

# Polymorphisms of *organic cation transporter 1* and the drugs response

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## ABSTRACT

Polymorphisms of proteins which have an important role in drug transport, metabolism, and disposition in the body could affect the drugs efficacy and toxicity. The organic cation transporter 1 (OCT1), encoded by *SLC22A1* gene, has been known as one of the polyspecific protein transporters which could affect some of the cationic drug response such as metformin, levodopa and imatinib. However, the findings of many studies an association of *OCT1* polymorphisms and drug response both in Caucasian and Asian were still inconsistent. Moreover, this study's topic in Asians was still uncommon. This review was aimed to explore the polymorphisms of *OCT 1* in Asians and Caucasians and to find the challenges of the next studies in Asians. The articles about *OCT1* polymorphisms were searched in the PubMed with the keywords; *OCT1* or *SLC22A1*, polymorphisms. There were ten articles of *OCT1* polymorphisms which are related to the drug response and most of the studies were performed in Caucasian subjects. In Caucasians, the rs622342 variant might associated with the response of metformin and levodopa. Moreover, the R61C and 420del variants still showed the inconsistent findings associated with metformin response. The non-synonymous variants which were found in Caucasians were not found in Asian. However, the new non-synonymous variants were found in Japanese, Chinese, Indian and Korean population and some of them were associated with the metformin response. The recent findings found in Caucasians cancer patients, were related to the association of non-synonymous variants haplotype and the 5-Hydroxytryptamine Receptor Antagonists drug response. The inconsistent results of *OCT1* polymorphisms studies could be related to the study's sample size and design of the studies. Further studies which exploring the association of *OCT1* polymorphisms and drug pharmacokinetic profiles and/or drug response, which were adjusted by genetic variants of proteins involved in drug transport, metabolism and disposition are still needed in both Caucasians and Asians. Additional large studies also considering non-genetic risk factors are warranted, to implement the results of the various studies into clinical practice.

**Key words:** *OCT1*- polymorphisms – Asians – Caucasians - drug response

## ABSTRAK

Polimorfisme protein yang berperan penting dalam transport, metabolisme dan disposisi obat dalam tubuh dapat mempengaruhi efektivitas dan toksisitas obat. *Organic cation transporter 1* (OCT1) yang dikode oleh gena *SLC22A1*, dikenal sebagai salah satu transporter protein polispesifik yang dapat mempengaruhi respon obat kationik seperti metformin, levodopa dan imatinib. Namun demikian, banyak penelitian menunjukkan hubungan polimorfisme *OCT1* dan respon obat baik pada orang Kaukasoid dan Asia tidak konsisten. Selain itu penelitian mengenai hal ini pada orang Asia masih jarang. Tinjauan pustaka ini bertujuan untuk mengkaji polimorfisme *OCT1* pada orang Asia dan Kaukasoid dan kemungkinan dilakukannya penelitian pada orang Asia. Pustaka mengenai polimorfisme *OCT1* diperoleh dari PubMed menggunakan kata kunci OCT1, SLC221 dan polimorfisme. Terdapat 10 artikel polimorfisme *OCT1* yang berkaitan dengan respon obat dan sebagian besar dilakukan pada subjek Kaukasoid. Pada orang Kaukasoid, varian rs622342 kemungkinan berhubungan dengan respon metformin dan levodopa. Lebih jauh, varian R61C dan 420del masih menunjukkan hubungan yang tidak konsisten. Varian *non-synonymous* yang ditemukan pada orang Kaukasoid tidak ditemukan pada orang Asia. Namun demikian varian *non-synonymous* ditemukan pada populasi Jepang, Cina, India dan Korea. Beberapa diantaranya dihubungkan dengan respon metformin. Penemuan terkini ditemukan pada penderita kanker orang Kaukasoid dan berhubungan dengan varian non-synonymous haploid dan respon obat antagonis reseptor hidroksitriptamin-5. Ketidakkonsisten hasil penelitian polimorfisme *OCT1* kemungkinan dapat dikaitkan dengan jumlah sampel dan rancangan penelitian. Penelitian lebih lanjut untuk menghubungkan polimorfisme OCT1 dan profil farmakokinetik dan atau respon obat yang dikendalikan oleh variasi genetik protein yang terlibat dalam transport, metabolisme, disposisi obat masih diperlukan baik pada orang Kaukasoid dan Asia. Penelitian yang lebih luas juga perlu dilakukan dengan mempertimbangkan faktor risiko no-genetik untuk dapat mengimplementasikan hasil berbagai penelitian dalam praktek klinik.

**Kata kunci :** *OCT1*- polimorfisme – orang Asia – orang Kaukasoid - respon obat

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## INTRODUCTION

The drug efficacy and toxicity could be affected by the variability of genes encoding proteins which have role in drug absorption, distribution, metabolism and excretion.<sup>1,2</sup> Organic Cation Transporter 1 (*OCT1*) is one of the polyspecific transporters which has important role in translocating drugs, toxins and neurotransmitter with cation organic structure.<sup>3,4</sup> The *OCT1*, encoded as *SLC22A1* was mostly found in the liver and was less expressed in kidney and human intestine.<sup>5</sup> The *SLC22A1* mediates the transport of small molecular weight hydrophylic organic cation from extracellular fluid to the hepatocyte.<sup>6</sup> Therefore, the polymorphism of *OCT1* gene could affect the pharmacokinetic parameters of the drug which were mainly metabolized in the liver and consequently, the response of the drugs would be affected as well. This polymorphism could increase the risk of adverse drug reactions because the concentrations of the drug in the serum may exceed the minimal toxic concentration or may decrease the drug response.<sup>7</sup> In the other hand, the *OCT1* also has role in detoxification of xenobiotics and chemotherapy agents.<sup>8</sup> Some of the drugs were known as substrate of this gene, like metformin, amantadine and pramipexole.<sup>9-10</sup> Recently, the study about metformin found that eventhough this drug is not metabolized and available in cationic form, it is largely transported into hepatocytes and renal tubular epithelium by *OCT1*.<sup>11-12</sup> One of the study of metformin pharmacogenetics showed that the variant of rs622342 of *OCT1* gene could modify the metformin response to the blood glucose level. Furthermore, the multidrug and toxin extrusion transporter (*MATE1*) gene was known to increase

the antihyperglycemic effect of metformin.<sup>12</sup> This finding was supported by studies in Caucasian which identified the *OCT1* polymorphisms which were related to the decrease effect of metformin.<sup>13-14</sup> The other previous study also found that the *OCT1* polymorphisms could predict the response of imatinib in chronic myeloid leukemia and the survival rate of patients used levodopa as anti-parkinson.<sup>9,15</sup> However, the effect of *OCT1* polymorphisms to the drug response in Asian is still being a challenge to the researcher. The previous studies in Japanese and Chinese found that the reduced-functions coding region of *OCT1* variants was more rare than those of Caucasians. Furthermore, these rare variants may alter the response of metformin as well.<sup>16</sup>

The aim of this review was to explore the polymorphisms of *OCT1* in Asians and Caucasians and to find the challenges of the next studies in Asians.

## MATERIALS AND METHODS

The articles about *OCT1* polymorphisms in the PubMed with the keywords; *OCT1* or *SLC22A1*, polymorphisms were searched. Ten articles of *OCT1* polymorphisms which are related to the drug response were found and most of the studies were performed in Caucasian subjects.

## RESULTS

The studies related to the *OCT1* polymorphisms and drug response are listed in TABLE 1. Two studies were performed in Asians and the others were performed in Caucasians. To date, with the limited number of *OCT1* polymorphism studies in Asian, the challenge of the topic is still opened.

TABLE 1. Studies of the *OCT1* polymorphisms and drug response

Author (year)	Variants	Drug	Subject	Outcome	Result
Zhou <i>et al.</i> , 2009	R61C and 420del	Metformin	Caucasian	Reduction of HbA1C level	These polymorphisms did not alter metformin response
Becker <i>et al.</i> , 2009	rs622342	Metformin	Caucasian	Reduction of glucose level and HbA1C level	The subject with minor C allele experienced less response of metformin
Tzvetkov <i>et al.</i> , 2009	R61C, G410S, G465R, M420del	Metformin	Caucasian	Renal clearance and plasma concentration	Subject with higher number of active alleles showed lower renal clearance and higher metformin plasma concentration
Kim <i>et al.</i> , 2009	rs683368	Imatinib mesylate	Caucasian	Laboratory test of imatinib response	GG genotype of the rs683368 was associated with less response of imatinib
Jablonski <i>et al.</i> , 2010	rs622342	Metformin	Caucasian	Development of diabetes disease	The rs622342 had no interaction with metformin intervention
Chen <i>et al.</i> , 2011	Q97K, P117L and R206C	Metformin	Japanese and Chinese	Michaelis- Menten parameter and uptake of metformin in cells	1. The uptake of metformin in cells by these variants was reduced significantly 2. P117 and R206C showed reduction of Vmax. 3. Q97K showed the increase of Km
Becker <i>et al.</i> , 2011	rs622342	Levodopa	Caucasian	Survival time	The subject with minor C allele had shorter survival time
Tzevetkov <i>et al.</i> , 2012	R61C, C88R, G410S, G465R, M420del	Ondansetron and tropisetron	Caucasian	Mean episode of vomiting after chemotherapy	Subjects with higher number of active alleles experienced more episode of vomiting than subjects with wildtype
Choi <i>et al.</i> , 2012	P283L, P341L	Metformin and lamivudine	Korean	The Clearance of metformine and lamivudine	Lamivudine uptake decreased in the variants of <i>OCT1</i> .

**DISCUSSION**

Most of the studies in the TABLE 1 were based on association of *OCT1* polymorphisms and metformin. Metformin mechanism was supposed to be related to activation of AMP-activated protein kinase (AMPK). This activation will suppress glucagon-stimulated glucose production, then it will increase the glucose-uptake in muscle and hepatic cells. The *OCT1* variants was supposed to mediate

metformin response in the first step of metformin action which involved the activation of AMPK.<sup>17</sup>

In the study of Caucasian patients with diabetes mellitus, the subjects with minor C allele of rs622342 experienced less response of metformin in reducing HbA1C and glucose levels.<sup>13</sup> In the other hand, the other study in Caucasian patients of diabetes mellitus found that the two reduced functions of *OCT1* polymorphisms, R61C and 420del, did not alter the metformin response in reducing HbA1C.<sup>14</sup> Contra-

dictively, the previous study in Caucasian showed that the subjects with the variants of R61C and 420del experienced the higher of area under the plasma concentration-time curve and higher maximum plasma concentration.<sup>18</sup> The different result of these two previous studies could be caused by the number of sample included in the study or the different design of study. The other study by Tzvetkov *et al* in Caucasian subjects also found that subject with higher number of active allele showed lower renal clearance and higher metformin plasma concentration. This study included R61C, G410S, G465R, M420del as the variants and were predicted as active and inactive function, such as OCT1\*1 (active), \*2, \*3, \*4 and \*5 (inactive).<sup>19</sup> Those allele variants could alter the disposition of OCT1 substrate. Therefore, the drug response will be changed.<sup>20</sup> The result of the metformin response study in Caucasian woman with polycystic ovarian syndrome which included similar SNPs also consistent with the Tzvetkov *et al* study.<sup>21</sup> In the future perspective, to conduct the study which exploring the pharmacokinetic parameters of metformin with considering the reduction of glucose levels and HbA1C levels is still being a good challenge in Caucasian.

In the study of metformin response in the Diabetes Prevention Program, there were 40 genes explored to understand the associations between the gene variants and metformin response. Most of the subjects in this study were Caucasians (55.9%) and 4.3% of Asians. The variants of *OCT1* which was associated to the metformin response were still robust. The SNP with rs622342 showed no interaction with metformin response.<sup>22</sup> The different results of this study and the study of Becker *et al*.<sup>9</sup> could be caused by the different condition of subjects participated in the studies. The expression of OCT1 is in the small intestine and small amount in the brain. The expression of OCT1 which involved in the differences of levodopa response was unknown. Therefore, to consider further study on rs622342 and exploring its association with glucose levels and HbA1C levels or considering the pharmacokinetic parameters of metformin is needed.

The study of *OCT1* polymorphism in Japanese and Chinese was conducted in understanding its role in metformin response. Nine SNPs were included in this study; -43T>G, S14F, R61C, S189L, G220V,

G410S, V408M, 420del and G465R. The study also identified the other non-synonymous variants. This study found that not all of the variants with decrease function in Caucasians were found in Japanese and Chinese patients with type 2 diabetes melitus. The nonsynonymous variants found in this study, Q97K, P117L and R206C, were associated with the reduced function of OCT1. Thus the uptake of metformin in subjects with these variants were significantly reduced.<sup>16</sup> We can conclude that the decreased functions of OCT1 variants in Caucasians were not found in Asians, furthermore the other nonsynonymous decreased functions of OCT1 variants were found in Japanese and Chinese with type 2 diabetes mellitus. The other study in Indian population found that P341L, M408V and 1386C>A variants in South Indian Tamilian. The allele frequencies of P341L and M408V were similar to the allele frequencies of Japanese and Korean population. However, the 1386C>A was not found in Japanese and Korean. The allele frequencies of P341L in Chinese and Vietnam population were lower than those in Indian. Nevertheless, there were no variants of M408V and 1386C>A found in Chinese and Vietnam. In Caucasian, the variants of P341L and 1386C>A were not found.<sup>23</sup> The other study reported that after haplotype analysis, the distribution of SNPs in Korean, Japanese and Chinese were similar.<sup>24</sup> This could be challenging for the next studies in Asians to find the new variants of *OCT1* which play role in drug response.

Imatinib, was largely used in treatment of chronic myeloid leukemia (CML). Around 20% CML patients did not get satisfactory response of imatinib because of the resistance.<sup>25</sup> The drug transporter variability was proposed as the variability of imatinib response. The active uptake of imatinib into cells was transported by OCT1 and this agent was metabolized by CYP3A4 and CYP3A5.<sup>26</sup> It was known that the drug disposition was mainly dependent on the role of liver metabolic enzymes and drug transporter. Imatinib was the weak substrate of OCT1 and the role of OCT1 was more related as surrogate expression of the others intracellular uptake transporter.<sup>27</sup> It was proved by pharmacogenetic study of imatinib in CML patients which showed that the GG genotype of rs683368 was associated to the loss response of imatinib together with the other predictive factors, such as

rs2231137 of *ABCG2* and the genotype of *CYP3A5*.<sup>15</sup>

The other previous study in Caucasian subjects was aimed to know the associations between *OCT1* variant of rs 622342 and the anti-parkinson drugs efficacy. Subjects who were prescribed levodopa for the first time were included in this study.<sup>28</sup> Levodopa is a substrate of OCT, even though the specific transporter is not clearly defined yet.<sup>9,28</sup> This study found that the subjects with minor C allele needed higher dose of prescribed anti-parkinson drug and also had shorter survival time after levodopa prescription. However, the authors of this study mentioned that the replication of this study will be needed because of the small number of participants might increase the possibility of false-positive findings.<sup>9</sup> According to the two previous mentioned studies in the metformin response, we could find that the minor C allele of rs622342 of *OCT1* may express the decrease function of OCT1 both in metformin and levodopa responses. The rs622342 was located in intron and it was known that this region had linkage of disequilibrium with the functional alleles.<sup>9</sup> This fact could affect the gene expression.

The recent study of *OCT1* role was performed by Tzvetkov *et al.*<sup>29</sup> toward ondansetron and tropisetron. The previous review found that the response of 5-Hydroxytryptamine Receptor Antagonists in Caucasian cancer patients could be affected by the polymorphisms of the 5-Hydroxytryptamine receptors, the Multi Drug Resistance 1 (MDR1) as the protein transporter uptake and *CYP2D6*.<sup>30</sup> Ondansetron and tropisetron were partly metabolized by *CYP2D6*, and these agents are being the OCT1 substrate. The R61C, C88R, G410S, G465R and M420del amino acid substitutions were included in Tzvetkov *et al.*<sup>29</sup> study. They performed the haplotype of these combinations and predicted the phenotype of the haplotype as fully active function and deficient function. This study concluded that the wildtype of *OCT1* showed less clinical efficacy of tropisetron than the two loss of functional variants. The tropisetron serum concentrations was higher in subjects with two loss of functional variants than those of wildtype. The effect of *OCT1* genotype was significantly higher in tropisetron than in ondansetron.<sup>29</sup> The previous study in Asians, showed that there were no associations between the polymorphisms of MDR1, 5-

Hydroxytryptamine B receptors and the *CYP2D6* predicted phenotypes and the ondansetron.<sup>31</sup> According to the study result of Tzvetkov *et al.*<sup>29</sup> this could be a challenge to know the association of *OCT1* polymorphisms and the ondansetron or tropisetron response in Asians, since there were still around 30% patients did not get satisfactorily response of ondansetron in acute phase of chemotherapy-induced nausea-vomiting.<sup>31</sup>

The newest study in Korean population, found that the P283L and P341L variants of *OCT1* could decrease the uptake of lamivudine.<sup>32</sup> The pharmacogenetic study of lamivudine is still limited. The previous study about pharmacogenetic of lamivudine was aimed to know the association between tumor necrosis factor-alpha promoter and lamivudine response. This study found that the non-responsive patients could be related to the variants of this gene.<sup>33</sup> It means that, lamivudine pharmacokinetic parameters information related to the pharmaco-genetic studies must be available to support the application of pharmacogenetic studies of lamivudine in clinical settings. However, the other genes which have role in lamivudine absorption, distribution, metabolism and excretion should be involved in the next studies.

## CONCLUSION

The studies of *OCT1* polymorphisms are going to widespread in the next further years. To apply the result findings in the metformin individualized therapy, we have to consider the ethnicities differences, because the non-synonymous variants found in Caucasians did not found in the Asians. However, the new non-synonymous variants were found in Asians and affected the metformin response. The studies about imatinib response and 5-Hydroxytryptamine Receptor Antagonists response will be the challenge in Asian. However, it is too early to implement the results of the various studies into clinical practice. Additional large studies also considering non-genetic risk factors are warranted.

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