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Association of *ABCG2* genetic polymorphisms with subjective symptoms and weight gain by bictegravir administration in Japanese HIV-1-infected patients

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Background

Adenosine triphosphate-binding cassette transporter G2(*ABCG2*) is known to be expressed in the liver, the apical membrane of the small intestine, and the blood-brain barrier, and bictegravir (BIC) and other integrase inhibitors have been shown to be substrates of *ABCG2*. It has been suggested that decreased *ABCG2* function may increase the permeability of the blood-brain barrier for BIC[1)]. Also, *ABCG2* (421C>A) frequency is high in Asian populations, including Japanese[2)] .The principal aim of the study was to investigate the association between subjective symptoms induced by BIC administration and genetic polymorphisms of *ABCG2*.

Patients & Methods

Participants

The study subjects were 77 Japanese patients with HIV-1 infections who were receiving BIC at NHO Osaka National Hospital from April 2019 to December 2023. We compared the frequency of subjective symptoms among three groups: with homozygous mutations(Homo) in *ABCG2* (421C>A) ; with heterozygous mutations(Hetero); and wild-type(Wild). In addition, weight gain during the first 24 weeks of treatment was also compared in treatment-naïve patients.This study was reviewed and approved by the institutional review board of the NHO Osaka National Hospital (approval number: 19017).

Genotyping

Saliva samples were collected from the patients, absorbedwith a filter paper, and subsequently dried. A portion ofthe filter paper containing the saliva sample was cut and used as a template in the polymerase chain reaction (PCR) used to determine the presence or absence of gene poly morphisms.

Demographics of participants(Table 1)

ABCG2 genotype	Homo	Hetero	Wild	*p-value*
Participants (n, %)	7	26	44	
Age (years)	43 [39–49]	35 [30–42]	40 [34–47]	0.61
Males (n, %)	6(86%)	25(96%)	43(98%)	0.31
Body weight (kg)	59 [56–68]	67 [63–75]	64 [59–73]	0.80
Body Mass Index	23 [18.7-26.0]	23 [21.6-25.3]	22 [20.4-25.0]	0.27
ART naïve patient	5(71%)	20(77%)	31(70%)	0.84
CD4 cell count (cells/μL)	384 [276–468]	316 [222–553]	374 [251–495]	0.90
Participants with HIV-1-RNA level <50 at time of sampling (n, %)	2(29%)	6(23%)	13(30%)	0.84
AIDS(n, %)	0(0%)	2(8%)	7(16%)	0.35
HBV infection (n, %)	0(0%)	2(5%)	2(5%)	0.69
HCV infection (n, %)	0(0%)	2(5%)	0(0%)	0.13
Use of antiretroviral agents prior to initiation of BIC administration (n, %)				
Tenofovir alafenamide	2	6	11	0.95
Boosted PI	1	3	8	0.88
NNRTI	0	2	4	0.71
INSTI	1	2	1	0.32

Median [IQR] IQR, interquartile range

- The median age of the 77 patients (74 were male) was 38 years (interquartile range 33-47 years); 56 (73%) patients introduced BIC in the first antiretroviral treatment.
- The subjects comprised seven (9%) homozygotes, twenty-six (34%) heterozygotes, and 44 (57%) patients for the wild-type *ABCG2* genotype.

Results

Table 2. Correlation between *ABCG2* polymorphisms and Subjective symptoms

	All	Homo	Hetero	Wild	*p-value*
Participants	77	7	26	44	
Increased Appetite	20(31%)	3(43%)	11(42%)	6(14%)	0.017
Insomnia	6(8%)	2(29%)	3(12%)	1(2%)	0.037
Vivid Dreams	4(5%)	1(14%)	2(8%)	1(2%)	0.32
Forgetfulness	2(3%)	1(14%)	1(4%)		0.078
headache	2(3%)			2(5%)	0.46
Drowsiness	2(3%)		2(8%)		0.13

- Subjective symptoms developed in 34 of 77 patients (44%) .The frequency of expression of Increased Appetite and Insomnia was significantly higher in homo and heterozygous than wild type.

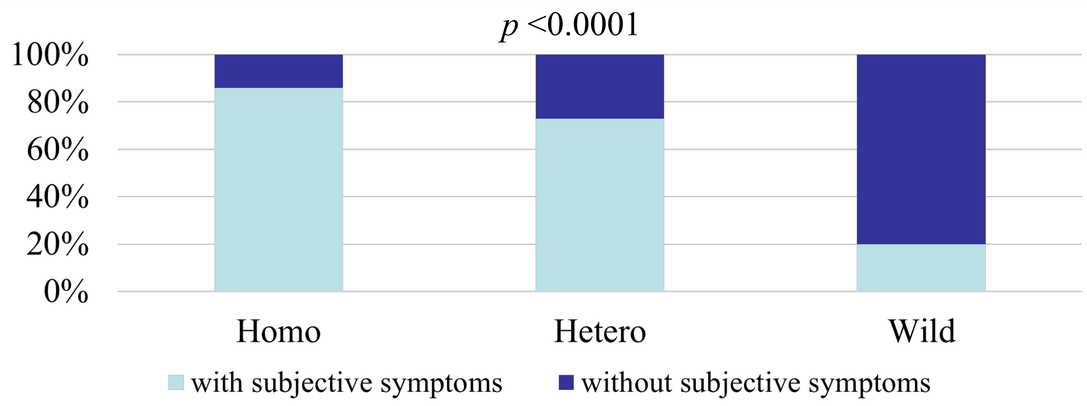

Fig.1 Association between ABCG2 polymorphisms and subjective symptoms developed ***p*-value by Cochran-Armitage test is shown**

- The frequencies of subjective symptoms in the three groups were: Homo, 86%; Hetero, 73%; and Wild, 20%. Significant difference in the frequency of subjective symptoms was evident in terms of *ABCG2* genetic polymorphisms (p<0.0001).

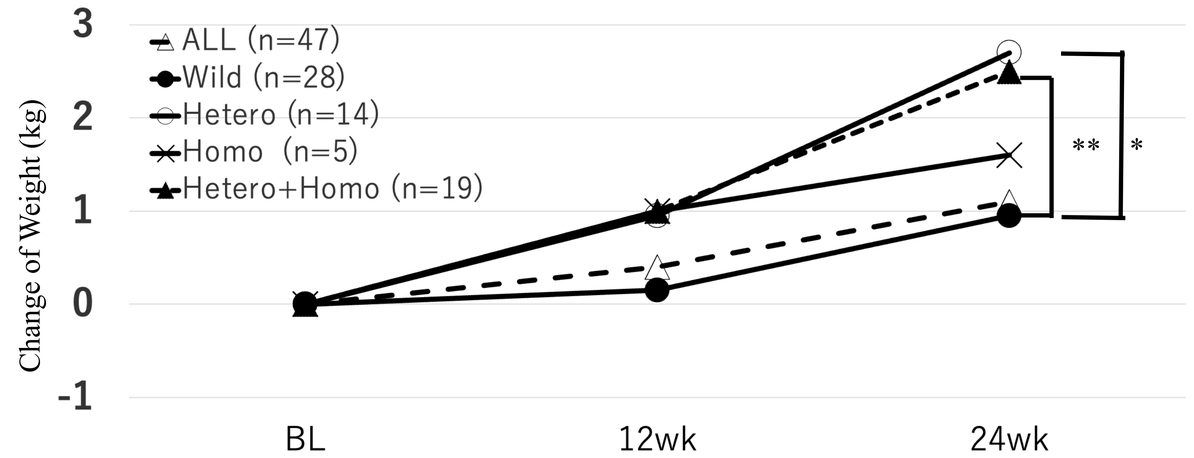

Fig.2 Association of *ABCG2* polymorphisms and weight change at day 1 to 24 week 24 in ART-naive Patients

- The median increase in body weight during the first 24 weeks of treatment was 2.5 kg for Homo + Hetero and 0.95 kg for Wild, and was significantly higher in the cases with the genetic mutation(p=0.006).

Limitations

This study was performed at a single institution with a limited number of Japanese patients.

Conclusions

ABCG2 genetic polymorphism may be a predictor of subjective symptoms and weight gain with BIC administration.

References

1) Kurose K, et al. Drug Metab Pharmacokinet, 2012;27:9-54.
2) Chang Huang, et al., Front Pharmacol, 2023, Mar 8:14:1118580.