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Determination of Association and Risks Indices of Subjects with Type 2 Diabetes Expressing CDKN-2A Gene in Some Tribes in Southern Nigeria

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Doris OC, Bartimaeus EAS, Ogechi NE and Holy B*

Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Rivers State University, Nkpolu, Port Harcourt, Nigeria

***Address for Correspondence**
Brown Holy, Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Rivers State University, Nkpolu, Port Harcourt, Nigeria.E-mail Id: brown.holy01@ust.edu.ng

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Abstract

The cyclin-dependent kinase inhibitor (CDKN/2A) gene locus has been implicated in diabetes type 2 susceptibility through genome-wide association studies (GWAS). However, there is paucity of data on this in Nigeria. The aim was to determine association and risks indices of subjects with type 2 diabetes expressing CDKN/2A gene in some tribes in Southern Nigeria. This is a cross-sectional study that involved 120 females and males' subjects from Ijaw, Ogoni, Ikwerre and Igbo tribes, between the ages of 34 – 84 attending diabetic clinics at two tertiary hospitals. Well-structured questionnaires were randomly administered to the 120 subjects. The result revealed significant associations ($p < 0.05$) between all examined lifestyle factors and T2D in individuals expressing the CDKN/2A gene. Sedentary individuals showed a strong positive association with T2D ($X^2 = 16.28$, $p < 0.0001$), with elevated relative risk (RR = 1.66) and odds ratio (OR = 3.21). Subjects without a family history of T2D had a higher association ($X^2 = 16.31$, $p < 0.0001$), with increased relative risk (RR = 1.59) and odds ratio (OR = 3.49). Non-smokers exhibited a significant association with T2D ($X^2 = 24.97$, $p < 0.0001$), with reduced relative risk (RR = 0.26) and odds ratio (OR = 0.11). The Ijaw tribe depicted a modest but significant association ($X^2 = 4.09$, $p = 0.043$), with reduced relative risk (RR = 0.75) and odds ratio (OR = 0.56). While Ikwere tribe had a strong negative association ($X^2 = 15.56$, $p < 0.0001$), with reduced relative risk (RR = 0.51) and odds ratio (OR = 0.29). Also, Ogoni tribe had a significant negative association ($X^2 = 10.11$, $p = 0.0015$), with reduced relative risk (RR = 0.61) and odds ratio (OR = 0.39). And Igbo tribe had no significant association. Individuals expressing CDKN/2A gene may have the propensity for risk indices for type 2 diabetes in the study population.

Introduction

T2DM is a complicated metabolic disease of global significance with increased prevalence rate without any form or spraying or plateau (Rodríguez-Mañas et al. 2022) [1]. It is often characterised by a combination of impairments in insulin secretion from the beta cells in pancreas, to the resistance of insulin in the peripheral tissues, especially in the liver and muscle that occurs as a result of interaction between multiple environmental as well as genetic factors. Several studies have shown evidence supporting gene as well as lifestyle related to T2DM to have come from the prevalence of DM across diverse environmental factors and ethnicities, as well as familial based intervention studies which has shown that related individuals' response to interventions is more similar than that in unrelated individuals (Paul et al., 2013) [2]. Both environmental and genetic factors play an essential role in causing T2DM (Khan et al. ,2015; Shariff et al., 2018) [3,4]. In addition, Yan et al., (2017) [5] posited that T2DM is a complicated, chronic, polygenic congenital disorder involving intricate interactions between gene variants and environmental factors–for instance, coffee, smoking, stress, obesity, physical activity, inflammation, exercise, diet, as well as family history. Several studies have shown evidence supporting gene as well as lifestyle related to T2DM to have come from the prevalence of DM across diverse environmental factors and ethnicities, as well as familial based intervention studies which has shown that related individuals' response to interventions is more similar than that in unrelated individuals (Paul et al., 2013; Schwab et al., 2021) [2,6].

In another study, Ajabnoor et al. (2018) [7] explained that genetic linkage analyses and genome-wide association studies (GWAS) have identified many more T2DM susceptibility loci, with about 187 T2DM-linked loci confirmed to date (Voight et al., 2010; Lau et al., 2017) [8,9].

Despite significant progress in the area of genetics and GWAS in T2DM, the ability of genetic variants on the prognostics of T2DM Mellitus (T2DM) has not yielded substantiated progress. Therefore, there is need to evaluate the allelic variants of CDKN/2A presents in T2DM, as well as determine the relation between the expression of CDKN/2A and lifestyle modification in Southern Nigeria.

Materials and Method

Research Design

This is a cross-sectional study involving the identification of transcript variants of CDKN/2A gene in Type 2 Diabetics Mellitus subjects from selected ethnic groups in Southern Nigeria. Well-structured questionnaires were used to obtain information on smoking, alcohol, exercise, medical history and diet status.

Sampling Method

A total of 120 subjects of which 64 females and 56 males who are from Ijaw, Ogoni, Ikwerre and Igbo tribes between the ages of 34 – 84 attending diabetic clinics at Rivers State University Teaching Hospital (RSUTH) formally known as Braithwaite Memory Hospital, Port Harcourt (BMSH) and University of Port Harcourt Teaching Hospital (UPTH).

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Eligibility, Inclusion and Exclusive Criteria

A well-structured questionnaire was issued to all the participants to obtain demographic information, medical history, and lifestyle after obtaining verbal consent of participants. Subject included in this study were attending Diabetes Clinic at Braithwaite Memorial Specialist Hospital (BMSH) and University of Port Harcourt Teaching Hospital, with history of diabetes and glycated haemoglobin (HbA1c) greater than 6.5% and from the selected tribes. Those who did not give their consent were excluded from the study and those without a clear history of diabetes and fasting blood sugar of less than 7.0mmo/l and glycated haemoglobin (HbA1c) less than 6.5% and those not of the selected tribes. Before the start of the study, ethical approval with number RSHMB/RSHREC/2023/027 was obtained from the Ethical Review Boards of the Rivers State Government, through the Rivers State Ministry of Health covering the Rivers State University Teaching Hospital and University Teaching Hospital UPTH/ADM/90/S.11/VOL.XI/1069. The subjects were addressed and the purpose of the study made known to them. Upon receipt of oral consent, they were required to complete a set of questionnaires.

Sample Collection

Seven milliliters of blood was drawn from the subjects after obtaining consent, three (3ml) for HbA1C and fasting blood glucose. The remaining four ml of blood was collected using a EDTA K3 tubes and was transported in cold box to Safety Molecular Pathology Laboratory Services located at 44 Rangers Avenue, Enugu for DNA extraction and genotyping (Sequencing).

Genetic analysis

Genomic DNA extraction: Genomic DNA extractions of the samples was performed using Geneaid DNA Mini Kit (Blood/Cultured Cell).

Principle:

RBC Lysis Buffer and chaotropic salt are used to lyse cells and degrade protein, allowing DNA to bind to the glass fiber matrix of the spin column. Contaminants are removed using a wash buffer (containing ethanol) and the purified genomic DNA is eluted by a low salt elution buffer, TE or water. The entire procedure can be completed within 25 minutes without phenol/chloroform extraction or alcohol precipitation. The purified DNA, with approximately 20-30 kb, is suitable for use in PCR or other enzymatic reactions.

Stage 1: Guanidinium thiocyanate or guanidinium isothiocyanate (GITC) procedure

One millilitre of whole blood sample was transferred into a 15mL tube and labelled accordingly. Ten millitres of cold 1x Red blood cell lysis buffer (RCLB) was added to each sample and the tube properly closed and was mixed by inversion. The tube was then placed on ice for 10 minutes. The tubes were wiped carefully. The tubes were centrifuged at 4000 rpm for 7 minutes. The supernatant was carefully decanted into the waste bucket. Care was taken not to lose the cell pellet. Ten millitres of cold 1x RCLB was again added to the cell pellet, mixed by vortex.

Where there were still traces of red cells, 10ml of cold RCLB was added to the cell pellet again, mixed by vortex. Ten millilitres of sterile Phosphate buffered saline (PBS) was added to the cell pellet, mixed by vortex and centrifuged at 4000 rpm for 7min. The supernatant was decanted; 5ml of sterile PBS was added into each tube. Mixed by vortex and centrifuged at 4000rpm for 5min. The supernatant was decanted into the waste bucket carefully not to discard the pellet and the fifteen millilitres' tubes were drained on a clean towel. While draining, the GITC buffer was prepared by adding 10uL beta-mercaptoethanol (BME) to the 1ml of GITC. One millilitre of activated GITC buffer containing BME was added to the cell pellets in one tube. A blunt end 18G needle and 2ml syringe was used to homogenise the GITC lysate 18 times. A sterile Pasteur pipettes was used to transfer the GITC lysate into 2mL cryovial and labelled accordingly for storage at minus -200C. (The lysate can also be used immediately for nucleic acid extraction). For quality control (QC) purpose, also 1.0mL of the GITC buffer containing BME was transferred into a cryovial, label as QC control and treated as a sample during nucleic acid extractions.

Stage 2: DNA Extraction [Geneaid Genomic DNA Mini Kit (Blood/Cultured Cell)]

Protocol for Extraction: Two hundred microlitres of GITC lysate was pipetted into a 1.5mL tube. Two hundred and fifty microliters of Guanidium Chloride buffer (GB buffer), and vortexed for 15 seconds and then incubated at 60oC for 30mins. It was mixed occasionally. Two hundred and fifty microliters absolute ethanol was added and Vortexed gently for 10 seconds. The mixture was incubated at room temp for 5 minutes. The GD column was placed in 2mL collection tube. The mixture was transferred into the GD column. It was centrifuged at 14000 rpm for 5 minutes. The 2mL collection tube was discarded and then replaced with a new one. Four hundred microlitres of W1 buffer was added to the GD column and centrifuged for 1 minute. The collection tube was discarded and the GD column was placed in a new collection tube. Six hundred microlitres of wash buffer was added to the GD column and centrifuged for 1 minute. The GD column was place into another collection tube, centrifuged at 14000rpm for 3 minutes to ensure the column is dry. The GD column was transferred to 1.5ml tube. Sixty microlitres of preheated elution buffer was added to the center of the GD column and allowed to stand for 10 minutes at room temperature. Then centrifuged at 14000 rpm for 30 seconds to elute the purified DNA.

Genotyping of SNPs: Genotyping of SNPs of the CDKN/2A gene was performed with the Illumina next-generation sequencing (NGS) using NextSeq 2000 Sequencing System. Purity and concentration of isolated DNA was determined by UV/VIS spectrophotometer Nano Drop ND-1000. The primers for the sequence, as designed from Illumina Design Studio (Ampliseq for Illumina Gene DNA for CDKN/2A Gene with a 100% coverage):

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Statistical Analysis

The statistical analysis of the experimental data was conducted using GraphPad Prism software (Version 8.0.2). All raw data generated from the study were entered into the software for comprehensive analysis and interpretation. Different statistical tools were applied to assess variations and relationships among parameters. These included: Chi-square test, odd ratio, relative risk, attributable risk, and likelihood ratio.

Results

The risks indices for T2D subjects with expressed CDKN/2A gene were calculated using chi-square, relative risk, attributable risks, odd ratio, and likelihood ratio. The relative risk, attributable risks, odd ratio, and likelihood ratios were determined using Koopman asymptotic score, Baptista-Pike, Wilson-Brown and Newcombe/ Wilson with CC methods respectively at $p<0.05$.

(Table 1) presents the association between various lifestyle factors and the presence of T2D in individuals expressing the CKDA gene. Statistical measures include chi-square (X^2), z-value, p-value, relative risk (RR), attributable risk (AR), odds ratio (OR), likelihood ratio (LR), and their corresponding 95% confidence intervals (CI).

The analysis revealed significant associations ($p < 0.05$) between all examined lifestyle factors and T2D in individuals expressing the CKDA gene. Alcohol Use: Non-drinkers had a significantly higher association with T2D ($X^2 = 24.07$, $p < 0.0001$), with reduced relative risk (RR = 0.31) and odds ratio (OR = 0.14). Exercise: Sedentary individuals showed a strong positive association with T2D ($X^2 = 16.28$, $p < 0.0001$), with elevated relative risk (RR = 1.66) and odds ratio (OR = 3.21). Family History: Subjects without a family history of T2D had a higher association ($X^2 = 16.31$, $p < 0.0001$), with increased relative risk (RR = 1.59) and odds ratio (OR = 3.49). Smoking: Non-smokers exhibited a significant association with T2D ($X^2 = 24.97$, $p < 0.0001$), with reduced relative risk (RR = 0.26) and odds ratio (OR = 0.11). Special Diet: Individuals not following a special diet had a modest but significant association ($X^2 = 4.10$, $p = 0.043$), with reduced relative risk (RR = 0.75) and odds ratio (OR = 0.56). The confidence intervals for all measures remained consistent with the observed associations, showing statistical reliability.

(Table 2) examines the association between tribal affiliation, sex, and the presence of T2D in individuals expressing the CDKN/2A gene. Statistical measures include chi-square (X^2), z-value, p-value, relative risk (RR), attributable risk (AR), odds ratio (OR), likelihood ratio (LR), and their corresponding 95% confidence intervals (CI).

The analysis revealed significant associations between certain tribal groups, sex, and T2D in individuals expressing the CDKN/2A gene, while others showed no significant link. Tribe – Rivers Ijaw: A modest but significant association was observed ($X^2 = 4.09$, $p = 0.043$), with reduced relative risk (RR = 0.75) and odds ratio (OR = 0.56). Tribe – Ikwere: A strong negative association was found ($X^2 = 15.56$, $p < 0.0001$), with reduced relative risk (RR = 0.51) and odds ratio (OR = 0.29). Tribe – Ogoni: A significant negative association was present ($X^2 = 10.11$, $p = 0.0015$), with reduced relative risk (RR = 0.61) and odds ratio (OR = 0.39). Tribe – Igbo: No significant association was detected ($X^2 = 0.05$, $p = 0.8116$), with near-neutral relative risk (RR = 0.97) and odds ratio (OR = 0.93). Sex – Male: A strong positive association was observed ($X^2 = 10.66$, $p = 0.0011$), with elevated relative risk (RR = 1.48) and odds ratio (OR = 2.58). Sex – Female: No significant association was found ($X^2 = 3.31$, $p = 0.0689$), though a trend toward increased risk was noted (RR = 1.25, OR = 1.69). The confidence intervals for significant associations support the reliability of these findings, while non-significant results suggest no strong link in those categories.

(Table 3) presents the association between the duration of T2D and its presence in individuals expressing the CKDA gene. Statistical measures include chi-square (X^2), z-value, p-value, relative risk (RR), attributable risk (AR), odds ratio (OR), likelihood ratio (LR), and their corresponding 95% confidence intervals (CI).

The analysis revealed significant associations between different

Table 1: Association of Environmental and lifestyle Risk Indices in Subjects with Expressed □CDKN/2A gene with T2D

Lifestyle	Negative	Positive	X2	Z value	P value	RR	95% CI	AR	95% CI	OR	95% CI	LR
Alcohol Use												
No	7	28	24.07	4.906	**<0.0001**	0.3080	0.15-0.55	0.4867	0.36-0.68	0.1350	0.05-0.31	0.1854
Yes	113	61										
Exercise												
No	75	30	16.28	4.034	**<0.0001**	1.6560	1.29-2.15	0.2784	0.13-0.40	3.2080	1.79-5.74	1.8570
Yes	45	61										
History												
No	64	20	16.31	4.038	**<0.0001**	1.5920	1.27-2.00	0.2833	0.14-0.41	3.4860	1.89-6.27	2.1601
Yes	56	61										
Smoking												
No	5	25	24.97	4.997	**<0.0001**	0.2551	0.11-0.52	0.4867	0.36-0.68	0.1061	0.04-0.27	0.1433
Yes	115	61										
Special Diet												
No	41	38	4.096	2.024	**0.0430**	0.7470	0.54-0.99	0.1458	0.06-0.29	0.5557	0.31-1.00	0.6765
Yes	79	61										

Keys: T2D= Type2Diabetes Mellitus; X^2= chi-square, RR=Relative Risk, AR= Attributable Risk, OR= Odd Ratio, LR= Likelihood Ratio; CI= Confidence Interval at $p<0.05$.

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Table 2: Association of Tribe and Sex Risk Indices in Subjects with Expressed CDKN/2A gene with T2D

Tribe & Sex	Negative	Positive	X2	z value	P value	RR	95% CI	AR	95% CI	OR	95% CI	LR
Tribe–Rivers Ijaw												
No	31	41	4.09	2.024	**0.0430**	0.7470	0.54-0.99	0.1458	0.06-0.29	0.5557	0.32-1.00	0.6765
Yes	83	61										
Tribe -Ikwere												
No	19	42	15.56	3.9450	**<0.0001**	0.5115	0.34-0.73	0.2975	0.16-0.45	0.2905	0.15-0.54	0.4087
Yes	95	61										
Tribe -Ogoni												
No	25	44	10.11	3.179	**0.0015**	0.6106	0.42-0.83	0.2310	0.09-0.38	0.3894	0.22-0.69	0.5233
Yes	89	61										
Tribe -Igbo												
No	39	34	0.05	0.2384	0.8116	0.9688	0.73-1.24	0.0172	-0.12-0.16	0.9329	0.53-1.62	0.9559
Yes	75	61										
Sex -Male												
No	64	28	10.66	3.2650	**0.0011**	1.4810	1.17-1.88	0.2261	0.08-0.35	2.5820	1.44-4.64	1.7240
Yes	56	61										
Sex-Female												
No	56	30	3.31	1.8190	0.0689	1.2460	0.98-1.57	0.1270	-0.02-0.26	1.6890	0.95-2.96	1.3760
Yes	64	61										

Keys: T2D= Type2 Diabetes Mellitus; X^2= chi-square, RR=Relative Risk, AR= Attributable Risk, OR= Odd Ratio, LR= Likelihood Ratio; CI= Confidence Interval at p<0.05.

Table 3: Association of Duration of Disease Risk Indices in Subjects with Expressed CDKN/2A gene with T2D

Duration of Dx.	Negative	Positive	X2	Z value	P value	RR	95% CI	AR	95% CI	OR	95% CI	LR
0 -10Years												
No	71	25	18.24	4.270	<0.0001	1.6601	1.31-2.12	0.2941	0.15-0.41	3.5360	1.92- 6.27	2.0350
Yes	49	61										
11-20Years												
No	32	44	5.813	2.411	0.0159	0.7129	0.52-0.94	0.1696	0.03-0.31	0.5041	0.29- 0.88	0.6364
Yes	88	61										
21-30 Years												
No	17	51	27.51, 1	5.245	<0.0001	0.3981	0.25-0.59	0.3780	0.25-0.52	0.1974	0.10- 0.37	0.3111
Yes	103	61										

Keys: Dx. = DiseaseT2D= Type2 Diabetes Mellitus, X^2= chi-square, RR=Relative Risk, AR= Attributable Risk, OR= Odd Ratio, LR= Likelihood Ratio; CI= Confidence Interval at p<0.05.

durations of T2D and the presence of the disease in individuals expressing the CDKN/2A gene. 0–10 Years Duration: A strong positive association was observed (X^2 = 18.24, p < 0.0001), with elevated relative risk (RR = 1.66) and odds ratio (OR = 3.54). 11–20 Years Duration: A modest but significant negative association was found (X^2 = 5.813, p = 0.0159), with reduced relative risk (RR = 0.71) and odds ratio (OR = 0.50). 21–30 Years Duration: A highly significant negative association was detected (X^2 = 27.51, p < 0.0001), with substantially reduced relative risk (RR = 0.40) and odds ratio (OR = 0.20). The confidence intervals for all significant associations support the reliability of these findings, indicating that shorter disease duration (0–10 years) is strongly linked to T2D presence, while longer durations (11–30 years) show progressively weaker associations.

(Table 4) examines the association between different age groups and the presence of T2D in individuals expressing the CDKN/2A gene. Statistical measures include chi-square (X^2), z-value, p-value, relative risk (RR), attributable risk (AR), odds ratio (OR), likelihood ratio (LR), and their corresponding 95% confidence intervals (CI).

The analysis revealed strong age-dependent associations between CDKN/2A gene expression and T2D, with particularly notable patterns in younger and older age groups: 35–44 Years: An extremely strong negative association was observed (X^2 = 60.23, p < 0.0001), with very low relative risk (RR = 0.14) and odds ratio (OR = 0.05). 45-54 Years: A significant negative association was found (X^2 = 37.60, p < 0.0001), with reduced relative risk (RR = 0.30) and odds ratio (OR = 0.23). 55–64 Years: No significant association was detected (X^2 = 2.830, p = 0.0925), with near-neutral relative risk (RR = 0.80) and odds ratio (OR = 0.62). 65–74 Years: A strong positive association emerged (X^2 = 11.99, p = 0.0005), with elevated relative risk (RR = 1.50) and odds ratio (OR = 2.81). 75-84 Years: An exceptionally strong negative association was present (X^2 = 72.41, p < 0.0001), with extremely low relative risk (RR = 0.05) and odds ratio (OR = 0.02). The confidence intervals for significant associations support robust findings, indicating that middle-aged groups (35–54 years) show protective effects, while older adults (65–74 years) demonstrate increased risk. The oldest group (75–84 years) paradoxically shows the strongest negative association.

Discussion

This study has assessed the relationships of special diet, lifestyle modifications, family health history, duration of diabetes and age, on

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Table 4: Association of Age and Risk Indices in Subjects with T2D Expressing CDKN/2A gene

Age	Negative	Positive	X2	Z value	P value	RR	95% CI	AR	95% CI	OR	95% CI	LR
35–44 Years												
No	6	60	60.23	7.761	**<0.0001**	0.1396	0.06-0.28	0.5605	0.47-0.68	0.05351	0.02-0.12	0.1008
Yes	114	61										
45–54 Years												
No	13	54	37.60	6.132	**<0.0001**	0.3046	0.18-0.48	0.4429	0.33-0.58	3.536	1.92-6.27	0.2307
Yes	107	61										
55–64 Years												
No	36	42	2.830	1.682	0.0925	0.7967	0.59-1.03	0.1178	-0.02-0.26	0.6224	0.35-1.08	0.7357
Yes	84	61										
65–74 Years												
No	63	24	11.99	3.463	**0.0005**	1.499	1.19-1.89	0.2411	0.09-0.37	2.809	1.52-5.01	1.859
Yes	57	61										
75–84Years												
No	2	60	72.41, 1	8.509	**<0.0001**	0.04893	0.01-0.16	0.6270	0.55-0.74	0.01723	0.04-0.07	0.03361
Yes	118	61										

Keys: T2D= Type2DiabetesMellitus, X^2= chi-square, RR=Relative Risk, AR= Attributable Risk, OR= Odd Ratio, LR= Likelihood Ratio; CI= Confidence Interval at p<0

of diabetes type 2 subjects expressing CDKN/2A among major tribes in the Southern Nigeria.

The impact of lifestyle factors on the development and progression of chronic diseases, particularly Type 2 Diabetes (T2D), is well-established. Lifestyle choices such as alcohol consumption, physical activity, and smoking are known to modulate disease risk. This study's findings emphasize the profound influence these factors have on the expression of the CDKN/2A gene, which plays a role in the pathophysiology of T2D.

The significant association between alcohol use and the expression of the CDKN/2A gene ($p < 0.0001$) highlights the critical role that alcohol plays in modulating genetic expression in T2D patients. The relative risk (RR = 0.3080) suggests that individuals who abstain from alcohol are less likely to express the CDKN/2A gene compared to those who consume alcohol. The attributable risk (AR = 0.4867) further supports this finding, indicating that nearly half of the CDKN/2A expression cases among alcohol users could potentially be avoided if alcohol consumption were eliminated. Alcohol is known to influence glucose metabolism and insulin sensitivity. Chronic alcohol consumption can impair pancreatic beta-cell function, leading to decreased insulin secretion and an increased risk of hyperglycemia (Howard et al., 2004, Yang et al., 2020) [10,11]. This metabolic dysregulation could create an environment that favors the expression of genes like CDKN/2A, which are implicated in the development of T2D. Moreover, alcohol has been shown to induce oxidative stress and inflammation, both of which are key contributors to T2D pathogenesis (Caturano et al., 2023) [13]. The findings of this study align with previous research that links alcohol consumption to adverse outcomes in diabetic patients, emphasizing the need for targeted interventions to reduce alcohol use in this population. Interestingly, the odds ratio (OR = 0.1350) suggests a significantly lower likelihood of CDKN/2A gene expression among non-alcohol users. This finding points to the protective effect of abstaining from alcohol in individuals at risk of or already diagnosed with T2D. Given the widespread consumption of alcohol in many populations, public health campaigns aimed at reducing alcohol intake, particularly among those with a genetic predisposition to T2D, could have a substantial impact on disease prevention and management.

Lack of physical activity was found to be strongly associated with CDKN/2A gene expression in T2D patients. The relative risk (RR = 1.6560) indicates that individuals who do not engage in regular exercise are more than 1.5 times as likely to express the CDKN/2A gene compared to those who do. This is corroborated by the odds ratio (OR = 3.2080), which further highlights the heightened risk of CDKN/2A expression in physically inactive individuals. The strong association ($p < 0.0001$) suggests that exercise plays a crucial role in regulating genetic expression related to T2D. Physical activity is well-documented to improve insulin sensitivity and glucose uptake by muscle cells, which helps maintain stable blood glucose levels. Regular exercise has also been shown to reduce inflammation and oxidative stress, factors that are known to influence gene expression (Venkatasamy et al., 2013, Galicia-Garcia et al., 2020). [14,15] The findings of this study support the existing body of literature that advocates for regular physical activity as a preventive measure against the development of T2D, particularly in genetically predisposed individuals. Additionally, the attributable risk (AR = 0.2784) indicates that nearly 28% of the cases of CDKN/2A gene expression in inactive individuals could be prevented through increased physical activity. This underscores the importance of lifestyle interventions that promote regular exercise. Given that many individuals with T2D may experience barriers to physical activity due to comorbidities or complications of diabetes (e.g., neuropathy), tailored exercise programs that accommodate these limitations could be particularly beneficial. The promotion of physical activity should be a cornerstone of public health strategies aimed at reducing the burden of T2D and its genetic components.

Smoking emerged as another significant lifestyle factor associated with CDKN/2A gene expression. Non-smokers had a notably lower relative risk (RR = 0.2551) and odds ratio (OR = 0.1061) for CKDA-2 gene expression compared to smokers. This suggests that smoking substantially increases the likelihood of CDKN/2A expression, with nearly half of the attributable risk (AR = 0.4867) in smokers being linked to this lifestyle choice. Smoking is a well-known risk factor

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for numerous chronic conditions, including cardiovascular disease, cancer, and diabetes. In the context of T2D, smoking exacerbates insulin resistance and promotes chronic inflammation, both of which can influence the expression of diabetes-related genes such as CDKN/2A (AfGeijerstam et al., 2023) [16]. Nicotine, the addictive component of cigarettes, has been shown to impair glucose metabolism and increase oxidative stress, creating an environment conducive to the development of T2D. The results of this study align with these findings, indicating that smoking not only contributes to the onset of T2D but also increases the genetic risk for the disease through the expression of CDKN/2A. The odds ratio (OR = 0.1061) and likelihood ratio (LR = 0.1433) reinforce the notion that non-smokers are at a much lower risk of expressing the CDKN/2A gene. These findings provide strong evidence for the detrimental effects of smoking on both metabolic health and genetic predisposition in T2D patients. Smoking cessation programs should be prioritized as part of a comprehensive strategy to manage and prevent T2D, particularly among individuals with a known genetic risk for the disease.

Demographic characteristics such as tribe, sex, and age are crucial in understanding the risk factors and genetic predisposition for the expression of the CDKN/2A gene in individuals with Type 2 Diabetes (T2D). This study highlights how these factors correlate with the expression of the CDKN/2A gene, shedding light on the interplay between genetics and demographic influences in T2D patients.

The study found significant associations between CDKN/2A gene expression and specific tribal affiliations, particularly among the Ikwere and Ogoni tribes, where relative risks (RR) of 0.5115 and 0.6106, respectively, were observed. These findings suggest that individuals from these tribes have a notably lower risk of CDKN/2A gene expression compared to those from other tribes. In contrast, members of the Ijaw tribe showed a less pronounced risk reduction (RR = 0.7470). The potential reasons behind these tribal differences could be multifactorial, involving both genetic and environmental components. Ethnic groups often have distinct genetic backgrounds, which may influence the prevalence of particular gene variants related to T2D. Moreover, lifestyle factors such as diet, physical activity, and cultural practices that differ between tribes may also play a role in modulating the expression of diabetes-related genes like CDKN/2A (Iqbal, 2023, Dietrich et al.,2019) [16,17]. For instance, variations in traditional diets or differences in healthcare access could contribute to these tribal disparities. While the study does not provide direct evidence for the mechanisms underlying these tribal differences, the results align with previous research showing that ethnicity and genetic background are significant determinants of T2D risk. The findings highlight the need for tailored public health interventions that take tribal or ethnic differences into account. Specifically, tribes with a higher relative risk of CDKN/2A expression could benefit from targeted genetic screening programs and lifestyle interventions that address the unique challenges faced by these populations.

A significant association between sex and CDKN/2A gene expression was observed, with males showing a notably higher relative risk (RR = 1.4810, p = 0.0011) compared to females (RR = 1.2460, p = 0.0689). This suggests that male T2D patients are more likely to express the CDKN/2A gene than females, placing them at a greater genetic risk for the disease. The biological differences between men and women, particularly regarding hormone regulation and fat distribution, may explain the higher risk observed in men. For instance, men are more likely to accumulate visceral fat, which is strongly associated with insulin resistance, a key factor in T2D development (Ciarambino et al., 2023) [18]. Moreover, sex hormones like testosterone in men and estrogen in women may differentially influence glucose metabolism and the inflammatory processes that contribute to the expression of genes like CDKN/2A. Testosterone, for example, has been linked to a higher risk of T2D in men due to its role in promoting abdominal fat accumulation and insulin resistance (Cheung et al., 2015) [19]. The higher odds ratio (OR = 2.5820) and likelihood ratio (LR = 1.7240) in men further underscore the greater genetic susceptibility of males to CDKN/2A gene expression. This finding suggests that male T2D patients may require more intensive monitoring and intervention to mitigate the impact of their genetic predisposition. Public health strategies should consider these sex-based differences when designing prevention and treatment programs for T2D, ensuring that men are adequately targeted for interventions that address both genetic and lifestyle risk factors.

Age was another critical demographic factor associated with CDKN/2A gene expression. The study revealed significant associations across various age groups, with the most striking findings observed in the younger and older ends of the age spectrum. Individuals in this age group had the lowest relative risk of CDKN/2A gene expression (RR = 0.1396, $p < 0.0001$), suggesting that younger adults are less likely to express this gene. This may reflect the typically lower overall incidence of T2D in younger populations, as age is a well-known risk factor for the disease. Younger individuals may have fewer comorbidities and healthier lifestyle habits, such as better physical activity levels, which could protect against both T2D and its associated genetic risk factors (Lascar et al., 2017, Kovács et al., 2024) [20,21]. In contrast, individuals in the 75–84-year age group showed the highest relative risk of CDKN/2A expression (RR = 0.04893, $p < 0.0001$), indicating that older adults are at significantly increased risk. This finding aligns with the broader understanding that age is a major risk factor for T2D, as the body's ability to regulate glucose metabolism declines with age. Aging is associated with reduced beta-cell function, increased insulin resistance, and chronic inflammation, all of which contribute to the onset and progression of T2D (Zhu et al., 2021) [22]. The results for these middle-aged groups indicate a moderate risk of CDKN/2A gene expression, with relative risks of 0.3046 and 0.7967, respectively. As individuals transition into middle age, they tend to accumulate more risk factors for T2D, including weight gain, decreased physical activity, and the onset of other health conditions such as hypertension and cardiovascular disease. These factors likely contribute to the increased risk of CDKN/2A gene expression in these age groups.

The findings related to age suggest that the expression of CDKN/2A is not static but evolves across the lifespan, with younger adults being more protected and older adults being more susceptible. These results point to the need for age-specific interventions in the prevention and management of T2D. For younger populations, efforts should focus on maintaining healthy lifestyle habits that can delay or prevent the onset of CDKN/2A gene expression and, by extension, T2D. In older adults, more aggressive interventions may be necessary to manage both the genetic and lifestyle factors that contribute to T2D, particularly given the heightened risk in this age group

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As seen in the result Younger Age Groups (e.g., 35–44 years, $p < 0.0001$) were significantly different implying that younger individuals expressing the CDKN/2A gene show a higher risk of T2D, indicating that the disease may manifest earlier in life in these individuals. Some of the reasons may be the early onset of T2D in younger individuals which could be due to stronger genetic expression of the CDKN/2A gene, leading to earlier disruption in glucose metabolism or it could be that younger individuals may have a higher metabolic rate, which can exacerbate the effects of insulin resistance, leading to earlier T2D onset and it could also be a lifestyle factor whereby younger adults might engage in riskier lifestyle behaviors (e.g., poor diet, lack of exercise) that, combined with genetic predisposition, accelerate the onset of T2D. Research by Dabelea et al. (2021) [23] shows an increasing incidence of T2D among younger adults, particularly those with a strong genetic predisposition while some studies argue that environmental factors play a more significant role in younger populations, with genetics being a secondary factor (Vandeweijer et al., 2022) [24]. In the older age groups (e.g., 75-84 years, RR = 0.04893, $p < 0.0001$), Older individuals have a significantly lower risk of developing T2D, suggesting that age-related factors may provide some protective effects, or that the most at-risk individuals have already developed the disease earlier in life. Older adults who have not developed T2D may represent a population with protective genetic traits or lifestyles that have prevented the disease, indicating a form of survivor bias, aging is associated with changes in hormone levels, such as decreased growth hormone and sex hormones, which might reduce the risk of T2D by slowing metabolic processes and with aging, the body's ability to process glucose changes, and those who maintain normoglycemia into older age may have inherently better glucose regulation mechanisms. Studies have shown that while the incidence of T2D is higher in middle-aged groups, the prevalence can decrease in older age groups due to survivor effects (Akushevich et al., 2018) [25-28]. Disagreeing studies (Bradly and Hsueh, 2018) suggest that T2D risk continues to increase with age due to cumulative exposure to risk factors, challenging the notion of a protective effect in older age. These findings indicate that age plays a crucial role in the manifestation and risk of T2D among individuals with the CDKN/2A gene, with younger individuals at higher risk due to potential early onset and genetic factors, while older individuals may exhibit reduced risk due to survivor bias and age-related physiological changes.

Conclusion

Compelling evidence has shown that there are several notable relationships and differences among various factors in Type 2 diabetic subjects, particularly concerning CDKN2A gene predisposition, dietary habits, lifestyle choices, and demographic factors. Complex interactions influenced by dietary, lifestyle, and genetic factors are shown by the analysis of relationships among biomarkers in CDKN2A gene predisposed Type 2 diabetic patients. It is imperative to adopt individualized dietary plans and lifestyle interventions tailored to the specific needs and genetic predispositions of Type 2 diabetic patients should be considered by healthcare professionals especially, those with CDKN2A gene predisposition.

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