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Detection of a potential fitness cost associated with warfarin-resistance mediated by Vkorc1 mutation

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ABSTRACT

We report on a cardiovascular phenotype in wild-derived warfarin resistant rats that carry a amino-acid exchange in the vitamin K epoxide reductase gene from tyrosine to cysteine at position 139 in the protein (Y139C) caused by a mutation in the cDNA position 416 from A to G. The mutation causes a 53% reduction of the *VKOR* enzyme activity, as reported previously by others, and we speculate that the heterozygous warfarin resistant rat has an ~25% reduced enzyme activity.

We observe a striking pattern where almost exclusively homozygous mutant males display mineralization of the aorta. In contrast, heterozygous and wildtype males, as well as females, were found free of mineralization. This is the first such evidence for the effect of changes in the protein sequence of the *Vkorc1*, the resulting reduction of enzyme activity, and mineralization of the aorta.

The spread of warfarin resistant rats by natural selection for the resistance mutations is both of evolutionary interest and of potential relevance to rat control with warfarin-based anticoagulants. Assuming that the mineralization of the aorta imposes a fitness loss to mutant rats the spread of resistance can be modeled with respect to the phenotypic data obtained. Moreover, as different rat strains carrying different mutations in the Vkorc1 gene have been found in Europe, it would be important to characterize these with respect to such a fitness cost to better predict which strains may have developed effective modifier genes that detach the selective advantage of resistance from the physiological cost of it.