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Genetic Association of TCF7L2 Polymorphisms (rs7901695 and rs7903146) with Type 2 Diabetes Mellitus in East Godavari, Andhra Pradesh, India

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KEYWORDS

Type 2 Diabetes Mellitus, TCF7L2 gene, rs7901695, rs7903146, genetic polymorphisms, East Godavari, Andhra Pradesh, case-control study, genotyping, real-time PCR.

ABSTRACT:

Objectives: This paper aims to compare T2DM and genotype connection in the TCF7L2 gene particularly the two SNP's that are, rs7901695 and rs7903146. The kind of research design used to undertake this study is a comparative analysis between 150 T2DM patients and 150 healthy individuals from the area of East Godavari, Andhra Pradesh, India.

Materials and Methods: A case-control study was done in 150 T2DM patients and 150 ethnically matched normal controls. Integral blood samples and genomic DNA were obtained, respectively, and TCF7L2 polymorphisms were detected by using real-time PCR. Statistical information was processed using the help of SPSS and comparisons were made between the demographic, lifestyle, and genotypic and allelic status of the two groups.

Results: T2DM patients were older, and more obese with a higher BMI value and parity than the control group of women. They also reported a higher rate of hysterectomies, a later age of menarche, and more. There were no other differences between the two groups about other demographic measures and lifestyles. Population genetic stratification and analysis of the allelic distribution of SNPs rs7903146 (OR=0.0075) and rs7901695 (OR= 0.0091) made it possible to establish the relationship between the T allele of the rs7903146 marker and the C allele of the marker rs7901695 with T2DM.

Conclusion; T2DM relates to different factors including age, weight, parity and abortions, age at menarche, menopausal status, and presence of other diseases. SNP analysis revealed that rs7903146, and rs7901695 of the gene TCF7L2 are strongly linked to T2DM.

Introduction:

It is a chronic condition of hyperglycaemia attributed to insufficient production of insulin or lack of utilization of the available insulin. T2DM is then estimated to be the cause of 90-95% of diabetes cases that are being experienced in the world today and mainly occurs in adults. However, an increase in child and adolescent obesity and sedentism play a role in improving the T2DM risk. Complications are also brought about by T2DM which leads to severe conditions like cardiovascular diseases, peripheral neuropathy, suffering from retinopathy, and nephropathy and as a result, patients get to experience a poor quality of life while putting a lot of pressure on health facilities. **(World Health Organization, 2023)** Depending on basically the categorization into the T2DM type, one finds an insulin secretory failure by the beta cell or insulin resistance in peripheral tissue, **(Bogardus & Lillioja, 1992; DeFronzo, 1991)** however, insulin levels are inevitably raised as opposed to Type 1 Diabetes wherein there is a complete absence of the hormone insulin. This continuous high blood glucose level which is maintained up to that period other than the postprandial period is due to insulin resistance. It has previously been used as a term that highlights the

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fact that cells in the body can only poorly recognize insulin and consequently maintain high blood glucose concentrations even when insulin levels are normal or elevated. The TCF7L2 gene can be regarded today as one of the primary T2DM risk-associated loci after linkage studies and genome-wide association studies (GWAS). The first investigations by Decode Genetics proved that there is a linkage to T2DM on chromosome 10 in the Icelandic population **(Reynisdottir et al., 2003)**. Further studies did reveal that certain SNP, especially in TCF7L2, known as rs7903146 and rs12255372, had a close link to T2DM **(Grant et al., 2006)**. These SNPs that lie in the non-coding regions displayed very significant Linkage disequilibrium and were found to be significantly associated with the disease. rs7903146-T & rs12255372-T alleles displayed the maximum Odds ratio which implied approximately 1.4. Additional analysis to substantiate TCF7L2 as a diabetogene was done by Froguel and partners by examining 392,935 SNP in a French population, whereby, not only was the association of TCF7L2 with T2DM proven, but other loci were also pointed out to be related to T2DM. **(Sladek et al., 2007)** These results were replicated in European population-based samples with more than 240 loci linked to T2DM of which TCF7L2 is one **(Mahajan et al., 2018)**. It has been reported that the TCF7L2 gene is significantly associated with T2DM in different populations sectional analysis of TCF7L2 had the most frequent replication across T2DM studies **(Zeggini & McCarthy, 2007).** Research shows that TCF7L2 polymorphisms, especially those that adhere to a multiplicative genetic model, are elements with over 20% risk of T2DM **(Tong et al., 2009)**.

Objectives:

This current study aims to categorize and contrast the risks related to T2DM and to determine the relationship of TCF7L2 gene polymorphisms, rs7901695, and rs7903146 with T2DM.

Materials and methods:

In this evaluation of the knowledge, attitude, and practice regarding Type 2 Diabetes a case-control study methodology was used with detailed questionnaires (total = 300) distributed on human subjects. This cohort specifically included 150 patients with Type 2 Diabetes who have provided written informed consent to participate and underwent phenotypic screening and molecular analysis. Criteria for 150 control groups were based on age and sex-matched individuals for Type 2 Diabetes chosen in random order from the population. The study received approval from the Institutional Ethics Committee of Andhra University (IEC No: 2) to draw blood from people for scientific analysis. 2ml of venous blood samples in the form of fresh whole blood were collected in heparinized tubes in the EDTA vials. The collected blood samples which were with EDTA tubes were spun at 3000 rpm for 3 mins. Subsequently, for each blood sample, the buffy coat was carefully scraped off the inner surface of the tubes and was transferred to a separate microcentrifuge, and the Genomic DNA was isolated from the buffy coat with the Machery Nagel kit (NucleoSpin Blood method). The calculation of the concentration of DNA using a spectrophotometer at the wavelength of 260nm. The obtained DNA quality was analyzed, and with the help of the given concentration of agarose gel, 0.8% (0.8g in 100 ml TEB 1X) until the completion of electrophoresis, and the outcomes were further examined under UV transilluminator. Primers for this study were designed using the WASP allele-specific tool available at http:///bioinfo.biotec.or.th/WASP. Single nucleotide polymorphisms were genotyped using allelic discrimination with a fast 7500 Real-Time PCR System (Roche Light Cycle nano). The set of probes and primers are self-designed primers from Sigma Aldrich and a master mix 2X TB Green Premix Ex Taq was used in the study. All procedures were performed following the instructions. All samples were genotyped twice in the presence of controls. The results of the samples were confirmed using the sequencing method. DNA was amplified as denaturation at 95°C for 5 seconds, annealing at 60°C for 20 sec, and extension at a temperature of 72°C for 20 sec (Data collection) (Cycle number 35). (Table 1) Samples from patients and controls, including molecular analyses of these samples tested epidemiologically were documented and compiled into an SPSS data format for a complete statistical analysis. As far as the details are concerned, the intermediate data analysis was done with SPSS (version 16) and involved simple frequency count and estimation of the basic quantitative characteristics; such as mean ± SD along with Chi-square and t-tests wherever required.

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Table 1. Primer sequences			
Primer	**Sequence**	**Annealing temperature**	**Amplicon length (bp)**
7903146F	GCTAAGCACTTTTTAGATAC		
7903146R	ACTATGTATTGTTGCCAGTC	60^0c	247
7901695F	AATGGTATCATAAAATCTAC		
7901695R	TGTGCAAAATGTTCATAGTA	64^0c	207

Results:

The characteristics of the study population are presented in Table 2.

Table 2. Patient characteristics					
CHARACTERISTICS		**STUDY GROUP TYPE2DIABETES**	**CONTROLS**	**t value**	**P**
Age (years)		233(±78.5); 25-55	79(±75.5);25-55	8.4732	.00001*
Weight (kgs)		164.9(±13.9); 55-100	137.56(±13.44) 55-100	-2.724	.00652*
Obesity		7.75(±1.25);35.33%	5.25(±1.25); 20%	1.3108	.105502
Religion	Hindu	156.5(±0); 83.33%	156.5(±0);94.33%	-0.791	.217062
	Muslim	7.25(±1.25); 2%	4.5(±1.5);1%	1.2780	.20054
	Christian	15(±0); 14.66%	15(±0); 4.66%	0.7245	.239015
Education	Literate	98.0(±0.5); 79%	98.1(±0.4); 72%	-0.671	.253409
	Illiterate	9.75(±1.75); 47.33%	6(±2); 28%	0.8992	.193108
Occupation	Homemaker	11.65(±0.15); 83.33%	11.28(±0.22);56.66%	0.5056	.308521
	Employee	31.5(±0.2); 7.33%	31.5(±0.2); 34%	-1.921	.033308
	Business	8(±2.5); 9%	3(±2.5); 0%	2.5067	.01208
	Farmer	12(±0); 6%	12(±0); 9.33%	-1.25	.114637
Economic status	Above average	11(±0); 7.33%	11(±0); 6.66%	0.000	.50000
	Average	13.38(±0.12);75.33%	13.61(±0.11);91.33%	0.8382	.204045
	Below average	17(±1); 17.33%	10.8(±5.2); 2%	1.3257	.127791
Area	Urban	5(±2.5); 23.33%	10(±2.5); 40.66%	1.6960	.05782
	Rural	10.89(±0.11); 35%	11.08(±0.08);61%	-1.098	.143185
Food habits	Mixed	9.83(±0.33); 87.33%	4.86(±3.14)91.33%	-0.632	.266306
	Vegetarian	10.75(±2.75);12.66%	4.86(±3.14); 8.66%	0.2606	.39983

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Addictions	Alcohol	9(±1.5); 3.2%	6(±1.5)	2.1213	.027702
	Smoking	7.2(±1.2); 1.33%	5 (±1.2)	1.7748	.048832
Family history of type 2 diabetes	With	9.62(±1.62); 78.66%	6.14(±1.86); 44.66%	-0.637	.264422
	Without	13.2(0.88); 21.33%	14.37(0.37); 53.33%	0.4801	.31928
Number of Pregnancies		160.88(±11.38)	138.27(±11.38)	2.5024	.00643*
Number of Miscarriages		137.6(±11.4)	160.17(±11.17)	3.258	.00062*
Age of Menarche		174.63 (±24.13)	126.37 (±24.13)	7.236	.00001*
Age of Menopause	Natural	40.47 (±1.47)30.6%	36.82 (±2.18); 20%	1.208	.120472
	Hysterectomy	46.53(±5.97);55.3%	72.4 (±19.9); 19.3%	4.684	.00009*
	Not yet	26(±0);14%	26(±0); 60.66%	-3.80	.00024*
Age of onset		233(±7835)		61.80	.00001*
Comorbidities	With	12.45(±2.95); 67.33%	4.86(±4.64); 8%	10.467	.00001*
	Without	9.92(±0.58); 32.7%	10.75(±0.25); 92%	0.2474	.40129

p – p value, probability value**; ***–significant values

The study group patients with Type 2 Diabetes had a higher average score on age, (p-value .00001) weight, (p-value .00652) and the number of pregnancies (p-value .00643) value than the score of the control group patients. This can also be explained by causes that are affiliated with type 2 diabetes, these being age and weight. The percentage of miscarriage in the control group was much higher than in the Type 2 Diabetes group throughout the study. (p-value .00062). The menarche ages of the study group were on average significantly higher than those of the control groups. (p-value .00001). Concerning hysterectomy, the results revealed a higher percentage of women in the study group who had been subjected to hysterectomy surgery than their counterparts in the control group. This aspect gives rise to some questions such as whether hysterectomy has any long-term metabolic impacts and if these impacts make women with hysterectomy to be at higher risk of developing type 2 diabetes. (p-value .00009). The study group patients had more comorbidities than the control group patients. This result further emphasizes that it is difficult to look at the effect of Type 2 Diabetes in isolation and emphasizes the importance of complete patient care. (p-value .00001)

Other factors such as religion, education level, occupation, economic status, area (rural or urban), diet, addictions, family history of diabetes, and age of menarche were not significantly different between the groups.

Genotype frequencies of the SNPs were consistent with the Hardy-Weinberg equilibrium. Allele frequency in rs7903146 (TCF7L2 C > T) in all of the investigated women is as follows: The distribution of genotypes, reveals a higher percentage of C/C genotype (47%) in the study group compared to the control group (0.66%). As far Regarding the T/T genotype, it is evident in the control group in 56%, while in the study group only in 14%. The percentage of the T allele (%T) is of considerably larger value in the control group (77.67%) as compared to the study group (33.33%). There is a highly significant genetic association between the C allele and Type 2 Diabetes with an odds ratio (OR) value of 0.0075 with a 95% confidence interval of 0.0010 to 0.0548. The p-value for the association is 0.0001 which indicates that there is a highly significant variation in the allele distribution between the two

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groups. The deviation from Hardy-Weinberg Equilibrium (HWE) in the study group indicated the possession of a genetic link to the disease and the p-value of 0.0023 confirmed that the control group is in the HWE. (Table 3)

Table 3. The distribution of genotypes and allele frequency in the study group and the control

SNP	Genotype	STUDY GROUP (Type 2 DM)		CONTROLS		OR	95% CI	p-value	HWE p-value
		L	%	L	%				
rs7903146 TCF7L2 C > T	C/C	71	47	1	0.66	0.0075	0.0010 to 0.0548	0.0001	0.0023
	C/T	58	38	65	43.33				
	T/T	21	14	84	56				
	%T	33.33		77.67					
rs7901695 TCF7L2 T >C	T/T	69	46	1	0.66	0.0091	0.0012 to 0.0666	0.0001	0.0029
	T/C	57	38	64	42.66				
	C/C	24	16	85	56.66				
	%C	35		78					

SNP-Single Nucleotide Polymorphism; DM – Diabetes Mellitus; OR−Odds Ratio; CI−Confidence Interval; p-value− Probability value; HWE p – value− Hardy-Weinberg Equilibrium probability of the control group

Allele frequency in rsrs7901695 (TCF7L2 T > C) in all of the investigated women is as follows: Static Percentage results exhibited that the T/T genotype is more vital in the study group (46%) than in the control group (0.66%). The frequency of the C/C genotype is higher in the control group (56.66%) as compared to the study group (16%). Therefore, it can be concluded that the percentage of the C allele and the comparative analysis of the percentage of C in the control and study groups are 78% and 35% respectively. The index of comparison between the exposure to the T allele and Type 2 Diabetes is the odds ratio OR equal to 0.0091 while showing marginal genetic relation with a 95% confidence interval in the range of 0.0012 to 0.0666 indicating a significant genetic association. Concerning the p-value of the linkage, it equals 0.0001 which contributes to the fact that there are apparent differences in allele frequencies between the groups. According to the information from the Control group's HWE p-value equal to 0.0029, this group is standardizing while the abnormality of the odds ratio of the study group indicated a genetic association of this group with Type 2 Diabetes. The distribution of genotypes and allele frequencies for SNPs rs7903146 and rs7901695 in TCF7L2 shows significant differences between the study group and the control group. The results support a strong genetic association between these SNPs and Type 2 Diabetes, with the study group exhibiting higher frequencies of specific genotypes linked to the disease. The deviation from the Hardy-Weinberg Equilibrium in the study group further supports the potential role of these SNPs in the genetic predisposition to Type 2 Diabetes. Genotype distribution is presented in Table 3.

Discussion:

The findings of the study suggest that various variables could help in the identification of the study subjects (patients with Type 2 Diabetes) from the Comparator subjects (people without Type 2 Diabetes). Some of these factors include the age of the patient, weight of the woman, the number of pregnancies that she has had, number of miscarriages, age at the start of menstruation, whether the woman is menopausal, age at diagnosis onset, and presence of other diseases among others.

A common detail that contributes to the onset of Type 2 Diabetes is the patient's age. Herting analysis revealed that the age of patients in the study group was studied to be significantly higher than that recorded in the control group. This corroborates the universally accepted perception about Type 2 diabetes where its occurrence

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is significantly hiked among the elderly due to reasons such as insulin resistance, and decreased capacity of beta-cells among the elderly **(American Diabetes Association, 2020)**. The elderly population is vulnerable to it, therefore it's important to develop age-segmented prevention and control measures. The other parameter that defines the difference between the study and the control groups is weight. The study also supported the fact that high body weight increases the risk of Type 2 Diabetes. Obesity is one of the prominent causes of insulin resistance and this factor is regarded as one of the most important pathogenetic factors of Type 2 Diabetes **(Kahn, et al.2006)**. It was noted that the pregnancies were more frequent and the miscarriages were also frequent in the studied group. Parity has been linked with Type 2 Diabetes, mainly if it is multiple as it could be resultant of cumulative pregnancy metabolism in the body of the woman **(Tobias, et al.2011)**.

Some things, that were found to be discriminators were; The age at which first menstruation occurs also referred to as menarche. According to some studies, the menarche that is related to the early first menstrual cycle makes a woman a candidate for Type 2 diabetes. This relationship could be attributed to estrogen exposure that affects insulin sensitivity and glucose metabolism since women are likely to have an extended duration of estrogen exposure compared to men **(He, C., Zhang, et al.2010)**. It was also observed that the menopausal status of the patients varied between the study and control groups. Another modifiable risk factor for postmenopausal women is Type 2 Diabetes; it is also noted that hormonal changes may influence insulin resistance and fat utilization **(Carr, M. C 2003)**. The majority of patients in the study group reported comorbidity of hypertension, dyslipidemia, and cardiovascular diseases compared to the control group. These comorbid conditions are usually modifiable and are related to Type 2 Diabetes by risk factors such as Obesity and lack of Physical activity **(Stokes & Preston, 2017).**

SNP rs7903146; SNP rs7901695 and Type 2 Diabetes

The TCF7L2 gene is currently considered to be a critical gene that is associated with T2DM, having a strong impact on the regulation of blood glucose levels and beta-cell function. (Jyothi, et al. 2013) Grant et al. (2006) were the first to describe the association of TCF7L2 variants with T2DM risk; (Grant, et al. 2006) this association has been since then confirmed in different ethnic populations (Florez, J. C. 2007). However, it is worth mentioning that the specific SNP rs7903146 (C/T) within the TCF7L2 has been indicated to have the strongest association with Caucasian ethnicity **(Florez, et al. 2012)**.

The given results found consistently significant and positive associations of the TCF7L2 gene variants with the risk of T2DM in all the compared studies and in different populations that approve the critical role of the gene in the development of T2DM (Cauchi, et al2007). However, there are studies, including the Asian population, to the best of knowledge have confirmed the pooled effects of TCF7L2 rs7903146 SNP on T2DM risk **(Tong, et.al. 2012)**.

In 2009, Tong et al. published a comprehensive meta-analysis involving 36 genetic association studies that examined the link between type 2 diabetes mellitus (T2DM) and four TCF7L2 polymorphisms (rs7903146, rs7901695, rs12255372, and rs11196205). This meta-analysis included a total of 39,123 controls and 35,843 cases from various ethnic backgrounds. The findings for the rs7903146 SNP revealed that individuals with the heterozygous genotype had just over a 1.4-fold increased risk of developing T2DM, while those with the T/T homozygous genotype had nearly a 2.0-fold increased risk compared to C/C homozygotes. The study also computed the population attributable risk (PAR) for the T/T and T/C genotypes, finding it to be 16.9% overall, with significant variations among ethnic groups: 23.2% for Caucasians, 14.1% for North Europeans, 2.5% for East Asians, 17.9% for Indians, and 27.0% for Africans. These results suggest that the rs7903146 polymorphism might account for approximately one-fifth of all T2DM risk globally, excluding East Asians **(Tong, et al. 2009)**. Additionally, the other three TCF7L2 variants analyzed were significantly associated with T2DM risk across different ethnicities. The authors suggested that rs7903146 and rs12255372 can serve as reference loci for investigating T2DM susceptibility, as they were associated with the highest pooled odds ratios **(Tong, et al.2009).**

A study that Song et al carried out in 2012 on 66 original articles carried out a meta-analysis that vindicated the T2DM association with the rs7903146

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SNP (OR = 1.41, 95% CI 1.37-1.46 for T). They observed significant differences in the T allele frequencies across various populations: the allele was found to be frequent, it ranged from 0.16-0.48% in Caucasians, Africans by origin, and Hispanics excluding the Pima Indians while it was very rare in the East Asian subjects, it was between 0.02-0.04. These frequency differences have, however, not affected the overall results of the association since the latter were similar for all ethnic groups. Also, Song et al. assessed the effect of the rs7903146 SNP on beta-cell function in 35,052 non-diabetic subjects participating in 31 studies. Carriers of the T allele had significantly reserved fasting insulin and HOMA-%B, as well as higher fasting glucose and 2-hour post-load glucose vs C/C homozygous **(Song, Y., et al. 2012)**.

This was done by Peng et al. who carried out a cumulative meta-analysis and an updated study on the relationship between the TCF7L2 variants and T2DM. This study covered eight TCF7L2 polymorphisms; the patient cohort consisted of 121,174 people (53,385 cases, 67,789 controls). They found significant associations between T2DM risk and six single nucleotide polymorphisms (SNPs) under an additive inheritance model: The polymorphic variations that it assigned included rs7903146, rs12255372, rs11196205, rs7901695, rs7895340, and rs4506565 (Peng, et al. 2013).

For the three most significant SNP loci the pooled ORs were the highest; for rs7903146, rs12255372, and rs4506565, the OR was equal to 1. 39 (95% CI 1. 34-1. 45), 1. 33 (95% CI 1. 27-1. 40), respectively. All these SNPs had high linkage disequilibrium in all the populations being studied. Nonetheless, more recently, specific ethnic studies, including American Pima Indians, were shown to be inconclusive when directly relating the mentioned SNPs of TCF7L2 to T2DM, which underlines the necessity for evaluating TCF7L2 in more diverse populations and ethnic backgrounds **(Peng, S., et al.2013)**.

The pathways by which TCF7L2 variants to T2DM are inconclusive as all the SNPs found in the TCF7L2 gene are intronic. Most significantly, no polymorphisms in the exonic part of this gene namely TCF7L2 have been linked to T2DM. This calls for the development of an understanding of how intronic variants affect the expression of the TCF7L2 gene **(Jyothi, et al.2013)**.

It was recently ascertained by Lyssenko et al. that, the increase in with the rs7903146 T allele, the TCF7L2 mRNA is significantly higher in the human pancreatic islets. This influx was observed to be correlated with blunted insulin secretion and also with incretin effect, as well as increased incidences of gluconeogenesis in the liver **(Lyssenko, et al. 2007)**. In the same way, Gaulton et al., observing the chromatin structure at the TCF7L2 locus in human islets, linked the T allele of the rs7903146 marker with a more open structure of the chromosome **(Gaulton, et al. 2010)**. To assess the enhancer activity, they employed the allele-specific luciferase reporter constructs to the two endocrine cell lines namely MIN6 and 832/13 suggesting that T allele constructs had higher enhancer activity than the C allele constructs. Of these, the T allele was found to regulate cis-acting sites and the local chromatin structure in human pancreatic islets regarding T2DM risks.

In addition to this, Palmer et al in the same study explored the tagging SNPs and figured out that the 4. The 3-kb region in the TCF7L2 gene, which has the rs7903146 SNP, was deemed most important for T2DM risk. In sequencing this part in 96 DNA samples of African Americans they confirmed that Imputation, Haplotype, and Condition analyses were aligned to the fact that ‘’the SNP rs7903146 is a trait-defining variant **(Palmer, et al. 2011).**

Thus, there are genetic pieces of evidence along with functional pieces of evidence explaining the functional implication of the rs7903146 SNP in T2DM.

Conclusion:

Thus, age, weight, number of pregnancies, miscarriages, age at menarche, menopausal status, the age of onset of Type 2 Diabetes, and presence of comorbidities were identified as critical variables that help distinguish patients with Type 2 Diabetes from the control group. Thus, there were differences in the genotypes and allele distribution of SNP rs7903146 and rs7901695 in the TCF7L2 gene between the studied and control groups. In addition, a high degree of consistency is maintained throughout these data proving a significant even near-absolute genetic relationship to Type 2 Diabetes here. Also, the deviation from HWE in the study group

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indicates possible gene-related susceptibility to Type 2 Diabetes distinct from any effects of population stratification that might be expected in a larger population and thus underlines the relevance of these genetic markers for the study of the epidemiology of the disease.

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