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PHARMACOGENETICS

Association between *CYP2B6* polymorphisms and Nevirapine-induced SJS/TEN: a pharmacogenetics study

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Abstract
Purpose Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor, widely prescribed for type 1 human immunodeficiency virus infection. A small proportion of individuals treated with NVP experience severe cutaneous adverse events, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Our aim was to verify whether genetic variability in NVP-metabolizing cytochromes or in transporter genes could be involved in susceptibility to SJS/TEN.
Methods Twenty-seven patients with NVP-induced SJS/TEN and 78 controls, all from Mozambique, were genotyped for the *ABCB1* and *ABCC10* transporter genes and for *CYP2B6*, *CYP3A4* and *CYP3A5* cytochrome gene variants. A case–control and a genotype–phenotype analysis were performed.
Results *CYP2B6* G516T and T983C single nucleotide polymorphisms (SNPs) were found to be associated with SJS/TEN susceptibility. The 983C allele in particular was found to be highly associated with a higher risk to develop SJS/TEN [odds ratio (OR) 4.2, P=0.0047]. The GT haplotype (wildtype for both SNPs) showed a protective effect, with an OR=0.33 (P=0.0016).
Conclusions This is the first study showing that genetic variability in a metabolizing enzyme can also contribute to NVP-induced SJS/TEN susceptibility.

Keywords Stevens–Johnson syndrome · Toxic epidermal necrolysis · Pharmacogenomics · Nevirapine · Single nucleotide polymorphisms · *CYP2B6* gene

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Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe cutaneous disorders characterized by acute skin blisters and mucous membrane erosions. They are complex hypersensitivity reactions that are caused by drugs in about 75 % of the cases; viral infections and mycoplasma pneumonia infection have also been reported as potential causes [1, 2]. In the general population TEN affects approximately 0.4–1.2 individuals per million every year, while SJS occurs more frequently, affecting one to six individuals per million every year [3, 4]. Skin lesions are frequent expressions of an adverse drug reaction and are characterized by acute exanthema which progress towards limited (SJS) or widespread (TEN) blistering and erosions of the skin and mucous membrane [5]. The mortality rate is almost 10 % for patients with SJS, approximately 30 % for patients with SJS/TEN-overlap and almost 50 % for patients with TEN [1]. Although these cutaneous reactions are rare, a number of drugs are more often associated with the onset of these disorders [6], including antibacterial sulfonamides, cabamazepine, fosphenytoin, lamortrigine, oxcarbazepine, phenobarbital, phenytoin, allopurinol and nevirapine (NVP) [7]. NVP is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is widely prescribed for type 1 human immunodeficiency virus (HIV) infection. Although

generally well tolerated and effective, some individuals exposed to NVP experience severe cutaneous adverse events, including SJS/TEN during the first few weeks of therapy [8, 9]: the reaction can begin 10–240 days after the introduction of NVP (median 12 days) [10].

Several features of NVP hypersensitivity suggest that genetic factors may play an important predisposing role and, in recent years, several studies have explored the influence of genetic variability on NNRTI treatment response [11], with the results suggesting that the development of SJS/TEN depends on an immune mechanism. Findings from studies in Han-Chinese and South-Eastern Asian populations indicate a correlation between some HLA alleles and SJS/TEN induced by allopurinol or by carbamazepine. In the case of allopurinol-induced SJS/TEN in a Han-Chinese population, the HLA-B*58:01 allele was identified in all patients with SJS/TEN and in only 12–15 % of tolerant patients [12, 13]. This association has also been reported in a European population [14]. Another HLA allele (B*15:02) has been identified in Thai [15], Malaysian [16] and Taiwan populations [17] as being associated with a larger susceptibility to SJS/TEN induced by carbamazepine. This correlation, however, has not been replicated in other populations. For example, studies performed on European patients with carbamazepine-induced SJS/TEN failed to confirm the association with HLA-B*15:02 [18, 19].

Two recent genome-wide association studies [20, 21] have identified further associations with SJS/TEN on chromosome 6 within the *HCP5* and *PSORS1C1* genes; the first study, performed on allopurinol–treated Japanese patients, described a strong association with both genes [20], whereas the second study, performed in an European large cohort of patients treated with allopurinol, carbamazepine or phenytoin drugs, reported a stronger association with the HCP5 gene [21].

Most studies have analysed the genetic contribution to NVP-hypersensitivity, including rash and other cutaneous adverse reactions [11, 22], but not focussed on SJS cohorts. HLA-DRB1*01 [22] and polymorphisms in the cytochrome P450 2B6 gene (*CYP2B6*) [11] have been associated with rash induced by NVP. Another recent study has identified the HLA-B*35:05 allele as being involved in NVP-induced rash in a Thai population with high specificity [23].

Other studies have highlighted the involvement of genetic factors in the development of hepatotoxicity after treatment with NVP [24–28]. A polymorphism in the *ABCB1* (ATP-binding cassette sub-family B member 1) gene [also known as *MDR1* (encoding multidrug resistance protein 1)] has been found to be associated with a minor risk to develop hepatic toxicity [24, 25]. The rs2125739 polymorphism in the *ABCC10* (encoding multidrug resistance-associated protein 7) gene has recently been described as significantly associated with plasma NVP concentration [29]. Several studies have highlighted a role in NVP-hepatotoxicity for a polymorphism in the *CYP2B6* gene [c.516G>T single nucleotide polymorphism (SNP)] [25–30], with the *CYP2B6* 516TT genotype found to be associated with higher plasma exposure to NVP [30].

To date, no studies have consistently investigated the involvement of genetic factors in the context of SJS/TEN induced by NVP: polymorphisms in genes of cytochromes that metabolize the NVP or in genes of transporters have as yet only been studied in relation to hepatotoxicity or cutaneous rash. For this reason, we have performed a retrospective study in a Mozambique population treated with NVP to verify whether genetic variability in cytochromes that metabolize NVP (*CYP2B6*, *CYP3A4*, *CYP3A5*) or in transporter (*ABCB1* and *ABCC10*) genes could be involved in susceptibility to SJS/TEN.

Material and methods

Patient recruitment and ethics statement

Subjects were recruited from patients accessing NVP-based combination treatment (azidothymidine/stavudine plus lamivudine and NVP) according to the reported criteria [DREAM: an integrated faith-based initiative to treat HIV/acquired immunodeficiency syndrome (AIDS) in Mozambique (www.who.int/hiv/pub/casestudies/mozambiquedream.pdf] in three Drug Resource Enhancement against AIDS and Malnutrition (DREAM) centers in Mozambique.

A protocol entitled “Study on genetics of nevirapine related adverse reactions in HIV women” was submitted to the National Health Bioethics Committee of Mozambique in 2007, within the framework of the DREAM programme. Approval was received in 2008, and the study was consequently authorized by the Minister of Health. Informed consent and specific permission to use genetic data was administered and signed by each participant in the study.

Cases were selected based on the diagnosis of the clinicians and reported in the database. The clinical diagnosis was based on the development of exanthema, mainly starting on the trunk, involving more than 10 % of the body surface, with mucosal involvement. In these patients, the skin lesions had not given pruritus and a skin detachment had been observed by the clinicians who made the diagnosis. Controls were randomized from the same health centers and were defined on the basis of the absence of SJS/TEN development during at least 4 years of treatment involving NVP. We retrospectively recruited 27 unrelated patients who had developed SJS/TEN and 78 controls. All patients were females. An anonymous code identifier was assigned to all patients. Laboratory analyses were performed using the coded identifiers only. The treatment protocol included the monitoring of the

transaminases values, viral loads and CD4 cells before and after starting the antiretroviral therapy. The clinical baseline characteristics of all patients are reported in Table 1. There were no significant differences in clinical features between cases and controls (Table 1).

DNA extraction and genotyping

DNA extraction was performed using the Wizard® Genomic DNA Purification kit (Promega, Madison, WI). Exons 4, 5 and 7 in the *CYP2B6* gene, exons 21 and 26 in the *ABCB1* gene and exon14 in the *ABCC10* gene were analysed by direct sequentcing. The rs2740574 and rs776746 SNPs in the *CYP3A4* and *CYP3A5* genes, respectively, were genotyped using the allelic discrimination assay by real-time PCR. Exon sequencing and SNP genotyping were performed as described by Ciccacci et al. [24].

Statistical analysis

Hardy–Weinberg equilibrium was verified for all examined SNPs by the Pearson χ^2 test. The same test was used to evaluate differences in allelic, genotypic and haplotypic frequencies between cases and controls (1 *df*, considering together the heterozygotes and variant homozygotes). Odds ratios (OR) with 95 % confidence intervals (CI) were calculated. We used analysis of variance to evaluate differences in the distribution of transaminase levels, viral loads and CD4 cells counts between cases and controls. A binary logistic regression analysis (stepwise method with forward approach) was performed taking into account the occurrence of SJS/TEN as the dependent variable and including in the model, as independent variables, the two *CYP2B6* variants (that resulted associated with SJS/TEN) and CD4 levels, age and body mass index (BMI). CD4 levels were considered by steps of 50 cells/μl. The cutoff for statistical significance was set at a p value of<0.05.

All statistical analyses were performed by the SPSS program (SSPS, Chicago, IL).

Haplotype analysis

Haplotypes were inferred using Arlequin [31] ver. 3.11. Differences in the haplotype distribution between cases and controls were evaluated by the χ^2 test.

Results

Case–control association analysis

The cases were 27 patients who had developed SJS/TEN during the first weeks of NVP treatment (after 29 days on average) and the controls were 78 patients who did not show any adverse reactions during a prolonged NVP treatment (at least 4 years). Clinical characteristics of cases and controls are reported in Table 1. Deviations from Hardy–Weinberg equilibrium for the SNPs examined were not observed. Table 2 shows the distribution of the genotypes and alleles in cases and controls.

Interestingly, the distribution of the *CYP2B6* G516T and T983C SNP genotypes highlighted a difference between cases and controls, suggesting that in our study cohort the *CYP2B6* variants were significantly associated with susceptibility to SJS/TEN. Heterozygotes and variant homozygotes for the G516T SNP were present at a higher frequency in cases than in controls (51.9 and 29.6 % vs. 48.7 and 16.7 %, respectively). Individuals carrying the variant alleles seemed to have about a twofold higher risk to develop the SJS/TEN (OR 1.8) although the difference did not reach significance (P=0.064). Moreover, the risk of an individual carrying the variant homozygote genotype was 3.32 respect to a wildtype subject (P=0.063). The results regarding the other *CYP2B6* SNP, T983C, were even more interesting in that the variant homozygote genotypes were only found in the cases (11.1 vs. 0 % in controls). Moreover, there was a higher frequency of heterozygotes in cases than in controls (14.8 vs. 10.3 %, respectively). The C allele was significantly associated with a higher risk to develop SJS/TEN (OR 4.2, P=0.0047).

Table 1 Clinical baseline characteristics of patients

Clinical characteristics at baseline	SJS/TEN	Controls	All	*P* (SJS/TEN vs. controls)
Age (years)	31 (27–36)	32 (27–36)	32 (27–36)	0.8
Viral load (log copies/ml)	4.1 (3.2–4.6)	3.58 (2.39–4.43)	3.72 (2.98–4.49)	0.41
CD4 cell count, median (cells/mm^3)	467 (326–721)	393 (227–591)	409 (230–634)	0.21
Body mass index	22.8 (21.5–25.4)	22.8 (21.6–26.3)	22.8 (21.6–25.9)	0.78
Alanine aminotransferase (U/l)	8.6 (6.9–12.8)	10.7 (7.3–15.4)	10.2 (7.1–15.2)	0.28
Aspartate aminotransferase (U/l)	20.5 (15.9–23.5)	20.3 (16.9–23.6)	20.4 (16.8–23.6)	0.91

SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis

Values are reported as the median with the interquartile range given in parenthesis

Table 2 Case–control association analysis

Gene	Single nucleotide polymorphisms	SJS/TEN controls	*n*	Genotypes			Odds ratio (95 % CI)	*P*[a]	Alleles		Odds ratio (95 % CI)	*P*
				wt/wt (%)	wt/var (%)	var/var (%)			wt (%)	var (%)		
CYP2B6	G516T (rs3745274)	SJS/TEN	27	18.5	51.9	29.6	2.33 (0.79–6.84)	0.12	44.4	55.6	1.8 (0.96–3.36)	0.064
		Controls	78	34.6	48.7	16.7			59.0	41.0		
	c.646-159G>C (rs58425034)	SJS/TEN	26	57.7	26.9	15.4	1.53 (0.61–3.8)	0.36	71.2	28.8	1.82 (0.88–3.77)	0.1
		Controls	77	67.5	28.6	3.9			81.8	18.2		
	c.646-106G>A (rs8192715)	SJS/TEN	27	40.8	44.4	14.8	0.79 (0.32–1.93)	0.6	63.0	37.0	0.78 (0.41–1.48)	0.45
		Controls	77	35.1	44.1	20.8			57.1	42.9		
	c.646-17C>T (rs12721646)	SJS/TEN	27	66.7	22.2	11.1	1.04 (0.41–2.64)	0.92	77.8	22.2	1.29 (0.6–2.75)	0.52
		Controls	77	67.5	28.6	3.9			81.8	18.2		
	A785G (rs2279343)	SJS/TEN	27	29.6	44.4	26.0	1.21 (0.47–3.14)	0.69	51.9	48.1	1.24 (0.66–2.31)	0.5
		Controls	77	33.8	46.7	19.5			57.1	42.9		
	T983C (rs28399499)	SJS/TEN	27	74.1	14.8	11.1	3.06 (0.99–9.48)	0.058	81.5	18.5	4.2 (1.56–11.3)	0.0047*
		Controls	78	89.7	10.3	0			94.9	5.1		
CYP3A4	G-392A (rs2740574)	SJS/TEN	27	51.9	48.1	0	1.08 (0.45–2.6)	0.86	75.9	24.1	0.86 (0.42–1.76)	0.68
		Controls	78	53.8	38.5	7.7			73.1	26.9		
CYP3A5	A6986G (rs776746)	SJS/TEN	26	57.7	34.6	7.7	1.65 (0.66–4.12)	0.28	75.0	25.0	1.52 (0.72–3.22)	0.27
		Controls	78	69.2	25.7	5.1			82.1	17.9		
ABCB1	T3421A (rs2229107)	SJS/TEN	27	77.8	22.2	0	1.2 (0.41–3.5)	0.74	88.9	11.1	1.09 (0.4–2.96)	0.86
		Controls	78	80.8	17.9	1.3			89.7	10.3		
	C3435T (rs1045642)	SJS/TEN	27	70.4	29.6	0	0.95 (0.36–2.46)	0.92	85.2	14.8	0.91 (0.38–2.16)	0.84
		Controls	78	69.2	29.5	1.3			84.0	16.0		
ABCC10	C3058T (rs2125739)	SJS/TEN	27	55.6	37	7.4	0.89 (0.37–2.14)	0.79	74.1	25.9	0.92 (0.46–1.86)	0.82
		Controls	78	52.6	39.7	7.7			72.4	27.6		

*Significant at $P < 0.05$

wt, Wildtype; var, variant; CI, confidence interval

[a] Heterozygotes and variant homozygotes were considered together (1 *df*) in the comparisons between genotypes (Pearson χ^2 - test or Fisher exact test when required)

Our study did not reveal any significant association with the SNPs in the other cytochrome (*CYP3A4* and *CYP3A5*) and in the transporter (*ABCB1* and *ABCC10*) genes.

Haplotype analysis

We have inferred haplotypes between the two *CYP2B6* SNPs associated with susceptibility to SJS/TEN. The comparison between the distribution of haplotypes in cases and controls is shown in Table 3. Only one subject (a SJS/TEN patient) carried the haplotype with both variant risk alleles. It is interesting to note that the wildtype haplotype showed a protective effect with respect to the susceptibility to SJS (OR=0.33, P=0.0016). The GC haplotype (containing the wildtype allele of the G516T SNP and the variant allele of the T983C SNP) seemed to contribute to SJS/TEN susceptibility more than the TT haplotype (containing the variant allele of G516T and the wildtype allele for T983C) (OR 3.7 vs. 1.67, respectively).

Genotypes analysis

Analyzing the distribution of genotypes of the two SNPs (G516T–T983C) together (Fig. 1), we observed that individuals who were wildtype for both SNPs (GG/TT) were only present in the control group [30.7 % (controls;24 subjects) vs. 0 % (cases)]. These individuals also carried a double dose of wildtype haplotype that was found to be highly protective in the haplotype analyses. On the contrary, individuals carrying the GG/CC and the TT/TC genotypes were present only among cases (about 15 %). These observations reflect the fact that individuals with a double dose of wildtype haplotype are likely to have some degree of protection against SJS/TEN susceptibility, while individuals with the GG/CC and TT/TC genotypes have a very high risk to develop SJS/TEN.

Logistic regression analysis

Binary logistic regression analysis (stepwise method with forward approach) was carried out with the occurrence of SJS/TEN considered to be the dependent variable and G516T and T983C variants, CD4 cell count, age and BMI taken as the independent variables. The final result of the stepwise analyses is shown in Table 4. One interesting observation is that all variables included in the final model contributed significantly to the development of SJS/TEN. The two *CYP2B6* genetic variants showed a high OR (Exp B) (OR=5.4, P=0.0012 and OR=4.7, P=0.026 for G516T and T983C, respectively), confirming that CYP2B6 variability played a role in SJS/TEN susceptibility among our study cohort. Variables included in our model explained about 17 % of the contribution to the disease susceptibility (Cox and Snell R^2).

Discussion

In the present study we investigated associations between genetic variants in drug-metabolizing enzymes and transporters and SJS/TEN in HIV-1 patients from Mozambique who had initiated NVP treatment. SJS/TEN is characterized by rapidly developing, painful or burning blistering exanthema with mucosal involvement and skin detachment. Although SJS and TEN are very rare conditions, they are associated with an overall high mortality, and affected individuals require intensive treatment [2]. Although SJS/TEN pathophysiology remains largely unknown, previous reports suggest an immune mechanism involving a drug-dependent cytotoxic cell response against epidermal cells. Some studies, especially those involving Han-Chinese and South-Eastern Asian populations, have reported an association between HLA-B alleles and SJS/TEN induced by allopurinol (HLA-B*58:01) or by carbamazepine (HLA-B*15:02). Evidence for such associations have not been replicated in other populations, suggesting that other alleles and other mechanisms could also be involved. We hypothesized that variability in genes involved in NVP metabolism and transportation could also influence susceptibility to SJS/TEN, as has been demonstrated for hepatic toxicity and cutaneous rash [24–28]. To this end, we performed a case–control association analysis to investigate the possible role of genetic variants in the cytochromes and transporters involved in NVP metabolism or transportation with respect to SJS/TEN susceptibility.

Table 3 Distribution of haplotypes between G516T and T983C single nucleotide polymorphisms in SJS/TEN patients and controls

Haplotype	SJS/TEN, *n* (%)	Controls, *n* (%)	*P*	*P* each vs. others	Odds ratio	95 % CI
GT	15 (27.8)	84 (53.9)	0.0008*	0.0016*	0.33	0.16–0.68
GC	9 (16.6)	8 (5.1)		0.017*	3.7	1.27–10.82
TT	29 (54)	64 (41)		0.15	1.67	0.89–3.11
TC	1 (1.8)			ND		

*Significant at $P < 0.05$

ND, Not determined

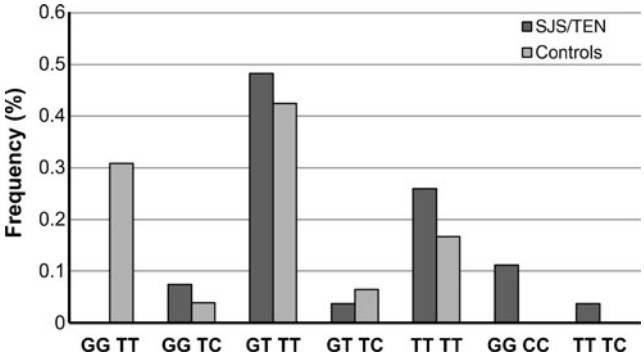

Fig. 1 Distribution of the G516T and T983C genotypes in SJS/TEN patients and controls

Our main finding is the strong association between the T983C *CYP2B6* SNP and susceptibility to NVP-induced SJS/TEN. The frequency of the 983C allele in our control population was 5.1 %, which is well in line with that reported previously [32]. Interestingly, in our study cohort the frequency of the C allele was considerably higher in patients with SJS (18.5 %) than in the controls. The risk of SJS/TEN in individuals with the variant allele was 4.2 with respect to those with the wildtype allele, suggesting that this SNP is highly associated with SJS/TEN susceptibility. Moreover, it was notable that the variant homozygous genotype was present only in cases (3/27 SJS/TEN patients). This SNP, described also as *CYP2B6**18, is only found in Africans and African-Americans and results in an amino acid change in the CYP2B6 protein (Ile328Thr). It has been shown to impact NVP and efavirenz pharmacokinetics [30, 33], and a heterozygous status is associated with a higher plasma concentration of both drugs. The variant homozygous genotype was correlated with higher plasma efavirenz concentration (P=0.0001) in two individuals (out of 57). It should be noted that the variant homozygous genotype is extremely rare, and there are as yet no data on plasma NVP concentration and CC genotype.

Another SNP, the G516T in the same *CYP2B6* gene, has shown a minor association with SJS/TEN susceptibility. Although the significance is borderline (P=0.064), the OR for the T allele variant is 1.8, and subjects carrying the GT or the TT genotypes have a risk equal to 1.99 and 3.32, respectively, in comparison with wildtype individuals (P=0.23 and P=0.063, respectively), highlighting a dose–allele effect.

Table 4 Final model of the binary logistic regression analysis (stepwise)

Variable	B	*P*	Exp B	95 % CI
G516T	1.694	0.012*	5.443	1.449–20.446
T983C	1.541	0.026*	4.67	1.201–18.156
CD4	0.102	0.045*	1.107	1.002–1.224

*Significant at $P < 0.05$

The regression analysis confirmed and strengthened our findings, showing that both of these two variants made a significant contribution to SJS/TEN susceptibility.

Our results are partially comparable with those reported recently by Yuan et al. who detected a correlation between the *CYP2B6* gene and NVP-associated severe cutaneous adverse events (defined as grade 3 or 4 rash, but not described as SJS/TEN) [11]. These authors found that two CYP2B6 SNPs, both in linkage with G516T, were significantly associated with cutaneous adverse events among populations of African, Asian and European descent [11]. They also found that the G516T SNP was associated with an increased risk of cutaneous adverse events, particularly in Africans. However, the T983C polymorphism (the most associated SNP in our study) was not assayed, probably because it is absent in non-African populations.

The haplotype analysis strengthened our results, highlighting that the wildtype haplotype conferred protection against SJS/TEN (OR=0.33, P=0.0016). On the contrary, the GC haplotype (wildtype for G516T and variant for T983C) conferred a high risk of developing SJS/TEN (OR=3.7, P=0.017).

The analysis of SNPs combined also produced an interesting result: individuals with the wildtype genotype for both SNPs were present only in the control group while, in contrast, only cases had the GG/CC and TT/TC genotypes. This result could suggest that individuals with the completely wildtype genotype could initiate the NVP-containing therapy with more safety than others, while an individual carrying the two risk genotypes combined should avoid NVP treatment. Obviously, further studies on larger samples and replications on other African populations are necessary to demonstrate the utility of such genotyping in clinical practice as a means to avoid SJS/TEN emergence.

Both of the *CYP2B6* SNPs associated with SJS produce a poor metabolizer protein and, as a consequence, individuals with such variants could reach an higher concentration of available drug. The mechanism by which this mechanism could influence susceptibility to SJS/TEN is not clear. One hypothesis could be that a higher level of circulating drug in predisposed subjects carrying a specific repertoire of HLA-alleles and/or T cell receptors [34] could facilitate an immune response: CYP2B6 variants could be responsible for a longer and massive exposure to drug or drug peptides that could elicit robust immune reactions. This notion is partially supported by a recent report of patients who were exposed to higher NVP levels showing an increased cutaneous rash risk (grade III) [9].

In conclusion, the strength of this study is the description, for the first time, of a relationship between CYP2B6 genetic variability and the emergence of SJS/TEN. The main potential bias of this study is the diagnosis of SJS. Our criteria for SJS diagnosis are given in the Patient recruitment and ethics statement section. Although it is truly hard to differentiate multiform major erythema from SJS, the clinical approach is

the only basis on which the two syndrome can be differentiated. Admittedly, another weakness of our study is the lack of HLA typing data which could be useful to integrate with our findings. Moreover, even if our sample size is not large enough to reach definitive conclusions, it is very important to consider that SJS and TEN are rare conditions, and a sample of 27 SJS/TEN patients can be considered sufficient for a preliminary study.

Conclusions

In this study we identified two *CYP2B6* gene variants (T983C and G516T) associated with susceptibility to SJS/TEN in a Mozambique population. In particular, we found that the 983C allele confers a significantly higher risk for developing SJS/TEN and that in our study cohort it was present in the homozygous status only in cases. SJS/TEN is a complex disorder: it is obvious that many genetic and non genetics factors are involved and that *CYP2B6* is only one of the players. Further studies are mandatory to explore the contribution of the HLA-system in order to integrate our results on the *CYP2B6* gene with the contribution of the immune system in the context of NVP-induced SJS/TEN. In conclusion, the results of this study show that genetic variability in a metabolizing enzyme gene can also be correlated with susceptibility to NVP-induced SJS/TEN and that it should be considered.

Competing interests None.

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