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Change in molecular weight due to important pfatp6 and pfmdr1 polymorphisms and susceptibility to antimalarial drug: Possible role of epigenetic phenomenon

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ABSTRACT

Malaria is an important tropical mosquito borne infection. It is still the present global public health issue. The management of malaria requires antimalarial drugs. The resistance to antimalarial drugs is a very big problem. The genetic variant is proposed to be an important factor affecting susceptibility to antimalarial drug. Here, the authors studied the change in molecular weight due to important pfatp6 and pfmdr1 polymorphisms and further implied the interrelationship with susceptibility to antimalarial drug. The greatest change can be seen in case of G639D (of pfatp6 polymorphism) while the least change can be seen in the case of N1042D (of pfmdr1 polymorphism). The results from some studies imply that there must be other factors that affect the susceptibility to antimalarial drugs. Those factors might be protein conformation factors, epigenetic factors or environmental factors. Further studies on these aspects should be carried out. It is concluded for possible role of epigenetic phenomenon.

1. Introduction

Malaria is a vector borne disease. It is an important tropical mosquito borne infection that can be seen worldwide. Since it affects millions of world population, this infection is still the present global public health issue to be managed. The management of malaria requires early diagnosis and prompt treatment by antimalarial drug. In clinical practice, the resistance to antimalarial drug is a very big problem [1,2]. The genetic variant is accepted as an important factor determining susceptibility to antimalarial drug [3,4]. This is the same principle as seen in any infection. When there is a genetic change, the change in protein level and further change in expression can be expected. This can result in difference in response to pharmacologic treatment and it is the important explanation of the drug resistance phenomenon. Of interest, genetic variant is common and can be seen in any organisms. The clinical importance of genetic variant should be mentioned in clinical medicine. Here, the authors performed a study to assess the change in molecular weight due to important *Plasmodium falciparum* calcium-ATPase (pfatp6) and *Plasmodium falciparum* multidrug resistance 1 transporter (pfmdr1) polymorphisms. The results can help further imply the interrelationship with susceptibility to antimalarial drug. Based on the observation, the possible role of epigenetic phenomenon can be proposed.

2. Materials and methods

This work is a bioinformatics modeling study. The focused study molecules are pfatp6 and pfmdr1. The authors used standard quantum chemical calculation to calculate the change in molecular weight due to important pfatp6 (R37K, G639D and S769N) and pfmdr1 (N86Y, Y184F, N1042D and D1246Y) polymorphisms. The calculation is based on standard technique as previously described by the previous publication by Wiwanitkit [5,6]. Briefly, calculation of the molecular weight based on basic quantum chemical calculation was done for each naïve polymorphism. Then simulating change of genetic content according to each variant was assigned and the recalculation of the new molecular weight for each variant was done by the same basic quantum chemical calculation. The difference of molecular weight is then calculated by "difference of molecular weight = molecular weight after assignment of simulating genetic variance

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– molecular weight of naïve polymorphism". The derived final difference molecular weight was used for further comparison.

3. Results

Based on the modeling, the molecular weight change from calculation is shown in Table 1. According to Table 1, either increasing or decreasing molecular weight changes can be observed. It can be seen that the changes range from −58.03 to 27.93 (the magnitudes of change are from 0.98 to 58.03). The greatest change can be seen in case of G639D (of pfatp6 polymorphism) while the least change can be seen in the case of N1042D (of pfmdr1 polymorphism).

Table 1
The molecular weight changes from calculation.

Polymorphism		Change in molecular weight
pfatp6 polymorphism	R37K	27.93
	G639D	−58.03
	S769N	−27.02
pfmdr1 polymorphism	N86Y	−49.07
	Y184F	16.00
	N1042D	−0.98
	D1246Y	−48.09

4. Discussion

Adjalley *et al.* said that "the acquisition of multidrug resistance by *Plasmodium falciparum* underscores the need to understand the underlying molecular mechanisms so as to counter their impact on malaria control [7]." The focus in clinical pharmacology is on the polymorphism that possibly relates to drug susceptibility and resistance. Of several underlying genetic factors, pfatp6 is mentioned in the literature as the target of artemisinin and related endoperoxide [8], and pfmdr1 is mentioned in the literature for altering drug transport from the parasite's cytosol into the digestive vacuole [9]. Both pfatp6 and pfmdr1 are widely studied for the effects of the polymorphisms on antimalarial drug activity.

Based on the present study, it seems that the polymorphisms should have effect, either on increased susceptibility or resistance. Nevertheless, this is discordant with the recent *in vivo* studies. Phompradit *et al.* found that only "mutation at codon 86 was associated with a significant increase in the susceptibility of parasite isolates" to antimalarial drugs [10]. Cui *et al.* also found no association of the S769N mutation in pfatp6 with resistance to artemisinins [11]. The results from those studies imply that there must be other factors that affect the susceptibility to antimalarial drugs. Those factors might be protein conformation factors, epigenetic factors or environmental factors. Further studies on these aspects should be carried out.

Conflict of interest statement

We declare that we have no conflict of interest.

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