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Prevalence of *OCT1* (rs628031) genetic polymorphism in south Indian population

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ABSTRACT

Genetic polymorphism is defined as the presence of a heterozygous deoxyribose nucleic acid (DNA) variant in greater than 1% of the population. Genetic polymorphism integrates genetic information in clinical decision-making. High polymorphism of organic cation transporters (*OCT*) transport genes may represent a significant portion of the variation in the pharmacokinetics and pharmacodynamics of substrate drugs transported by *OCT1*. The scarcity of research and the difference of effect in the genetic variability of the rs628031 polymorphism in various groups provide compelling reasons to perform the study. The purpose of this study is to find the prevalence of rs628031 polymorphism in the South Indian population. The phenol-chloroform technique was used to extract DNA from 48 healthy individuals in the research. Polymerase chain reaction was used to amplify the acquired DNA samples. After digestion with a tailored restriction enzyme, restriction fragment length polymorphism was utilized to discover genetic polymorphisms. The minor allele frequency of rs628031 was 0.67, indicating its deviation with the Hardy–Weinberg principle. The frequency of variant alleles discovered in this study was comparable to that seen in the Javanese population. The study's major findings provide the groundwork for future pharmacogenetic investigations in this group, as well as contribute to a better understanding of the role of the rs628031 polymorphism in drug response and benefit in developing a customized treatment regimen with improved efficacy and safety.

INTRODUCTION

The human genome, a complicated entity made up of 23 chromosomes, is made up of approximately three billion deoxyribose nucleic acid (DNA) base pairs, with an estimated number of 20,000–25,000 genes that code for various proteins. Interestingly, about 99.9% of the human genome is similar in all humans, and the remaining 0.1% difference accounts for each person's uniqueness (MedlinePlus, 2021). Few DNA variants can be detrimental and can result in life-threatening diseases, while others can help in the development of desirable characteristics (Koepsell, 2019). When the variant occurs in more than 1% of the population, it is referred to as genetic polymorphism (MedlinePlus, 2021). The single nucleotide polymorphisms (SNPs) in specific genes impact the expression of various illnesses as well as safety and efficacy of drug therapy (Koofee and Mubarak, 2019). According to reports, at least 10% of the population possesses gene variations that lead to complications (Fridovich-Keil, 2020). Despite significant advances, contemporary pharmacotherapy still confronts several obstacles, including catastrophic or even fatal adverse drug responses and non-responses to the empirical therapy. Interindividual variability in drug treatment has been attributed to genetic polymorphism. Such variabilities in the outcomes of the drug therapy among the different populations are referred as "pharmacoethnicity" and occur due to drug-gene interactions. Various enzymes and transporters involved in drug metabolism and transport exhibit polymorphisms that affect an individual's response to a certain medication. The discovery and analysis of clinically relevant polymorphisms assist in the development of personalized therapy (Fridovich-Keil, 2020). The benefits of testing for the genetic polymorphisms include improved health care outcomes through the use of gene therapy, the identification

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of new therapeutic targets, the development of new medications, defining new dosage regimens, and so on (Koepsell, 2019). Recent genetic polymorphism research has focused on leveraging these genetic variations through big data analytics in order to develop tools for identifying critical population diversity patterns connected to treatment response (Bachtiar, 2019).

The organic cation transporter 1 (*OCT1*) are the members of the *SLC22A* family of solute carrier transporters (*SLC*s). The most essential *SLC*s implicated in drug elimination are *OCT*s (Koepsell, 2019). *OCT1* is one of the most abundantly expressed poly specific transporter protein in the liver that plays an important role in the hepatic uptake of cationic and neutral small molecules, and also in their renal excretion (Tzvetkov *et al*., 2009).

OCT1 gene has been reported with about 34 polymorphisms in 10 different ethnic groups reported with altered drug transportation capacity that resulted in interindividual variability in pharmacokinetics (PK) and or pharmacodynamic (PD) outcomes of drugs (Koepsell, 2019). Extensive research on the populations of Japanese, Chinese, and Korean ethnicity were done, and genetic variations have mostly been found in such Asian populations apart from the European population (Mato *et al*., 2018). The effects of *OCT1* polymorphisms on the PK and PD of Metformin in comparison to other medications have been thoroughly studied (Tzvetkov *et al*., 2009). Indian researchers have examined rs683369 (480 G > C, L160F), rs2282143 (P341L, 1022C > T), rs628031 (M408V, 1222A > G), rs622342 (1386C > A), rs1867351 (156T > C, S52S), and four other intronic variants (Sur, 2014). The allele frequency of the rs628031 polymorphism was reported as 80.3% in the Tamilian population of south India (Umamaheswaran *et al*., 2011) and the rs628031 polymorphism has been found to affect the responsiveness of substrate medicines such as Metformin, Levodopa, Imatinib, Lamotrigine, and others (Koepsell, 2019).

Only few literature findings are available that suggest heterogeneity in the frequency and impact of the rs628031 *SNP* among ethnicities, (Chen *et al*., 2010; Mato *et al*., 2018; Ningrum *et al*., 2017; Reséndiz-Abarca *et al*., 2019; Shokri *et al*., 2016; Tarasova *et al*., 2012; Tzvetkov *et al*., 2009; Umamaheswaran *et al*., 2011). Among the Indians, only a couple of studies, one from north India and another from south India, have reported the prevalence statistics for rs628031 polymorphisms (Sur, 2014, Umamaheswaran *et al*., 2011).

The primary objective of this study is to determine the prevalence of rs628031 polymorphism in healthy south Indian males. The scarcity of research and the difference of effect in the genetic variability of the rs628031 polymorphism in various groups provide compelling reasons to perform the study. The period elapsed since the last study in the south Indian population warrants another study in the south Indian population. Furthermore, the Umamaheswaran *et al*. (2011) study included only south Indian Tamilians, whereas this study included participants from all the major states of south India including Tamil Nadu in order to get more generalized results for the south Indian population. As a matter of fact, it is important to investigate the incidence and degree of this *SNP's* effect in the south Indian population in order to create a medication regimen with improved therapeutic efficacy and minimum side effects for the drugs that are *OCT1* substrates.

MATERIALS AND METHODS

Subjects

Inclusion criteria: Adult male volunteers between the age group of 18 and 35 years in good health based on medical history, physical examination, electrocardiography (ECG), and routine laboratory tests (complete blood count, blood glucose, liver function tests, renal function tests, and urinalysis) were included in the study. The subjects' south Indian heritage was confirmed through interviews, and those who had lived in south India for at least three generations were included. All participants were certified as fit to participate in the study by a competent physician.

Exclusion criteria: Smokers, alcoholics, or subjects taking any drugs for chronic conditions were excluded from the study.

Out of the 60 volunteers screened, 58 were certified as fit to participate in the study out of which 10 volunteers were the drop-outs and thus 48 volunteers participated in the study.

Ethical Clearance

The study protocol was approved by the institutional review board of the academic institution where the study was held (JSSCP/IRB/09/2019-20). All the study participants were well-informed about the purpose, nature, and outcomes of the study prior to the process of getting informed consent forms.

Sampling methods

A qualified phlebotomist withdrew 2 ml of blood from each participant in K3-EDTA (Ethylenediaminetetraacetic acid)-coated blood collection tubes and labelled them accordingly. The blood samples were centrifuged at 12,000 rpm for 1 minute to separate the plasma from the blood cells. The sedimented white blood cells were used for DNA harvesting.

Isolation of DNA from whole blood

The DNA extraction was carried out by Phenol-Chloroform method that involves digesting eukaryotic cells or tissues with proteinase K in the presence of EDTA and solubilizing membrane and denaturing proteins with a detergent such as sodium dodecyl sulphate. The nucleic acids were then purified by the phase extraction method using organic solvents', viz., phenol, chloroform, isoamyl alcohol, and 100% ethanol. Buffers such as saline sodium citrate buffer (sodium chloride, sodium citrate) and Tris-EDTA buffer (Tris-acetate and EDTA (TAE)) were used in the procedure to maintain the pH.

Primers

The primers used for *OCT1*—rs628031 polymorphism detection were designed using the nucleotide sequences obtained from GENBANK, the accession number for the human *OCT1* gene was found as NC_000006.12. The sequences of the forward and reverse primers designed for this study were F5′- TCATCACCATTGACCGCGTG -3′ and R5′- ACACTTTCCCCACACTTCGAT -3′, respectively (Sakhala Enterprises, Bengaluru).

DNA amplification

The isolated DNA samples were amplified using polymerase chain reaction (PCR) and restriction fragment length polymorphism technique was used to identify the genetic polymorphism. DNA was amplified using the reaction mixture consisting of 0.1 µl of Taq DNA polymerase, 15 µl of genomic DNA, 1 µl of each dNTP (GENEI LABS, Bengaluru), 0.5 µl of each primer (Sakhala Enterprises, Bengaluru), and 5 µl of PCR buffer with MgCl2 and the volume made to 50µl using sterile water. PCR for *OCT1*—rs628031 gene was performed by initial denaturation of the sample at 95°C for 5 minutes, followed by 30 cycles of 95°C for 30 seconds denaturation, 54°C for 35 seconds annealing, and 72°C for 60 seconds extension, with a final extension step of 72°C for 5 minutes.

Restriction enzyme

The restriction enzyme was designed using www.restrictionmapper.org. The DNA sequence under question was pasted in the restriction mapper, and a list of all the enzymes that cleaved the sequence was obtained for both wild and variant types. The restriction enzyme that is not common in both lists was selected. The obtained DNA samples were fragmented using restriction enzyme Msc1 (GENEI LABS, Bengaluru) in case of wild type allele.

Genotyping and agarose gel electrophoresis

To detect the presence of polymorphism, 25 µl mixture with 10 µl PCR amplified product, 1µl restriction enzyme (Msc1), 5 µl assay buffer, and 9 µl distilled water was prepared and placed at 37°C bath for about 2 hours to facilitate digestion. After 2 hours, it was placed in a 65°C bath for about 5 minutes to destroy the enzyme and stop digestion. The sample was then allowed to cool. After digestion with a restriction enzyme, the resulting DNA fragments were separated by agarose gel electrophoresis. 1% agarose gel was cast and 2 µl of loading dye was added to 10 µl of PCR product. The PCR product was loaded in the odd-numbered wells, while the PCR products digested by the restriction enzyme were loaded in the adjacent even-numbered wells. The gel was run in a 1× TAE buffer at 50 V by observing the bromophenol blue for the movement of the DNA fragments. The banding patterns were observed for DNA fragmentation under Ultraviolet light (using a photo documentation system) to determine the presence of rs628031 polymorphism.

Statistical analysis

The average baseline characteristics of the study subjects were calculated using descriptive statistics such as the mean and standard deviation. Hardy–Weinberg equilibrium was used to compare the genotype data with the expected frequencies. Chi-square test was used to compare the differences between observed and expected frequencies. A *p*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

A total of 60 volunteers were screened for fitness. Based on the physician's advice, two volunteers were excluded from the study due to lack of fitness. The average age of the subjects was 18.5 $\pm$ 0.91 years. All general parameters and biochemical investigations revealed that all such parameters were within the normal limits.

Genotyping

In 48 samples, DNA was isolated, and genetic polymorphism was studied. The genotype frequencies of rs628031 *GG* homozygous variant, *AG* heterozygous variant, and *AA* homozygous wild are 66.66%, 2.08%, and 31.25% (n = 32, 1 and 15), respectively, as shown in figure 1–6. p, q CHWE: Check was used to calculate Hardy–Weinberg equilibrium. To compare the expected and observed values, the Chi-square test was used. The observed and expected values differed significantly, and the *p*-value was greater than 0.05, indicating rs628031 deviation from Hardy–Weinberg equilibrium.

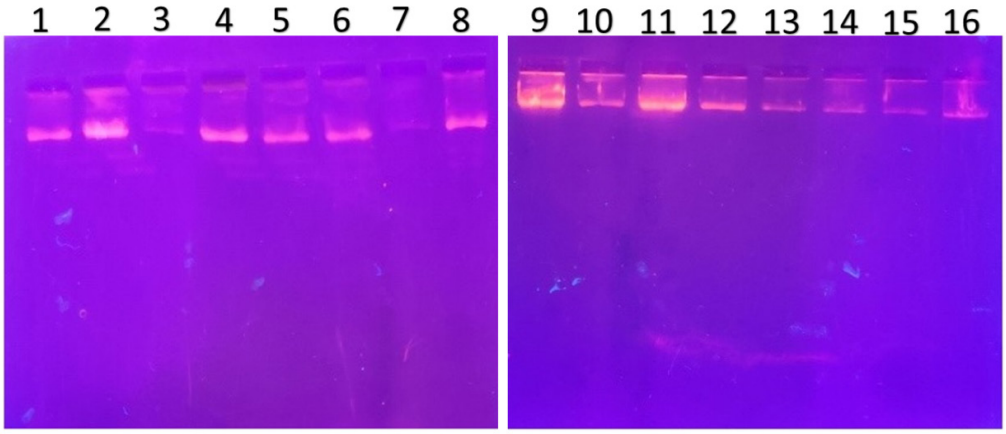

Figure 1. PCR amplified-RFLP treated DNA samples of *OCT1* rs628031 gene results by agarose gel electrophoresis (1%): The lanes 1, 3, 5, 7, 9, 11, 13, 15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. From the results, a single clear band was observed, this indicates, lanes 2, 4, 6, 8, 10, 12, 14, 16, all samples found to be *GG* homozygous variants. No fragmentation was detected after treatment with restriction enzyme specific for *OCT1* polymorphism.

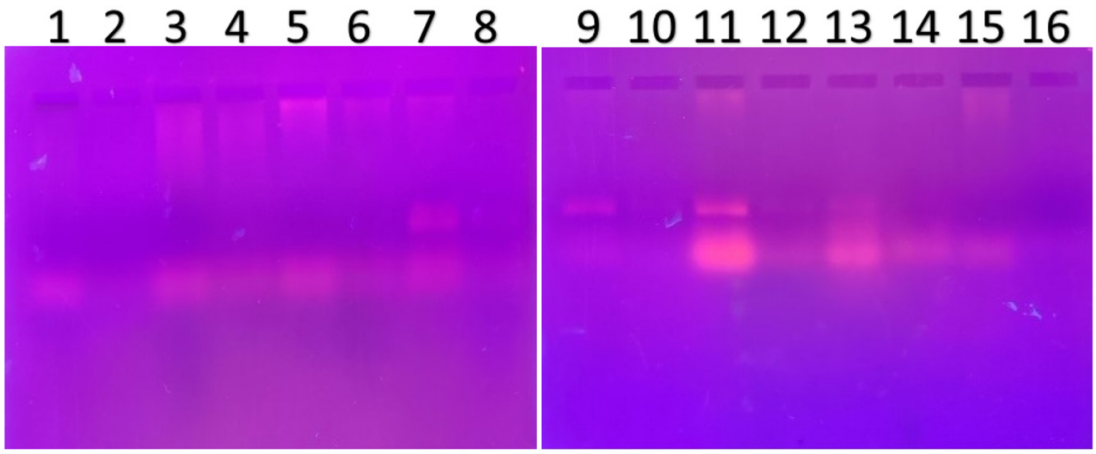

Figure 2. PCR amplified-RFLP treated DNA samples of *OCT1* gene results by agarose gel electrophoresis (1%): The lanes 1, 3, 5, 7, 9, 11, 13, 15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. From the results, clear evidence of fragments was observed, this indicates, lanes 2, 4, 6, 8, 10, 12, 14, 16, all samples were found to be *AA* homozygous wild. Fragmentation was detected after treatment with a restriction enzyme specific for *OCT1* polymorphism

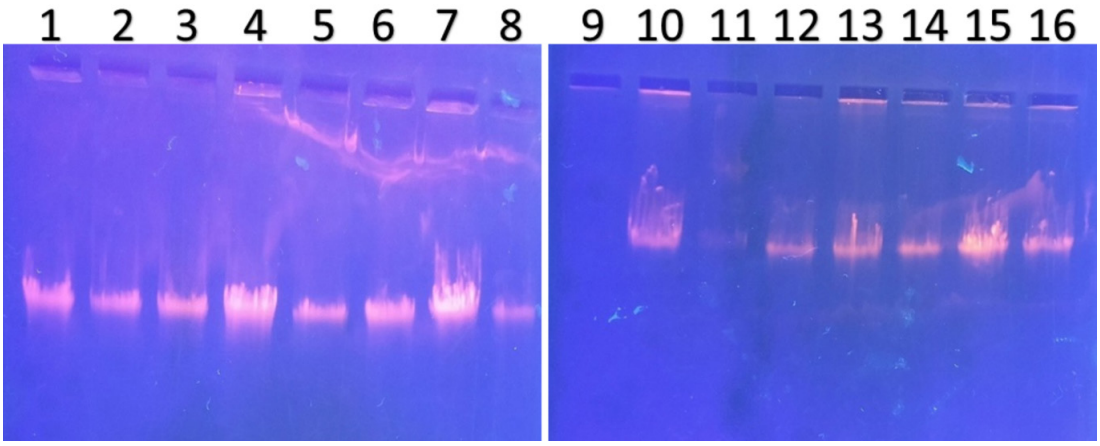

Figure 3. PCR amplified-RFLP treated DNA samples of *OCT1* gene results by agarose gel electrophoresis (1%): The lanes 1,3,5,7,9,11,13,15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. From the results, a single clear band was observed, this indicates, lanes 2, 4, 6, 8, 10, 12, 14, 16, all samples found to be *GG* homozygous variants. No fragmentation was detected after treatment with restriction enzyme specific for *OCT1* polymorphism.

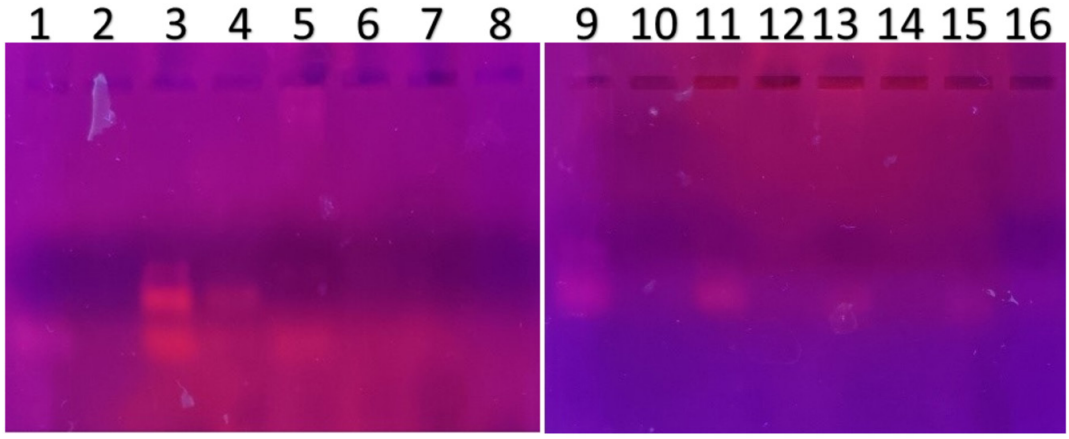

Figure 4. PCR amplified-RFLP treated DNA samples of *OCT1* gene results by agarose gel electrophoresis (1%): The lanes 1, 3, 5, 7, 9, 11, 13, 15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. Lane 4 was found to be an *AG* heterozygous variant; evidence of fragmented DNA strand was detected after restriction enzyme treatment specific for *OCT1* polymorphism. The remaining 2, 6, 8, 10, 12, 14, 16 lanes' samples were found to be *AA* homozygous wild with clear evidence of fragmented DNA strand after restriction enzyme digestion.

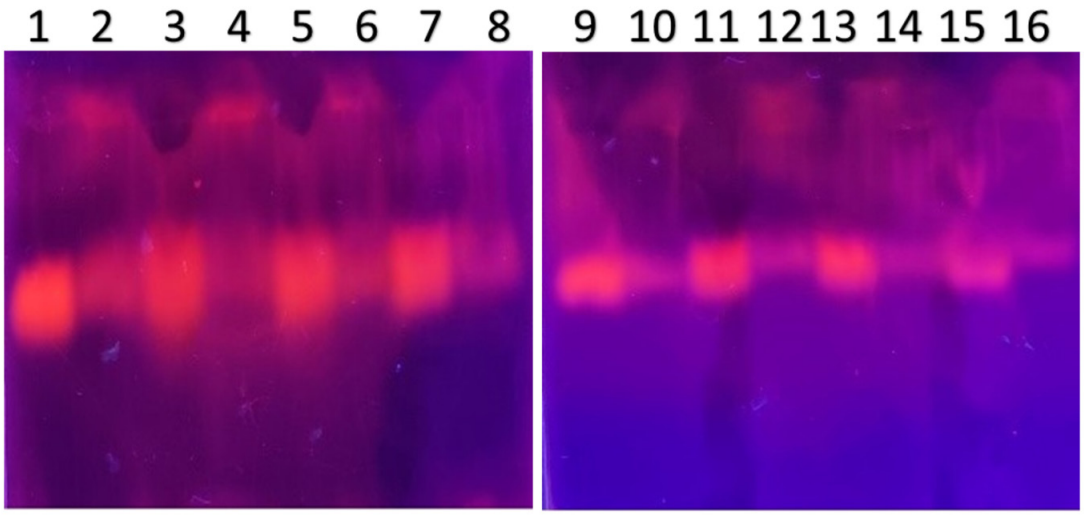

Figure 5. PCR amplified-RFLP treated DNA samples of *OCT1* gene results by agarose gel electrophoresis (1%): The lanes 1, 3, 5, 7, 9, 11, 13, 15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. From the results, a single clear band was observed, this indicates, lanes 2, 4, 6, 8, 10, 12, 14, 16, all samples found to be *GG* homozygous variants. No fragmentation was detected after treatment with restriction enzyme specific for *OCT1* polymorphism.

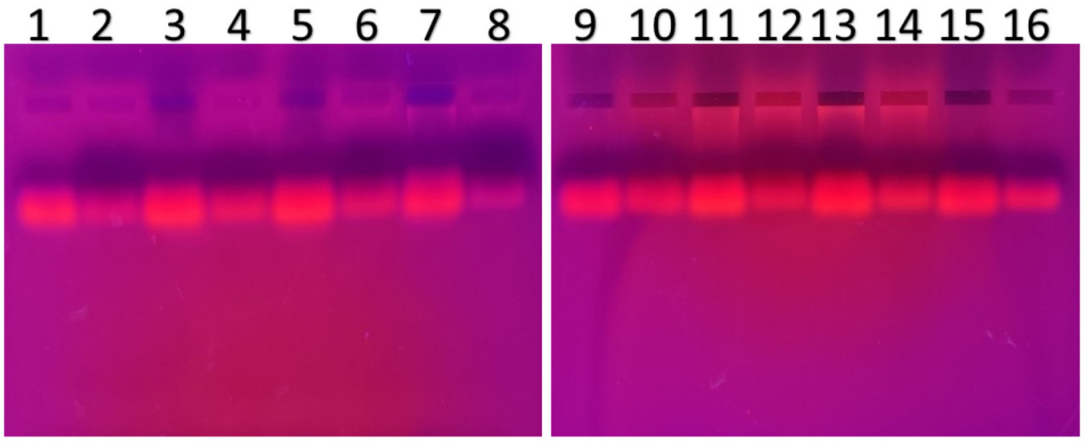

Figure 6. PCR amplified-RFLP treated DNA samples of *OCT1* gene results by agarose gel electrophoresis (1%): The lanes 1, 3, 5, 7, 9, 11, 13, 15 are loaded with PCR amplified DNA and the lanes 2, 4, 6, 8, 10, 12, 14, 16 contain restriction enzyme-treated DNA of the volunteers. From the results, a single clear band was observed, this indicates, lanes 2, 4, 6, 8, 10, 12, 14, 16, all samples found to be *GG* homozygous variants. No fragmentation was detected after treatment with restriction enzyme specific for *OCT1* polymorphism.

DISCUSSION

OCT1 (rs628031) genetic polymorphism influences the PK and PD of its substrate drugs. Multiple studies have shown significant interethnic differences in *OCT1* genetic variants. In this study, the minor allele frequency of rs628031 polymorphism was found to be 0.67 in the south Indian population. This frequency of rs628031 polymorphism is higher when compared to that predicted by the Hardy–Weinberg equilibrium that indicates a deviation. The Hardy–Weinberg equilibrium is a concept that states that in the absence of disrupting influences, genetic variation in a population will remain constant from generation to generation. Though statistical variance from Hardy–Weinberg predictions typically implies a violation of the theorem's assumptions, the reverse is not always true. The possible causes of this deviation include the study's small sample size or the possibility of natural selection of the minor allele over the generations based on the five principles of Hardy–Weinberg equilibrium. The frequency of the minor allele of rs628031 was determined to be 60.47% in the Javanese population, which is similar to the findings of this study (Ningrum *et al*., 2017). In a study among the diabetic population, in the Han Chinese community, found a frequency of about 72% (Zhou *et al*., 2015). In an Iranian population, the G allele frequency of rs628031 was 41% in the metformin-responding group and 51% in the non-responding group (Shokri *et al*., 2016). The minor allele frequency for rs628031 in a Latvian population was found to be 0.42 in the control group and 0.275 in the case group (Tarasova *et al*., 2012). Findings from a 1,000 genomes project in the Chinese - Japanese community, the minor allele frequency of rs628031 was determined to be 0.15. (Chen *et al*., 2010). Minor allele frequencies of 0.43 and 0.80 were found in two earlier investigations done in India (Sur, 2014; Umamaheswaran *et al*., 2011). To summarize, studies in Chinese, Mexican, and Japanese populations, as well as a previous study in south India, revealed

a greater frequency (73%–83%) of variant allele rs628031 than this study (Chen *et al*., 2010; Reséndiz-Abarca *et al*., 2019; Umamaheswaran *et al*.; 2011, Zhou *et al*. 2015) whereas, the prevalence of this polymorphism was lower (39%–40%) in European nations (Becker *et al*., 2011; Tarasova *et al*., 2012) as well as among (43%–51%) Iranian and North Indian groups (Shokri *et al*., 2016; Sur 2014). Based on the study's findings and the existing literature, the rs628031 polymorphism has a diverse distribution. To further understand the prevalence and clinical significance of rs628031, genotyping studies should be undertaken in smaller, more focused areas, as a generalized model cannot be developed by extrapolating existing data.

Limitations

This study was only able to examine 48 samples, as compared to the 60 samples that were scheduled to be analyzed at the beginning of the project. A larger sample size would allow for more generalizable findings on the prevalence of the rs628031 polymorphism in the south Indian population.

CONCLUSION

The study results show that the minor allele frequency of rs628031 polymorphism was 0.67 which is comparable to that of the Javanese population. At the same time, it differs from the prevalence found in other populations. This demonstrates the importance of conducting polymorphism studies in a specific population.

Further studies are needed to determine the effect of the rs628031 polymorphism on the PK and PD of drugs widely transported by the *OCT1*, such as Metformin. These types of research can help in the development of precision medicine and designing customized dosing regimen in individuals known to have the rs628031 polymorphism. Given the high prevalence of the rs628031 polymorphism among the study subjects, individuals who take *OCT1* substrate drugs may be urged to undertake a genotyping test in the future, if its effects on PK and PD of relevant drugs are studied in a wider population.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

ETHICAL APPROVALS

The study protocol was approved by the institutional review board of the academic institution where the study was held (JSSCP/IRB/09/2019-20).

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