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# *MDR1 (ABCB1)* polymorphisms: functional effects and clinical implications

Aniel Jessica Leticia Brambila-Tapia*

*Instituto de Biotecnología, Universidad Nacional Autónoma de México.

***ABSTRACT***

MDR1 *gene encodes for P glycoprotein (P-gp), which plays an important role in bioavailability and cell-toxicity limitation of a wide range of drugs and xenobiotics. Three single nucleotide polymorphisms (SNPs) in the coding region (C3435T, C1236T and G2677T/A) are the most widely studied SNPs in MDR1 and have been related to substrate and inhibitor-dependent functional modifications in* in vitro *studies and reduced expression in tissues. The three SNPs exhibit the highest frequencies in Asian and Caucasians populations and the lowest in African populations. In regard to the clinical implications of MDR1 SNPs, it was found in large meta-analysis that C3435T SNP was associated with a slight increase in the susceptibility to ulcerative colitis and cancer and was related with slight modifications in tacrolimus pharmacokinetics and platinum-based chemotherapy response in lung cancer. On the other hand, C3435T SNP has shown controversial results in many other cases of disease susceptibility and drug pharmacokinetics where no meta-analyses have been performed. There is less information about C1236T and G2677T/A SNPs, which, although investigated in some diseases and drug pharmacokinetics, have a very limited number of published meta-analyses. Further studies should include analysis of the haplotype 1236T-2677T/A-3435T as well as other SNPs in* MDR1, *other transporters and drug metabolizers that may be related with the outcome variable.*

***Key words.*** *MDR1 (ABCB1) polymorphism. C3435T. C1236T. G2677T/A. Disease susceptibility. Pharmacokinetics.*

***Polimorfismos del gen MDR1 (ABCB1): efectos funcionales e implicaciones clínicas***

**RESUMEN**

El gen *MDR1* codifica para la glicoproteína P (P-gp), la cual juega un papel importante en la biodisponibilidad y limitación de la toxicidad en la célula de un amplio rango de fármacos y xenobióticos. Los tres polimorfismos de nucleótido simple (SNP) en la región codificadora (C3435T, C1236T y G2677T/A) son los polimorfismos más ampliamente estudiados en el gen MDR1 y se han asociado con modificaciones funcionales dependientes de substrato o de inhibidor, en estudios *in vitro* y expresión reducida en tejidos. Los tres SNPs tienen las más altas frecuencias en asiáticos y caucásicos y las más bajas en africanos. Con respecto a las implicaciones clínicas de estos polimorfismos, se encontró en grandes meta-análisis que el polimorfismo C3435T se asoció con un leve incremento en la susceptibilidad a colitis ulcerativa y cáncer, así como con ligeras modificaciones en la farmacocinética del tacrolimus y en la respuesta a la quimioterapia basada en platino en cáncer de pulmón. Por otro lado, el polimorfismo C3435T ha mostrado resultados controversiales en la susceptibilidad a muchas otras enfermedades y la farmacocinética de drogas, donde no se han realizado meta-análisis. Existe menos información sobre los SNPs C1236T y G2677T/A, los cuales, aunque investigados en algunas enfermedades y farmacocinéticas, han sido incluidos en un número muy limitado de meta-análisis. Futuros estudios deberán incluir el análisis del haplotipo 1236T-2677T/A-3435T, así como de otros SNPs en el gen *MDR1,* en otros transportadores y metabolizadores de fármacos que pudieran estar relacionados con la variable respuesta.

**Palabras clave.** Polimorfismos del gen *MDR1 (ABCB1).* C3435T. C1236T. G2677T/A. Susceptibilidad a enfermedades. Farmacocinética.

## INTRODUCTION

Genetic polymorphisms of drug-metabolizing enzymes such as cytochrome P450 superfamily (CYP) and drug transport proteins are responsible for inter-individual differences of pharmacokinetics. It has been estimated that ~500-1,200 genes encode for transport proteins. The main members include multidrug resistance proteins (MDRs), multidrug resistance-related proteins (MRPs), organic anion transporters (OATs), organic anion transporter polypeptides (OATPs), organic cation transporters (OCTs) and peptide transporters (PepTs). From all previous transporters, P-glycoprotein (P-gp) or multidrug resistance transporter (MDR1) has one of the best studied genotype-phenotype correlations.[1] The objective of this review is to discuss the main aspects of MDR1 single nucelotide polymorphism (SNP) from its functional effect until its clinical implications in pharmacokinetics and disease susceptibility, with special emphasis on the meta-analyses performed to date.

## P-GLYCOPROTEIN

P-gp belongs to a large group of transport proteins known as the ATP binding cassette *(ABC)* superfamily, which shares common structural and functional properties. To date, 48 human *ABC* genes have been identified and classified into seven subfamilies *(ABCA* to *ABCG)* where P-gp is defined as *ABCB1*.[2] P-gp is a 170-kD transmembrane protein composed of 1,280 amino acids forming two halves, each comprised of six hydrophobic transmembrane α-helices and an ATP binding domain. P-gp works as an energy-dependent efflux pump that plays an important role in the bioavailability and cell-toxicity limitation of a wide range of substances, drugs and xenobiotics including ions, sugars, glycans, phospholipids, proteins, anticancer drugs, antibiotics, corticosteroids, immunosuppressors, anti-HIV protease inhibitors, calcium-channel blocker agents, among others.[3,4] It is also expressed in many tissues including intestine, blood-brain barrier, liver, kidney, leucocytes, pancreas, adrenal cortex and placenta, where it exerts its protective effects.[5,6]

## *MDR1* GENE TRANSCRIPTION AND POLYMORPHISMS

P-gp is encoded by the *MDR1*/*ABCB1* gene located on 7q21 with a length ~100 kb including 28 exons.[3] The *MDR1* promoter contains a GC box for specificity protein 1 (Sp1), an inverted CCAAT box for Y-box binding protein 1 (YB-1) and nuclear factor Y (NF-Y). The main transcription factors involved in MDR1 expression are the early growth response factor-1 (EGR1), the nuclear factor for interleukin-6 expression (NF-IL6), the nuclear factor-erythroid 2-related factor (NF-R2) and the orphan nuclear receptor, steroid and xenobiotic receptor SXR/PXR.[2] Diverse endogenous and exogenous *MDR1* expression inducers have been identified. Endogenous expression inducers include reactive oxygen species, insulin, epidermal growth factor (EGF), tumor necrosis factor a (TNF-α), heat shock, cytokines and growth factors, whereas exogenous expression inducers include digoxin, irradiation, endotoxin, cisplatin, rifampicin and doxorubicin, whereas verapamil decreases P-gp expression.[1,2] So far, 66 *MDR1* SNPs including 24 synonymous have been identified in the coding sequence. From these, the most widely investigated for their clinical implications are the synonymous SNPs: C3435T and C1236T and the non-synonymous SNP G2677A/T.[6,7]

### *MDR1* SNPs and their functional implications

#### C3435T SNP

C3435T SNP (rs1045642), the most widely investigated SNP of the MDR1 gene, is located in exon 26 and represents a synonymous SNP with no effect in amino acid change at position 1145 (Ile) in the second ATP binding domain.[5] The polymorphic allele 3435T has been associated with decreased P-gp expression in tissues studies including placenta, liver and leukocytes[8-10] although other studies have not found any effect on gene expression in liver, heart and intestine.[11-13] Most *in vitro* studies have failed to confirm an association with protein expression,[14,15] although Wang, *et al.,* suggested a decrease in mRNA stability with the 3435T allele.[10] With respect to functional effects, it was detected a diminished function *in vitro*[16] and a difference in substrate specificity and protein conformation when combined with either C1236T and/or G2677T/A SNPs.[14,15] This effect in synonymous SNP was explained by alterations in folding processes by ribosome stalling in rare codon usage, which leads to a different tertiary conformation that changes protein function with a decrease in inhibitor effect (cyclosporine A and verapamil).[14,15] On the other hand, the discordance observed in the expression effect of C3435T

SNP when studied in tissues or *in vitro* has been explained by the transcription-inducer effect of some *MDR1* substrates. These substrates would be decreased when Pg-p activity is increased as reported in certain conditions for the 3435T allele and would produce a subsequent reduction in mRNA.[8] This reduction in mRNA could also be observed with some endogenous transcription inducers such as cytokines or growth factors, which have shown an altered secretion in lymphocytes with the 3435TT genotype.[17] The previous effect could only be observed in *in vivo* (tissues) studies where these factors are present, so a lack of alteration in gene expression in *in vitro* studies would be expected as shown in most of them.[10,14,15] Nevertheless, this hypothesis still needs to be proven. Another confusion variable probably responsible for the discrepancy between *in vitro* and in tissue studies in protein expression is the presence of other *MDR1* SNPs and haplotypes in the latter.

### G2677T/A SNP

The non-synonymous G2677T/A SNP (rs2032582) is located in exon 21, which encodes a region before the TM9 and TM104 and represents an amino acid change of alanine by serine or threonine (Ala893Ser/Thr) as three different nucleotides can be found at this position (G, T or A). This SNP has shown controversial results in functional effects. Kim, *et al.*[18] identified an increased efflux function of P-gp in the presence of 2677T allele. Conversely, Salama, *et al.*,[16] found a diminished function for the 2677T allele, whereas other authors such as Wang, *et al.*,[10] Morita, *et al.*,[19] and Kimchi-Safarty, *et al.*,[20] did not find any effect. In some studies with inhibitors, the use of cyclosporine A showed an increased inhibition in the transport of calcein for 2677T allele but, together with the 2677A allele, showed a decreased inhibition in the transport of paclitaxel, suggesting a substrate-dependent effect.[21] Furthermore, biochemical analysis showed that the presence of the 2677T or 2677A allele may alter drug transport by affecting induced ATPase activity.[22] This effect, when combined with other functional SNPs, mainly C3435T, presents a greater impact as shown in the change of the tridimensional structure leading to a diminished effect of some inhibitors (cyclosporine A and verapamil).[14,15] With regard to G2677T/A SNP and gene transcription, Hemauer, *et al.*,[8] identified that the 2677T/A variant was associated with a significant reduction (16%) in placental P-gp protein expression compared with the wild type. Conversely, Meissner, *et al.*,[12] found an association between 2677TT/AT genotypes and an elevated MDR1 expression in heart tissues; however, additional in tissue and *in vitro* studies have not demonstrated any evident effect.[13-15] The controversial results in tissue reports and gene expression may be due to the effect of other confounder SNPs; nevertheless, as reported in the *in vitro* studies, SNP G2677T/A may not have any effect on gene expression. With respect to the functional implications, SNP G2677T/A appears to have some effect, but further experiments are needed.

### C1236T SNP

The synonymous C1236T SNP (rs1128503) is located on exon 12 that encodes for the TM6 region, which is essential for substrate binding.[5] This SNP does not exhibit an amino acid change at position 412 (Gly). Few studies in regard to the 1236T allele and P-gp expression have been performed. Controversial results are reported when comparing in tissue and *in vitro* studies with a decreased expression and increased function in human placenta with the 1236T allele[8] and an apparent lack of effect in cell studies in regard to protein expression.[10,14,15] With respect to functional implications, this SNP has been shown to affect protein folding due to the use of a rare codon when combined with the SNP C3435T[14,15] with a diminished effect of some inhibitors and other probable functional effects, such as the diminished function observed by Salama, *et al.* in an *in vitro* study.[16] Differences observed in the silent SNPs C1236T and C3435T may be explained by the importance of the region where they are located because they produce an alteration of the tridimensional structure caused by the pause in co-translational folding. These differences are also related to the scarcity of the codon used. In this line, despite the fact that the codon produced by the change in C1236T SNP is rarer than that produced in C3435T SNP (reduction of 18 *vs.* 12%, respectively),[14] the SNP C3435T may have a greater effect in protein folding due to its position in the gene.

## *MDR1* SNP FREQUENCIES IN DIFFERENT POPULATIONS

The distribution of the main *MDR1* SNPs C3435T, G2677T/A, and C1236T shows a wide variability in different populations. The lowest frequencies of polymorphic alleles are found in African and African-Americans (0.1-0.2 for each of the three

polymorphic alleles) and the highest in Asians and Caucasians (~0.5 for each of the three polymorphic alleles). African and African-American populations have shown the largest number of MDR1 SNPs detected as compared with other populations.[3] Frequencies of MDR1 SNPs in a Mexican-American population[23] have a greater similarity to Caucasians and Asians than to African-Americans in concordance with the origin of this population. The haplotype containing the three wild-type or reference variants (CGC) is the most frequent in African or African-American populations (43.6-79.3%) followed by South Americans (25-65%) and Caucasians (32.5-45%). Asians showed the lowest frequency of the wild-type haplotype (16-25.9%) and the highest frequency of the polymorphic haplotype (TTT) (32.2-45.3%). As expected, this frequency was followed by Caucasians (23.1-42.19%), South Americans (6-35%) and Africans (4.5-8.7%).[5] It has been suggested that the increased frequency of the 3435CC genotype in African population confers a selective advantage against gastrointestinal infections, this considering that the 3435C allele has been associated with increased P-gp expression and a better protection of intestinal epithelium against pathogens.[24]

## MDR1 SNPs AND DISEASE SUSCEPTIBILITY

### Inflammatory bowel disease

Inflammatory bowel diseases (IBD) are represented by Crohn's disease (CD) and ulcerative colitis (UC). Their physiopathology is related with autoimmunity, impaired epithelial barrier and chronic inflammatory pathways. It has been shown that *mdr1a*$^{-/-}$ knockout mice were susceptible to spontaneous UC-like inflammation under pathogen-free conditions, presumably due to a defect in the intestinal epithelial barrier because these mice have a normal immune response.[1] Furthermore, *MDR1* expression is significantly diminished in patients with active UC compared with inactive UC or a control group,[25] as well as in other inflammatory bowel diseases (CD, diverticulitis and collagenous colitis).[26] Susceptibility to IBD and C3545T SNP is consistent with the notion that a lower P-gp expression decreases the protection from the accumulation of toxic materials within the intestine.[2] With respect to *MDR1* SNPs, a meta-analysis of nine association studies of C3435T SNP showed a significant association of the 3435T allele with UC (OR:1.12, 95% CI: 1.02-1.23) but not with CD.[27] This association was also found in another meta-analysis of six studies[28] (OR: 1.17 95% CI: 1.06-1.31). Three independent studies are common in both meta-analyses. In contrast, no association was found for UC or CD and the SNP G2677T/A in a meta-analysis of five association studies[28] (Table 1). The association observed between the 3435T allele and UC is low but comparable with other genetic SNPs associated with the disease.[29,30] It is important to mention that the role of non-genetic factors including smoking, pathogenic and intestinal flora, hygiene factors and diet seems to be greater than the role of genetic factors reported to date for IBD development.[31]

### Cancer

P-gp expression has been related with an alteration in apoptosis and cancer. P-gp was found to protect cells against caspase-dependent apoptosis induced by cytotoxic drugs, Fas-receptor ligation, TNF and ultraviolet radiation. Its expression was also upregulated by apoptotic stimuli. Furthermore, mutations of p53, which is the most frequent genetic alteration detected in human cancers, induce *MDR1* promoter transactivation with an increased expression in neoplastic cells leading to resistance in chemotherapy and radiation.[1,2] Nevertheless, the association between cancer and the 3435T allele may be explained by a diminished expression or function of P-gp, with a subsequent increase of carcinogens and toxins within the cell.[2] To date, a large meta-analysis of 39 independent studies conducted in relation with *MDR1* SNPs and cancer risk,[32] found an association between the 3435T allele and overall cancer risk (OR: 1.18, 95% CI: 1.04-1-34). When compared according to the specific cancer subtype, it was found an association of the 3435T allele with breast cancer (OR: 1.42, 95% CI: 1.04-1.94), renal cancer (OR: 1.77 95% CI: 1.28-2.46) and hematological malignancies (OR: 1.27, 95% CI: 1.10-1.46).[32] The risk related to 3435T allele in unspecific cancer is relatively low but is comparable to most genetic SNPs associated with cancer,[33,34] and is higher when compared according to specific cancer types, mainly with renal cancer. On the other hand, it is also important to consider confounding variables that could affect the real risk of each polymorphism. These include the use of specific treatments, age, diet and smoking status. In this regard, the meta-analysis including 3,149 postmenopausal breast cancer patients and 5,489 controls did not show association between C3435T and G2677T/A SNPs and breast cancer associated with hormone replacement therapy.[35] These results could indicate a dimi-

nished effect of *MDR1* SNPs in hormone-associated breast cancer. Corroborating the results of Sheng, *et al.*,[32] in 12 studies, an increased risk for leukemia in the 3435T allele was found in a meta-analysis of ten studies,[36] which shares nine studies with the study of Sheng, *et al.*[32] In this meta-analysis, subgroup comparisons were performed, finding a higher risk in chronic leukemia (OR: 1.94; 95% CI: 1.32-2.85) than in acute leukemia (OR: 1.19; 95% CI: 1.01-1.40).[36] In the previous meta-analysis evaluating hematological malignancies,[32,36] the study of Leal-Ugarte, *et al.,* in a Mexican population was included[37] where no association with acute lymphoblastic leukemia was found although, when combined with the rest of the studies, the 3435T allele achieved significance. Finally, in the meta-analysis conducted by He, *et al.,* in colorectal cancer, no association was found between C3435T SNP and this cancer.[38] These results were also according to the meta-analysis performed by Sheng, *et al.*[32] that shares 7/11 studies included in the study of He, *et al.*[38] (Table 1).

In general, it is considered that the 3435T allele represents a risk factor for developing cancer; nevertheless, this risk is low as shown for most genetic SNPs related to the disease,[34] but could achieve a greater importance when combined with independent genetic and environmental risk factors. It is noteworthy that some environmental factors such as smoking[39] and diet[40] show a similar or even higher risk than most genetic factors in cancer development. It is important to consider that despite the wide range of genetic and environmental factors currently associated with cancer, more genetic variants and environmental exposures still need to be investigated in order to determine personalized risks for specific cancer types.

In addition to IBD and cancer, *MDR1* SNPs have been investigated in relation with the risk for developing a wide range of diseases including Parkinson disease,[41] HIV-1 infection and progression,[42] hypertension[43] and rheumatoid arthritis[44] among others; nevertheless, additional studies are required in order to have a better approximation of their effect.

## MDR1 POLYMORPHIMS AND PHARMACOKINETICS AND DRUG RESPONSE

*MDR1* SNPs have been investigated in the pharmacokinetics of a wide range of drugs. Large meta-analyses in pharmacokinetics of digoxin,[45] anticonvulsants,[46] cyclosporine A,[47] and clopidrogel adverse events[48] have shown no association with C3435T SNP (Table 1) despite the diminished effect of some of these drugs (cyclosporine A and anticonvulsants) in the double (1236T-3435T) or triple haplotype (1236T-2677A/T-3435T).[15] Nevertheless, the pharmacokinetics of tacrolimus showed increased concentrations and diminished dose administration of tacrolimus in 3435TT individuals when compared with those with the genotype 3435CT and these last individuals presented increased concentrations when compared with individuals with the 3435CC genotype at different times posttransplantation.[49] Moreover, in a meta-analysis of 419 individuals describing the relation of MDR1 C3435T SNP and response to platinum-based chemotherapies in advanced non-small cell lung cancer, Wei, *et al.*[50] found an association of the 3435C allele with higher chemotherapy response (OR: 2.22; 95% CI: 1.46-3.37) but not for overall survival (HR:1.11; 95% CI: 0.78-1.56), when stratifying by ethnic group, the association was significant in Asians (OR: 2.63; 95% CI: 1.56-4.45) but not in Caucasians (OR: 1.61; 95% CI: 0.79-3.28).[50] It is important to consider that five studies were included for chemotherapy response, whereas only two studies were included in the survival analysis, which diminishes the representativeness of overall survival. These results were further confirmed in the meta-analysis performed by Yin, *et al.*[51] that shares 4/5 studies included with the study of Wei, *et al.*[50] As in this last study, they also found that 3435CC carriers showed significantly increased drug response (OR: 1.82, 95% CI: 1.17-2.85), a difference that was only observed in Asians (OR: 1.97, 95% CI: 1.11-3.5). This study also found a higher response in individuals with the 2677GG genotype (OR: 2.6, 95% CI: 1.44-4.74) in the three studies included (all in Asians). On the other hand, Chen, *et al.* did not find an association between the 3435T allele and response to chemotherapy and advanced breast cancer in a meta-analysis of seven studies including 464 patients with advanced breast cancer.[52]

Together these results suggest that MDR1 SNPs may have a slight influence on some drug pharmacokinetics and response in specific populations; nevertheless, it seems to be substrate-dependent because different alleles have been associated with different drugs. This, considering the results in the meta-analysis of tacrolimus,[49] where the 3435T allele showed increased concentrations and diminished dose administration and the results in the study of platinum-based chemotherapy response in lung cancer,[50,51] where the 3435C allele showed increased response. It is important to consider that drug response was not evaluated in the meta-analysis of

**Table 1.** MDR1 polymorphism meta-analysis in regard to disease risk, pharmacokinetics and chemotherapeutic response.

| Author/Year | Disease/ Drug | Cases (n) | Controls (n) | Main results | Other findings |
|---|---|---|---|---|---|
| Onnie, 2006[27] | IBD | CD: 2,311<br>UC: 1,743 | 2,931 | Significant association was found between 3435T allele and UC (OR: 1.12, 95% CI: 1.02-1.23) but not with CD. | |
| Annese, 2006[28] | IBD | UC (C3435T): 1,530<br>CD (C3435T): 1,473<br>UC (G2677T): 1,377<br>CD (G2677T): 1,621 | C3435T: 2,019<br>G2677: 1,746 | Significant association with 3435T allele(OR 1.17, 95% CI: 1.06-1.31) and 3435TT genotype (OR: 1.36, 95% CI: 1.05-1.76) was demonstrated for UC. | No association for 2677T allele or G2677T genotypes. |
| Sheng, 2012[32] | Cancer | 9,265 | 13,502 | 3435TT genotype was associated with a higher cancer risk than 3435CC or 3435CTgenotype (OR: 1.18, 95% CI: 1.04-1.34). With an increase in cancer risk for 3435T allele (OR: 1.13,95% CI: 1.04-1.23). | More pronounced effect in hematological malignancies (OR: 1.27, 95% CI: 1.10-1.46), breast cancer (OR: 1.42, 95% CI: 1.04-1.94) and renal cancer (OR: 1.77, 95% CI: 1.28-2.46). |
| He, 2011[38] | Colorectal cancer | 3,175 | 3,715 | No association between 3435T allele and colorectal cancer risk; when one study was removed there was a trend for association (OR: 1.30, 95% CI: 1.02-1.67) in Asians. | No association found between polymorphisms G2677T/A and rs3789243 and colorectal cancer risk. |
| Qian, 2012[36] | Leukemia | 1,815 | 2,095 | 3435T allele significantly increased risk of leukemia in all tested models: dominant model: 3435CT/3435TT *vs.* 3435CC (OR: 1.29; 95% CI: 1.11-1.50). Association with risk for lymphocytic leukemia (OR: 1.31, 95% CI: 1.10-1.55) was shown. | Increased risk for acute disease (OR: 1.19, 95% CI: 1.01-1.40), chronic disease (OR: 1.94, 95% CI: 1.32-2.85) and Caucasians (OR: 1.33, 95% CI: 1.12-1.57). |
| Pharmacokinetics and chemotherapeutic responce | | | | | |
| Chowbay, 2005[45] | Digoxin | $AUC_{0-4h}$: 121<br>$AUC_{0-24h}$: 71<br>$C_{max}$: 106<br>Single dose studies: 97 | NA | No significant effect of C3435T-related genotypes and digoxin concentrations measured in $AUC_{0-4h}$ and $AUC_{0-24h.}$ | Fixed effects model showed that $AUC_{0-4h}$ was significantly higher in subjects with 3435CC genotype, than in those with 3435 CT genotype. Cmax value tended to be lower for subjects 3435CC than those with 3435TT genotypes. |

| | | | | | |
|---|---|---|---|---|---|
| Li, 2012[49] | Tacrolimus | 1,327 patients | NA | Subjects with 3435CC genotype had lower concentration to dose ratio and need higher tacrolimus doses than subjects with 3435CTand 3435TT genotype at 6 months posttransplantation and 3435CT genotype had significantly higher concentrations compared with 3435CC genotype 1 week posttransplantation. | Subjects with 3435CC genotype had significantly higher dose administration compared with subjects with 3435TT genotype at 1 month posttransplantation. Subjects with genotype 3435CT had significantly higher dose administration than subjects with 3435TT genotype at 1 week, 1 month, 6 months and 1 year posttransplantation. |
| Jiang, 2008[47] | Cyclosporine | 1,036 patients | NA | No major influence of C3435T polymorphism and pharmacokinetic parameters. | $AUC_{0-12h}$ values were lower in 3435CC genotype than those with at least one T allele. $C_0$ was lower in Caucasians with the 3435CC genotype. |
| Haerian, 2010[46] | Anticonvulsants | 3,231 drug-resistant patients 3,524 drug-responsive patients or healthy controls | NA | No significant association with 3435T allele and drug resistance under fixed effects model (OR:1,06, 95% CI 0.98-1.14), or random-effects model (OR: 1.10, 95% CI: 0.93-1.30). | No difference in overall findings or stratified by ethnicity. |
| Wei, 2011[50] | Response to chemotherapy in non-small cell lung cancer | 222 patients for overall survival effects 419 patient for overall objective effect | NA | Overall effect on overall survival was not significant for 3435CC *vs.* 3435CT/TT genotypes (HR: 1.11; 95% CI: 0.78-1.56) For objetive response, overall effect was significant for 3435CC *vs.* 3435CT/TT (OR: 2.22,95% CI: 1.46-3.37). | Subgroup analysis produced significant results in Asians (OR: 2.63; 95% CI: 1.56-4.45) but not in Caucasians (OR: 1.61, 95% CI: 0.79-3.28). |
| Yin, 2012[51] | Response to chemotherapy in non-small cell lung cancer | C3435T: 379 patients G2677T/A: 218 patients | NA | 3435CC carriers showed significantly increased drug response (OR: 1.82, 95% CI: 1.17-2.85), this difference was only observed in Asians (OR: 1.97, 95% CI:1.11-3.5) | 2677GG genotype showed higher response (OR: 2.6, 95% CI: 1.44-4.74). All the reports were performed in Asians. |
| Chen, 2012[52] | Chemotherapy response in advanced breast cancer | 464 patients | NA | No association for 3435CC *vs.* 3435CT/TT and response to chemotherapy (OR: 1.18, 95% CI: 0.76-1.84). | Subgroup analysis by ethnicity did not change the results pattern, and comparisons of 3435CC *vs.* 3435CT/TT in Caucasians showed (OR: 0.81, 95% CI: 0.36-1.85) and in Asians (OR: 1.59, 95% CI: 0.90-2.80). |
| Luo, 2011[48] | Risk of adverse clinical events in clopidogrel-treated patients | 10,153 patients | NA | No association for C3435T SNP with risk of overall recurrent ischemic events was shown in clopidogrel-treated patients (OR: 1.13, 95% CI: 0.78-1.64). | Significant association was identified between the 3435T allele and risk of short-term recurrent ischemic vents (OR1.55,95% CI:1.09-2.20). No association was shown for Stent thrombosis or bleeding. |

IBD: inflammatory bowel disease. UC: ulcerative colitis. CD: Crohn's disease. NA: not applicable. AUC: area under the curve. OR: odds ratio. HR: hazard ratio. CI: confidence interval.

tacrolimus and similarly the drug concentrations were not evaluated in the meta-analysis of platinum-based chemotherapy response[49,50] (Table 1). It is also important to consider that the determination of concomitant medication with P-gp inhibitors is also required in further pharmacokinetic studies in order to discard confusion biases.

To date, many other drugs have been studied in relation to the *MDR1* polymorphisms including antiretroviral therapy,[42] fexofenadine[18] and irinotecan[53] as well as in paroxetine response in depressive disorder[54] methotrexate response in rheumatoid arthritis[44] and steroid response in nephrotic syndrome.[55] Nevertheless, specific meta-analyses including all the studies performed so far are required in order to achieve a consensus.

Considering that few meta-analyses have been conducted in drug pharmacokinetics and genetic polymorphisms (~30) with CYP450 and MDR1 being the main genes involved, it is possible that a personalized drug administration according to the individual's genetic background will take longer than previously thought.

## CONCLUSIONS

MDR1 SNPs C3435T, C1236T and G2677T/A are the most widely investigated in the *MDR1* gene. MDR1 SNPs have shown functional alterations *in vitro* in a substrate-dependent manner and are related with decreased tissue expression, although most i*n vitro* studies have shown no effect on protein expression. Additional controlled studies using specific inhibitors and substrates are needed in order to achieve a better approximation of its functional effects. These SNPs have been investigated in a wide range of diseases and drug pharmacokinetics. C3435T SNP has shown a slight increased risk to develop UC and cancer and has shown a slight effect on tacrolimus pharmacokinetics and platinum-based chemotherapy response in lung cancer; additionally it has demonstrated controversial results in other diseases and drug pharmacokinetics where no meta-analyses have been performed. C1236T and G2677T/A have been less investigated than C3435T SNP with conflicting results in some diseases and drug pharmacokinetics, but they have been included in a very limited number of meta-analyses. It is necessary to study the influence of these SNPs in other drugs pharmacokinetics and disease susceptibilities as well as to perform meta-analyses including the studies with controversial results. It is also needed to perform an evaluation of a wider range of *MDR1* SNPs including the haplotype 1236T-2677T/A-3435T and other drug transporters and enzymes that may be related with the outcome variable in order to discard a confusion bias.

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## REFERENCES

1. Sakaeda T, Nakamura T, Okumura K. MDR1 genotype-related pharmacokinetics and pharmacodynamics. *Biol Pharm Bull* 2002; 25: 1391-400.
2. Sakaeda T. MDR1 genotype-related pharmacokinetics: fact or fiction? *Drug Metab Pharmacokinet* 2005; 20: 391-414.
3. Pauli-Magnus C, Kroetz DL. Functional implications of genetic polymorphisms in the multidrug resistance gene MDR1 (ABCB1). *Pharm Res* 2004; 21: 904-13.
4. Li YH, Wang YH, Li Y, Yang L. MDR1 gene polymorphisms and clinical relevance. *Yi Chuan Xue Bao* 2006; 33: 93-104.
5. Fung KL, Gottesman MM. A synonymous polymorphism in a common MDR1 (ABCB1) haplotype shapes protein function. *Biochim Biophys Acta* 2009; 1794: 860-71.
6. Pechandová K, Buzková H, Slanar O, Perlík F. Polymorphisms of the MDR1 gene in the Czech population. *Folia Biol (Praha)* 2006; 52: 184-9.
7. Wolf SJ, Bachtiar M, Wang J, Sim TS, Chong SS, Lee CG. An update on ABCB1 pharmacogenetics: insights from a 3D model into the location and evolutionary conservation of residues corresponding to SNPs associated with drug pharmacokinetics. *Pharmacogenomics J* 2011; 11: 315-25.
8. Hemauer SJ, Nanovskaya TN, Abdel-Rahman SZ, Patrikeeva SL, Hankins GD, Ahmed MS. Modulation of human placental P-glycoprotein expression and activity by MDR1 gene polymorphisms. *Biochem Pharmacol* 2010; 79: 921-5.
9. Hitzl M, Drescher S, van der Kuip H, Schäffeler E, Fischer J, Schwab M, et al. The C3435T mutation in the human MDR1 gene is associated with altered efflux of the P-glycoprotein substrate rhodamine 123 from CD56+ natural killer cells. *Pharmacogenetics* 2001; 11: 293-8.
10. Wang D, Johnson AD, Papp AC, Kroetz DL, Sadée W. Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C>T affects mRNA stability. *Pharmacogenet Genomics* 2005; 15: 693-704.
11. Owen A, Goldring C, Morgan P, Chadwick D, Park BK, Pirmohamed M. Relationship between the C3435T and G2677T(A) polymorphisms in the ABCB1 gene and P-glycoprotein expression in human liver. *Br J Clin Pharmacol* 2005; 59: 365-70.
12. Meissner K, Jedlitschky G, Meyer zu Schwabedissen H, Dazert P, Eckel L, Vogelgesang S, et al. Modulation of multidrug resistance P-glycoprotein 1 (ABCB1) expression in human heart by hereditary polymorphisms. *Pharmacogenetics* 2004; 14: 381-5.
13. Siegmund W, Ludwig K, Giessmann T, Dazert P, Schroeder E, Sperker B, et al. The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. *Clin Pharmacol Ther* 2002; 72: 572-83.
14. Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science* 2007; 315: 525-8.

15. Hung CC, Chen CC, Lin CJ, Liou HH. Functional evaluation of polymorphisms in the human ABCB1 gene and the impact on clinical responses of antiepileptic drugs. *Pharmacogenet Genomics* 2008; 18: 390-402.
16. Salama NN, Yang Z, Bui T, Ho RJ. MDR1 haplotypes significantly minimize intracellular uptake and transcellular P-gp substrate transport in recombinant LLC-PK1 cells. *J Pharm Sci* 2006; 95: 2293-308.
17. Pawlik A, Baskiewicz-Masiuk M, Machalinski B, Kurzawski M, Gawronska-Szklarz B. Involvement of C3435T and G2677T multidrug resistance gene polymorphisms in release of cytokines from peripheral blood mononuclear cells treated with methotrexate and dexamethasone. *Eur J Pharmacol* 2005; 528: 27-36.
18. Kim RB, Leake BF, Choo EF, Dresser GK, Kubba SV, Schwarz UI, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. *Clin Pharmacol Ther* 2001; 70: 189-99.
19. Morita N, Yasumori T, Nakayama K. Human MDR1 polymorphism: G2677T/A and C3435T have no effect on MDR1 transport activities. *Biochem Pharmacol* 2003; 65: 1843-52.
20. Kimchi-Sarfaty C, Gribar JJ, Gottesman MM. Functional characterization of coding polymorphisms in the human MDR1 gene using a vaccinia virus expression system. *Mol Pharmacol* 2002; 62: 1-6.
21. Gow JM, Hodges LM, Chinn LW, Kroetz DL. Substrate-dependent effects of human ABCB1 coding polymorphisms. *J Pharmacol Exp Ther* 2008; 325: 435-42.
22. Sakurai A, Onishi Y, Hirano H, Seigneuret M, Obanayama K, Kim G, et al. Quantitative structure-activity relationship analysis and molecular dynamics simulation to functionally validate nonsynonymous polymorphisms of human ABC transporter ABCB1 (P-glycoprotein/MDR1). *Biochemistry* 2007; 46: 7678-93.
23. Kroetz DL, Pauli-Magnus C, Hodges LM, Huang CC, Kawamoto M, Johns SJ, et al. Pharmacogenetics of membrane transporters investigators. Sequence diversity and haplotype structure in the human ABCB1 (MDR1, multidrug resistance transporter) gene. *Pharmacogenetics* 2003; 13: 481-94.
24. Schaeffeler E, Eichelbaum M, Brinkmann U, Penger A, Asante-Poku S, Zanger UM, et al. Frequency of C3435T polymorphism of MDR1 gene in African people. *Lancet* 2001; 358: 383-4.
25. Yamamoto-Furusho JK, Villeda-Ramírez MA, Fonseca-Camarillo G, Sánchez-Muñoz F, Dominguez-Lopez A, Barreto-Zuñiga R, et al. High gene expression of MDR1 (ABCB1) is associated with medical treatment response and long-term remission in patients with ulcerative colitis. *Inflamm Bowel Dis* 2010; 16: 541-2.
26. Blokzijl H, Vander Borght S, Bok LI, Libbrecht L, Geuken M, van den Heuvel FA, et al. Decreased P-glycoprotein (P-gp/MDR1) expression in inflamed human intestinal epithelium is independent of PXR protein levels. *Inflamm Bowel Dis* 2007; 13: 710-20.
27. Onnie CM, Fisher SA, Pattni R, Sanderson J, Forbes A, Lewis CM, et al. Associations of allelic variants of the multidrug resistance gene (ABCB1 or MDR1) and inflammatory bowel disease and their effects on disease behavior: a case-control and meta-analysis study. *Inflamm Bowel Dis* 2006; 12: 263-71.
28. Annese V, Valvano MR, Palmieri O, Latiano A, Bossa F, Andriulli A. Multidrug resistance 1 gene in inflammatory bowel disease: a meta-analysis. *World J Gastroenterol* 2006; 12: 3636-44.
29. Zhu H, Lei X, Liu Q, Wang Y. Interleukin-10-1082A/G polymorphism and inflammatory bowel disease susceptibility: a meta-analysis based on 17,585 subjects. *Cytokine* 2013; 61: 146-53.
30. Xue LN, Xu KQ, Zhang W, Wang Q, Wu J, Wang XY. Associations between vitamin D receptor polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. *Inflamm Bowel Dis* 2013; 19: 54-60.
31. Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? *Dig Dis* 2009; 27: 215-25.
32. Sheng X, Zhang L, Tong N, Luo D, Wang M, Xu M, et al. MDR1 C3435T polymorphism and cancer risk: a meta-analysis based on 39 case-control studies. *Mol Biol Rep* 2012; 39: 7237-49.
33. Mocellin S, Verdi D, Pooley KA, Landi MT, Egan KM, Baird DM, Prescott J, et al. Telomerase reverse transcriptase locus polymorphisms and cancer risk: a field synopsis and meta-analysis. *J Natl Cancer Inst* 2012; 104: 840-54.
34. Zhang K, Zhou B, Wang Y, Rao L, Zhang L. The XRCC1 Arg280His polymorphism contributes to cancer susceptibility: an update by meta-analysis of 53 individual studies. *Gene* 2012; 510: 93-101.
35. Marie-Genica. Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk Polymorphisms in the BRCA1 and ABCB1 genes modulate menopausal hormone therapy associated breast cancer risk in postmenopausal women. *Breast Cancer Res Treat* 2010; 120: 727-36.
36. Qian X, Cao S, Yang G, Dong J, Jin G, Shen Y, Hu Z. Variant genotypes of MDR1 C3435T increase the risk of leukemia: evidence from 10 case-control studies. *Leuk Lymphoma* 2012; 53: 1183-7.
37. Leal-Ugarte E, Gutiérrez-Angulo M, Macías-Gómez NM, Peralta-Leal V, Durán-González J, De La Luz Ayala-Madrigal M, et al. MDR1 C3435T polymorphism in Mexican children with acute lymphoblastic leukemia and in healthy individuals. *Hum Biol* 2008; 80: 449-55.
38. He T, Mo A, Zhang K, Liu L ABCB1/MDR1 polymorphism and colorectal cancer risk: a meta-analysis of case-control studies. *Colorectal Dis* 2011; 7: e38150.
39. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008; 122: 155-64.
40. Reiss R, Johnston J, Tucker K, DeSesso JM, Keen CL. Estimation of cancer risks and benefits associated with a potential increased consumption of fruits and vegetables. *Food Chem Toxicol* 2012; 50: 4421-7.
41. Lee CG, Tang K, Cheung YB, Wong LP, Tan C, Shen H, et al. MDR1, the blood-brain barrier transporter, is associated with Parkinson's disease in ethnic Chinese. *J Med Genet* 2004; 41: e60.
42. Kedmi M, Maayan S, Cohen SB, Hauzi M, Rund D. MDR1 and CYP3A4 polymorphisms are associated with HIV seropositivity in Israeli patients but do not influence the course of HIV disease. *AIDS Patient Care STDS* 2007; 21: 653-8.
43. Kivistö KT, Niemi M, Schaeffeler E, Pitkälä K, Tilvis R, Fromm MF, et al. CYP3A5 genotype is associated with diagnosis of hypertension in elderly patients: data from the DEBATE Study. *Am J Pharmacogenomics* 2005; 5: 191-5.
44. Pawlik A, Wrzesniewska J, Fiedorowicz-Fabrycy I, Gawronska-Szklarz B. The MDR1 3435 polymorphism in patients with rheumatoid arthritis. *Int J Clin Pharmacol Ther* 2004; 42: 496-503.
45. Chowbay B, Lit H, David M, Cheung YB, Lee EJ. Meta-analysis of the influence of MDR1 C3435T polymorphism on digoxin pharmacokinetics and MDR1 expression. *Br J Clin Pharmacol* 2005; 60:159-71.
46. Haerian BS, Roslan H, Raymond AA, Tan CT, Lim KS, Zulkifli SZ, et al. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. *Seizure* 2010; 19: 339-46.

47. Jiang ZP, Wang YR, Xu P, Liu RR, Zhao XL, Chen FP. Meta-analysis of the effect of MDR1 C3435T polymorphism on cyclosporine pharmacokinetics. *Basic Clin Pharmacol Toxicol* 2008; 103: 433-44.
48. Luo M, Li J, Xu X, Sun X, Sheng W. ABCB1 C3435T polymorphism and risk of adverse clinical events in clopidogrel treated patients: a meta-analysis. *Thromb Res* 2011; 129: 754-9.
49. Li Y, Hu X, Cai B, Chen J, Bai Y, Tang J, et al. Meta-analysis of the effect of MDR1 C3435 polymorphism on tacrolimus pharmacokinetics in renal transplant recipients. *Transpl Immunol* 2012; 27: 12-8.
50. Wei HB, Lu XS, Shang LH, Xu G, Hu J, Che DH, et al. Polymorphisms of ERCC1 C118T/C8092A and MDR1 C3435T predict outcome of platinum-based chemotherapies in advanced non-small cell lung cancer: a meta-analysis. *Arch Med Res* 2011; 42: 412-20.
51. Yin JY, Huang Q, Zhao YC, Zhou HH, Liu ZQ. Meta-analysis on pharmacogenetics of platinum-based chemotherapy in non small cell lung cancer (NSCLC) patients. *PLoS One* 2012; 7: e38150.
52. Chen G, Quan S, Hu Q, Wang L, Xia X, Wu J. Lack of association between MDR1 C3435T polymorphism and chemotherapy response in advanced breast cancer patients: evidence from current studies. *Mol Biol Rep* 2012; 39: 5161-8.
53. Mathijssen RH, Marsh S, Karlsson MO, Xie R, Baker SD, Verweij J, et al. Irinotecan pathway genotype analysis to predict pharmacokinetics. *Clin Cancer Res* 2003; 9: 3246-53.
54. Kato M, Fukuda T, Serretti A, Wakeno M, Okugawa G, Ikenaga Y, et al. ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 398-404.
55. Choi HJ, Cho HY, Ro H, Lee SH, Han KH, Lee H, et al. Polymorphisms of the MDR1 and MIF genes in children with nephrotic syndrome. *Pediatr Nephrol* 2011; 26: 1981-8.

*Reimpresos:*

**Aniel Jessica Leticia Brambila-Tapia**
Av. Universidad, Núm. 2001
Col. Chamilpa
Cuernavaca, Mor.
Phone: (55) 5627-1777, Ext. 38306
P.C.:62210
E-mail: anieljessica@hotmail.com

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