# Cytochrome P450 2D6 and MDR1 Gene Mutation in Relation to Mortality in Patients with Crimean-Congo Hemorrhagic Fever: A Preliminary Study

## Kırım Kongo Kanamalı Ateşi Hastalarında Sitokrom P450 2D6 ve MDR1 Gen Mutasyonlarının Mortalite ile İlişkisi: Bir Ön Çalışma

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**ABSTRACT Objective:** The aim of this study was to investigate the role of multidrug transporter P-glycoprotein 1 (MDR1), cytochrome P450 isozyme 2D6 (CYP2D6) and C-C chemokine receptor 5 (CCR5) genes in the mortality of patients with Crimean-Congo Hemorrhagic Fever (CCHF). **Material and Methods:** Fifteen patients under drug therapy and conventional supportive measures were investigated. Diagnosis of the patients was confirmed by ELISA and/or reverse transcription-polymerase chain reaction (RT-PCR) technique. Clinical and laboratory features of three cases with fatal outcomes were compared with those of twelve patients with non-fatal CCHF. Genomic DNA was isolated from pheripheral blood samples and PCR based reverse hybridization strip assay was used for the genotyping. **Results:** The mortality rate was 20% (3/15) in this study. In two fatal cases the MDR1 gene had homozygous point mutation and in one fatal case heterozygous point mutation. All the fatal cases had poor drug metabolizer genotypes of CYP2D6 gene. Of the twelve surviving patients, three had heterozygous mutation in the MDR gene while only one had homozygous mutation of the same gene. Drug metabolizer genotypes of CYP450 gene were normal in all surviving patients. In fatal cases, ratios of mutable MDR1 and poor drug metabolizer genotypes of CYP450 genes were higher than those in non-fatal cases. The CCR5 gene was normal in all cases. **Conclusion:** Hypoexpression of CYP2D6 alleles and mutation in MDR1 gene could cause impaired drug metabolism and/or lead to therapeutic failure in the CCHF patients. MDR1 and CYP2D6 genes may play a crucial role in pharmacokinetics, immunological response and drug metabolism in the management of CCHF infection. Further studies are necessary to substantiate these findings.

**Key Words:** Genes, MDR; hemorrhagic fever virus, Crimean-Congo; cytochrome P-450 CYP2D6

**ÖZET Amaç:** Bu çalışmada, Kırım Kongo Kanamalı Ateşi (KKKA) hastalarında multidrug transporter (MDR1) geni, sitokrom P450 izoenzim 2D6 geni (CYP2D6) ve kemokin reseptör 5 (CCR5) geninin mortalite üzerindeki rolünü araştırmak amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmaya enzim işaretli immün deney ya da revers transkripsiyon polimeraz zincir reaksiyonu (RT-PZR) ile tanısı kesinleştirilmiş ve tedavi gören 15 KKKA hastası alındı. Çalışmada ölen 3 hasta ile yaşayan 12 hasta klinik ve laboratuvar özellikleri açısından karşılaştırıldı. Hastaların genomik DNA'ları PZR temelli revers hibridizasyon strip testi kullanılarak genotiplendirildi. **Bulgular:** Çalışmamızdaki mortalite oranı %20 (3/15) bulundu. Ölen 3 hastanın 2'sinde MDR1 geninde homozigot mutasyon, 1'inde ise heterozigot mutasyon saptandı. Ölen hastaların her üçünde de CYP2D6 geninin düşük düzeyde sunulduğu ve zayıf ilaç metabolizasyonu yapan tipte olduğu bulundu. Yaşayan 12 hastanın sadece birinde MDR1 geninde homozigot mutasyon, 3'ünde ise heterozigot mutasyon mevcuttu. Ölen hastalardaki MDR1 mutasyonu ve sitokrom P450 geninin zayıf ilaç metabolizasyonu yapan formunun oranları, yaşayan hastalara göre daha yüksekti. CCR5 geni ise tüm hastalarımızda normal bulundu. **Sonuç:** KKKA hastalarında, CYP2D6 allelinin azalmış sunumu ve MDR1 geninde olan mutasyonlar ilaç ya da toksik maddelerin metabolizasyonunda bozukluğa yol açarak tedavide başarısızlığa sebep olabilir. MDR1 ve CYP2D6 genleri, immünolojik cevap ve ilaç metabolizasyonu üzerine olan etkileri nedeni ile KKKA hastalarının tedavisinde önemli bir rol oynayabilir. Ancak bulgularımızın daha fazla hasta ile yapılacak çalışmalarla desteklenmesi gerekmektedir.

**Anahtar Kelimeler:** Multidrug direnç geni; Kırım Kongo Kanamalı Ateşi; sitokrom P450 2D6 polimorfizm



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Crimean-Congo hemorrhagic fever (CCHF) a viral hemorrhagic fever diseases caused by infection with the CCHF virus (CCHFV). Humans are infected by tick-bites, contact with blood or tissue from acute phase of CCHF patients or viremic livestock. The most common clinical features of the disease are hemorrhage, myalgia, fever, disseminated intravascular coagulation and vascular dysfunction. CCHF is a common disease and has been reported in about 30 countries in Africa, Asia, Europe and Middle East.[1,2]

The P-glycoprotein is a membrane protein that plays a crucial role on pumping the xenobiotics at the blood-brain barrier. P-glycoprotein is encoded by MDR1 gene. The gene product does not only contribute to drug resistance during chemotherapy of tumors but it is also expressed in healthy tissues with secretory function. Polymorphisms of MDR1 gene have been reported to be associated with the synergistic effect in predisposing patients to toxic neurological complications during drug therapy and/or chemotherapy.[3] Chemokines play a critical role in many pathophysiological processes such as infectious diseases. Cytochrome P450 (CYP) enzymes system is responsible for drug activation and metabolism.

In the recent years, outbreaks of CCHF have been reported in Turkey. Midilli and colleagues reported similar genetic structures of CCHF viruses in patients with CCHF in Turkey.[4] However, different mortality rates (from 2.8% to 12%) were reported from Turkey.[5,6] On the other hand, the mortality rate of the disease could be up to 50%.[7] There is no genetic study on host organisms to explain how genetic differences and/or polymorphism can act on the diversity of the disease mortality. The aim of our study was to find out the possible role of some genes such as multidrug transporter P-glycoprotein 1, CYP450 isozyme 2D6 and C-C chemokine receptor 5 in the defense mechanism against infectious diseases, drug metabolism and immune response in CCHF patients. This study also represents the first molecular approach in CCHF mortality.

## MATERIAL AND METHODS

### PATIENTS, CLINICAL DIAGNOSIS AND LABORATORY ASSESSMENT

This study was conducted in the Cumhuriyet University Hospital in Sivas city located in the central Anatolia, between May and November 2007. The study protocol was approved by the Hospital Ethics Committee of the Cumhuriyet University, Faculty of Medicine. Informed consents were obtained from the patients. Fifteen CCHF patients (7 male and 8 female) aged between 25 and 73 were in the study. Sera from suspected CCHF cases were sent to the Virology Laboratory of Refik Saydam Hygiene Central Institute, Ankara, Turkey for serologic and virologic analyses. The definitive diagnosis of CCHF infection was based upon typical clinical and epidemiological findings and detection of CCHF virus-specific IgM by enzyme linked immunosorbent assay (ELISA) or of genomic segments of the CCHF virus by RT-PCR either in the acute or convalescent phase of the disease.

### MUTATION ANALYSIS

Total genomic DNA was extracted from 100 µl peripheral blood samples by the Invitek kit extraction technique (Invitek, Invisorb spin blood, Germany) and was stored at -20°C until genetic analysis was performed. Three different gene regions [multidrug transporter P-glycoprotein 1-MDR 1, cytochrome P450 izoyme 2D6 (CYP2D6) and C-C chemokine reseptor 5 (CCR5-32 bp del)] were simultaneously amplified and biotin-labeled in a single multiplex amplification reaction (Viennelab, PGX-HIV StripAssay, Austria). Extensive(1*/1*, 1*/3*, 1*/4*, 1*/5*, 1*/6*) and poor (3*/3*, 3*/4*, 3*/5*, 3*/6*, 4*/4*,4*/5*, 4*/6*, 5*/5*, 5*/6*, 6*/6*) metabolizer alleles of cytochrome P450 izoyme 2D6 were analyzed. PCR was performed in a Perkin Elmer 9600 and the protocol consisted of an initial melting step of 2 minutes at 94°C; followed by 35 cycles of 15 seconds at 94°C, 30 seconds at 58°C, and 30 seconds at 72°C; and a final elongation step of 3 minutes at 72°C. The mutation analysis was performed by StripAssay technique (Vienna Lab, PGX-HIV StripAssay GmbH, Austria) which is based on the

**TABLE 1:** Demographic and clinical characteristics, symptoms, signs and laboratory findings, and ribavirin treatment for 15 patients with Crimean-Congo hemorrhagic fever.

| | Fatal (n= 3) | Non-fatal, (n= 12) |
|---|---|---|
| Mean age (range), y | 49 (33-73) | 42 (25-73) |
| Sex, n (%) | | |
| Female | 2 (67) | 5 (42) |
| Male | 1 (33) | 7 (58) |
| Most common symptoms, n (%) | | |
| Myalgia | 3 (100) | 12 (100) |
| Headache | 0 (0) | 3 (25) |
| Fever | 3 (100) | 11 (92) |
| Diarrhea | 0 (0) | 1 (8) |
| Nausea and/or vomiting | 2 (67) | 9 (75) |
| Malaise | 3 (100) | 12 (100) |
| Physical finding, n (%) | | |
| Fever,[a] | 3 (100) | 11 (92) |
| Conjunctival hyperemia | 1 (33) | 7 (58) |
| Fascial hyperemia | 1 (33) | 5 (42) |
| Hepatomegaly | 2 (67) | 2 (17) |
| Splenomegaly | 0 (0) | 1 (8) |
| Rash | | |
| Maculopapular | 2 (67) | 4 (33) |
| Petechia or Ecchymosis | 2 (67) | 5 (42) |
| **Bleeding** | | |
| Epistaxis | 0 (0) | 2 (17) |
| Hemoptysis | 1 (33) | 0 (0) |
| Hematuria | 1 (33) | 0 (0) |
| Hematemesis | 1(33) | 0 (0) |
| Risk factors for CCHF | | |
| History of tick bite | 1 (33) | 5 (42) |
| History of tick removal from animal | 2 (67) | 1 (8) |
| No tick exposure | 0 (0) | 6 (50) |
| Laboratory features | | |
| Thrombocytopenia,[b] | 3 (100) | 12 (100) |
| Leucopenia,[c] | 2 (67) | 10 (83) |
| Elevated AST,[d] | 3 (100) | 12 (100) |
| Elevated ALT,[e] | 3 (100) | 8 (67) |
| Prolonged prothrombin time | 1 (33) | 4 (33) |
| Prolonged aPTT,[f] | 1 (33) | 8 (67) |
| Ribavirin therapy | 2 (67) | 10 (83) |

[a] Arm pit, $\geq 38°C$

[b] Thrombocytopenia, platelet count < $150 \times 10^9$

[c] Leukopenia, leukocyte count < $4 \times 10^3$

[d] Aspartate aminotransferase

[e] Alanine aminotransferase

[f] Activated partial thromboplastin time

reverse-hybridization principle automatically. The normal, heterozygous and homozygous mutant/non-mutant genotype profiles of each gene were determined using the enclosed Collector™ sheet for the fatal and non-fatal CCHF patients. Study variables were not analyzed statistically due to the small size of study population.

## RESULTS

Three of 15 cases died due to severe infection. Nine (60%) patients had CCHF virus-specific IgM antibodies, two (13.3%) were found to be positive by RT-PCR for CCHF virus and 4 (26.7%) patients yielded positive results by both tests in the acute and/or convalescent phase of the disease. Demographic and clinical characteristics, laboratory findings and status of ribavirin treatment of the patients were given in Table 1. All patients had malaise and myalgia. Of the fatal cases, two (case 11 and 14) had homozygous point mutation in the MDR gene, while the remaining one (case 12) had heterozygous mutation of the same gene (Figure 1, lane 3, 4 and 5). All fatal CCHF patients had also poor drug metabolizer genotypes of the CYP450 gene (Figure 1, lane 3, 4 and 5). All surviving patients had normal drug metabolizer genotypes of CYP450. Among survivors, only one patient (case 15) had homozygous mutation in the MDR gene while three patients had heterozygous mutation. Although case numbers were not adequate for statistical analysis, ratios of homozygous and/or heterozygous mutation of MDR1 and poor drug metabolizer genotypes of CYP450 genes were higher in fatal cases (Table 2). No mutation profile was found in the CCR5 gene region in all studied cases (Figure 1, lanes 1-5). Current results demonstrated that there were no variations in the genes encoding the chemokine CCR5 in both fatal and non-fatal CCHF infections.

## DISCUSSION

CCHF is a potentially fatal disease affecting multiple organs and systems. Although the infection of the endothelium has an important role in CCHF pathogenesis and capillary fragility, the specific mechanisms underlying the pathogenesis of the CCHF virus and

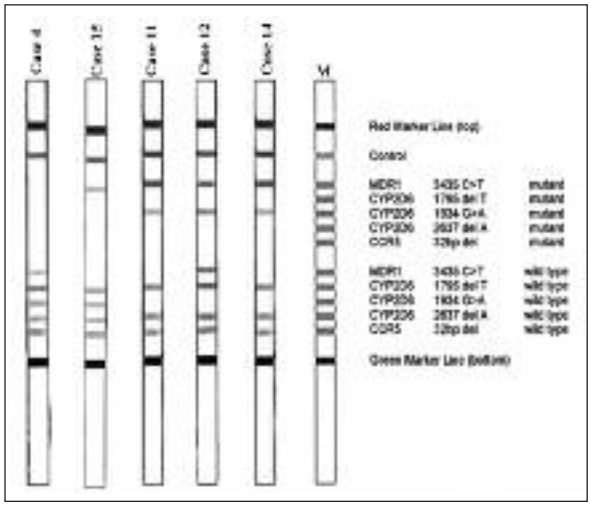

**FIGURE 1:** Shows mutable and non-mutable gene profiles of target genes in fatal and non-fatal CCHF patients of the current study.

**Lanes**

Lane 1- Non-mutant profiles of MDR1, CYP450 and CCR5 genes of non-fatal case 4.
Lane 2- Homozygous point mutation in MDR1 and normal drug metabolizer genotype (*1/1*) in non-fatal case 15. The CYP450 and CCR5 genes are in normal appearance.
Lane 3- Homozygous point mutation in MDR1 and poor drug metabolizer genotype (*4/6*) in fatal case 11. The CCR5 gene is in normal appearance.
Lane 4- Shows heterozygous point mutation in MDR1 and poor drug metabolizer genotype (*4/6*) in fatal case 12. The CCR5 gene is in normal appearance.
Lane 5- Homozygous point mutation in MDR1 and poor drug metabolizer genotype (*4/6*) in fatal case 14. The CCR5 gene is in normal structure.

**TABLE 2:** The mutation prevalence of MDR1, CYP450, and CCR5 genes in fatal and non-fatal Crimean-Congo hemorrhagic fever patients in the current study.

| | CCHF Patients | |
|---|---|---|
| **Gene Types** | **Fatal (n= 3)** | **Non-fatal (n= 12)** |
| MDR1 | | |
| wt/wt | 0 (0) | 8 (67) |
| wt/mt | 1 (33) | 3 (25) |
| mt/mt | 2 (67) | 1 (8) |
| CCR5 | | |
| wt/wt | 3 (100) | 12 (100) |
| wt/mt | 0 (0) | 0 (0) |
| mt/mt | 0 (0) | 0 (0) |
| CYP2D6 | | |
| Extensive metabolizer alleles (1*/1*, 1*/3*, 1*/4*, 1*/5*, 1*/6*) | 0 (0) | 12 (100) |
| Poor metabolizer alleles (3*/3*, 3*/4*, 3*/5*, 3*/6*, 4*/4*, 4*/5*, 4*/6*, 5*/5*, 5*/6*, 6*/6*) | 3 (100) | 0 (0) |

wt: Wild- type allele, mt: Mutant allel.

variable mortality in CCHF patients are still unclear. General supportive therapy is the mainstay of patient management in CCHF infection. There is currently no specific antiviral therapy for CCHF approved for use in humans by the FDA. However, the antiviral drug ribavirin, a synthetic purine nucleoside analogue, has been most promising over the years. Ribavirin was been shown to inhibit in vitro viral replication of CCHF in Vero cells. Additionally, several case reports suggested ribavirin as an effective drug for treating CCHFV infections.[1] However, some patients failed to respond to ribavirin therapy. The specific genome variability of the host organism could play a crucial role in the varying responses to drug treatment.

The P-glycoprotein, a membrane transporter encoded by the MDR1 gene, mediates drug efflux from cells and plays a major role in Multi Drug Resistance in inflammatory bowel disease, implications for disease risk and therapeutic outcome in HIV, and an increased risk for renal cell carcinoma in humans.[8] Lee et al have shown that HIV viral production was greatly reduced when MDR1 was overexpressed.[9] This suggests that cells with high levels of MDR1 expression are relatively resistant to HIV infection. It has also recently been reported that cells overexpressing MDR1 are resistant to some enveloped viruses that enter via the plasma membrane.[9] The CCHFV is also an enveloped virus and most possibly enter the cells by a transmembrane glycoprotein mediated patway.[1] Furthermore, in patients with renal cell carcinoma, MDR1 expression was significantly decreased when compared with healthy controls.[8] A susceptibility to renal cell carcinoma is consistent with the hypothesis that a lower MDR1 expression level offers less protection from the accumulation of toxic/carcinogenic materials in renal tissues.[8,10] In addition, impaired expression of a gene or genes that play a crucial role in drug metabolizing systems or clearing toxic materials may also be effective in response to drug and/or fatality of CCHF infection.

Johnstone et al suggested that MDR1 protected cells against caspase-dependent apoptosis induced by cytotoxic drugs, fas ligation, tumor necrosis factor (TNF), and ultraviolet (UV) irradiation.[11] Alt-

hough there is no clear evidence on the possible role of apoptosis on CCHF mortality, some researchers have accepted the possible effects of apoptosis on immune depression and host organism death in some virus mediated haemorrhagic fever infections.[12-14] Several reports suggested that the supression of MDR1 was associated with a decrease in the activity of NK cells and CD8 T cells.[15,16] Lymphocytes play an important role in immune responses by directly killing virus infected or tumor cells or by secreting cytokines. In addition, Randolph et al have reported a role for MDR1 in the migration of dendritic cells.[17] These observations might suggest that MDR1 could play an important role in the immunological response in virus mediated infections. According to the above findings it is also possible to discuss that the homozygous or heterozygous mutated MDR1 gene could lead to and/or mediate the death of CCHF patients.

Cytochrome P450 (CYP) enzymes system is responsible for drug activation and metabolism. These enzymes are predominantly expressed in the liver but can also be found in the intestines, lungs and in some other organs.[18] This enzyme metabolizes a wide variety of substances including therapeutic drugs, procarcinogens and neurotoxins.[19] The CYP2D gene locus contains three alternative alleles of CYP2D6, CYP2D7, and CYP2D8 encoding a functional protein on drug metabolizers.[20] CYP2D6 exhibits genetic polymorphism and the polymorphisms can be classified according to one of four levels of activity: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs).[21] Individuals with normal CYP2D6 activity are designated extensive metabolizers. PMs inherit two deficient CYP2D6 alleles and as a result, metabolize drugs at a notably slower rate and this leads to drug accumulation and toxicity.[22] In our study, all fatal CCHF patients had poor drug metabolizer genotypes of the CYP450 gene, which suggesets loss of function of drug metabolizing during the therapy in these three fatal CCHF patients.

Chemokines are small basic polypeptides that induce the targeted migration of leukocytes.[23] They also play a critical role in many pathophysiological processes such as allergic responses, infectious and autoimmune diseases, angiogenesis, inflammation, tumor growth and hematopoietic development. In our study, all current CCHF patients showed CCR5 gene domain with normal structure.

In this study, the mortality rate of CCHF patients was 20% (3/15) due to severe infection. Homozygous point mutation in multidrug transporter gene was found in two fatal cases and the one fatal case had heterozygous point mutation. All fatal patients had poor drug metabolizer genotypes of CYP450 2D6 izozyme alleles. Three of the twelve surviving patients had heterozygous mutation in the MDR gene while only one patient had homozygous mutation. Drug metabolizer genotypes of CYP450 gene were normal in all surviving patients. In fatal cases, ratios of mutable MDR1 and poor drug metabolizer genotypes of CYP450 genes were higher than those in non-fatal cases. The CCR5 gene had a normal appearance in all cases. Most possibly the combined effect of impaired expression of cytochrome P450 as a poor metabolizer and homozygous MDR1 gene mutation in supression of NK and CD8 T cells played an important role in the mortality of those cases.

Mean age, sex, clinical characteristics, and laboratory findings in fatal and non-fatal patients were comparable. In our study, ratios of homozygous or heterozygous mutation of the MDR1 and poor drug metabolizer genotypes of CYP450 genes were higher in fatal cases. In conclusion, our data suggest that P-glycoprotein 1 and CYP450 isozyme 2D6 may play a crucial role in pharmacokinetics, immunological response and drug metabolism during CCHF infection and treatment but further and more detailed studies are necessary to substantiate these findings.

***Conflict of interest:*** No conflict of interest to declare.

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