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INCIDENCE OF MATURITY ONSET DIABETES OF THE YOUNG (MODY) AMONG THE SELECTED YOUNG ADULTS

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ABSTRACT

This study investigated the incidence of maturity onset diabetes of the young (MODY) among young adults aged 18-35 years in Thoothukudi City, Tamil Nadu in the year 2021. Data was collected with the help of a well-structured interview schedule among 506 young adult participants. Four of the 506 participants, who met the MODY parameters (BMI below 30, two to three generations with diabetes, age below 35) were proceeded with additional genetic testing. Among the four, two were reported to have genetic mutations. One of the participants had a type 2 diabetes gene variation (AKT2 gene) and another had a MODY gene variation (KLF11 gene). Both Participants had a strong paternal side family history with diabetes and parents with diabetes. It indicates that having a strong family history of diabetes increases the likelihood that MODY and other kinds of diabetes will develop through heredity by some percent chance. The overall significance of this study is that it highlights the importance of early and accurate diagnosis for better treatment and management of this type of diabetes and also contributes to the spreading of knowledge on MODY.

Keywords – Diabetes,Gene Variation, Identification, Maturity Onset Diabetes of the Young (MODY).

INTRODUCTION

Genetical mutations can induce a monogenic type of diabetes called Maturity Onset Diabetes of the Young, affecting people below the age of 35 years with the 14 different subtypes of MODY such as: “MODY 1 (Hepatocyte Nuclear Factor 4 Alpha or HNF4A), MODY 2 (Glucokinase or GCK), MODY 3 (Hepatocyte Nuclear Factor 1 Alpha or HNF1A), MODY 4 (Pancreatic and Duodenal homeobox 1 or PDX1) , MODY 5 (Hepatocyte Nuclear Factor 1 Beta or HNF1B), MODY 6 (Neuronal Differentiation 1 or NEUROD1), MODY 7 (Kruppel-like factor KLF11), MODY 8 (Carboxyl Ester Lipase or CEL), MODY 9 (Paired box gene 4 or PAX4), MODY 10 (Insulin gene or INS), MODY 11 (B Lymphocyte Kinase or BLK), MODY 12 (ATP Binding Cassette subfamily C member 8 or ABCC8), MODY 13 (KCNJ11), MODY 14 (APPL1) (Naylor *et al.,* 2018)”. Among the 14 subtypes, three genetic variations (Hepatic Nuclear Factor 1 Alpha, Hepatic Nuclear Factor 4 Alpha and Glucokinase) cause MODY in 95 % of all cases

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(Delvecchio *et al.,* 2020). Delvecchio *et al.,* (2020) also points out, "misdiagnosis of MODY with type 1 and type 2 diabetes can result in suboptimal glycemic control and unnecessary use of insulin or oral hypoglycemic agents." This misdiagnosis from the lack of awareness of clinical and genetic features of MODY from other diabetes types leads to inappropriate treatment. Because of this many misdiagnosis of MODY among young adults and the delaying the use of specific medications. Therefore, timely detection and raising awareness of MODY to avoid misdiagnosis is important for appropriate treatment and understanding of the disease. According to Urakami, (2019), "MODY runs in the strong family history of diabetes, insulin independence, absence of autoantibodies, lack of ketoacidosis, normal BMI and persistent mild fasting hyperglycemia. After a clinical diagnosis, next-generation sequencing is required to confirm the cases of MODY ". However, the effective diagnostic method for detecting MODY has yet to be researched and there is a need for more accurate and effective diagnostic strategies.

The study aimed to discover the incidence of MODY cases among young adults in Thoothukudi City, India. The overlapping symptoms of MODY often lead to misdiagnosis with both type 1 and type 2 diabetes. This study helps in knowing the role of heredity in the onset of diabetes and contributes to the improvisation of accurate management and treatment of the rare form of diabetes in the later years. Understanding the incidence of MODY in this young adult population can inform healthcare professionals about the importance of considering MODY in the differential diagnosis of young-onset diabetes.

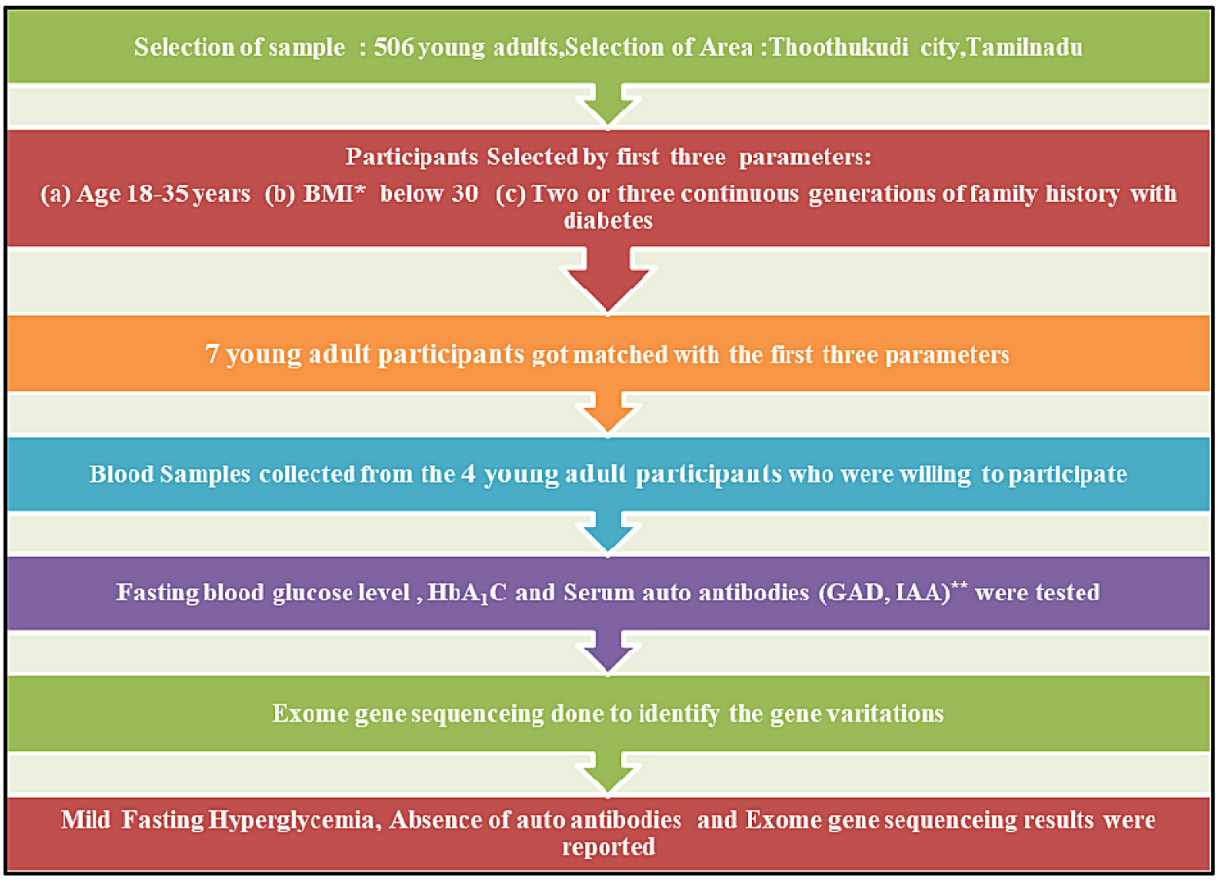
MATERIAL AND METHODS

Research Area and Sample Selection

The cross-sectional study aimed to find the incidence of Maturity Onset Diabetes of the Young (MODY) among young adults in Thoothukudi City, Tamil Nadu, India in April to July 2021. The individuals at risk for Maturity Onset Diabetes of the Young (MODY) were selected using a convenience non-random sampling method. The sample size was calculated using Yamane's sample size calculation method. According to census of Thoothukudi City conducted in 2011, the city's population was 2,37,830. Taking this population size into consideration and applying the formula of Yamane [Sample Size (n)=N/(1+N*(e^2))], the sample size of the study was 384. The sample size was expanded to include total of 500 participants to increase statistical power and to ensure the enough cases of MODY were captured for meaningful analysis. This would increase the generalizability and credibility of the findings of the study. The study focuses on to find the maturity onset diabetes of the young participants. Kant *et al.,* (2022) says, "children, adolescents and young adults who were not obese commonly developed maturity-onset diabetes of the young. And among them, young adults were the group affected more". Therefore, young adults between the ages of 18 and 35 years made up the target group.

Analysing the Data

Data were gathered with a help of well structure interview schedule which elicits information such as background information, anthropometry and clinical information. Socio-demographic information includes gender, marital status, educational status, income, etc. The four factors that comprise anthropometry were height, weight, waist to hip ratio (WHR) and body mass index (BMI). Clinical information includes biochemical parameters and family history with diabetes. Anthropometry and clinical data were performed to determine the patients who were at risk for maturity onset diabetes of the young.



**BMI (Body Mass Index),*

***Auto antibodies (IAA-Insulin Antibodies, GAD-Glutamic Acid Decarboxylase)*

Figure 1. Procedure adopted for the selection of participants for High-Risk Maturity Onset Diabetes of the Young

Young adults between 18 and 35 years, Body Mass Index less than 30, two or three continuous generations with diabetes, mild fasting persistent hyper glycemia and absence of autoantibodies (Kant *et al.,* 2022) were the parameters taken into account while identifying maturity onset diabetes of the young. As this study was carried out in the general population, the study consists of a mixed population (participants may or may not have clinical data). The first three parameters, young adults in the age group of 18-35 years, Body Mass Index - less than 30 (Kant *et al.,* 2022), two or three continuous generations with diabetes were considered to filter the data (Figure 1).

Collection of Blood Sample

Blood samples were drawn from the selectedparticipants with the help of a professional lab technician early in the morning on an empty stomach. Fasting blood glucose level, HbA_1C and Serum autoantibodies (GAD, IAA) were the tests to be run. A total of 15 ml of blood was drawn for the test. The collected blood specimen was stored in blood vials and taken to run the test by the lab technician. To meet the maturity onset diabetes of the young, parameters such as fasting blood glucose level, HbA_1C and serum autoantibodies (GAD, IAA) were measured. The participants' genes were also examined using the next-generation

Table 1- Testing Procedures and Normal Values of Blood Parameters

S.No	Blood Parameters	Testing Procedure	Normal Values
1	Fasting Blood glucose level	Glucose Oxidase and Peroxidase test (GOD-POD)	70 to 100 mg/dl
2	Serum HbA_1C (Glycosylated Hemoglobin)	High-Performance Liquid Chromatography test (HPLC)	4 to 5.7.0%
3	Serum GAD-65 (Glutamic Acid Decarboxylase-65)	Enzyme Immuno Assay (EIA)	<10 IU/ml
4	Serum Insulin AutoAntibodies	Enzyme Immuno Assay (EIA)	<12 U/ml
5	Next Generation Maturity Onset Diabetes of the Young (MODY) sequencing	Exome gene sequencing	Positive or Negative

Reference for normal values-Fasting Blood glucose level and Serum HbA1C (American Diabetes Association, 2022), Serum GAD-65 and Serum Insulin AutoAntibodies(Belhiba *et al.,* 2020)

exome gene sequencing method to look for variations in the MODY or other diabetes genes.

RESULTS AND DISCUSSION

Background Information of the Young Adult Participants

Background information such as gender, family type, marital status, educational status and family income was given in Table 2.

Among the 506 selected participants, 55.7% were female participants and 44.3% were male participants. The majority of participants (99.6%) belonged to nuclear families, with a small percentage (0.4 %) from joint families. This aligns with the study by Jamila *et al.,* (2017), where the participants from urban areas were influenced by nuclear families. Most participants were married (78.9%), while 21.1 % were unmarried. A study by Singh *et al.,* (2023) also found out that there was a high proportion of marriage was increasing between the age of 18-35 years. Regarding educational status, 49.1 % had attended only school, followed by 29.4% undergraduates, 12.4 % uneducated, 7.5 % postgraduates and 1.4 % with higher education. The educational status of the participants in this study aligns with Negi and Nambiar (2021) regarding the educational distribution among breast cancer patients. In terms of income, 75.3 % of participants were from families earning more than Rs.10,000 per month, while 24.5 % were from families earning between Rs.5,000 and Rs.10,000. This income level distribution correlates with the study of Sarkar and Samanta (2023).

Mean of Anthropometric Measurements of the Young Adult Participants

Body Mass Index was calculated using anthropometric data (height in centimetres and weight in kilograms). The Waist to Hip Ratio of the young adult participants was calculated using both the waist circumference in inches and the hip circumference in inches. The mean of these anthropometric measurements was

Table 2. Background information of the Young Adult Participants

S.No	Background information		Frequency (n=506)	Percent
1	Gender	Male	224	44.3
		Female	282	55.7
2	Family Type	Nuclear	504	99.6
		Joint	2	0.4
3	Marital Status	Bachelor/Spinster	107	21.1
		Married	399	78.9
4	Educational Status	Uneducated	63	12.4
		School	249	49.1
		Undergraduate	149	29.4
		Postgraduate	38	7.5
		Higher Education	7	1.4
5	Income Status	Less than Rs.5,000	Nil	Nil
		Rs. 5,000-Rs.10,000	124	24.5
		More than Rs.10,000	382	75.3

Table 3- Mean of Anthropometric Measurements of the Young Adult Participants

Anthropometric Measurements	Mean of Anthropometric Measurements of the Young Adult Participants(n=506)			
	Male (n=224)	Ideal Anthropometric Measurements of Male	Female (n=282)	Ideal Anthropometric Measurements of Female
Height(cm)169±7	172.5 [a]	159±7	157 [a]	
Weight (Kg)67.92±11.9	65 [b]	60.82±12.1	55 [b]	
Body Mass Index (Kg/m^2)	24.88±3.8	22.9 [a]	24.19±4.5	22.6 [a]
Waist (inches)	33.63±4.0	34.5 [a]	34.05±4.8	33.2 [a]
Hip (inches)36.37±5.1	36.6 [a]	37.59±4.5	38.9 [a]	
Waist to Hip Ratio	0.93±0.7	0.94 [a]	0.91±0.7	0.85 [a]

Reference of Ideal Anthropometric Measurement values- a-(National Institute of Nutrition (NIN), 2020); b- (International Institute for Population Sciences (IIPS) and Macro International, 2017)

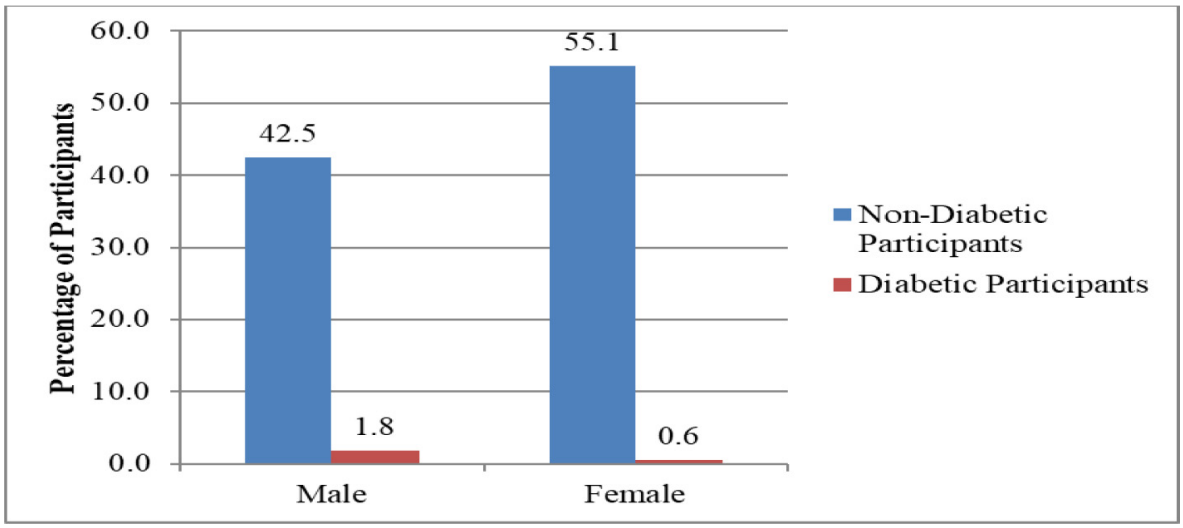


Figure 2- Incidence of Diabetes among the Selected Young Adult Participants

compared with the ideal anthropometric measurements of the male and female in India.

The analysis of anthropometric measurements revealed that young adult participants were close to their ideal values. Male participants were slightly shorter (169 cm) and heavier (67.82 kg) than the ideal, with a BMI of 24.88 kg/m^2. Female participants were slightly taller (159 cm) and lighter (60.82 kg) than the ideal, with a BMI of 24.19 kg/m^2. Both genders had healthy BMI (within 18.5-24.9 range) and healthy waist-to-hip ratio (males 0.93, females 0.91). BMI values between 18.5 and 24.9 were considered healthy and WHR values over 1.0 for male participants and over 0.8 for female participants were linked to higher

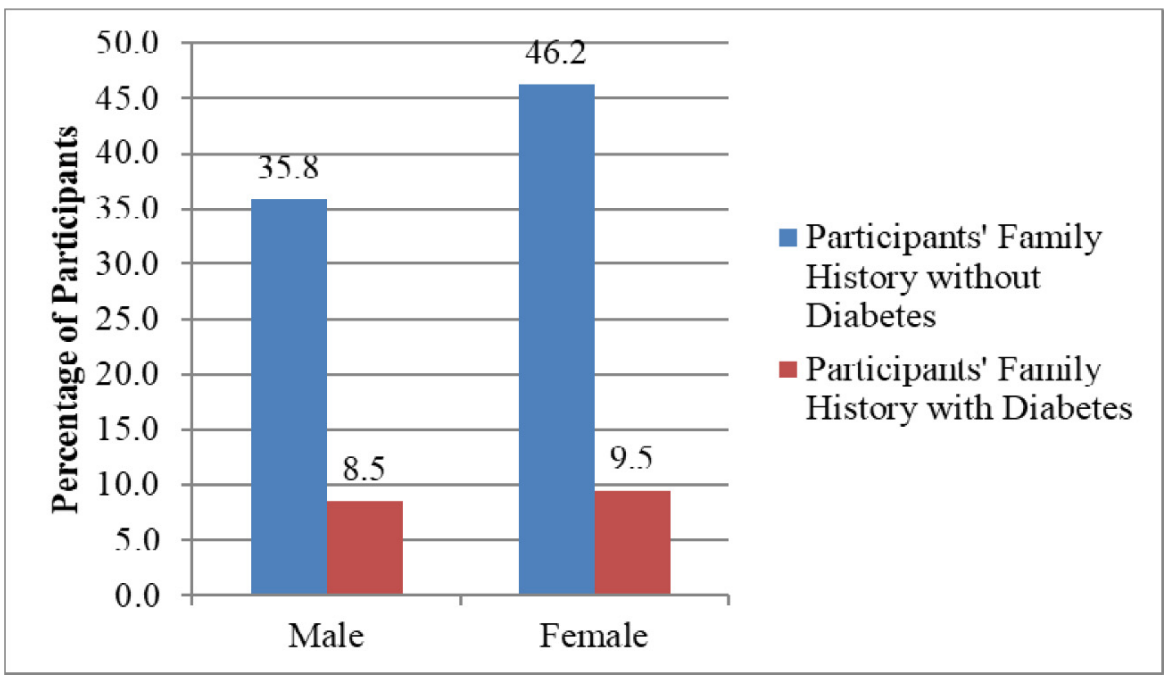


Figure 3 - Percentage of Participant's Family History with Diabetes

health risks so the participants were still within the healthy range but closer to the upper limit.

Incidence of Diabetes among the Selected Young Adult Participants

Diabetes has become alarming in all age groups; Figure 2 shows the diabetes incidence among 18-35 years participants.

The majority of the study participants were not affected by diabetes. There incidence of diabetes was slightly higher in male participants (1.8%) compared to female participants (0.6%). This aligns with the previous studies indicating a lower incidence of diabetes in younger populations (Maiti *et al.,* 2023).

Percentage of Participant's Family History with Diabetes

Family History was the leading cause of diabetes prevalence among people in the world(Abdulaziz Alrashed *et al.,* 2023). The figure illustrates the family history of diabetes among the selected young adult participants.

Almost 82% of the participants had no history of diabetes in the family line. Conversely, only 18% had a history of diabetes in the family line. Interestingly, a slightly higher percent of female participants (9.5%) had diabetes in their family line compared to the male participants (8.5%). The prevalence of family lines of diabetes among females aligns with the study of Moonesinghe *et al.,* (2018).

Body Mass Index and Family History of Diabetes among the selected Young Adults

Table 4 states the number of generations of diabetes prevalence among the young adult participants' families. It also gives information as to whether the generations of diabetes were continuous or not continuous in the family line. Table 4 shows the number of participants who satisfied the two parameters of Maturity Onset Diabetes of the Young (MODY).

The majority of 180 male and 236 female young adult participants had no diabetic family history. About 39 male and 37 female young adult participants had one generation with diabetes who majorly falls under the normal weight category. Two male and four young adult female participants in normal weight, obesity and obesity class II had two generations with diabetes but not in the continuous family line.

Another three male and three female young adult participants in underweight and obesity conditions had two continuous generations with diabetes. Only one female young adult participant under the normal weight category had three continuous generations with diabetes. These seven young adult participants had satisfied the two maturity onset diabetes of the young parameters (Body Mass Index below 30 and two or three continuous generations of diabetes). These cases resonate with the study of Asgarian*et al.,* (2024), which showed a continuous family line of diabetes linked to normal BMI, could indicate a number of specific genetic forms of diabetes such as MODY.

Health Status of the Selected Participants

Blood test results and the background information of the participants who were doubted as risk subjects were given in Table 5.

Blood Glucose Level and Genetic Report Interpretations of Subsample:

The fasting blood glucose levels, HbA_1C, and autoantibodies level testing of the participants shows that Participant 1 and 2 has a history of diabetes in a family that spans two to three generations. Participant 1 (a 34year old, male) with a normal weight (BMI 2.94 kg/

Table 4- Body Mass Index and Family History of Diabetes among the selected Young Adults

Body Mass Index (BMI)	Generations with Diabetes												Total
	No generations with diabetes		First generation		Second generation (Not Continuous)		Second generation (Continuous)		Third generation (Not Continuous)		Third generation (Continuous)		
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
Underweight (Below 18.5)	13	26	0	2	0	0	0	1	0	0	0	0	42
Normal weight (18.5-24.9)	106	114	21	16	2	0	0	0	0	0	0	1	260
Pre obesity (25.0-29.9)	49	70	14	17	0	2	2	3	0	0	0	0	157
Obesity Class I (30.0-34.9)	12	25	2	2	0	0	0	0	0	0	0	0	41
Obesity Class II (35.0-39.9)	1	1	2	0	0	2	0	0	0	0	0	0	6
Total	181	236	39	37	2	4	2	4	0	0	0	1	506

Table 5-Background information and Blood Test Report of the Selected Participants

S.No	Variables		Participant 1	Participant 2	Participant 3	Participant 4
1	Gender		Male	Female	Female	Female
2	Age (years)		34	32	29	21
3	Body Mass Index (BMI) (kg/m^2)		22.84 (Normal weight)	24.46 (Normal weight)	27.64 (Preobesity)	17.63 (Underweight)
4	Diabetic or Non diabetic		Diabetic	Nondiabetic	Nondiabetic	Nondiabetic
5	No.of Generations with Diabetes		Two continuous generations with diabetes (Paternal Grandfather, Paternal Grand Mother, Father, Mother)	Three continuous generations with diabetes (Paternal Grandfather, Paternal Grand Mother, Father, Mother, Brother)	Two continuous generations with diabetes (Paternal Grandfather, Father)	Two continuous generations with diabetes (Paternal Grand Mother, Father)
6	General Random Blood Glucose level (mg/dl)		223	135	100	120
7	Fasting Blood Glucose level (mg/dL)		180.56	107	83.60	96
8	Serum HbA_1C (%)		9.4	5.7	5.0	5.5
9	Estimated Average Glucose		223	117	97	111
10	Serum Glutamic Acid Decarboxylase-65 (IU/ml)		<5.00	<5.00	10.00	<5.00
11	Serum Insulin Auto Antibodies(U/ml)		1.73	1.50	0.53	2.66
12	Exome gene /sequencing	Gene	KLF11	AKT2	Negative	Negative
		Genomic Location	Chr2:10192597	Chr19:40747891		
		Variant	NM_003597.4:c.1502C>T;p.Pro501Leu	NM_001626.6:c.527G>T;p.Arg176Leu		
		Exon	4	6		
		Type of Mutation	Missense	Missense		
		Zygosity	Heterozygous	Heterozygous		

m^2) has mild fasting persistent hyperglycaemia (Fasting blood glucose level- 180.56 mg/dL, HbA_1C-9.4 %). Participant 2 (32year old female) with a normal weight (BMI 24.46 kg/m^2) has slight rise in the blood sugar levels (Fasting blood glucose level- 107 mg/dL, HbA_1C-5.7 %)which might be an alarm for a pre-diabetic condition. The blood glucose levels of pre-diabetic disease [Fasting blood glucose level- 100 to 125 mg/dL (American Diabetes Association, 2022), HbA_1C-5.7% to 6.5% (American Diabetes Association, 2022)] stated by the American Diabetes Association and Indian Council for Medical Research. Participant 3, a 29 years old female with a Body Mass Index of 27.64 kg/m^2 (pre-obesity) and participant 4, a 21 years old female with a Body Mass Index of 17.63 kg/m^2 (underweight) had normal blood sugar levels while comparing it with the normal blood glucose stated by the American Diabetes Association and Indian Council for Medical Research [Fasting blood glucose level- 70 to 100 mg/dL (American Diabetes Association, 2022), HbA_1C- 4% to 5.7% (American Diabetes Association, 2022)]. The auto antibodies (serum GAD and serum insulin autoantibodies) of four participants were reported to be absent.

Exome gene sequencing revealed a missense mutation in participant 1 in the KLF11 gene (Chr2:10192597; p.Pro501Leu), which is linked to type seven maturity onset diabetes of the young. A study by Sun *et al.,* (2021), also reported that KLF11 gene variation was responsible for type seven MODY (Sun *et al.,* 2021). This finding emphasizes the significance of considering MODY in the different diagnoses of early onset diabetes, especially when patients present with a strong family record of diabetes and negative autoantibody test. Participant 1's case emphasizes the potential role of genetic predisposition in MODY development, even in the absence of obesity, a prior misdiagnosis of type 2 diabetes. Participant 2 had a variation in the AKT2 gene (chr19:4074789; p.Arg176 Leu) linked to type 2 diabetes mellitus. This finding suggests the complexity of genetic contributions to diabetes development. While AKT2 gene variation might influence the participant's susceptibility to type 2 diabetes. A study by Liu *et al.,* (2023), also reported that AKT2 gene variation was linked to type 2 diabetes (Liu *et al.,* 2023). A noteworthy observation is the presence of diabetes in both parents of Participant 1 (Mother with IRS1 gene variation in chr2:226797016 linked to type 2 diabetes) and Participant 2. Participant 1 and his mother has variations in chromosome 2. This finding aligns with previous research suggesting an increased risk of diabetes in offspring if both parents are diabetic (Urakami, 2019). However, the exact mechanism of parental diabetes influences offspring risk remains unclear in Participant 2. Participants 3 and 4 didn't show any variations in the gene.

CONCLUSIONS

The findings revealed a low incidence of diabetes (2.4%) among the selected young adult participants, with a slightly higher prevalence in males (1.8%) compared to females (0.6%). Finally, this study clarifies the potential contribution of genetic predisposition in MODY development among young adults in Thoothukudi City situated in Tamil Nadu India. Identifying a MODY gene variation in one participant underscores the importance of considering MODY in the diagnostic method of young onset diabetes, particularly when individuals with a successive generation of family with diabetes and negative autoantibodies. Further research is needed to explore the link between genetic and environmental facts in MODY gene variations in the Indian population. Additional studies in this area will enhance the detection and

management of MODY patients, ultimately resulting in lower mortality rates and more focused interventions.

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