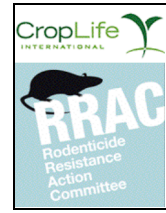


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Overview of mutations found in VKORC1 of rats and mice, their known occurrence and mediation of resistance to anticoagulants

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ABSTRACT

More than 30 missense mutations in the gene VKORC1 in humans, rats and mice have been found until today, 16 of which have been confirmed to confer a certain degree of resistance or insensibility to warfarin. Some of these mutations also seem to form the precondition for the occurrence of resistance to other compounds, such as coumatetralyl, bromadiolone or difenacoum. A change of amino acids at positions 120 to 139 is connected to the strongest degree of resistance observed.

Rat (*Rattus norvegicus*) samples provided by many people from different countries and analysed by Simone Rost at the Institute of Human Genetics of the University of Wuerzburg reveal that the tyrosin-cystein substitution at position 139 in VKORC1 is probably the most widespread mutation. It is common in Denmark and northwestern Germany, and was found in parts of Hungary, France and England. Other widespread mutations are the tyrosin-phenylalanin substitution at position 139, which is common in France and Belgium and was also found in Korea, the leucin-glutamic acid substitution at position 128 ("Scottish-type resistance", Scotland, northern England and parts of France) and the leucin-glutamic acid substitution at position 120 (Hampshire- and Berkshire-resistance, Southern England, parts of France and locally in Belgium. The well known Welsh-type resistance can be attributed to a tyrosin-serin substitution at position 139, however, the effect upon the degree of resistance seems to be less pronounced than in the other two substitutions at position 139 mentioned above. The occurrence of resistance described for the Chicago (Illinois, USA) area seems to be due to an arginin-prolin substitution at position 35 that was also detected in a wild rat from central France. Again the degree of resistance mediated by this mutation seems to be relatively low.

Information in mice (*Mus musculus musculus/domesticus*) is still very limited. Breeding colonies of resistant mice at Reading University and at the Central Science Laboratory in York, UK derived from wild mice in the UK were found to carry a tyrosin-cystein substitution at position 139 and a leucin-serin amino acid substitution at position 128 respectively. Both these mutations were recently found in populations of mice from the Rhineland, Germany. The tyr139cys mutation was also found in a mouse from Terceira/Azores, indicating that it is probably widespread. Other mutations found in German mice, particularly at positions 58 and 61 seem to have an effect on the degree of resistance which is still awaiting confirmation.

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