	13.5±52.7	11.1±51.6
(Yako et al., 2015)	South Africa	African	152	328	+	+	1	1	60.1 (11.8)	53.2 (13.5)
(Moran et al., 2015)	Venezuela	Hispanic	70	73	+	+	1	1	53.9 ± 10.5	50.8 ± 8.55
(Nanfa et al., 2015)	Cameroon	African	60	60	-	+	/	1	60 (53 – 67)	50 (45 – 54)
(Demirsoy & Aras, 2016)	Turkey	Asian	100	100	+	-	1	/	54,24	51,32

(Abd El Razek et al., 2016)	Egypt	Arab	90	100	+	-	1	/	31.4±4.6	23.98 ±3.59
(Welter et al., 2016)	Brazil	Hispanic	201	201	+	+	1	1	56.0(49.0-64.0)	53.0 (35.0–62.0)
(El-Lebedy & Ashmawy, 2016)	Egypt	Arab	180	210	+	+	1	1	55.3 ± 6.1	53.40 ± 5.2
(Phani et al., 2016)	India	Asian	578	578	+	-	1	/	54.25 ±11.5	53.6 ±13.1
(Altalalqa, 2017)	Palestine	Arab	100	100	+	-	1	/	NM	
(Bulgăr et al., 2017)	Romania	caucasian	53	30	+	-	1	/	60.7 ± 8.2	53.9 ±11.5
(Wu et al., 2017)	China	Asian	205	226	+	+	1	1	56.44±9.45	54.23±8.92
(Wang et al., 2017)	China	Asian	927	955	+	-	1	/	51.19±9.77	50.41±9.82
(Kaya et al., 2017)	Turkey	Asian	169	119	+	+	1	1	NM	
(Golbon et al., 2018)	Iran	Persian	240	240	+	-	1	/	58.3± 12.7	54.1± 11.3
(Anjum et al., 2018)	China	Asian	339	191	+	+	1	1	48.4 ±110.2	47.7 ±10.6
(Barna et al., 2018)	India	Asian	250	250	-	+	/	1	NM	
(Plengvidhya et al., 2018)	Thailand	Asian	500	500	+	-	1	/	57.2 ± 12.2	53.0 ± 8.4
(Isakova et al., 2018)	Kazakhstan	Asian	114	109	+	-	1	/	NM	
(Al Ali et al., 2019)	UAE	Arab	153	264	+	-	1	/	60.70 ± 11.06	48.94 ± 13.12

(Syamsurizal et al., 2019)	Indonesia	Asian	66	66	+	-	1	/	NM	
(Chandrasekaran & Gopinath, 2019)	India	Asian	98	98	+	-	1	/	50.34 + 9.84	54.97 + 8.227
(Xu et al., 2019)	Cuba	Hispanic	169	172	+	+	1	1	65.05±11.95	62.98±10.85
(Shahid et al., 2019)	Pakistan	Asian	170	170	+	-	1	/	35 to 55	25 to 55
(Wrzosek et al., 2019)	Poland	caucasian	129	345	+	-	1	/	47.0 (39.0-53.0)	44.0 (38.0-55.0)
(Foroughmand et al., 2019)	Iran	Persian	150	150	+	-	1	/	52.46 ± 7.37	56.75 ± 7.37
(Cai et al., 2019)	China	Asian	337	491	+	+	1	1	50.0 (42.0-57.0)	48.0 (43.0-57.0)
(Komala et al., 2019)	India	Asian	44	44	+	+	1	1	49.7 (+ 8.5)	45.2 (+ 8.3)
(Verma et al., 2020)	India	Asian	400	400	+	-	1	/	40.2 ± 9.5	39.7 ± 8.0
(Gravand et al., 2020)	Iran	Persian	146	146	+	+	1	1	52.62 ± 9.241	56.59 ± 7.230
(Mustafa & Younus, 2020)	Iraq	Arab	106	106	+	-	1	/	53.86 ± 1.12	50.07 ± 1.04
(Engwa et al., 2021)	Niger	African	73	75	-	+	/	1	NM	
(Verma et al., 2021)	India	Asian	251	221	+	+	1	1	NM	
(Sharma et al., 2021)	India	Asian	250	250	+	-	1	/	49.88±9.537	49.23±10.56
(Abdullah & Ali, 2021)	Iraq	Arab	100	100	+	-	1	/	47.7 ± 9.27	24.9 ± 3.5

(Obirikorang et al., 2021)	Ghana	African	106	110	+	+	1	1	53.90 ± 12.31	45.80 ± 12.14
(Lehrer & Rheinstein, 2021)	England, Wales, and Scotland	Caucasian	27759	451276	+	-	1	/	NM	
(Phu et al., 2021)	Myanmar	Asian	100	113	+	-	1	/	57.47± 10.71	47.05± 8.94
(Elhourch et al., 2021)	Moroco	Arab	150	100	+	+	1	1	58.32 ± 11.38	52.16 ± 12.78
(Sun et al., 2021)	China	Asian	28	52	+	+	1	1	55± 13.5	48± 14.67
(Hameed et al., 2021)	Pakistan	Asian	118	58	+	+	1	1	57.48 ± 9.09	42.81 ± 9.82
(Bawady et al., 2022)	Egypt	Arab	47	23	-	+	/	1	60 (53 – 66)	60 (44 – 63)
(Alshenawy et al., 2022)	Egypt	Arab	66	34	+	-	1	/	56.44 ± 9.91	47.74 ± 9.78
(Maghraby et al., 2022)	Egypt	Arab	124	126	+	-	1	/	57.37 ± 6.70	53.15 ± 8.45
(Bankura et al., 2022)	India	Asian	200	200	+	+	1	1	49.7 ± 10.1	51.5 ± 7.5
(Akhundova et al., 2022)	Azerbaijan	Asian	110	115	+	-	1	/	63.45± 8.9	59.77± 11.9
(Chowdhry et al., 2023)	India	Asian	154	154	-	+	/	1	52.00 ± 9.97	53.32 ± 4.06
(Jan et al., 2023)	Pakistan	Asian	100	100	+	-	1	/	58± 12.40	56± 13.43
(Chaudhary et al., 2024)	Kuwait	Arab	203	162	+	-	1	/	57.3 (±10.16)	40.3 (±9.8)
(Souza et al., 2024)	Brazil	Hispanic	209	201	+	+	1	1	62.33 ± 10.7	61.40 ± 12.5
(Kumar et al., 2024)	India	Asian	194	180	+	-	1	/	54.5 ± 10.7	44.68 ±10.9

(Farag et al., 2024)	Egypt	Arab	50	50	+	-	1	/	56.38 ± 11.39	49.0 ± 11.47
Total			39591	463251						

1*: rs7903146, 2*: rs12255372.

HWE*: Hardy-Weinberg Equilibrium.

NM*: Not Mentioned.

2. Distribution of genotypic and allelic frequencies in the meta-analysis studies

Table 7 and 8 shows the distribution of genotypic frequencies (CC, GG, CT, GT and TT) and allelic frequencies (C, G and T) of the TCF7L2 gene from the 60 studies selected for our meta-analysis.

Table 7: Genotypic and allelic frequencies of the rs7903146 polymorphism of the TCF7L2 gene in patients and controls in the selected studies.

AUTHOR/ YEAR	Patient genotype			Control genotype			Alleles for Patient		Alleles for Control	
	CC	CT	TT	CC	CT	TT	C	T	C	T
(Ouhaibi-Djellouli et al., 2014)	16	41	19	228	287	129	73	79	743	545
(Assmann et al.,2014)	382	415	156	261	215	59	1179	727	737	333
(Khan, 2015)	92	120	38	144	87	19	304	196	375	125
(Rezazadeh et al., 2015)	30	65	22	77	36	4	125	109	190	44
(Siewert et al., 2015)	28	60	20	48	36	4	116	100	132	44
(Kaftan, 2015)	84	12	4	75	4	1	180	20	154	6
(Pourahmadi et al., 2015)	109	68	23	126	59	15	286	114	331	89
(Yako et al., 2015	66	74	12	184	129	15	206	98	497	159
(Moran et al., 2015)	26	35	9	46	22	5	87	53	114	32
(Demirsoy & Aras, 2016)	69	20	11	82	9	9	158	42	173	27
(Abd El Razek et al., 2016)	25	41	24	21	57	22	91	89	99	101
(Welter et al., 2016)	95	82	24	95	82	24	272	130	272	130

(El-Lebedy & Ashmawy, 2016)	48	126	6	112	95	3	222	138	319	101
(Phani et al., 2016)	404	157	17	450	120	9	965	191	1020	138
(Altalalqa, 2017)	23	52	25	35	47	18	98	102	117	83
(Bulgăr et al., 2017)	23	25	5	22	5	3	71	35	49	11
(Wu et al., 2017)	104	90	11	126	93	7	298	112	345	107
(Wang et al., 2017)	495	311	121	576	265	114	1301	553	1417	493
(Kaya et al., 2017)	58	95	18	57	47	16	211	131	161	79
(Golbon et al., 2018)	62	89	89	79	93	68	213	267	251	229
(Anjum et al., 2018)	160	117	62	110	56	25	437	241	276	106
(Plengvidhya et al., 2018)	429	67	4	456	44	0	925	75	956	44
(Isakova et al., 2018)	91	20	3	89	16	4	202	26	194	24
(Al Ali et al., 2019)	58	76	19	84	137	43	192	114	305	223
(Syamsurizal et al., 2019)	43	16	3	56	6	0	102	22	118	6
(Chandrasekaran & Gopinath, 2019)	32	43	15	52	38	2	107	73	142	42
(Xu et al., 2019)	58	69	42	76	73	23	185	153	225	119
(Shahid et al., 2019)	95	55	20	85	74	11	245	95	244	96

(Wrzosek et al., 2019)	67	50	12	219	113	13	184	74	551	139
(Foroughmand et al., 2019)	26	85	39	13	100	37	137	163	126	174
(Cai et al., 2019)	197	83	16	287	147	12	477	115	721	171
(Komala et al., 2019)	17	27	0	42	2	0	61	27	86	2
(Verma et al., 2020)	140	250	10	213	182	5	530	270	608	192
(Gravand et al., 2020)	26	81	39	13	96	37	133	159	122	170
(Mustafa & Younus, 2020)	26	74	6	48	54	4	126	86	150	62
(Verma et al., 2021)	61	173	17	42	152	27	295	207	236	206
(Sharma et al., 2021)	133	90	27	166	73	11	356	146	405	95
(Abdullah & Ali, 2021)	8	68	18	71	15	9	84	104	157	33
(Obirikorang et al., 2021)	26	66	14	49	56	5	118	94	154	66
(Lehrer & Rheinstein, 2021)	11942	12644	3173	230399	184076	36801	36528	18990	644874	257678
(Phu et al., 2021)	17	76	7	52	58	3	110	90	162	64
(Elhourch et al., 2021)	50	64	36	36	59	5	164	136	131	69
(Sun et al., 2021)	25	2	1	46	6	0	52	4	98	6
(Hameed et al., 2021)	18	89	11	24	27	7	125	111	75	41
(Alshenawy et	15	25	26	2	13	19	55	77	17	51

al., 2022)										
(Maghraby et al., 2022)	49	53	22	72	46	8	151	97	190	62
(Bankura et al., 2022	80	88	32	102	79	19	248	152	283	117
(Akhundova et al., 2022)	30	56	24	44	62	9	116	104	150	80
(Jan et al., 2023)	11	66	23	50	39	11	88	112	139	61
(Chaudhary et al., 2024)	62	73	68	63	78	21	197	209	204	120
(Souza et al., 2024)	20	79	110	18	73	110	119	299	109	293
(Kumar et al., 2024)	47	32	115	70	23	87	126	262	172	197
(Farag et al., 2024)	6	23	21	9	24	17	35	65	42	58
Total	16304	16858	4689	236002	187885	37929	49466	26238	659918	263743

Table 8: Genotypic and allelic frequencies of the rs12255372 polymorphism of the TCF7L2 gene in patients and controls in the selected studies.

AUTHOR/ YEAR	Patient genotype			Control genotype			Alleles for Patient		Alleles for Control	
	GG	GT	TT	GG	GT	TT	G	T	G	T
(Rafati et al., 2015)	90	26	11	62	7	2	206	48	131	11
(Rezazadeh et al., 2015)	28	71	18	71	40	6	127	107	182	52
(Siewert et al., 2015)	20	76	12	44	40	4	116	100	128	48
(Yao et al., 2015)	572	270	35	611	238	22	1414	340	1460	282
(Pourahmadi et al., 2015)	130	59	11	148	46	6	319	81	342	58
(Yako et al., 2015)	92	50	10	221	92	15	234	70	534	122
(Moran et al., 2015)	33	29	8	46	24	3	95	45	116	30
(Nanfa et al., 2015)	31	3	24	46	3	8	65	51	95	19

(Welter et al., 2016)	105	73	23	97	84	20	283	119	278	124
(El-Lebedy & Ashmawy, 2016)	60	114	6	139	69	2	234	126	347	73
(Wu et al., 2017)	87	85	33	122	85	19	259	151	329	123
(Kaya et al., 2017)	72	65	31	30	51	28	209	127	111	107
(Anjum et al., 2018)	158	135	50	105	63	23	451	235	273	109
(Barna et al., 2018)	167	52	31	168	66	16	386	114	402	98
(Xu et al., 2019)	55	70	44	74	80	17	180	158	228	114
(Cai et al., 2019)	207	79	9	305	126	13	493	97	736	152
(Komala et al., 2019)	24	19	1	32	10	2	67	21	74	14
(Gravand et al., 2020)	45	74	27	50	82	14	164	128	182	110
(Engwa et al., 2021)	34	1	38	57	1	17	69	77	115	35
(Verma et al., 2021)	126	109	16	94	106	21	361	141	294	148
(Obirikorang et al., 2021)	61	38	7	81	24	5	160	52	186	34
(Elhourch et al., 2021)	42	80	28	30	64	6	164	136	124	76
(Sun et al., 2021)	26	2	0	46	6	0	54	2	98	6
(Hameed et al., 2021)	55	47	3	56	6	1	157	53	118	8
(Bawady et al., 2022)	19	22	6	12	9	2	60	34	33	13
(Bankura et al., 2022	99	77	24	118	67	15	275	125	303	97
(Chowdhry et al., 2023)	74	66	14	96	52	6	214	94	244	64
(Souza et al., 2024)	138	58	13	134	55	12	334	84	323	79
Total	2650	1850	533	3095	1596	305	7150	2916	7786	2206

In all case-control studies for the rs7903146 polymorphism included in the meta-analysis, the control cohorts and patients with T2D exhibited higher genotypic frequencies for the CT and TT genotypes compared to the CC genotype, with control studies showing much higher frequencies than the case studies (Figure 7 and 9). Additionally, we observe that the frequency of the T allele is

higher than that of the C allele in both the patient and control populations across all studies (Figure 8 and 10).

In almost all case-control studies for the rs12255372 polymorphism in the meta-analysis, both the control cohorts and the T2D patients exhibited higher genotypic frequencies for the GG and GT genotypes compared to the TT genotype, except in the studies by Nanfa et al. (2015) and Engwa et al. (2021) (Figure 11), where the TT genotype was more frequent than the GT genotype in the controls. We also note that the frequency of the G allele is higher than that of the T allele in both the patient and control populations across all studies (Figure 12).

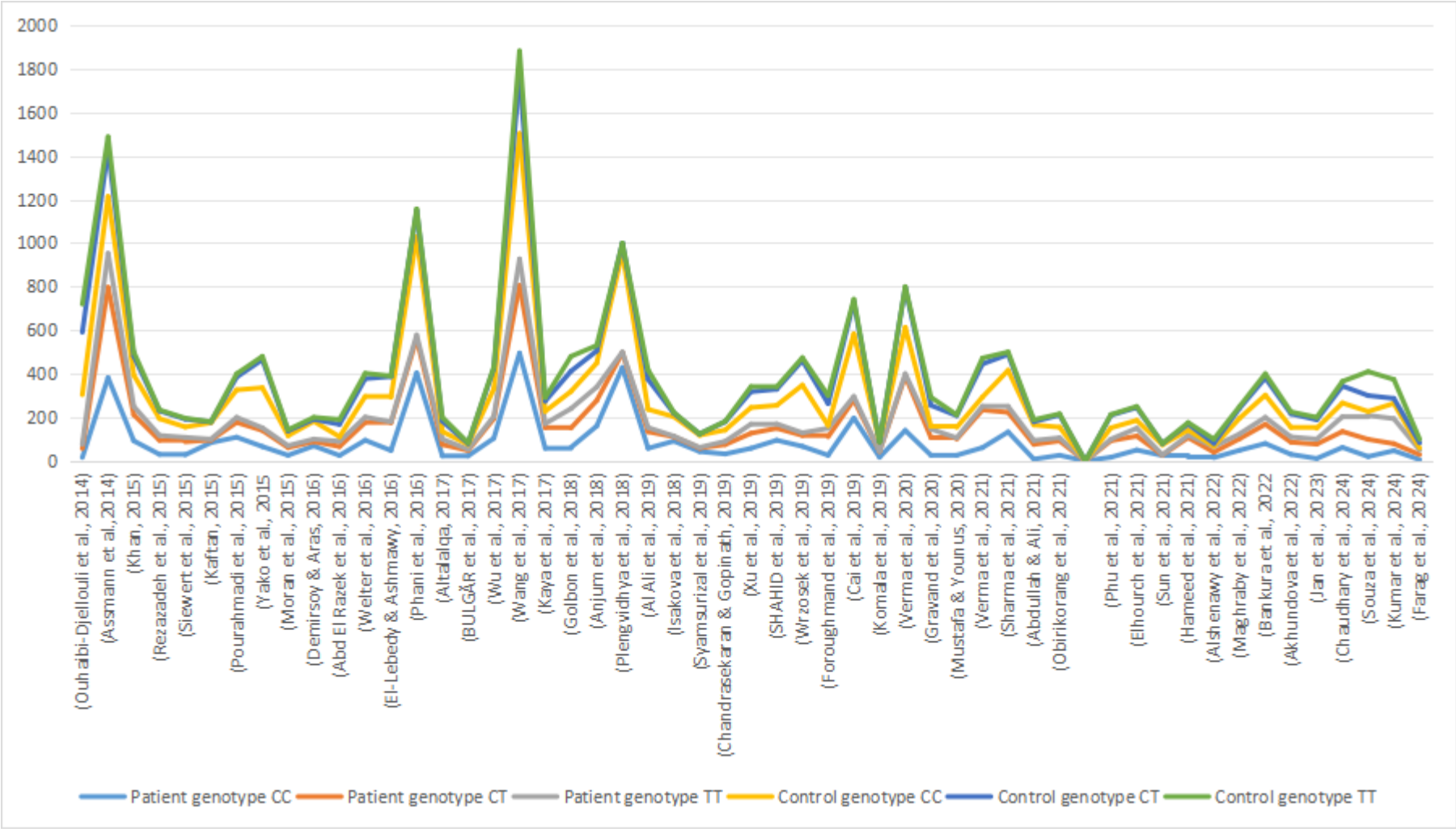

Figure 7: Graphical representation of genotypic frequencies (CC,CT and TT) in cases and controls of the different selected studies.

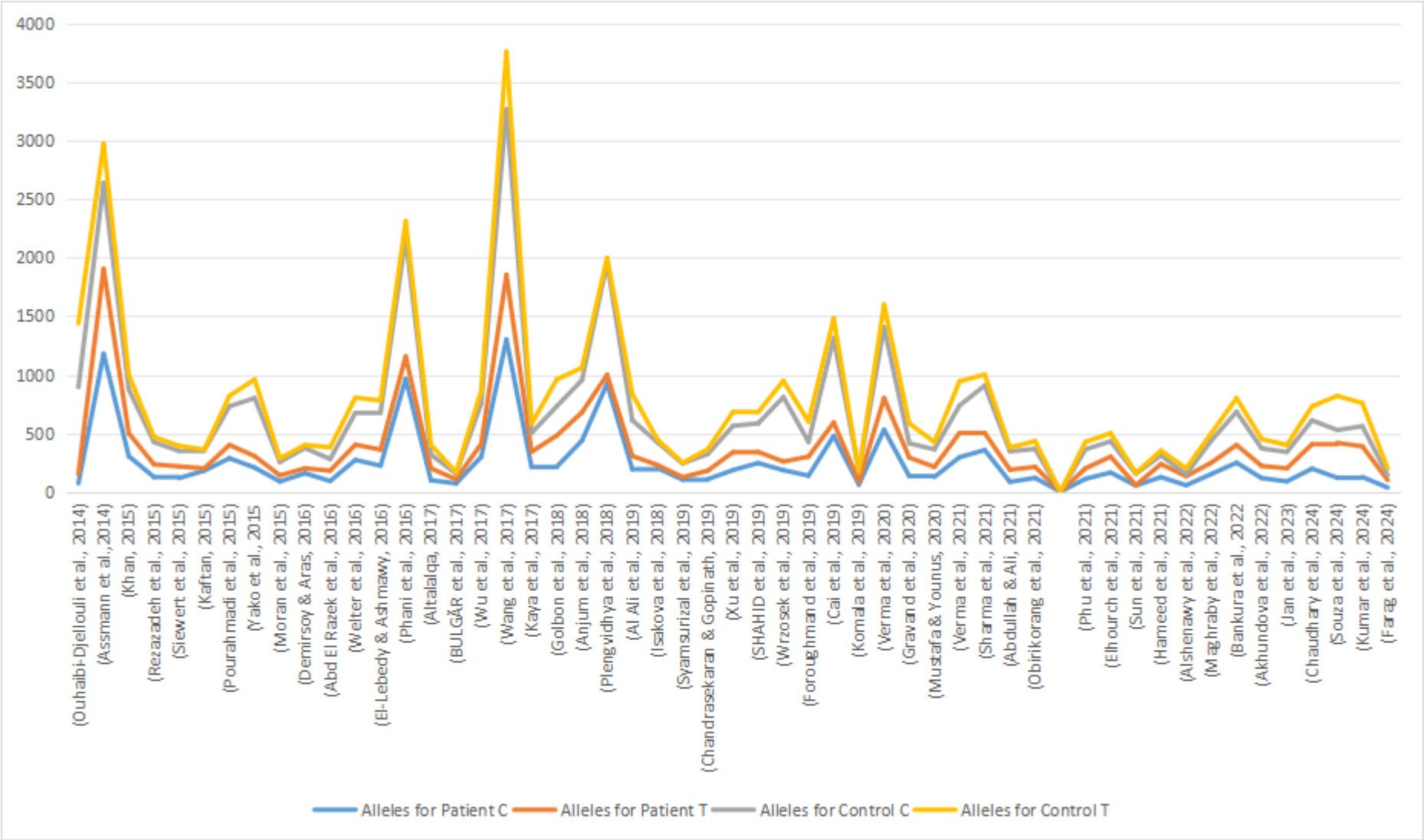

Figure 8: Graphical representation of allelic frequencies (C and T) in cases and controls of the different selected studies.

Due to the extensive size of the genotype and allelic number data of (Lehrer & Rheinstein, 2021), requiring it to be analyzed independently to avoid overshadowing the information contained within the other datasets.

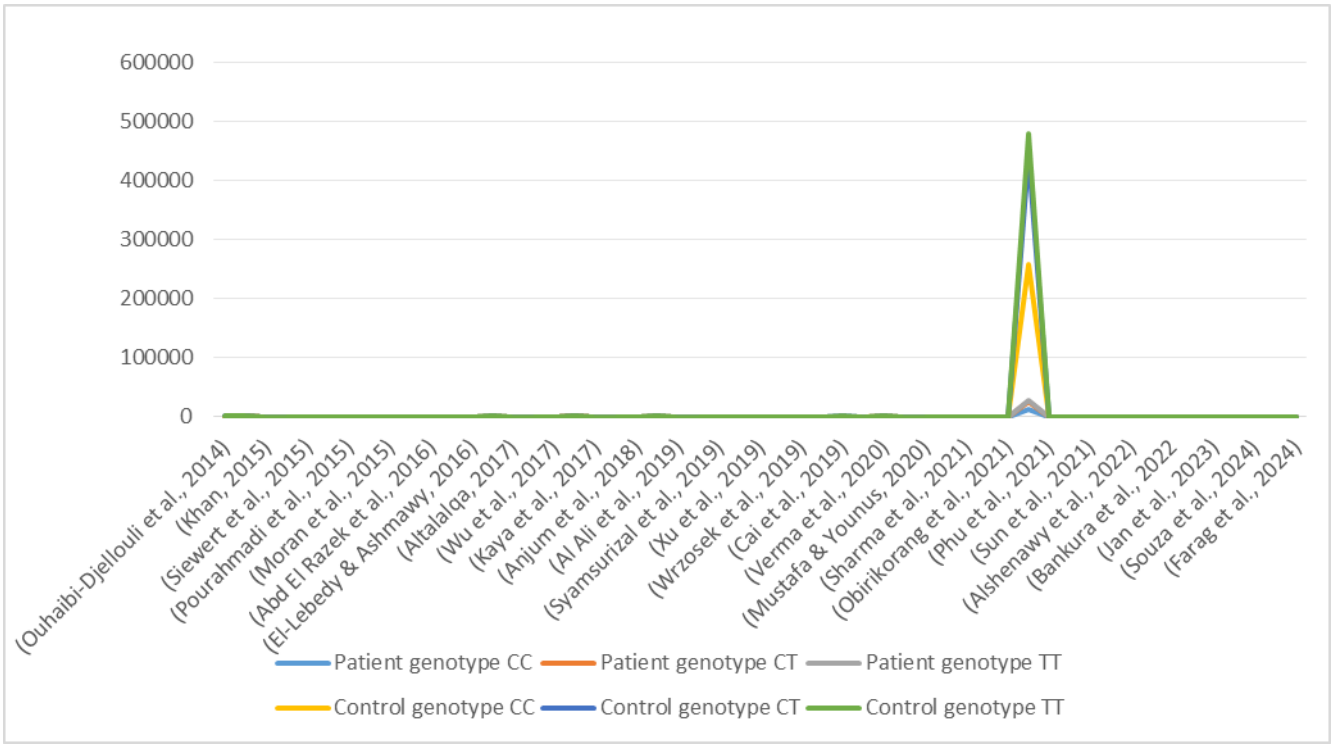

Figure 9: Graphical representation of genotypic frequencies (CC, CT and TT) in cases and controls for the study of (Lehrer & Rheinstein, 2021).

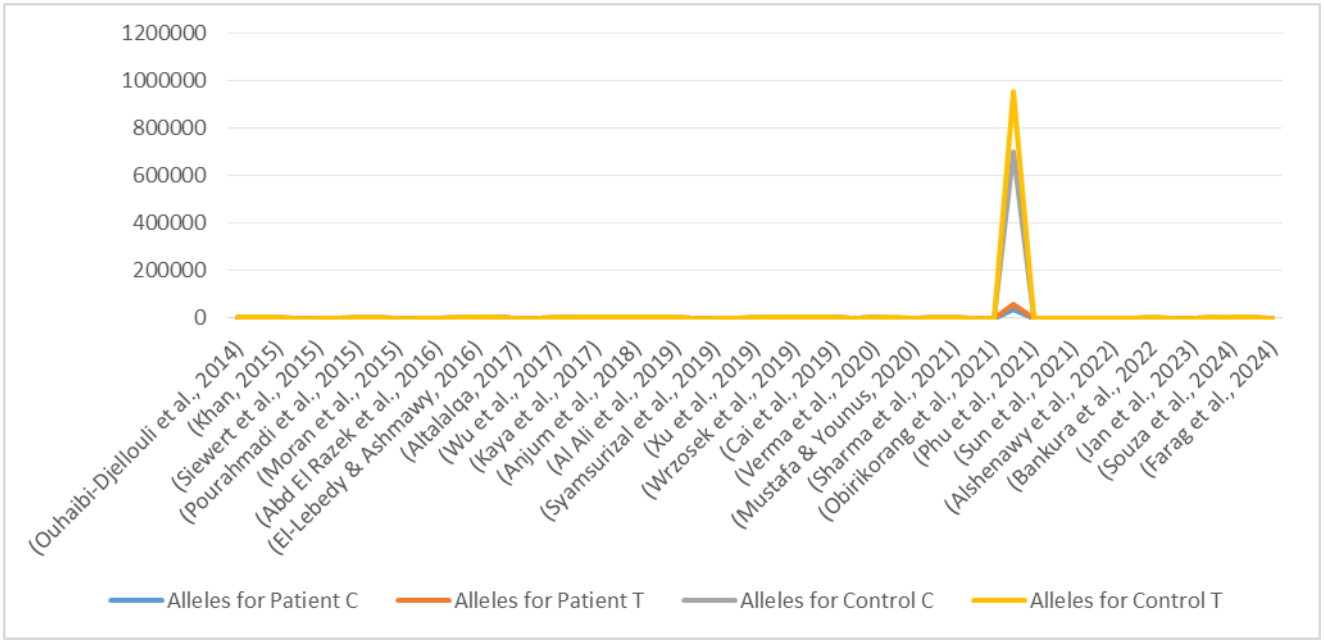

Figure 10: Graphical representation of allelic frequencies (C and T) in cases an controls for the study of (Lehrer & Rheinstein, 2021).

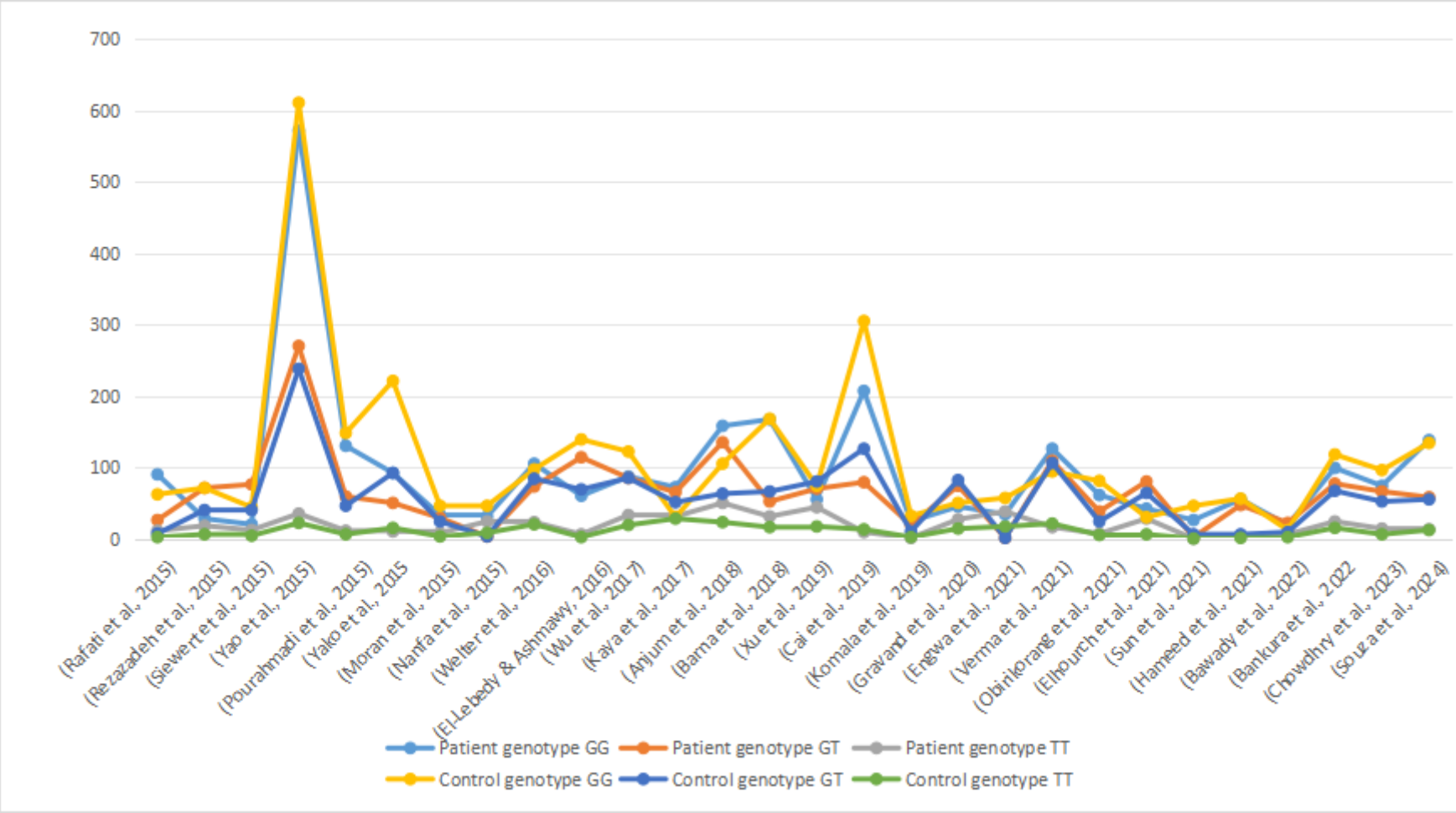

Figure 11: Graphical representation of genotypic frequencies (GG, GT and TT) in cases and controls of the different selected studies.

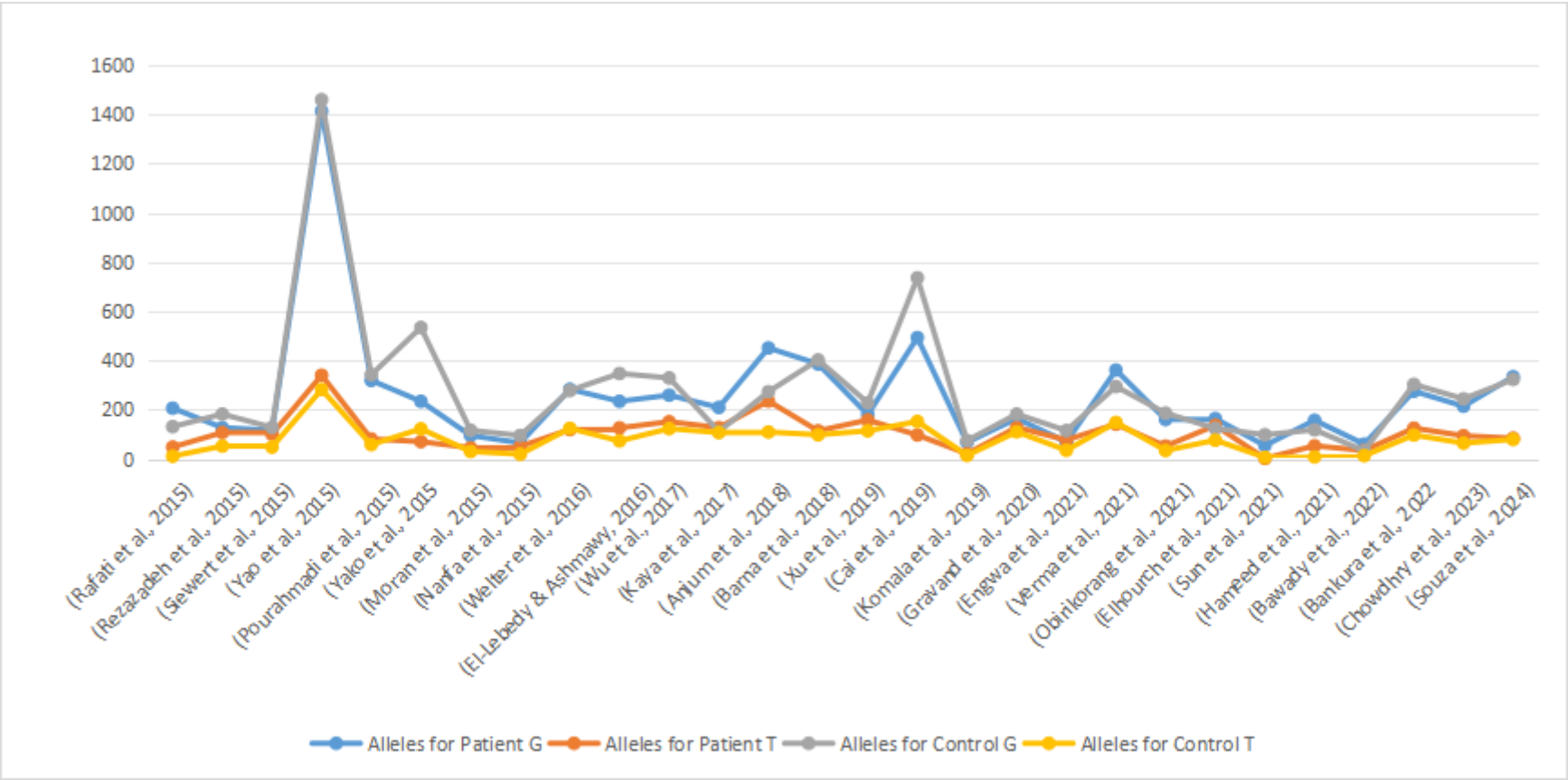

Figure 12: Graphical representation of allelic frequencies (G and T) in the cases and controls of the different selected studies.

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3. Effect of the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene on the risk of T2D

Tables 9 and 10 were used to assess the influence of the rs7903146 and rs12255372 polymorphisms of the *TCF7L2* gene on the risk of developing T2D. This assessment was based on the odds ratios (OR), 95% confidence intervals (95% CI), and *p*-values for both the homozygous mutant TT genotype and the T allele.

Table 9: Effect of the TT genotype and the T allele of the rs7903146 polymorphism of the TCF7L2 gene on the occurrence of T2D.

AUTHOR/ YEAR	Genotype TT			Allele T		
	OR	95% CI	*p*-values	OR	95% CI	*p*-values
(Ouhaibi-Djellouli et al., 2014)	2.0988	1.0431-4.2233	0.0377	1.4754	1.0534-2.0663	**0.0236***
(Assmann et al.,2014)	1.8065	1.2879-2.5340	0.0006	1.3647	1.1641-1.6000	**0.0001**
(Khan, 2015)	3.1304	1.7015-5.7595	0.0002	1.9342	1.4757-2.5352	< **0.0001**
(Rezazadeh et al., 2015)	14.1167	4.4885-44.3983	< 0.0001	3.7655	2.4827-5.7111	< **0.0001**
(Siewert et al., 2015)	8.5714	2.6594-27.6267	0.0003	2.5862	1.6764-3.9897	< **0.0001**
(Kaftan, 2015)	3.5714	0.3905-32.6656	0.2596	2.8519	1.1170-7.2814	**0.0284**
(Pourahmadi et al., 2015)	1.7725	0.8809-3.5664	0.1086	1.4824	1.0773-2.0399	**0.0156**
(Yako et al., 2015	2.2303	0.9926-5.0111	0.0521	1.4870	1.1021-2.0064	**0.0094**
(Moran et al., 2015)	3.1846	0.9646-10.5135	0.0573	2.1703	1.2903-3.6504	**0.0035**
(Demirsoy & Aras, 2016)	1.4525	0.5689-3.7085	0.4351	1.7032	1.0031-2.8920	**0.0487**
(Abd El Razek et al., 2016)	0.9164	0.4039-	0.8345	0.9587	0.6408-	0.8372

		2.0792			1.4341	
(Welter et al., 2016)	**1.0000****	0.5309-1.8837	1.0000	1.0000	0.7441-1.3439	**1.0000**
(El-Lebedy & Ashmawy, 2016)	4.6667	1.1206-19.4340	0.0343	1.9633	1.4421-2.6731	< **0.0001**
(Phani et al., 2016)	2.1040	0.9275-4.7726	0.0751	1.4629	1.1554-1.8523	**0.0016**
(Altalalqa, 2017)	2.1135	0.9474-4.7151	0.0676	1.4672	0.9885-2.1777	0.0571
(Bulgăr et al., 2017)	1.5942	0.3397-7.4820	0.5544	2.1959	1.0177-4.7383	**0.0450**
(Wu et al., 2017)	1.9038	0.7127-5.0858	0.1990	1.2118	0.8915-1.6472	0.2199
(Wang et al., 2017)	1.2351	0.9310-1.6385	0.1431	1.2217	1.0591-1.4093	**0.0060**
(Kaya et al., 2017)	1.1056	0.5138-2.3789	0.7973	1.2653	0.8948-1.7891	0.1831
(Golbon et al., 2018)	1.6677	1.0543-2.6379	0.0288	1.3739	1.0658-1.7712	**0.0142**
(Anjum et al., 2018)	1.7050	1.0096-2.8793	0.0460	1.4359	1.0922-1.8879	**0.0096**
(Plengvidhya et al., 2018)	9.5658	0.5135-178.2089	0.1302	1.7617	1.2011-2.5838	**0.0038**
(Isakova et al., 2018)	0.7335	0.1596-3.3714	0.6904	1.0404	0.5775-1.8746	0.8950
(Al Ali et al., 2019)	0.6399	0.3391-1.2078	0.1684	0.8121	0.6082-1.0842	0.1581
(Syamsurizal et al., 2019)	9.0920	0.4574-180.7092	0.1478	4.2418	1.6557-10.8677	**0.0026**
(Chandrasekaran & Gopinath, 2019)	12.1875	2.6134-56.8355	0.0015	2.3066	1.4634-3.6357	**0.0003**
(Xu et al., 2019)	2.3928	1.2968-4.4152	0.0052	1.5637	1.1485-2.1290	**0.0045**

(Shahid et al., 2019)	1.6268	0.7370-3.5909	0.2284	0.9855	0.7054-1.3770	0.9320
(Wrzosek et al., 2019)	3.0172	1.3144-6.9262	0.0092	1.5942	1.1487-2.2125	**0.0053**
(Foroughmand et al., 2019)	0.5270	0.2360-1.1770	0.1182	0.8616	0.6239-1.1898	0.3656
(Cai et al., 2019)	1.9425	0.8993-4.1959	0.0911	1.0165	0.7813-1.3225	0.9028
(Komala et al., 2019)	2.4286	0.0463-127.3113	0.6605	19.0328	4.3615-83.0549	**0.0001**
(Verma et al., 2020)	3.0429	1.0185-9.0912	0.0463	1.6132	1.2964-2.0074	< **0.0001**
(Gravand et al., 2020)	0.5270	0.2360-1.1770	0.1182	0.8579	0.6185-1.1902	0.3589
(Mustafa & Younus, 2020)	2.7692	0.7163-10.7057	0.1398	1.6513	1.1031-2.4718	**0.0148**
(Verma et al., 2021)	0.4335	0.2104-0.8933	0.0235	0.8039	0.6211-1.0404	0.0971
(Sharma et al., 2021)	3.0636	1.4657-6.4034	0.0029	1.7484	1.3017-2.3483	**0.0002**
(Abdullah & Ali, 2021)	17.7500	6.0051-52.4659	< 0.0001	5.8903	3.6711-9.4511	< **0.0001**
(Obirikorang et al., 2021)	5.2769	1.7107-16.2775	0.0038	1.8588	1.2513-2.7610	**0.0021**
(Lehrer & Rheinstein, 2021)	1.6635	1.5972-1.7325	< 0.0001	1.3011	1.2777-1.3248	< **0.0001**
(Phu et al., 2021)	7.1373	1.6589-30.7073	0.0083	2.0710	1.3859-3.0948	**0.0004**
(Elhourch et al., 2021)	5.1840	1.8528-14.5043	0.0017	1.5744	1.0878-2.2786	**0.0161**
(Sun et al., 2021)	5.4706	0.2149-139.2524	0.3035	1.2564	0.3393-4.6523	0.7325
(Hameed et al., 2021)	2.0952	0.6784-	0.1986	1.6244	1.0269-	**0.0381**

		6.4707			2.5694	
(Alshenawy et al., 2022)	0.1825	0.0372-0.8944	0.0359	0.4667	0.2439-0.8929	**0.0213**
(Maghraby et al., 2022)	4.0408	1.6646-9.8094	0.0020	1.9686	1.3413-2.8893	**0.0005**
(Bankura et al., 2022	2.1474	1.1338-4.0671	0.0190	1.4825	1.1035-1.9917	**0.0090**
(Akhundova et al., 2022)	3.9111	1.5970-9.5785	0.0028	1.6810	1.1507-2.4558	**0.0072**
(Jan et al., 2023)	9.5041	3.6002-25.0899	< 0.0001	2.9001	1.9236-4.3725	< **0.0001**
(Chaudhary et al., 2024)	3.2903	1.8022-6.0072	0.0001	1.8036	1.3390-2.4294	**0.0001**
(Souza et al., 2024)	0.9000	0.4517-1.7934	0.7645	0.9347	0.6885-1.2690	0.6652
(Kumar et al., 2024)	1.9687	1.2393-3.1273	0.0041	1.8155	1.3518-2.4383	**0.0001**
(Farag et al., 2024)	1.8529	0.5498-6.2444	0.3197	1.3448	0.7594-2.3815	0.3096

* $p < 0.05$, TT vs CC, ** OR = 1

The results from the 38 case-control studies included in our meta-analysis show a significant association between the rs7903146 polymorphism and the risk of T2D in the majority of studies. The calculated ORs and 95% CIs demonstrate statistically significant differences between patients and controls in most studies, with *p*-values below 0.05 (Table 9).

However, the study by Welter et al. (2016) showed no effect, as both groups were equally exposed (OR = 1, $p = 1$). Additionally, several studies including Abd El Razek et al. (2016), Altalalqa (2017), Wu et al. (2017), Kaya et al. (2017), Isakova et al. (2018), Al Ali et al. (2019), Shahid et al. (2019), Foroughmand et al. (2019), Cai et al. (2019), Gravand et al. (2020), Verma et al. (2021), Sun et al. (2021), Souza et al. (2024), and Farag et al. (2024) did not show a statistically significant association between the rs7903146 polymorphism and T2D risk. In these studies, the *p*-values were greater than 0.05, indicating no significant difference between patients and controls.

As a reminder, the 95% confidence interval is used to estimate the precision of the odds ratio. A narrow CI indicates high precision, whereas a wide CI indicates low precision.

Table 10: Effect of the TT genotype and the T allele of the rs12255372 polymorphism of the TCF7L2 gene on the occurrence of T2D.

AUTHOR/ YEAR	Genotype TT			Allele T		
	OR	95% CI	*p*-values	OR	95% CI	*p*-values
(Rafati et al., 2015)	3.7889	0.8115-17.6913	0.0902	2.7749	1.3907-5.5370	**0.0038***
(Rezazadeh et al., 2015)	7.6071	2.7369-21.1436	0.0001	2.9488	1.9739-4.4054	< **0.0001**
(Siewert et al., 2015)	6.6000	1.8929-23.0125	0.0031	2.2989	1.5012-3.5202	**0.0001**
(Yao et al., 2015)	1.6994	0.9850-2.9317	0.0567	1.2449	1.0461-1.4815	**0.0136**
(Pourahmadi et al., 2015)	2.0872	0.7509-5.8012	0.1583	1.4972	1.0341-2.1677	**0.0325**
(Yako et al., 2015)	1.6014	0.6939-3.6959	0.2697	1.3094	0.9398-1.8243	0.1111
(Moran et al., 2015)	3.7172	0.9164-15.0774	0.0661	1.8316	1.0719-3.1295	**0.0268**
(Nanfa et al., 2015)	4.4516	1.7728-11.1783	0.0015	3.9231	2.1230-7.2494	< **0.0001**
(Welter et al., 2016)	1.0624	0.5492-2.0550	0.8573	0.9427	0.6976-1.2739	0.7010
(El-Lebedy & Ashmawy, 2016)	6.9500	1.3635-35.4266	0.0196	2.5595	1.8354-3.5694	< **0.0001**
(Wu et al., 2017)	2.4356	1.2999-4.5634	0.0055	1.5594	1.1687-2.0808	**0.0025**
(Kaya et al., 2017)	0.4613	0.2372-0.8972	0.0226	0.6304	0.4464-0.8902	**0.0088**
(Anjum et al., 2018)	1.4447	0.8318-2.5091	0.1915	1.3051	0.9939-1.7136	0.0554

(Barna et al., 2018)	1.9491	1.0275-3.6973	0.0410	1.2115	0.8939-1.6419	0.2161
(Xu et al., 2019)	3.4824	1.8006-6.7348	0.0002	1.7556	1.2874-2.3940	**0.0004**
(Cai et al., 2019)	1.0201	0.4282-2.4301	0.9642	0.9527	0.7207-1.2594	0.7337
(Komala et al., 2019)	0.6667	0.0571-7.7888	0.7465	1.6567	0.7805-3.5168	0.1887
(Gravand et al., 2020)	2.1429	1.0013-4.5859	0.0496	1.2914	0.9276-1.7978	0.1298
(Engwa et al., 2021)	3.7474	1.8380-7.6402	0.0003	3.6667	2.2268-6.0376	< **0.0001**
(Verma et al., 2021)	0.5684	0.2814-1.1482	0.1153	0.7759	0.5880-1.0239	0.0729
(Obirikorang et al., 2021)	1.8590	0.5628-6.1401	0.3091	1.7779	1.0989-2.8767	**0.0191**
(Elhourch et al., 2021)	3.3333	1.2281-9.0473	0.0181	1.3530	0.9393-1.9490	0.1044
(Sun et al., 2021)	1.7547	0.0338-91.0336	0.7802	0.6049	0.1180-3.1013	0.5467
(Hameed et al., 2021)	3.0545	0.3082-30.2721	0.3400	4.9793	2.2806-10.8713	**0.0001**
(Bawady et al., 2022)	1.8947	0.3273-10.9686	0.4756	1.4385	0.6677-3.0987	0.3531
(Bankura et al., 2022)	1.9071	0.9487-3.8336	0.0700	1.4199	1.0399-1.9386	**0.0274**
(Chowdhry et al., 2023)	3.0270	1.1099-8.2555	0.0305	1.6746	1.1604-2.4169	**0.0059**
(Souza et al., 2024)	1.0519	0.4634-2.3880	0.9037	1.0283	0.7296-1.4492	0.8735

* P< 0.05, TT vs CC.

The results of the 16 case-control studies included in our meta-analysis show a significant association between the rs12255372 polymorphism of the TCF7L2 gene and the occurrence of T2D. The calculation of the OR and 95% CI in these studies allows us to observe statistically significant differences between patients and controls, as all *p*-values are below 0.05 and therefore considered significant (Table 10).

However, the studies by Yako et al. (2015), Welter et al. (2016), Anjum et al. (2018), Barna et al. (2018), Cai et al. (2019), Komala et al. (2019), Gravand et al. (2020), Verma et al. (2021), Elhourch et al. (2021), Sun et al. (2021), Bawady et al. (2022), and Souza et al. (2024) did not show any significant association between the rs12255372 polymorphism of the TCF7L2 gene and the occurrence of T2D. The calculation of the OR and 95% CI in these studies did not reveal any statistically significant differences between patients and controls, as all *p*-values were above 0.05 and therefore considered non-significant.

4. Results of the Meta-Analysis

Tables 11 and 12 were used to assess the influence of the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene on the risk of developing T2D. Several previous studies have reported contradictory findings regarding the association between T2D risk and genetic variants. To address this, we grouped 60 case-control studies according to genetic models and conducted subgroup analyses based on ethnicity to identify potential sources of heterogeneity.

Table 11: Results of the association of the rs7903146 polymorphism of the TCF7L2 gene with T2D.

	Total			Asian			Arab			Hispanic		
	OR (95% CI)	*p*-values	χ^2*	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2
C vs T	1.3272 (1.3066-1.3481)	< 0.0001	**IC***	1.4546 (1.3698-1.5446)	< 0.0001	150.214	1.3695 (1.2441-1.5075)	< 0.0001	41.2894	1.2476 (1.1231-1.3859)	< 0.0001	17.0405
CC vs TT	1.7895 (1.7293-1.8518)	< 0.0001	**IC**	1.7885 (1.5625-2.0472)	< 0.0001	72.4489	1.7908 (1.4715-2.1795)	< 0.0001	34.1582	1.4332 (1.1702-1.7552)	0.0005	12.1575
CC vs CT	1.2988 (1.2701-1.3282)	< 0.0001	527.2418	1.5098 (1.3927-1.6367)	< 0.0001	100.4454	1.4475 (1.2474-1.6797)	< 0.0001	23.8187	1.3194 (1.1221-1.5514)	0.0008	11.2711
CC vs CT+TT	1.3812 (1.3523-1.4107)	< 0.0001	902.1481	1.5635 (1.4499-1.6860)	< 0.0001	135.4842	1.5320 (1.3319-1.7621)	< 0.0001	35.8741	1.3547 (1.1673-1.5721)	0.0001	16.0176
CC+CT vs TT	1.5802 (1.5299-1.6322)	< 0.0001	781.613	1.5292 (1.3408-1.7442)	< 0.0001	40.5275	1.4536 (1.2179 - 1.7348)	< 0.0001	17.3454	1.2429 (1.0329-1.4955)	0.0213	5.3158

* Impossible to calculate: the controle groupe was 10 x time greater than the case groupe, whiche exceed the chi square limitations.

* χ^2: chi-square.

	Caucasian			African			Persian		
	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2
C vs T	1.5533 (1.5246-1.5825)	< 0.0001	813.6468	1.7146 (1.3566-2.1670)	< 0.0001	20.5536	1.3122 (1.1465-1.5020)	0.0001	15.5805
CC vs TT	1.6609 (1.5949-1.7296)	< 0.0001	612.9627	3.2924 (1.7519-6.1876)	0.0002	14.7892	1.6030 (1.2312-2.0871)	0.0005	12.3485
CC vs CT	1.3237 (1.2901-1.3581)	< 0.0001	460.9658	1.9166 (1.3830-2.6560)	0.0001	15.443	1.2301 (0.9890-1.5298)	0.0627	3.4668
CC vs CT+TT	1.3798 (1.3466-1.4139)	< 0.0001	674.3559	2.0508 (1.4945-2.8141)	< 0.0001	20.0622	1.3402 (1.0943-1.6415)	0.0046	8.0342
CC+CT vs TT	1.4522 (1.3975-1.5090)	< 0.0001	366.9232	2.3422 (1.2795-4.2877)	0.0058	7.9898	1.4215 (1.1279-1.7916)	0.0029	8.9244

Table 12: Results of the association of the rs12255372 polymorphism of the TCF7L2 gene with T2D.

	Total			Asian			Arab			Hispanic		
	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2
G vs T	1.4394 (1.3503-1.5345)	< 0.0001	125.228	1.2709 (1.1655-1.3858	< 0.0001	29.536	2.0107 (1.5982-2.5295)	< 0.0001	36.0898	1.3636 (1.1653-1.5957)	0.0001	14.999
GG vs TT	2.0410 (1.7567-2.3713)	< 0.0001	89.447	1.5915 (1.2930-1.9589)	< 0.0001	19.47	5.9835 (2.8829-12.4185)	< 0.0001	27.5639	2.0096 (1.4058-2.8727)	0.0001	15.006
GG vs GT	1.3538 (1.2438-1.4735)	< 0.0001	49.243	1.2283 (1.0976-1.3746)	0.0003	12.844	2.2754 (1.6643-3.1109)	< 0.0001	26.9319	1.2168 (0.9801-1.5107)	0.0754	3.164
GG vs GT+TT	1.4641 (1.3521-1.5852)	< 0.0001	88.564	1.2862 (1.1569-1.4298)	< 0.0001	21.734	2.5194 (1.8564-3.4191)	< 0.0001	35.8413	1.3478 (1.0995-1.6522)	0.0041	8.267
GG+GT vs TT	1.8217 (1.5734-2.1092)	< 0.0001	65.867	1.5002 (1.2235-1.8394)	0.0001	14.356	3.8338 (1.8857-7.7946)	0.0002	15.6303	1.8428 (1.3060-2.6001)	0.0005	12.389

	African			Persian		
	OR (95% CI)	*p*-values	χ^2	OR (95% CI)	*p*-values	χ^2
G vs T	2.0969 (1.6958-2.5928)	< 0.0001	47.694	1.6163 (1.3353-1.9565)	< 0.0001	24.4769
GG vs TT	3.2615 (2.1832-4.8722)	< 0.0001	35.609	2.7032 (1.6925-4.3175)	< 0.0001	18.3233
GG vs GT	1.4243 (1.0367-1.9568)	0.0291	4.786	1.4847 (1.1543-1.9098)	0.0021	9.505
GG vs GT+TT	1.9254 (1.4699-2.5219)	< 0.0001	22.891	1.6528 (1.3029-2.0966)	< 0.0001	17.2389
GG+GT vs TT	2.9731 (2.0088-4.4003)	< 0.0001	31.647	2.3151 (1.4649-3.6588)	0.0003	15.535

The pooled data from these 60 studies showed that the rs7903146 and rs12255372 polymorphisms in the *TCF7L2* gene are significantly associated with an increased risk of developing T2D. All *p*-values for the five genetic models are below 0.05, indicating strong associations for both polymorphisms.

For **rs7903146**, the following results were obtained:

- C vs T: OR = 1.3272, 95% CI = 1.3066–1.3481, $p < 0.0001$, χ^2 = not calculable (IC)
- CC vs TT: OR = 1.7895, 95% CI = 1.7293–1.8518, $p < 0.0001$, χ^2 = IC
- CC vs CT: OR = 1.2988, 95% CI = 1.2701–1.3282, $p < 0.0001$, $\chi^2 = 527.2418$
- CC vs CT+TT (dominant): OR = 1.3812, 95% CI = 1.3523–1.4107, $p < 0.0001$, $\chi^2 = 902.1481$
- CC+CT vs TT (recessive): OR = 1.5802, 95% CI = 1.5299–1.6322, $p < 0.0001$, $\chi^2 = 781.613$

For **rs12255372**, the associations are also significant:

- G vs T: OR = 1.4394, 95% CI = 1.3503–1.5345, $p < 0.0001$, $\chi^2 = 125.228$
- GG vs TT: OR = 2.0410, 95% CI = 1.7567–2.3713, $p < 0.0001$, $\chi^2 = 89.447$
- GG vs GT: OR = 1.3538, 95% CI = 1.2438–1.4735, $p < 0.0001$, $\chi^2 = 49.243$
- GG vs GT+TT (dominant): OR = 1.4641, 95% CI = 1.3521–1.5852, $p < 0.0001$, $\chi^2 = 88.564$
- GG+GT vs TT (recessive): OR = 1.8217, 95% CI = 1.5734–2.1092, $p < 0.0001$, $\chi^2 = 65.867$

Our results revealed that the rs7903146 and rs12255372 polymorphisms are highly associated with type 2 diabetes across all ethnic groups in all genetic models except for the heterozygous model, in which Persians for the rs7903146 polymorphism and Hispanics for the rs12255372 polymorphism showed an absence of association.

Ethnic Subgroup Analysis

Asians: Both rs7903146 and rs12255372 polymorphisms showed significant associations with T2D across all five genetic models.

Arabs: Similar to Asians, strong associations were observed in all models for both polymorphisms.

Hispanics: Significant associations were found for all five models for rs7903146. For rs12255372, only four models showed significant associations; while the heterozygous GG vs

GT model did not (OR = 1.2168, CI = 0.9801–1.5107, p = 0.0754), indicating no significant association in that case.

Africans: Both polymorphisms were strongly associated with T2D in all five models, with generally higher odds ratios, suggesting a stronger genetic effect.

Persians: Significant associations were found for all five models for rs12255372. For rs7903146, only four models showed significant associations; while the heterozygous CC vs CT model did not (OR = 1.2301, CI = 0.9890-1.5298, p = 0.0627), indicating no significant association in that case.

Caucasians: Significant associations were observed for rs7903146 in all models. Data on rs12255372 was either not reported or incomplete in this section.

Comparative Ethnic Risk Ranking

For **rs7903146**:

- African populations showed the highest ORs in all five models, suggesting the greatest genetic susceptibility.
- Caucasians ranked second in the allelic model, followed by Asians, Arabs, Persians, then Hispanics
- In the homozygous model, Arabs followed Africans, then Asians, Caucasians, Persians and then Hispanics.
- In the Heterozygous, dominant, and recessive models, Asians ranked second, followed by Arabs, Caucasians and then Hispanics in the heterozygous and dominant models and Persians in the recessive model. In which Hispanics and Persians ranked the last in each other's model

For **rs12255372**:

- Africans ranked highest in the allelic model, followed by Arabs, Persians, Hispanics, and Asians.
- In the dominant, recessive, homozygous, and heterozygous models, Arabs ranked highest, followed by Africans in all but the heterozygous model
- In the homozygous, dominant and recessive models: Arabs > Africans > Persians > Hispanics > Asians.
- In the heterozygous model: Arabs > Persians > Africans > Asians > Hispanics.

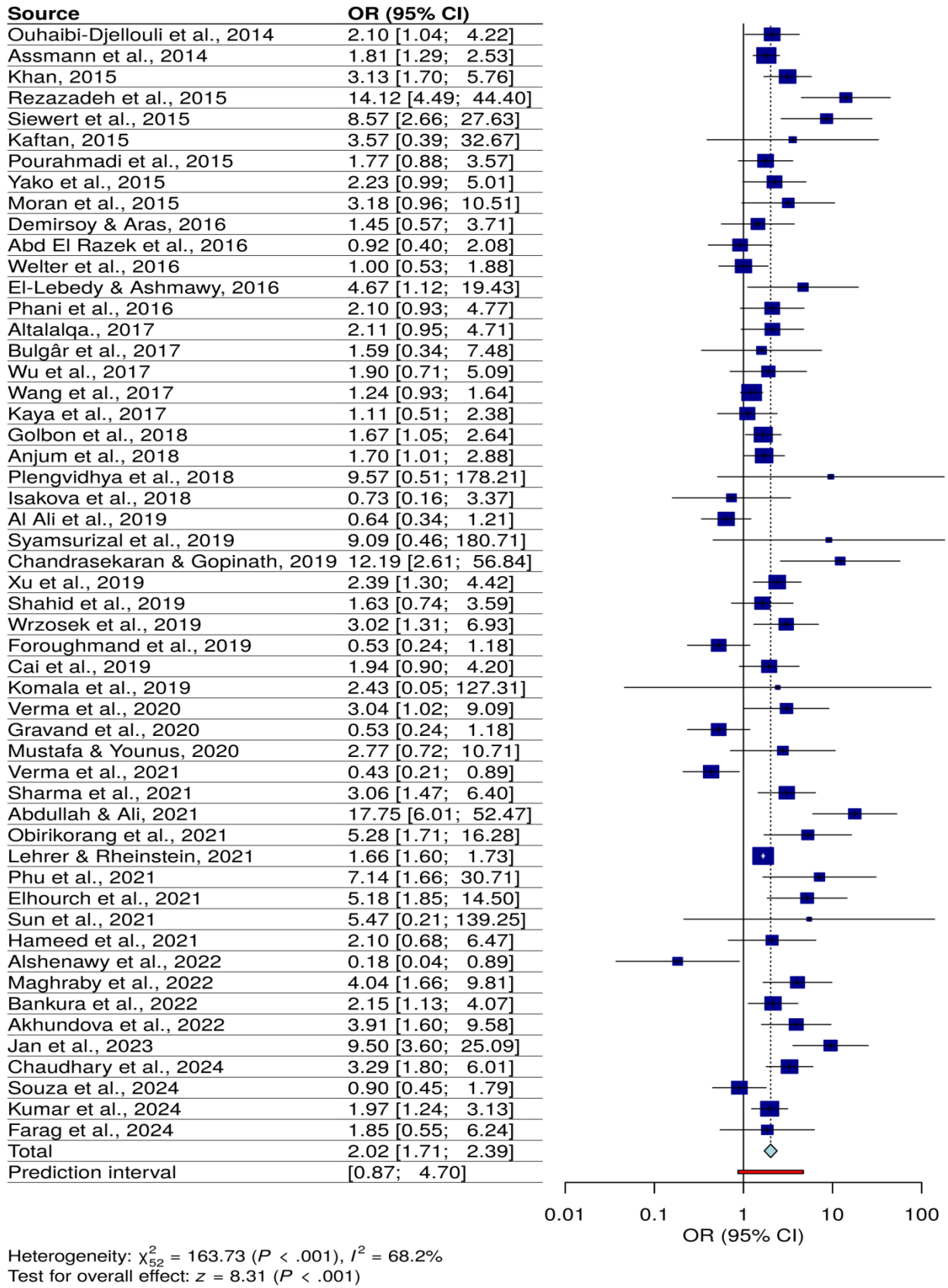

Figure 13: Forest plot for the association of the rs7903146 polymorphism of the TCF7L2 gene and the risk of T2D

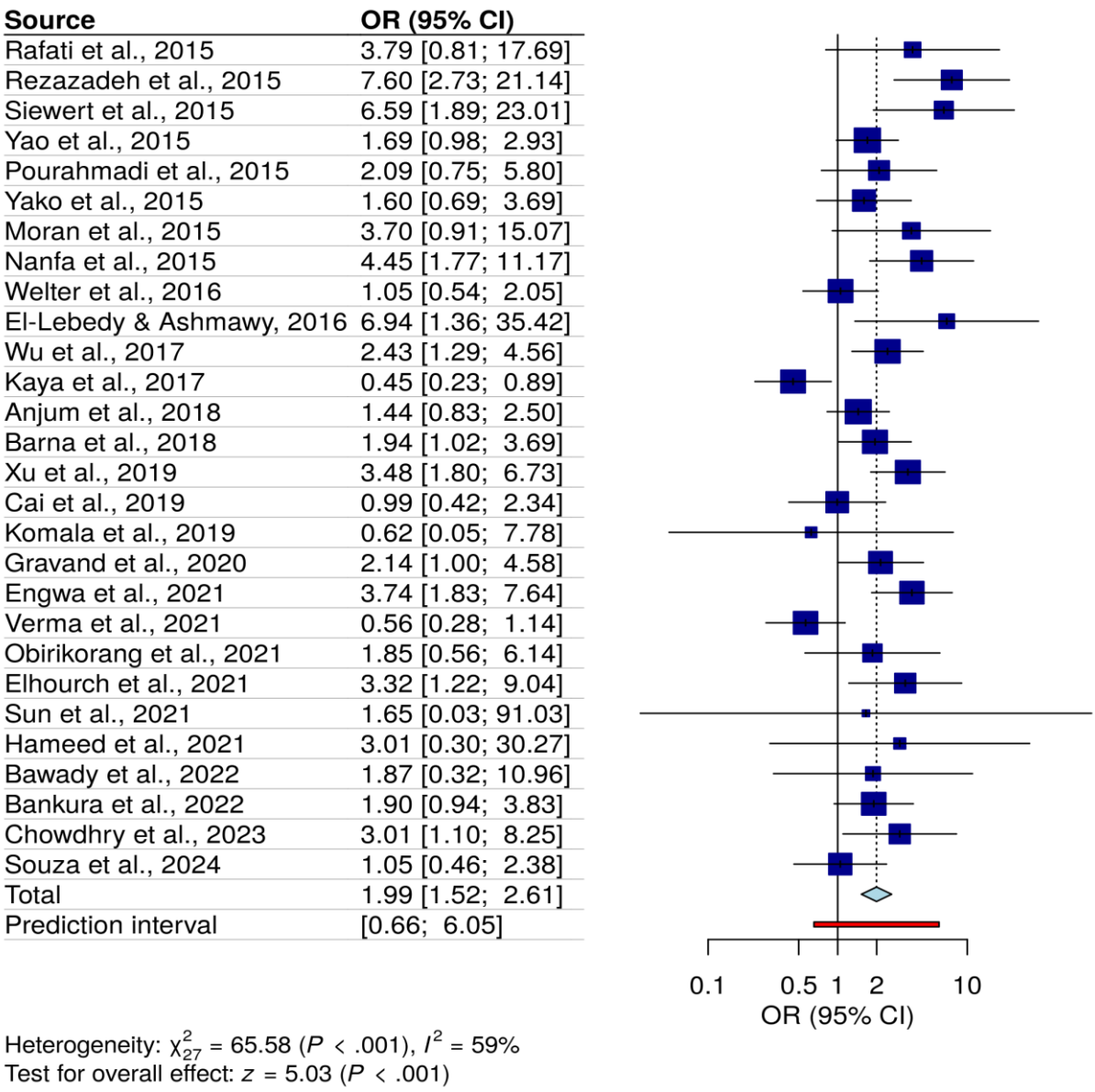

Figure 14: Forest plot for the association of the rs12255372 polymorphism of the TCF7L2 gene and the risk of T2D

The pooled OR in figure 13 was equivalent to 2.02 (95% CI: 1.71-2.39) which shows a statistically significant overall impact (P < 0.001) that align with the results of our meta-analysis. High heterogeneity (I^2 = 68.2%) indicates considerable variation in outcomes between studies.

The pooled OR in figure 14 was equivalent to 1.99 (95% CI: 1.52-2.61) which shows a statistically significant overall impact (P < 0.001) that align with the results of our meta-analysis. Moderate heterogeneity (I^2 = 59%) indicates variation in outcomes between studies.

5. Publication bias

Figure 15 and 16 represent a funnel plot that was used to access the presence or absence of the publication bias.

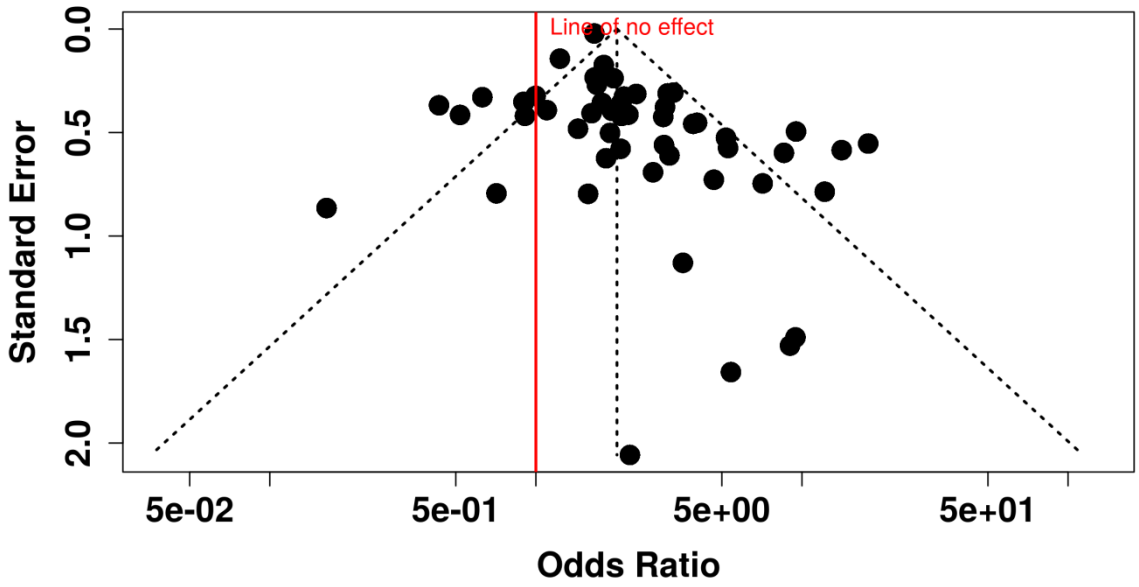

Figure 15: Funnel plot for the association of the rs7903146 polymorphism of the TCF7L2 gene and the risk of T2D

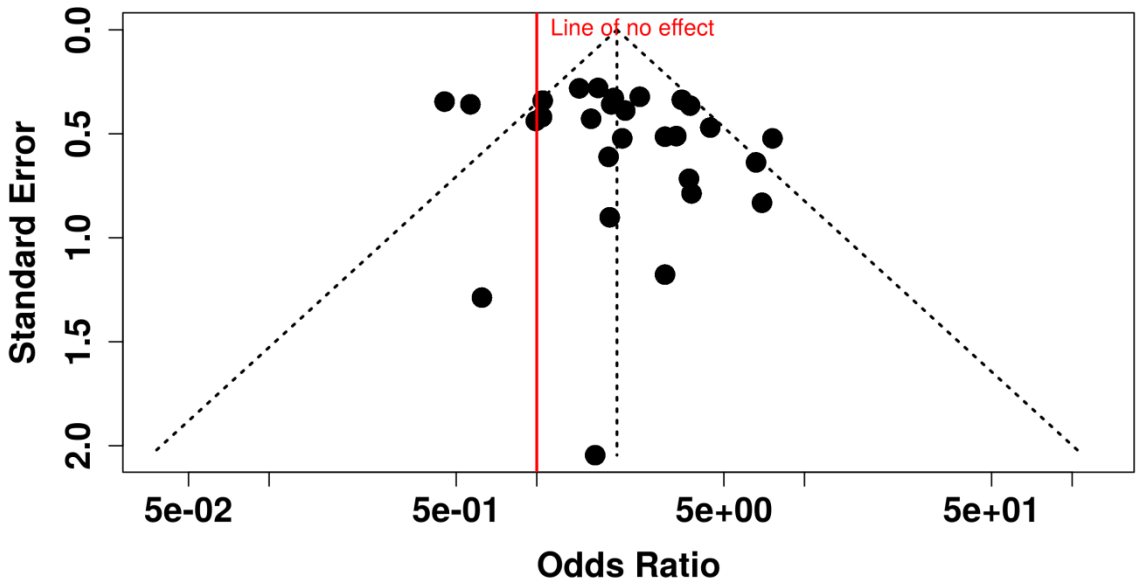

Figure 16: Funnel plot for the association of the rs12255372 polymorphism of the TCF7L2 gene and the risk of T2D.

Egger's test was used to examine the possible publication bias in the evaluation of the association between the rs7903146 (figure 15) and rs12255372 (figure 16) polymorphisms of the TCF7L2 gene and the occurrence of T2D. Two results were found in the funnel plot figures. Figure 15 suggests a possible publication bias in studies about the rs7903146 polymorphism, and Egger's test supports the presence of asymmetry.

In contrast, Figure 16 indicates the absence of publication bias in studies about the rs12255372 polymorphism, and Egger's test does not support the presence of asymmetry in the funnel plot.

6. Discussion

The multifactorial nature of T2D underscores the importance of genetic determinants, thus encouraging researchers to identify the responsible genes. The *TCF7L2* gene is a well-known genetic risk factor that is involved in the Wnt signaling pathway. Therefore, many association studies have reported a relationship between the *rs7903146* and *rs12255372* polymorphisms of the *TCF7L2* gene and T2D. Some of these studies have yielded seemingly conflicting results, perhaps partly due to small sample sizes or racial and regional differences. For this reason, we performed a meta-analysis to assess the relationship between *TCF7L2* polymorphisms and T2D risk.

Our meta-analysis suggests that the *rs7903146* polymorphism of the *TCF7L2* gene is statistically associated with an increased risk of developing T2D. This finding is consistent with the results of previous meta-analyses by Cauchi et al. (2007) in multiple ethnicities; Wang, Hu, et al. (2013) in Chinese populations; Abuhendi et al. (2019) in Arabs; Ding et al. (2018) in multiple ethnicities; and Asamoah et al. (2020) in sub-Saharan Africans, who demonstrated an association between the T allele of *TCF7L2* and susceptibility to T2D. However, our results are inconsistent with those of other meta-analyses that found no association between the *rs7903146* polymorphism and T2D. For instance, Peng et al. (2013) reported no association in Hispanic populations.

We were not able to confirm the heterozygote model for Persians, as other studies used broader ethnic classifications, and countries were not consistently specified in the included articles. Typically, Persians or Iranians are classified under Asian ethnicity. Therefore, several

articles contradicted our findings by reporting an association in Asian populations. For example, Yanasegaran et al. (2024) confirmed the association in an Asian cohort.

Our meta-analysis also suggests that the *rs12255372* polymorphism of the *TCF7L2* gene is statistically associated with an increased risk of developing T2D. This aligns with previous meta-analyses by Tong et al. (2009) across multiple ethnicities; Wang, Zhang, et al. (2013) in various populations; Ouyang et al. (2016); Abuhendi et al. (2019) in Arabs; and Xi and Ma (2020), who found an association between the T allele and T2D susceptibility. However, our results contradict those of Dou et al. (2013), who found no association in Chinese populations. We also found, through the meta-analysis by Peng et al. (2013), that the *rs12255372* polymorphism was not associated with T2D in Hispanic, Arab, and African populations. This supports our findings for Hispanics but contradicts them for the other groups.

The discrepancies between meta-analyses may be due to various factors, such as sample size, ethnicity, control sources (hospital-based vs. population-based), genotyping methods, participants' lifestyle and diet, and the different settings across countries.

The identification of *rs7903146* and *rs12255372* polymorphisms as significant genetic risk factors for T2D underscores the importance of genetic screening. This could facilitate early detection and the implementation of preventive strategies such as dietary modification and increased physical activity. Given the global prevalence of T2D, standardizing such preventive procedures could contribute to reducing mortality.

However, our meta-analysis has certain limitations that should be considered when interpreting the results. First, the presence of publication bias for the *rs7903146* polymorphism may affect the overall conclusions and weaken the findings. Second, our study lacks data from some populations, and certain ethnic groups included had small sample sizes, which could lead to underestimation or overestimation of the effect. Finally, we did not investigate the potential impact of gene–gene and gene–environment interactions, which could influence the association between the *TCF7L2* gene polymorphisms and T2D.

Conclusion and perspectives

Conclusion and perspectives

Given the anticipated increase in the prevalence of T2D in the coming years, it is crucial to investigate all potential contributors to its etiology. In this context, research into the role of genetic variations in disease susceptibility remains a promising and expanding field.

Therefore, we conducted this meta-analysis to assess the association between the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene and the risk of T2D. To achieve this, we collected all relevant case-control studies published between 2014 and 2024. A total of 60 eligible studies were included in the analysis.

Our results revealed a significant association between the rs7903146 polymorphism and T2D. This association was further confirmed through subgroup analyses based on ethnicity. The association was observed in all six ethnic groups (Asians, Arabs, Hispanics, Caucasians, Africans, and Persians) across five genetic models, except for Persians, where no association was found under the heterozygote model.

Regarding the rs12255372 polymorphism, our meta-analysis also demonstrated a significant association with T2D. This was supported by ethnicity-based subgroup analyses, showing associations across five genetic models for Asians, Arabs, Persians, and Africans, and in four models for Hispanics. However, the heterozygote model did not show a significant association in the Hispanic group.

In conclusion, this meta-analysis provides robust evidence that the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene are strongly associated with T2D susceptibility. For future association studies, strict selection criteria for both cases and controls should be applied. Moreover, broader ethnic representation should be considered to ensure the generalizability of findings. Nevertheless, this study has certain limitations. A publication bias was detected in the analysis of the rs7903146 polymorphism. Additionally, the small sample sizes in some ethnic subgroups may limit the reliability of the estimated effects.

Based on our findings, we propose the following future perspectives:

• Include studies with larger sample sizes to increase statistical power.

• Incorporate data from underrepresented populations, such as Americans and Europeans, to provide

a more comprehensive understanding of this association.

• Investigate gene–gene and gene–environment interactions to better elucidate the complex relationship between these polymorphisms and T2D risk.

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Summary

Résume

Contexte : La prévalence du diabète de type 2 (DT2) a augmenté au fil des années, influencée par des facteurs génétiques et environnementaux. Par conséquent, de nombreuses études d'association ont été menées pour évaluer la relation entre les polymorphismes rs7903146 et rs12255372 du gène TCF7L2 et le DT2. Ainsi, nous avons réalisé cette méta-analyse pour synthétiser les résultats de ces études d'association.

Méthodes : Les articles publiés entre 2014 et 2024 ont été identifiés via des recherches sur PubMed et Google Scholar. Un total de 39 591 cas et 463 251 témoins ont été inclus dans la méta-analyse. Soixante études éligibles ont été classées en six sous-groupes ethniques : Asiatiques, Arabes, Hispaniques, Caucasiens, Africains et Persans.

Résultats : Une association significative a été observée pour les deux polymorphismes. Pour rs7903146, des associations ont été observées dans les cinq modèles génétiques : dominant (OR = 1,3812, IC 95 % = 1,3523–1,4107, p < 0,0001), récessif (OR = 1,5802, IC 95 % = 1,5299–1,6322, p < 0,0001), homozygote (OR = 1,7895, IC 95 % = 1,7293–1,8518, p < 0,0001), hétérozygote (OR = 1,2988, IC 95 % = 1,2701–1,3282, p < 0,0001) et allélique (OR = 1,3272, IC 95 % = 1,3066–1,3481, p < 0,0001). De même, pour rs12255372, des associations significatives ont été trouvées sous les modèles allélique (OR = 1,4394, IC 95 % = 1,3503–1,5345, p < 0,0001), homozygote (OR = 2,0410, IC 95 % = 1,7567–2,3713, p < 0,0001), hétérozygote (OR = 1,3538, IC 95 % = 1,2438–1,4735, p < 0,0001), dominant (OR = 1,4641, IC 95 % = 1,3521–1,5852, p < 0,0001) et récessif (OR = 1,8217, IC 95 % = 1,5734–2,1092, p < 0,0001).

Conclusion : La méta-analyse suggère que les polymorphismes rs7903146 et rs12255372 sont significativement associés au DT2 dans plusieurs groupes ethniques, y compris les Asiatiques, les Arabes, les Hispaniques, les Caucasiens, les Africains et les Persans.

Mots-clés: Méta-analyse, DT2, TCF7L2, rs7903146, rs12255372

الملخص

الخلفية: إزداد إنتشار داء السكري من النوع الثاني على مر السنين، متأثرا بعوامل جينية و بيئية. لذلك أجريت العديد من دراسات الإرتباط لتقييم العلاقة بين تعدد الاشكال الجينية rs7903146 و rs12255372 في جين TCF7L2 و داء السكري من النوع الثاني. و لذلك قمنا بإجراء هذا التحليل الوصفي لجمع نتائج هذه الدراسات.

الطرق : تم تحديد المقالات المنشورة بين عامي 2014 و 2024 من خلال البحث في PubMedو Google Scholer شمل التحليل 39591 حالة و 463251 ضابطة. تم تصنيف ستون دراسة مؤهلة إلى ست مجموعات عرقية فرعية : الأسيويون، و العرب، و اللاتينيون، و القوقازيون، و الأفارقة، و الفرس.

النتائج : لوحظ ارتباط كبير لكلا تعدد الاشكال الجينية، بالنسبة ل rs7903146 لوحظت ارتباطات في جميع النماذج الجينية الخمسة: السائد (OR = 1,3812,CI 95 % = 1,3523–1,4107, p < 0,0001)، المتنحي(OR = 1,5802 (CI 95 % = 1,5299–1,6322, p < 0,0001) ، متماثل الزيجوت –CI 95 % = 1,7293 , OR = 1,7895 (p < 0,0001 ,1,8518) ، متغاير الزيجوت(OR = 1,2988, CI 95 % = 1,2701–1,3282, p < 0,0001)، و الأليلي (OR = 1,3272, IC 95 % = 1,3066–1,3481, p < 0,0001). بالنسبة ل rs12255372 وجدت الإرتباطات أيضا في النماذج لجينية الخمسة: السائد(OR = 1,4641, CI 95 % = 1,3521–1,5852, p < 0,0001)، المتنحي (OR = 1,8217, CI 95 % = 1,5734–2,1092, p < 0,0001)، متماثل الزيجوت (OR = 2,0410 CI 95 % = 1,7567–2,3713, p < 0,0001)، متغاير الزيجوت (–CI 95 % = 1,2438 OR = 1,3538, (1,4735, p < 0,0001)، و الأليلي (OR = 1,4394,CI 95 % = 1,3503–1,5345, p < 0,0001).

الإستنتاج: يشير التحليل إلى أن تعدد الاشكال لجينيةrs7903146و rs12255372 يرتبطان بشكل كبير بداء السكري من النوع الثاني عبر مجموعات عرقية متعددة، بما في ذلك لأسيويون، و العرب، و اللاتينيون، و القوقازيون، و الأفارقة، و الفرس.

الكلمات المفتاحية:داء السكري من النوع الثاني، جين TCF7L2، تعدد الاشكال الجيني rs7903416 وrs12255372 .

College year: 2024-2025	**Presented by:** KHELFAOUI Hibat Errahmane.

Association of the rs7903146 and rs12255372 Polymorphisms of the TCF7L2 Gene with Type 2 Diabetes Risk: A Meta-Analysis

Thesis for obtaining the Master's degree in Genetics

Summary

Background: The prevalence of type 2 diabetes (T2D) has been increasing over the years, influenced by both genetic and environmental factors. Consequently, many association studies have been conducted to evaluate the relationship between the rs7903146 and rs12255372 polymorphisms of the TCF7L2 gene and T2D. Therefore, we performed this meta-analysis to synthesize the findings of these association studies.

Methods: Articles published between 2014 and 2024 were identified through searches on PubMed and Google Scholar. A total of 39,591 cases and 463,251 controls were included in the meta-analysis. Sixty eligible studies were classified into six ethnic subgroups: Asians, Arabs, Hispanics, Caucasians, Africans, and Persians.

Results: A significant association was observed for both polymorphisms. For rs7903146, we observed associations across all five genetic models: dominant (OR = 1.3812, 95% CI = 1.3523–1.4107, p <0.0001), recessive (OR = 1.5802, 95% CI = 1.5299–1.6322, p <0.0001), homozygote (OR =1.7895, 95% CI = 1.7293–1.8518, p <0.0001), heterozygote (OR = 1.2988, 95% CI =1.2701–1.3282, p < 0.0001), and allelic (OR = 1.3272, 95% CI = 1.3066–1.3481, p < 0.0001). Similarly, for rs12255372, significant associations were found under the allelic (OR = 1.4394, 95%CI = 1.3503–1.5345, p < 0.0001), homozygote (OR = 2.0410, 95% CI = 1.7567–2.3713, p < 0.0001), heterozygote (OR = 1.3538, 95% CI = 1.2438–1.4735, p < 0.0001), dominant (OR =1.4641, 95% CI = 1.3521–1.5852, p < 0.0001), and recessive (OR = 1.8217, 95% CI =1.5734–2.1092, p < 0.0001) models.

Conclusion: The meta-analysis suggested that the rs7903146 and the rs12255372 polymorphisms are significantly associated with T2D across multiple ethnic groups, including Asians, Arabs, Hispanics, Caucasians, Africans, and Persians.

Keywords: Meta-analysis, T2D, TCF7L2, rs7903146, rs12255372.

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