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Association between the *TP53* Arg72Pro (rs1042522) Polymorphism and Type 2 Diabetes Mellitus: Implications for Molecular Imaging Biomarkers

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion. Genetic factors, including variations in the *TP53* gene, may influence metabolic pathways linked to disease progression. The p53 protein regulates apoptosis, DNA repair, and cellular metabolism, suggesting potential relevance as a molecular biomarker in imaging-based disease assessment. A hospital-based preliminary cross-sectional study was conducted from June to August 2024 among participants recruited at Ruhengeri Level Two Teaching Hospital and Rwamagana Level Two Teaching Hospital, Rwanda, while molecular analyses were performed at the Molecular Biology Laboratory of INES-Ruhengeri. Type 2 diabetes mellitus (T2DM) cases were defined according to standard diagnostic criteria, including fasting plasma glucose ≥ 126 mg/dL, glycated hemoglobin (HbA1c) ≥ 6.5%, or current use of antidiabetic medication. Non-diabetic controls were individuals without a history of diabetes and with normal fasting blood glucose or HbA1c values where available. The study included 21 participants (12 T2DM cases and 9 controls). Genomic DNA was extracted from peripheral blood samples. Genotyping of the *TP53* Arg72Pro polymorphism (rs1042522) was performed using allele-specific polymerase chain reaction (PCR). Fisher's exact test and odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate associations. T2DM prevalence was higher among females (57.14%) than males (42.86%). The Proline (CCC) allele predominated in both T2DM patients (62.5%) and controls (72.22%), while the Arginine (CGC) allele was less frequent. The heterozygous Arg/Pro genotype was more frequent among T2DM cases (75.0%) than controls (55.6%), although no statistically significant association was identified ($p > 0.05$). Hardy-Weinberg equilibrium analysis showed no deviation among controls. This preliminary pilot study found no significant association between *TP53* Arg72Pro polymorphism and T2DM susceptibility in the studied population. However, its known role in metabolic regulation highlights potential relevance for molecular imaging biomarkers targeting p53-mediated pathways. Further large-scale studies integrating genetic profiling with molecular imaging techniques are warranted.

Keywords

Type 2 Diabetes Mellitus, *TP53* Gene, Arg72 Pro Polymorphism, Molecular Imaging Biomarkers, Insulin Resistance, Genetic Association, PCR Genotyping

1. Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by chronic hyperglycemia, resulting from insulin resistance and impaired insulin secretion. The condition is associated with reduced life expectancy due to an increased risk of complications such as cardiovascular disease, stroke, peripheral neuropathy, renal impairment, blindness, and limb amputation. Globally, T2DM has reached pandemic proportions, affecting an estimated 463 million individuals in 2019, with projections indicating a continued rise driven by rapid urbanization, sedentary lifestyles, and dietary transitions. Key predictors of disease onset and progression include elevated fasting plasma glucose, impaired glucose tolerance, obesity, and reduced insulin sensitivity [1].

Although Africa has historically borne a greater burden of infectious diseases, the continent is currently experiencing a significant increase in the prevalence of T2DM. According to the International Diabetes Federation, approximately 24 million adults aged 20 - 79 years in Africa are living with diabetes, corresponding to a regional prevalence of 4.5%. Notably, over half (54%) of these cases remain undiagnosed, highlighting substantial gaps in early detection and management. In East Africa, rapid urbanization and lifestyle changes have further contributed to the rising burden of T2DM, posing major public health challenges. The tumor suppressor gene *TP53*, commonly referred to as p53, is widely recognized as the "guardian of the genome" due to its critical role in maintaining genomic stability. The codon 72 polymorphism (Arg72Pro) of the *TP53* gene has been extensively studied, particularly in the context of cancer biology. The p53 protein regulates essential cellular processes, including cell cycle arrest, DNA repair, and apoptosis.

Alterations in the *TP53* gene—such as point mutations, deletions, or epigenetic modifications—can lead to loss of tumor suppressor function and, in some cases, gain of oncogenic properties that promote cell survival and proliferation [2] (**Figure 1**).

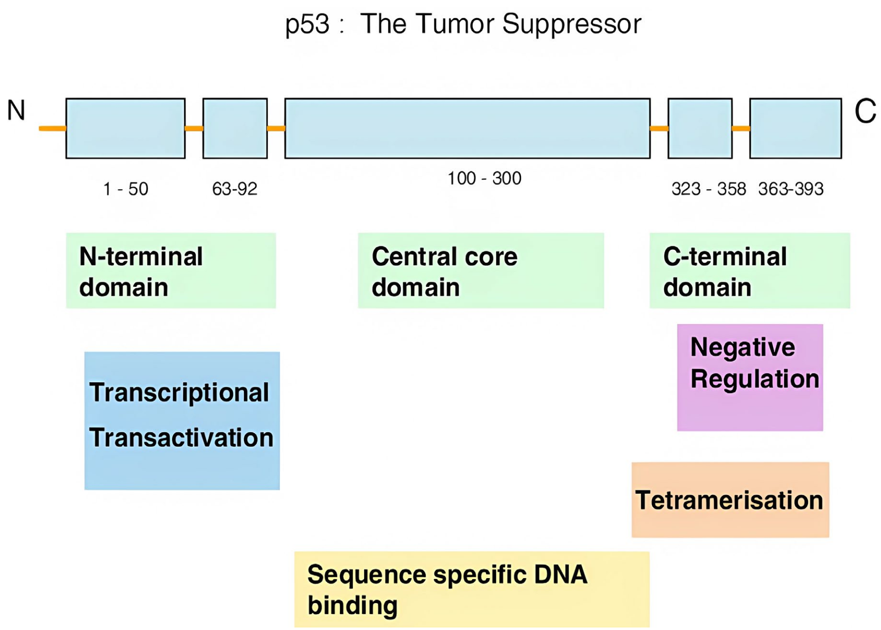

Figure 1. Structure and function of the p53 [2].

Beyond its established role in cancer, p53 has emerged as a key regulator in a wide range of physiological processes, including aging, immune response, development, reproduction, and neurodegeneration [2]. More recently, increasing attention has been directed toward the role of p53 in metabolic regulation. Evidence suggests that p53 influences glucose metabolism and insulin sensitivity, thereby contributing to the development of metabolic disorders. Notably, experimental studies have demonstrated that p53 mediates diet-induced insulin resistance in transgenic mice, providing early evidence for a mechanistic link between p53 activity and T2DM pathogenesis [3].

Given its involvement in both metabolic regulation and cellular stress responses, the *TP53* gene represents a potential target for molecular imaging approaches aimed at characterizing metabolic dysfunction and disease progression in T2DM. Understanding the relationship between *TP53* polymorphisms, such as Arg72Pro, and T2DM may provide valuable insights into novel imaging biomarkers and personalized diagnostic strategies [4].

2. Materials and Methods

2.1. Study Area

This study was conducted at Rwamagana Level Two Teaching Hospital and Ruhengeri Level Two Teaching Hospital, located in Rwamagana and Musanze

Districts, respectively. Molecular analysis was performed in the Molecular Biology Laboratory of INES-Ruhengeri, located in Musanze District, Rwanda.

2.2. Study Design and Study Period

A hospital-based cross-sectional study was conducted from June to August 2024 to determine the susceptibility of the *p53* gene among patients diagnosed with Type 2 Diabetes Mellitus (T2DM) attending Rwamagana and Ruhengeri Level Two Teaching Hospitals.

2.3. Study Population

The study population consisted of male and female participants recruited from Ruhengeri Level Two Teaching Hospital and Rwamagana Level Two Teaching Hospital. The case group included patients aged 40 years and above previously diagnosed with Type 2 Diabetes Mellitus according to standard diagnostic criteria, including fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or current use of antidiabetic medication. The control group consisted of apparently healthy non-diabetic individuals without a known history of diabetes mellitus and with normal fasting blood glucose or HbA1c values where available.

2.4. Sample Size

A total of 21 participants were enrolled in this preliminary pilot study, comprising 12 T2DM patients and 9 non-diabetic controls. The sample size was determined based on participant availability and feasibility within the study period. Because of the limited sample size, the study was designed primarily as an exploratory investigation to assess the potential association between *TP53* Arg72Pro polymorphism and T2DM susceptibility.

2.5. Eligibility Criteria

2.5.1. Inclusion Criteria

Participants included:

- Patients aged 40 years and above diagnosed with Type 2 Diabetes Mellitus;
- Non-diabetic individuals of any age serving as controls;
- Participants who voluntarily consented to participate.

2.5.2. Exclusion Criteria

Patients presenting with metabolic disorders other than diabetes mellitus were excluded from the study.

2.6. Ethical Considerations

Ethical approval was obtained from the ethical review committees of INES-Ruhengeri, Ruhengeri Level Two Teaching Hospital, and Rwamagana Level Two Teaching Hospital. Written informed consent was obtained from all participants prior to sample collection. Confidentiality and privacy of participant information were maintained throughout the study.

2.7. Sample Collection and Transportation

Venous blood samples were collected aseptically into EDTA tubes from all participants. Demographic and clinical information, including age, sex, and glycated hemoglobin (HbA1c), were recorded. Samples were stored at −20˚C to −80˚C until the required sample size was achieved. Thereafter, specimens were transported under cold-chain conditions using insulated containers with ice packs to the Molecular Biology Laboratory at INES-Ruhengeri for analysis.

2.8. Laboratory Analysis

2.8.1. DNA Extraction

Genomic DNA was extracted from whole blood samples using the QIAamp DNA Mini Kit according to the manufacturer's protocol. Briefly, 20 µL of QIAGEN protease was added to a 1.5 mL microcentrifuge tube containing 200 µL of whole blood, followed by the addition of 200 µL of Buffer AL. The mixture was vortexed thoroughly and incubated at 56˚C for 10 minutes. Subsequently, 200 µL of ethanol (96% - 100%) was added, mixed thoroughly, and transferred into a QIAamp Mini spin column. Sequential washing steps were performed using 500 µL of Buffer AW1 and 500 µL of Buffer AW2, followed by centrifugation at 8000 rpm and 14,000 rpm, respectively. DNA was finally eluted using 200 µL of Buffer AE and stored at −20˚C until amplification.

2.8.2. Polymerase Chain Reaction (PCR)

Quality-control measures were implemented throughout the genotyping procedure. Positive and negative PCR controls were included in each amplification run to monitor amplification performance and contamination. Genotypes were assigned according to the presence of allele-specific bands visualized during agarose gel electrophoresis. Samples with unclear band patterns were repeated independently to confirm genotype accuracy and reproducibility.

1) Preparation of PCR Master Mix

Allele-specific PCR was performed to detect *p53* codon 72 polymorphism (Arginine/Proline). Two separate reaction mixtures were prepared for each sample targeting the Proline and Arginine alleles.

Each 20 µL reaction mixture contained:

- 12 µL nuclease-free water
- 5 µL All Taq buffer
- 0.5 µL forward primer
- 0.5 µL reverse primer
- 2 µL template DNA

Primer sequences used were:

Proline allele:

- Forward: 5' GCCAGAGGCTGCTCCCCC 3'
- Reverse: 5' CGTGCAAGTCACAGACTT 3'

Arginine allele:

- Forward: 5' TCCCCCTTGCCGTCCCAA 3'

- Reverse: 5’ CTGGTGCAGGGGCCACGC 3’

2) PCR Amplification Conditions

Amplification was performed using an allele-specific thermal cycler under the following conditions:

- Initial denaturation: 95˚C for 10 minutes
- 40 cycles of:
  - Denaturation: 95˚C for 30 seconds
  - Annealing: 60˚C for 30 seconds
  - Extension: 72˚C for 30 seconds
- Final extension: 72˚C for 7 minutes
- Hold: 4˚C for 15 minutes

The total PCR run time was approximately 1 hour and 50 minutes.

2.8.3. Agarose Gel Electrophoresis

PCR amplicons were analyzed by agarose gel electrophoresis. A 2% agarose gel was prepared by dissolving 2 g agarose powder in 100 mL of 1× Tris-Acetate-EDTA (TAE) buffer, followed by heating and addition of ethidium bromide for nucleic acid staining.

Approximately 7 μL of PCR product was mixed with 1 μL loading dye and loaded into gel wells alongside a 6 μL DNA ladder. Electrophoresis was performed at 400 V for 20 minutes. DNA bands were visualized under ultraviolet illumination using a gel documentation system.

Expected fragment sizes were:

- Proline allele: 177 kb177\kb177 kb
- Arginine allele: 141 kb141\kb141 kb

Band patterns were interpreted to determine the *p53* genotype of each participant.

2.9. Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics. Descriptive statistics were used to summarize demographic and clinical characteristics separately for T2DM cases and controls. Given the small sample size and low expected cell frequencies, associations between the *TP53* Arg72Pro (rs1042522) polymorphism and T2DM were assessed using the chi-square test or Fisher’s exact test, as appropriate. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were computed to estimate the strength of associations. Hardy-Weinberg equilibrium (HWE) analysis was performed in the control group to evaluate the consistency of genotype distribution. Statistical significance was set at $p < 0.05$.

3. Results and Discussion

3.1. Demographic Characteristics of Study Participants

A total of 21 participants were enrolled in this study, including 12 patients diagnosed with Type 2 Diabetes Mellitus (T2DM) and 9 non-diabetic controls. The demographic characteristics of study participants are summarized in **Table 1**.

Table 1. Demographic characteristics of study participants.

GENDER	Frequency (%)
Male	9 (42.9)
Female	12 (57.14)
Age group	**Frequency (%)**
15 - 30	5 (23.8)
31 - 45	7 (33.33)
46 - 60	5 (23.8)
>60	4 (19.04)
TOTAL	21 (100)

The demographic characteristics of study participants were analyzed separately for T2DM cases and controls. Among T2DM patients, females were more represented than males, whereas the control group demonstrated a relatively balanced sex distribution. The mean age of T2DM participants was higher than that of controls because eligibility criteria restricted diabetic participants to individuals aged 40 years and above.

Females represented the majority of participants (57.1%), while males accounted for 42.9%. This female predominance may be attributed to hormonal factors, obesity prevalence, and metabolic susceptibility previously reported among women with T2DM However, this finding differs from that reported by the researcher, who observed a higher prevalence of T2DM among males [5].

Age distribution demonstrated that the 31 - 45 years age group was the most represented (33.3%), suggesting increased susceptibility during middle adulthood, likely due to lifestyle-related risk factors including dietary habits, stress, and reduced physical activity. Participants aged > 60 years represented the smallest proportion (19.0%), which may reflect reduced survival or under diagnosis among older individuals. Similar age-related trends have been reported in Rwanda [5].

3.2. Distribution of *TP53* Codon 72 Genotypes among Study Participants

3.2.1. Gel Electrophoresis Findings

Allele-specific PCR followed by agarose gel electrophoresis successfully identified *TP53* codon 72 polymorphisms among study participants. The amplified fragments corresponded to expected molecular sizes:

- Proline allele: 177 bp177\bp177 bp
- Arginine allele: 141 bp141\bp141 bp

These findings confirmed successful amplification and differentiation of both alleles (**Figure 2**).

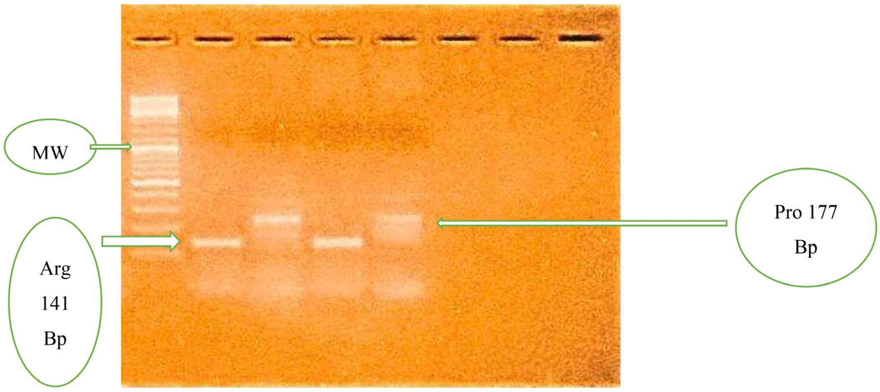

Figure 2. Representative agarose gel electrophoresis showing *TP53* codon 72 polymorphism bands.

3.2.2. Genotype Distribution

The genotype distribution of *TP53* codon 72 among T2DM patients and controls is presented in **Table 2**.

Table 2. Frequency distribution of *TP53* Codon 72 genotypes in the study population.

Group	Genotype	Frequency (%)
T2DM (n = 12)	Homozygous Proline (CCC/CCC)	3 (25.0)
	Heterozygous (CCC/CGC)	9 (75.0)
Controls (n = 9)	Homozygous Proline (CCC/CCC)	4 (44.4)
	Heterozygous (CCC/CGC)	5 (55.6)

Among T2DM patients, the heterozygous genotype (CCC/CGC) was predominant (75%), compared to 55.6% among controls. The homozygous Proline genotype (CCC/CCC) was more frequent in controls (44.4%) than in T2DM patients (25.0%). No homozygous Arginine genotype (CGC/CGC) was detected in either group.

The predominance of the heterozygous genotype among diabetic patients suggests a possible contribution of *TP53* polymorphism to T2DM susceptibility. Similar findings were reported by [6] who observed increased frequency of Arg72 carriers among diabetic patients. The absence of the homozygous Arginine genotype may reflect population-specific genetic distribution or the limited sample size.

3.3. Allelic Frequency Distribution

Allelic distribution of *TP53* codon 72 among T2DM patients and controls is shown in **Table 3**.

Table 3. Allelic frequency distribution of *TP53* codon 72.

Group	Proline (CCC), n (%)	Arginine (CGC), n (%)	p-value
T2DM	15 (62.5)	9 (37.5)	0.092
Controls	13 (72.2)	5 (27.8)	

The Proline (CCC) allele was the most frequent allele in both T2DM patients and controls. Although the Arginine allele was relatively more common in T2DM patients, the difference was not statistically significant (p = 0.092).

These findings suggest that while the Proline allele may be predominant in the studied population, its association with T2DM susceptibility remains inconclusive. Similar non-significant associations have been reported by [7], indicating that *TP53* polymorphism may contribute only modestly to diabetes risk.

3.4. Association between *TP53* Codon 72 Polymorphism and Type 2 Diabetes Mellitus

The association between *TP53* codon 72 genotypes and T2DM status was evaluated using chi-square analysis and Fisher's exact test, where possible, as shown in **Table 4**.

Table 4. Association between *TP53* codon 72 genotype and T2DM.

Genotype	T2DM (n)	Controls (n)	χ^2	df	p-value
Heterozygous (CCC/CGC)	9	5	0.875	1	0.350
Homozygous Proline (CCC/CCC)	3	4			

The heterozygous Arg/Pro genotype was more frequent among T2DM patients compared with controls; however, no statistically significant association was observed ($p > 0.05$). Odds ratio analysis where required, demonstrated a non-significant increase in T2DM susceptibility among heterozygous carriers, with wide confidence intervals reflecting the limited sample size. Hardy-Weinberg equilibrium analysis of the control group showed no significant deviation, suggesting acceptable genotype distribution within the studied population. The absence of statistical significance may be attributed to the small sample size and limited statistical power of this preliminary pilot investigation.

Additionally, the relatively similar genotype distribution between cases and controls suggests that *TP53* codon 72 polymorphism alone may not be a strong independent predictor of T2DM risk. These findings agree with previous studies by Punja *et al.* (2021) and Speliotes *et al.* (2010), both of which reported no significant relationship between *TP53* codon 72 polymorphism and T2DM susceptibility. However, larger multicenter studies are needed to validate these findings.

4. Conclusion

This preliminary pilot study evaluated the distribution of *TP53* Arg72Pro (rs1042522) polymorphism among patients with Type 2 Diabetes Mellitus and non-diabetic controls in selected areas of Rwanda. Although the heterozygous Arg/Pro genotype appeared more frequent among T2DM patients, no statistically significant association was identified between *TP53* Arg72Pro polymorphism and T2DM susceptibility. Due to the limited sample size and exploratory nature of the study, the findings should be interpreted cautiously. Larger multicenter studies integrating advanced molecular and statistical approaches are required to further clarify the potential contribution of *TP53* polymorphisms to T2DM pathogenesis and molecular biomarker development.

Acknowledgements

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Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

The research was conducted with the support and contributions of staff from INES-Ruhengeri and the University of Rwanda.

Funding Statement

This study did not receive any external funding.

Conflicts of Interest

The author declares that there is no conflict of interest.

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