Molecular characterization of Glucose-6-Phosphate Dehydrogenase: do single nucleotide polymorphisms affect hematological parameters in HIV positive patients?

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Abstract

Objectives: This descriptive, cross-sectional study aimed at evaluating the prevalence of G6PD deficiency, the 376A → G, 202G → A single nucleotide polymorphisms (SNPs) among HIV patients attending care at a teaching hospital in Ghana and determine if the SNPs are associated with a deranged hematological profile.

Results: Out of the 200 participants, 13.0% (26/200) were G6PD deficient based on the methemoglobin reductase technique, with 1.5% (3/200) and 11.5% (23/200) presenting with partial and full enzyme defect, respectively. Among the 13.0% participants with G6PD deficiency, 19.2% (5/26), 30.8% (8/26), and 19.2% (5/26) presented with 376A → G only [Enzyme activity (EA): 1.19 U/g Hb], 202G → A only [EA: 1.41 U/g Hb], and G202/A376 SNPs [EA: 1.14 U/g Hb], respectively. Having the 376A → G mutation was associated with lower red blood cell (RBC) count [3.38 x106/μL (3.16-3.46) vs 3.95 x106/μL (3.53-4.41), p=0.010], but higher mean cell volume (MCV) [102.90 (99.40-113.0) vs 91.10 fL (84.65-98.98), p=0.041] and mean cell hemoglobin (MCH) [33.70 pg (32.70-38.50) vs 30.75 pg (28.50-33.35), p=0.038] whereas possessing the 202G → A mutation was associated with higher MCV only [98.90 fL (90.95-102.35) vs 91.10 fL (84.65-98.98), p=0.041] compared to G6PD non-deficient participants.

Introduction

Human Immunodeficiency virus (HIV) is a chronic viral infection and a serious public health concern. Currently, approximately 37.9 million people are living with HIV worldwide [1]. In Ghana, 330 000 people are living with HIV [2].

HIV infection is associated with persistent inflammation and immune activation leading to production of reactive oxygen molecules and oxidative stress [3, 4]. Additionally, HIV positive individuals are predisposed to a plethora of other infections which may result in oxidative stress. The sequelae of these oxidative stress are particularly alarming and life-threatening in people comorbid with Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency. The prevalence rate of G6PD deficiency is 5–25% in tropical Africa and Asia [5–7]. In Ghana, the prevalence of G6PD deficiency is 15–26% [8, 9].

Over 400 G6PD variants have been identified [10] and the polymorphisms are predominantly defined to specific geographic locations [11]. About 186 of these variants are associated with G6PD deficiency due to decreasing enzyme activity or stability [5, 12, 13]. In sub-Saharan Africa, the predominant G6PD variants are B, A, and A-, with frequencies greater than 1% [14]. The G6PD B variant possesses the 376A cDNA sequence and has been shown to have normal enzyme activity. Likewise, the G6PD A variant, which carries a cDNA mutation A376G, has about 85% of the normal enzyme activity. On the contrary, the G6PD A- variants carry the G6PD A backbone with an added single nucleotide mutation. The most common G6PD A- variant possesses the A376G/G202A mutation and has been reported to have 10% of normal enzyme activity in their red blood cells (RBC), although their white blood cells (WBC) maintain

100% normal enzyme activity [15]. Other A- variants peculiar to sub-Saharan Africa are the A376G/T968C, A376G/G680T, and A376G/A543T [16].

In some conditions such as malaria, before primaquine administration, G6PD deficiency is screened for. However, the advantage of screening HIV positive patients for G6PD deficiency is often overlooked despite reports indicating worse clinical outcomes in people comorbid with HIV and G6PD deficiency [17–19]. Importantly, HIV and G6PD deficiency have individually being linked with deranged hematological profile. HIV affects all hematological cell lines, as evidenced by anaemia, neutropaenia, lymphopaenia, and thrombocytopaenia [20–23] whereas G6PD deficiency is associated with attenuated levels of haemoglobin (Hb), haematocrit (HCT), mean cell volume (MCV), and mean cell haemoglobin (MCH) [24]. Notwithstanding, studies on G6PD deficiency in HIV patients is limited in Africa, where both conditions are prevalent and none has been conducted in Ghana.

This study, thus, aimed at evaluating the prevalence of G6PD deficiency, the 376A → G, 202G → A single nucleotide polymorphisms (SNPs) among HIV patients attending care at a teaching hospital in Ghana and determine if the SNPs are associated with deranged hematological profile.

Methods

Study Design/Area

This descriptive, cross-sectional study was carried out between June 2018 and May 2019 at the HIV clinic of Komfo Anokye Teaching Hospital (KATH) in Kumasi.

Study Population

The sample size for the study was calculated using Fischer's sampling formula ($N = Z^2PQ/d^2$), where Z is the critical value of the normal distribution (1.96 at 95% CI); P is the estimated prevalence of G6PD deficiency in Ghana (15%) [8]; d is the absolute precision or sampling error tolerated = 5%. From the above equation, a total of 200 consecutive consenting HIV positive Ghanaians, aged 15 years and above, were recruited during their routine clinic visit days. All participants were on ART. Participants on sulfate and copper containing medications, those who were very ill and pregnant women were exempted from the study. Participants' selection protocol is shown in Additional file 1: Fig. S1.

Sample collection and assay

Six milliliters (6 ml) of venous blood was obtained from each participant under aseptic conditions for laboratory assessments. Complete blood count was evaluated using XN 2000 fully automated Sysmex Haematology analyzer (Sysmex Corporation, Kobe, Japan). G6PD screening was performed with the methemoglobin reductase technique as described by Brewer et al. [25] and patients were grouped into "normal", "partial defect" and "full defect" based on the color of the test solution as described by Antwi-Baffour et al. [26] (Details in Additional file 1: Table S1). G6PD enzyme activity assay was done for

samples that were G6PD deficient (both “full” and “partial defect”) during screening by the methemoglobin reductase technique using the Pointe Scientific G6PD kinetic kit according to manufacturer’s instructions (Standardized with an intra-assay % CVs of 2.5%-9.2% and inter-assay %CVs of 2.1%-11.4%) (Pointe Scientific Limited, UK). In preparation for G6PD genotyping, DNA was extracted from the blood samples that were G6PD deficient during screening. Extraction was based on the double salt precipitation method as previously described [27]. A large number of single nucleotide polymorphisms (SNPs) have been identified to be associated with G6PD deficiency in Africa [10, 11, 16]. However, 376A → G, 202G → A SNPs are the most commonly reported in Ghana [14, 28] and were thus selected for this study. For the 376A → G mutation, the forward and reverse primer sequences used were 5'-CCCAGGCCACCCCAGAGGAGA-3' and 5'-CGGCCCCGGACACGCTCATAG-3', respectively whereas those for the 202G → A mutation were 5'-CACCACTGCCCCTGTGACCT-3' and 5'-GGCCCTGACACCACCCACCTT-3', respectively (Inqaba Biotech Ltd, South Africa). The PCR cycling conditions were; one cycle of initial denaturation at 94 °C for 5 minutes, denaturation at 94 °C for 45 seconds, annealing at 56 °c for 30 seconds and extensions at 74° C for 45 seconds followed by five cycles of final extension at 74° c for 5minutes (For 35 cycles). The amplified products were separated by electrophoresis on 1% agarose gels stained with ethidium bromide and visualized under UV light for the presence of bands indicative of 376A → G and 202G → A mutations (Additional file 1: Fig. S2).

Statistical Analysis

Statistical analysis and graphical presentation were performed using the R Language for Statistical Computing version 3.5.2 (R Core Team, Vienna, Austria) [29]. Categorical data were presented as frequencies (percentages). Normality of continuous data was evaluated using Shapiro-Wilk’s test. All continuous data were non-parametric and were presented as medians (interquartile ranges). Significance of differences of hematological parameters between various variants of G6PD were tested with Kruskal-Wallis tests, followed by Dunn’s post-hoc multiple comparison tests. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

A total of 200 participants with an average age of 42.0 (35.0–50.0) years were included in this study. A higher proportion were females (84.0%) and had basic education (65.5%). The average RBC count, Hb, MCV, MCH, platelet (PLT) count, and WBC count were 3.88×10^6/μL, 12.0 g/dL, 91.75 fL, 31.25 pg, 222.0×10^3/μL, and 5.13×10^3/μL, respectively (Table 1).

Table 1
Baseline characteristics of the study population

Variables	Frequency (n = 200)	Percentage (%)
Demographic		
Sex		
Female	168	84.0
Male	32	16.0
Age (years)*	42.0	35.0–50.0
Educational level		
Illiterate	44	22
Basic	131	65.5
Secondary	19	9.5
Tertiary	6	3.0
Hematological*		
RBC count ($x10^6/\mu L$)	3.88	3.47–4.34
Hb (g/dL)	12.00	10.97–13.10
MCV (fL)	91.75	85.05–100.0
MCH (pg)	31.25	28.80-34.33
PLT count ($x10^3/\mu L$)	222.0	196.80–591.00
WBC count ($x10^3/\mu L$)	5.13	4.83–6.17
*Data presented as median and interquartile ranges		

Out of the 200 participants screened using the methemoglobin reductase technique, 13.0% (26/200) were G6PD deficient, with 1.5% (3/200) and 11.5% presenting with partial and full enzyme defects, respectively (Fig. 2a). Among the 13.0% (23/200) with G6PD deficiency, 19.2% (5/26), 30.8% (8/26), and 19.2% (5/26) presented with 376A → G only, 202G → A only, and G202/A376 SNPs, respectively (Fig. 2b). Upon stratification by sex, 4, 7, 4, and 5 of the females, and 1, 1, 1, and 2 of the males had the 376A → G only and 202G → A only, G202/A376 SNPs, and no band, respectively (Fig. 2c). The likelihood of being phenotypically classified as G6PD full defect was higher among participants having the G202/A376 SNPs compared to the 202G → A SNP (Additional file 1: Table S2).

Participants with only the 376A → G mutation presented with significantly lower RBC count [3.38 × 10^6/μL (3.16–3.46) vs 3.95 × 10^6/μL (3.53–4.41), p = 0.010], but higher MCV [102.90 (99.40–113.0) vs 91.10 fL (84.65–98.98), p = 0.041] and MCH [33.70 pg (32.70–38.50) vs 30.75 pg (28.50-33.35), p = 0.038] compared to G6PD non-deficient participants. On the other hand, participants with only the 202G → A mutation had significantly higher MCV [98.90 fL (90.95-102.35) vs 91.10 fL (84.65–98.98), p = 0.041]. No statistically significant association was found between haemoglobin level, PLT, and WBC counts and G6PD variants (Fig. 3).

Discussion

This study reports a 13.0% prevalence of G6PD deficiency, comprising 5% and 11.5% partial and full enzyme defect, respectively, based on methemoglobin reductase technique. Our finding is consistent with a retrospective study by Tungsiripat et al. among HIV patients in the United States. After screening 212 Blacks infected with HIV, they found 28 (13.2%) to be G6PD deficient [30]. In another study by Serpa et al. [31] in the United States, 6.8% of all HIV-infected adults had G6PD deficiency which is lower compared to this present study. The disparity in the prevalence rates could be linked to the fact that Serpa et al. included participants of diverse race (African Americans, Hispanics, Whites and Asian-Pacific). Evidence suggests that the prevalence of G6PD deficiency is very low among whites compared to blacks [30, 32]. Thus, the inclusion of Caucasians may have attenuated the prevalence rate found in their study. Our finding also falls within the prevalence range of 5–25% found in tropical Africa, the Middle East, tropical and sub-tropical Asia, some parts of the Mediterranean, and in Papua New Guinea [5–7].

In this study, among the participants with G6PD deficiency, we found 19.2% to harbor the G6PD A- allele (G202/A376) which is associated with reduced enzyme activity [15]. A study by Xu et al. in the Dominican Republic also reported a similarly high prevalence of the G6PD A- variant among HIV-infected patients [33]. Of note, we also observed that, among those with G6PD deficiency based on the methemoglobin reductase technique, 30.8% presented with no band on electrophoresis. It is possible that these patients harbored other G6PD variants such as the A376G/T968C, A376G/G680T, and A376G/A543T which are also peculiar to sub-Saharan Africa [16]. Importantly, seven and four of the females versus one and two of the males had the G6PD A and G6PD A- allele, respectively. Congruently, more females than males with the G6PD A- variants have been reported in previous studies in Ghana [14, 28]. An explanation could be the higher number of females in this study compared to males. The consistently higher number of HIV positive females compared to males in Kumasi justifies the gender disparity [34, 35].

Another finding of this study is that the presence of only the 376A → G mutation was associated with lower RBC count, but higher MCV and MCH whereas possessing only the 202G → A mutation was only associated with significantly higher MCV. The relatively greater deranged hematological profile in the participants with the 376A → G compared to the 202G → A could be attributed to the comparatively lower G6PD enzyme activity among participants with the 376A → G mutation compared to the 202G → A mutation, although not statistically significant (Additional file 1: Fig. S3). In a study to find the association between G6PD deficiency and hematological parameters in children from Botswana,

Motshoge et al. made similar observations [36]. The increased MCV due to the 202G → A mutation is also in harmony with a GWAS study by Ding et al.[37]. Other reports such as those by Ajlaan [38] and Domingos et al. [39] are in line with our study findings.

Conclusion

This study reports a 13.0% prevalence of G6PD deficiency, comprising 1.5% and 11.5% partial and full enzyme defect, respectively, based on the methemoglobin reductase technique among HIV patients in Ghana. Among G6PD deficient HIV patients, the prevalence of G202/A376 SNPs is 19.2%. The 376A → G mutation is associated with lower RBC count, but higher MCV and MCH whereas the 202G → A mutation is associated with higher MCV.

Limitations

Unavailability of data on important modifying genotypes such as HbS; alpha-thalassemia 3.7 deletion as well as data on ART; its adherence and CD4 count is a limitation of this study. This study is also limited by the relatively small sample size and the cross-sectional design used which precluded comparison with non-HIV group. Larger sample sizes in future studies will be ideal.

Abbreviations

HIV
Human Immunodeficiency virus
G6PD
Glucose-6-phosphate dehydrogenase
SNP
Single nucleotide polymorphisms
Hb
Hemoglobin
HCT
Hematocrit
RBC
Red blood cell
WBC
White blood cell
PLT
Platelet
MCV
Mean cell volume
MCH
Mean cell hemoglobin

Declarations

Ethics approval and consent to participate

This study was approved by the Committee on Human Research Publication and Ethics (CHRPE) of the School of Medical Sciences, Kwame Nkrumah University of Science and Technology. Written informed consent was obtained from all participants who opted to participate after the aims and objectives of the study was explained to them.

Consent for publication

Not applicable.

Availability of data and material

The datasets supporting the conclusions of this article are included within the article and its supporting file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

OAM, AYD and KOD designed the study, supervised the research and laboratory analysis and revised the manuscript. KM, CN, SKA, MN, YH, DON, LAB and MEAA were involved in the collection of data, laboratory analysis and revision of the manuscript. EWO was involved in the statistical analysis and interpretation, drafting and revision of the manuscript. All authors read and approved the final manuscript.

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Additional File

Additional file 1. Flowchart of the protocol for the selection of study subjects; Gel image of SNPs used in this study; Comparison of G6PD enzyme activity by the presence of 376A → G only and 202G → A only and G202/A376 SNPs.

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Figures

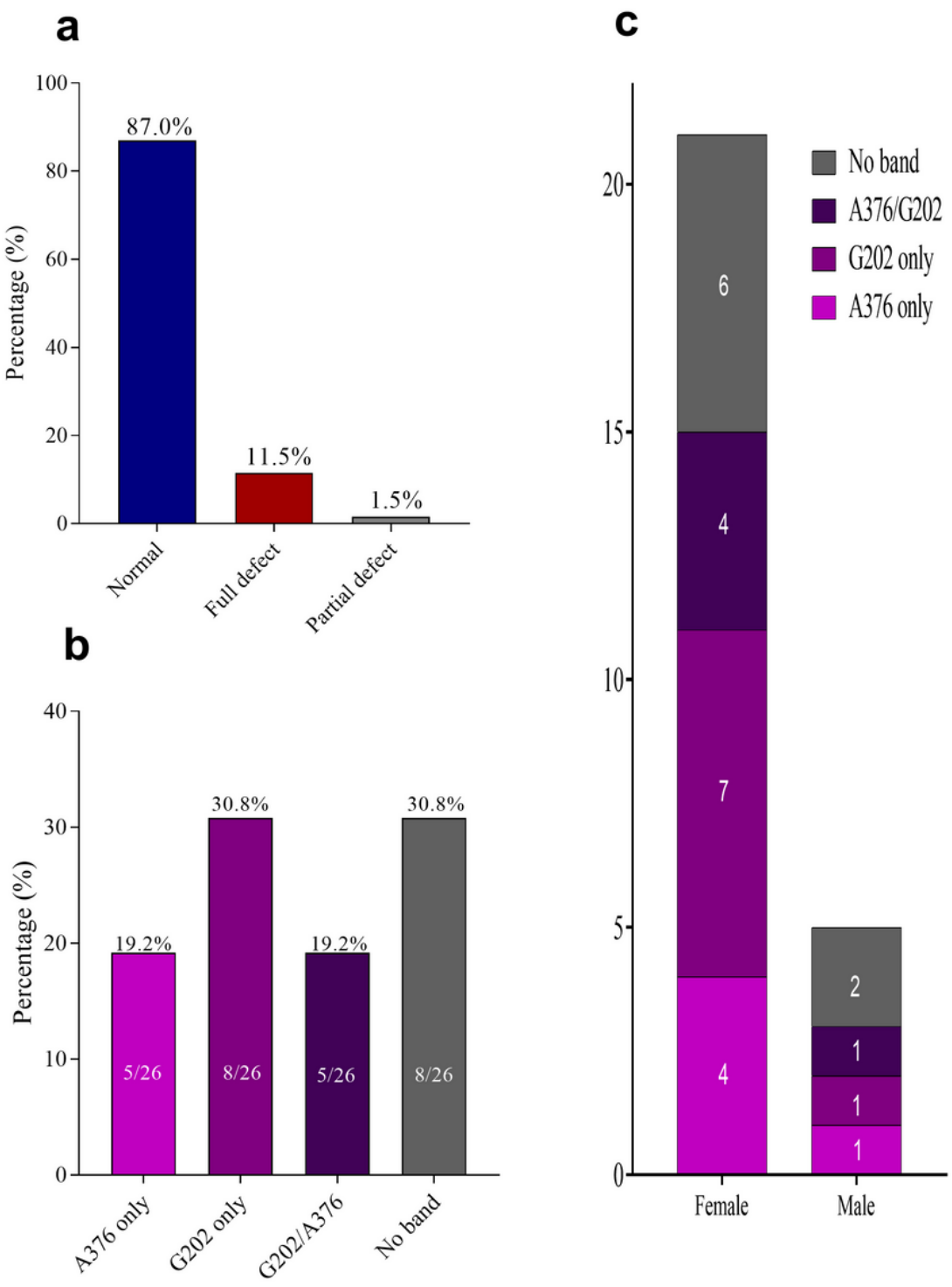

Figure 1

Prevalence of G6PD deficiency. (a) Phenotypic prevalence of G6PD deficiency based on methemoglobin reductase technique (b) Genotypic prevalence of 376A → G, 202G → A, G202/A376 G6PD variants (c) Genotypic prevalence of 376A → G, 202G → A, G202/A376 G6PD variants by sex.

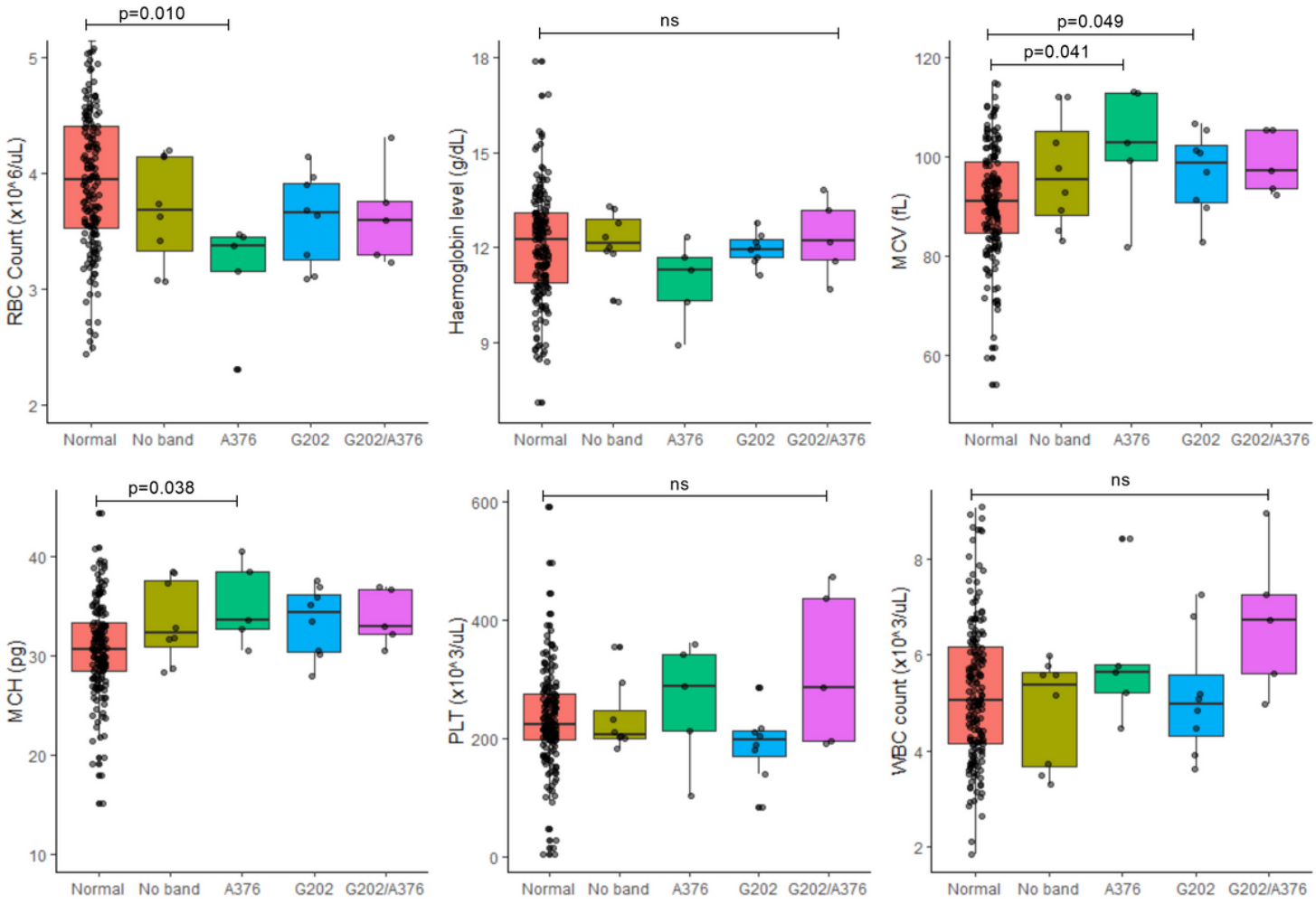

Figure 2

Comparison of hematological parameters by G6PD genotype.

Supplementary Files

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