Identification and Characterization of a Defective CYP3A4 Genotype in a Kidney Transplant Patient With Severely Diminished Tacrolimus Clearance.

Abstract:
Cytochrome P450 3A4 (CYP3A4) is a major drug-metabolizing enzyme that is widely investigated. So far, no homozygous inactive variant has been described. We report on a 19-year-old kidney transplant patient suffering from Alport syndrome, who experienced unexpected high tacrolimus plasma trough levels during immunosuppressant therapy. Because nonadherence, liver failure, or drug-drug interactions could be excluded, we hypothesized a diminished metabolism of the drug caused by mutations in the main detoxification enzyme, CYP3A4. Exome sequencing revealed a novel single-nucleotide polymorphism (c.802C>T) resulting in a premature stop codon in CYP3A4 exon 5. Accordingly, no CYP3A4 protein could be detected in kidney biopsy tissue, and there was lack of expression in HepG2 cells transiently transfected with the mutated CYP3A4. In addition, the patient harbored inactive CYP3A5*3, resulting in loss of function of the entire CYP3A locus, explaining the deteriorated tacrolimus clearance. This is, to our knowledge, the first case of a complete failure of CYP3A4 in humans.

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