



## CYP2D6\*4 polymorphism is associated with statin-induced muscle effects.

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### Abstract

Statin use is associated with a variety of overtly related muscle symptoms including muscle pain, myalgia, creatine kinase elevations without pain with myolysis and myositis (rhabdomyolysis), a potentially fatal side effect that led to the withdrawal of cerivastatin in 2001. Unintended drug response phenotypes have an impact on patient compliance and sometimes patient health and the assessment of risk on an individual basis could enhance therapeutic benefit. We therefore investigated whether common single nucleotide polymorphisms were associated with the expression of broadly grouped atorvastatin-induced muscle events in a case-control study (n=263 samples, n=388 SNPs). Of a number of associations identified in a discovery sample (51 atorvastatin-induced muscle and 55 normal) only those corresponding to the CYP2D6\*4 allele were significantly associated in the sample (24 atorvastatin-induced muscle and 133 normal) (Discovery P=0.004, odds ratio=3.6; Validation P=0.036, odds ratio=2.7; total P=0.001, odds ratio=2.5). The frequency of the CYP2D6\*4 allele was about 50% in atorvastatin-induced muscle patients but only 28% in controls, similar to that of other patient types (28.5%). The association was independent of various demographic variables and not explained by gross demographic, clinical or population-structure differences among cases and controls. Surprisingly, the CYP2D6\*4 allele appeared similarly distributed among controls and patients expressing simvastatin-induced muscle events (n=169, frequency in case participants=49.2%, P=0.067, odds ratio=1.7). Our results suggest that the CYP2D6\*4 allele is associated with broadly related muscle events caused by at least two structurally dissimilar HMG-CoA reductase inhibitors, and as such, may have implications for a better understanding of this statin-wide phenomena.

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