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RESEARCH

VKORC1 mutations in house mice in the Auckland Region (Aotearoa/New Zealand)

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Abstract: Introduced house mice are widespread in Aotearoa/New Zealand, and they have significant impacts on native wildlife. The most common toxins for controlling rodents are anticoagulant rodenticides (AR). Even though AR are an efficient tool, resistance to these substances in rodent populations has been detected in many countries. This phenomenon represents a major factor in reducing the success of pest management, and it is mostly related to missense mutations in the VKORC1 gene. Despite the crucial importance of effective house mouse management, genetic AR resistance in mice in Aotearoa/New Zealand is poorly understood. In this study, we undertook a genetic survey of six sites across the Auckland region to investigate the presence of VKORC1 mutations potentially involved in AR resistance. We found a total of five different missense mutations across four of the six sites. Three mutations leading to amino acid changes have been recorded in rodents previously while two are novel. Among these, the well-known Tyr139Cys, involved in resistance to some powerful AR like bromadiolone, is found with a high allelic frequency in central Auckland. Our results suggest that even across a moderate geographic region, there can be important genetic diversity and clustering in AR resistance. Anticoagulant rodenticides are a critical tool in introduced rodent management, but their use must be deliberated and genetic screening of rodent populations should increasingly be an important part of AR management operations.

Keywords: anticoagulants, genetics, pest control, resistance, rodents

Introduction

The most common method for controlling rodents is the use of anticoagulant rodenticides (AR) (McGee et al. 2020). These substances operate by inhibiting the vitamin K 2,3-epoxide reductase (VKORC) complex, a protein involved in the vitamin K synthesis cycle, which is crucial for blood clotting. Despite the efficiency of AR, the response to these substances in pest control may be influenced by a combination of either genetic and toxicokinetic factors (McGee et al. 2020). In fact, the extensive use of AR can lead to the development of resistance in rodent populations (Buckle, 2013; Goulois et al. 2017). The emergence of resistance to AR (comprising elevated tolerance or even immunity) is a major factor in unsuccessful pest management and was first observed in Wales (UK) in the late 1950s. Since then, numerous cases have been identified in various countries and across different rodent species (Iacucci et al. 2018; McGee et al. 2020; Díaz & Kohn 2021; Rached et al. 2022; Chua et al. 2022; Sran et al. 2022; Yiğit et al. 2023; Krijger et al. 2023; Carromeu-Santos et al. 2023; Aivelo et al. 2023).

Resistance is mainly due to the presence of Single Nucleotide Polymorphisms (SNPs) in one or more of the three exons of the VKORC1 gene. This gene encodes the subunit 1 of the VKORC protein, and missense SNPs result in amino acid substitutions that alter the conformation of VKORC. This frequently leads to a reduced basal activity of the protein, potentially resulting in a decreased VKORC-AR affinity and thus conferring resistance to all first-generation AR (1AR) and some second-generation AR (2AR) (Pelz et al. 2005). The advent of AR resistance diminishes the effectiveness of invasive rodent management, primarily because resistant populations can survive exposure to AR, and secondly, because the excessive and ineffective use of toxic baits poses a risk of bioaccumulation and poisoning of non-target species (Pelz & Prescott 2015). Genotyping the VKORC1 gene allows for the detection of known resistance-conferring mutations, thereby improving rodent management strategies. However, while every missense SNP causes amino acid substitutions, this does not necessarily mean they always confer resistance. Indeed, the actual effects of newly identified SNPs can only be determined through in vivo tests or biokinetic simulations (Bailey & Eason 2000). Without these analyses, their role in resistance can only be hypothesized based on previous studies. Nonetheless, the identification of any missense SNP still provides valuable information to be considered in planning rodent management.

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Introduced house mice (*Mus musculus*) are one of the most globally widespread invasive species (Lowe et al. 2000; Russell in press). They are a major agricultural pest (Brown et al. 2022) and disease host (Moinet et al. 2024). On islands they are a major reptile and invertebrate predator (St Clair 2011; Monks et al. 2024) but are often not the primary target of pest management where invasive rats are also present (Samaniego et al. 2024). Selective control of introduced rats can lead to increases in mouse abundance through competitor-release effect (Caut et al. 2007, Goldwater et al. 2012; Wilson et al. 2018). In fact, mice are also more resistant to AR (Fisher 2005), which amplifies the competitor-release effect from selective control targeting rats. These effects can be so strong that mice are often survivors of rodent eradication efforts (MacKay et al. 2007; Elliott et al. 2015).

In Aotearoa/New Zealand, introduced mice are widespread (Murphy & Nathan 2021) with different genetic identities due to multiple introductions from different sources (King et al. 2016; Veale et al. 2018) that may impact the efficiency of their management (MacKay et al. 2013). Mice have been successfully eradicated from a number of small offshore islands (Broome et al. 2019) but on the larger main islands their management tends to be neglected due to the absence of cost-efficient landscape tools (Samaniego et al. 2024). At some multi-predator eco-sanctuary management sites, mice are the sole remaining introduced mammal species when others have been removed (Innes et al. 2024).

To date, the only available genetic survey of AR resistance in Aotearoa/New Zealand focused on three rat species, in which a few mutations with very low frequencies emerged (Cowan et al. 2017). The presence, identity and prevalence of VKORC1 mutations in mice in Aotearoa/New Zealand remains poorly understood, though resistance has previously been detected in this species in the South Pacific (Wheeler et al. 2019). Given the widespread targeting of rats, but less so mice, in pest management (Russell et al. 2015), and the unregulated use of AR on private land (Cowan et al. 2017), it is likely that AR resistance is present and selected for in introduced house mice across Aotearoa/New Zealand. We undertook a genetic survey of six sites across the Auckland region, with different histories of rodent management and AR use, to investigate the presence of the VKORC1 mutations that code for AR resistance.

Methods

Samples were collected from 2022 to 2023 in five different locations in the Auckland Region, while samples from 2011 were available from a previous study at a sixth site where mice no longer exist (Table 1). Our sites comprised three offshore islands (Waiheke, Moturemu and Rotoroa), two regional parks (Shakespear and Tāwharanui) and one zoological park (Auckland Zoo). In the study area mice belong to *M. musculus domesticus* according to autosomal and mitochondrial genome, with small traces (approx. 2–3%) of *M. m. castaneus* nuclear ancestry (Veale et al. 2018) and varied origins reflected in mitochondrial D-loop haplotypes (MacKay et al. 2013). All our sites had a history of AR use which could pre-dispose them to selection AR resistance.

All the samples were stored in 96% pure ethanol until use. Genomic DNA was extracted using Quick-DNA^{TM} Miniprep Plus Kit by Zymo Research following the provider's instructions. For each sample, three fragments (253 bp, 801 bp and 308 bp long) of the VKORC1 gene were amplified. The primers used for PCRs are shown in Table 2. Each of the fragments contained one of the three exons of the VKORC1 gene, allowing the sequencing of the entire encoding region (486 bp long). Exons 1, 2 and 3 are 174 bp, 110 bp and 202 bp long respectively and they encode in total 161 amino acids.

Table 1. Sample size (*n*), geographic coordinates, year of collection and pest management history for each location.

Location	Coordinates	*n*	Year	History
Rotoroa Island	36.813 S, 175.197 E	12	2011	Norway rats eradicated with 2AR in 2010, mice survived and eradicated in 2013.
Waiheke Island	36.802 S, 175.028 E	14	2022	Rats and mice managed with AR.
Moturemu Island	36.422 S, 174.393 E	15	2022	Norway rats and mice eradicated with 2AR in 1992. Mice reinvaded between 2014-2019.
Shakespear Regional Park	36.607 S, 174.824 E	10	2023	Ship and Norway rats eradicated with 2AR in 2011, mice persisted.
Tāwharanui Regional Park	36.372 S, 174.831 E	15	2023	Ship and Norway rats eradicated with 2AR in 2004, mice persisted.
Auckland Zoo	36.864 S, 174.720 E	15	2023	Rats and mice historically managed with AR until 2018.

Table 2. Primers used in this study for VKORC1 amplification.

VKORC1	Forward	Reverse	Annealing Temperature	Reference
Exon 1	TCTTCCCTCCTGTSYCTGGG	AAATYATCTGGYAACCTGGC	56°C	Iannucci et al. 2019
Exon 2	CTGTGCTGAGGGGACAAAGT	TTGCCATAAAACTGAGATTGTGA	49°C	Iannucci et al. 2019
Exon 3	TTTCACCAGAAGCACCTGCTGYC	ACACTTGGGCAAGGSTCATGTG	61°C	Grandemange et al. 2010

Sequence chromatograms were manually examined and analysed using FinchTV (version 1.4.0; Geospiza Inc., 2006) to confirm the presence of mutations in both homozygous and heterozygous states. The FASTA files for each sequence were exported, and exons 1, 2, and 3 were combined to create a single sequence encompassing the entire VKORC1 coding region. A complete VKORC1 sequence, including all three exons, was downloaded from GenBank (accession number: NM_178600.2) and used as the wild type (WT) reference. An alignment was then built in MEGA (version 11.0.13; Tamura et al. 2021) comparing all sequences to the WT. Finally, we translated the DNA sequences into amino acid sequences to identify missense SNPs. For every location, the allelic frequency of the identified mutations was calculated.

Results

A total of 228 PCR products were successfully sequenced from 81 mouse samples. Specifically, we obtained 75 sequences for exon 1, 73 for exon 2 and 80 for exon 3. Overall, 28.4% (n = 23) of the mice included in this study had at least one VKORC1 mutation and 23.5% (n = 19) of the total had at least one missense mutation. Tāwharanui Regional Park is the only location where no SNPs were found, while the other five sampled areas had at least one mutant mouse. Particularly, nine different SNPs were identified: four synonyms (Leu17Leu, Ala18Ala, Leu22Leu, and Glu37Glu) and four missense SNPs are found in exon 1 (Ala14Thr, Leu20Ile, Ala21Thr, and Ala26Ser), no SNPs in exon 2 and one missense SNP is found in exon 3 (Tyr139Cys). Therefore, most of the mutations we detected are located in exon 1. The synonym mutations Leu17Leu and Leu22Leu only occur in one heterozygous individual each from Rotoroa and Moturemu Islands respectively, while Ala18Ala only occurs in two heterozygous individuals from Rotoroa Island. Conversely, the synonym mutation Glu37Glu follows a different pattern: it is always associated with Ala21Thr, and they are found in two homozygous individuals from the Auckland Zoo. The missense mutation Ala14Thr is found in three heterozygous individuals from Moturemu Island, and it is the only missense SNP found here. Similarly, Leu20Ile and Ala26Ser are also found in one heterozygous individual each and they represent the only missense SNPs from Waiheke Island and Shakespear Regional Park respectively. The missense mutation Tyr139Cys is the only SNP found in exon 3 and it was only detected in the Auckland Zoo. This mutation is found here with a very high allelic frequency (60%) and it is found in twelve individuals, half of which are homozygous. Detailed information about the allelic frequencies of every mutation in each location is provided in Figure 1 and Table 3.

Discussion

Our study identified a surprisingly high diversity of VKORC1 missense mutations associated with and potentially contributing to AR resistance across a moderately sized metropolitan region. Moreover, a high site-specificity in both the identity and frequency of these SNPs also emerged. According to the available literature, the two missense mutations Ala14Thr and Leu20Ile are novel, having not been recorded previously in any rodent species. Therefore, it is difficult to assess their role in resistance to AR. However, the site Ala14 has been observed to have an accelerated selection in the desert rodent *Nannospalax galili* (Chen et al. 2022). As a matter of fact, it is known that some rodent species living in arid areas show elevated physiological tolerance to AR, which seems to be due to some unknown selective pressures that rodents may experience in desert habitats. So, the mutation Ala14Thr may lead to some form of resistance. To our current state of knowledge, this hypothesis remains totally speculative and needs to be validated by biokinetic tests. All the other missense SNPs found in this study have already been detected in previous studies. The mutation Ala21Thr has been described in mice from Serbia and

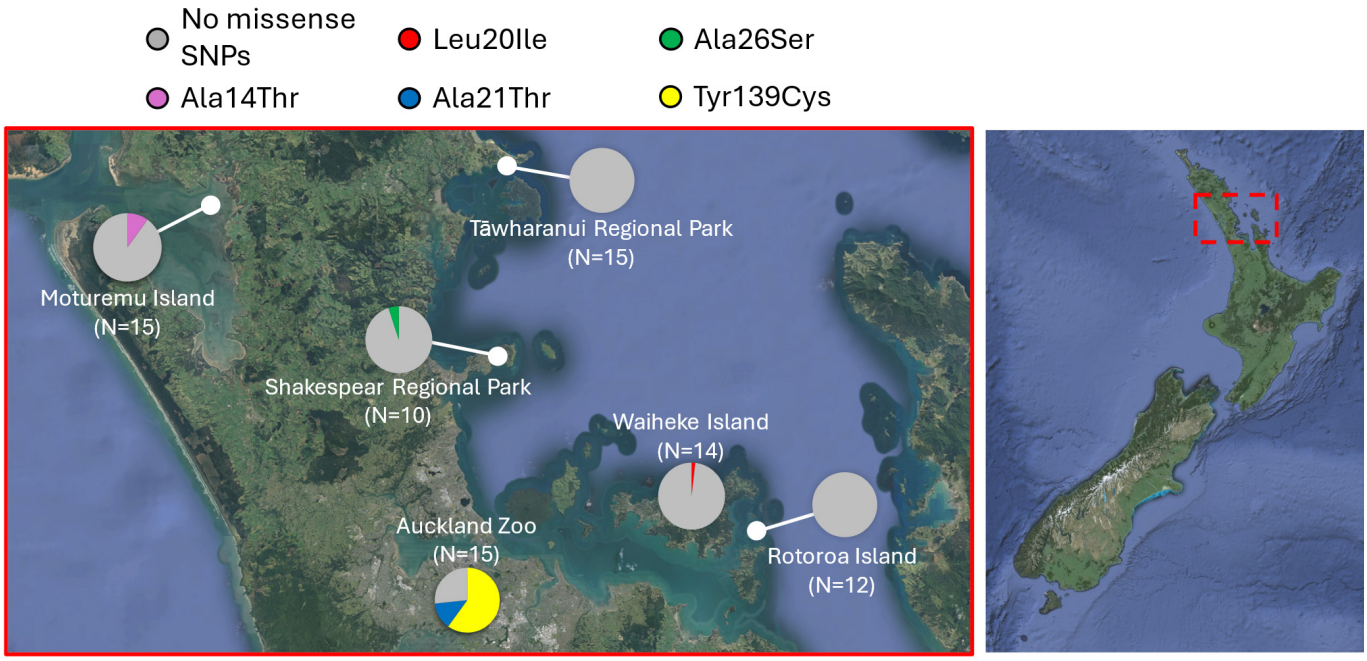

Figure 1. Allelic frequencies and distribution of the missense SNPs in the study area.

Table 3. List of the SNPs found in this study. Missense SNPs are reported in bold. Some SNPs co-occurred in the same individual. n: number of samples, WT: number of wild type individuals, HET: number of heterozygous individuals, HOM: number of homozygous individuals.

Sites			**Ala14Thr**		**Leu17Leu**		**Ala18Ala**		**Leu20Ile**		**Ala21Thr**		**Leu22Leu**		**Ala26Ser**		**Glu37Glu**		**Tyr139Cys**	
	n	**WT**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**	**HET**	**HOM**
Rotoroa Is.	12	9	-	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Waiheke Is.	14	13	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Moturemu Is.	15	11	3	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-
Shakespear	10	9	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Tāwharanui	15	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Auckland Zoo	15	1	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	2	6	6
TOTAL	81	58	3	-	1	-	2	-	1	-	-	2	1	-	1	-	-	2	6	6
Type of resistance			Unknown		-		-		Unknown		Bromadiolone		-		No resistance		-		Warfarin, Coumatetralyl, Chlorophacinone, Bromadiolone	
References			This study		This study		Gallozzi et al. 2024		This study		Šćepović et al. 2016; Díaz and Kohn 2021		This study		Goulois et al. 2017		Díaz and Kohn 2021; Carromeu-Santos et al. 2023		Pelz et al. 2005; Rost et al. 2009; Šćepović et al. 2016; Goulois et al. 2017; Mooney et al. 2018; Blažić et al. 2023	

it is known to give a high level of tolerance to bromadiolone (Šćepović et al. 2016). Interestingly, we found this mutation always associated with the silent mutation Glu37Glu. This condition was observed also in the USA by Díaz and Kohn (2021) and corresponds more closely to the sequence of *M. m. castaneus* than *M. m. domesticus*. In particular, Ala21Thr and Glu37Glu correspond the nucleotide positions 61 and 111 of the VKORC1 gene, which appear to be diagnostic. This is in accordance with the low but detectable nuclear ancestry for *M. m. castaneus* observed in Veale et al. (2018) in the North Island. So, the fact that the presence of these mutations can be the result of a previous *castaneus* genome introgression into *domesticus* genome can't be excluded. A similar VKORC1 condition has been already observed in Europe with the *spretus* × *domesticus* introgression, which is directly involved in AR resistance and can be positively selected when AR are used (Goulois et al. 2017). The mutation Ala26Ser is part of the resistance-giving *spretus* variant of VKORC1. Nonetheless, this mutation alone, as we observed it in Shakespear Regional Park, is not able to provide resistance (Goulois et al. 2017).

The mutation Tyr139Cys, found in the Auckland Zoo at high frequency, is the most common resistance-related SNP in mice and Norway rats (*Rattus norvegicus*) worldwide and it is known to confer resistance also in heterozygous condition to all the 1AR and some of the 2AR, like bromadiolone (Pelz et al. 2005; Markussen et al. 2008; Rost et al. 2009; Hodroge et al. 2011; McGee et al. 2020). As discussed before, the other mutation found in the Auckland Zoo, Ala21Thr, is related to resistance to bromadiolone, as well, making this location the only site with a high prevalence of AR resistance and more than one mutation. This site also had the longest-standing history of pest management and is bordered by some of Auckland's earliest urban intensification. This suggests that a positive AR-mediated selection is probably acting on resistance-giving SNPs in mice from this area. Fortunately, because of the risk of AR to park animals, the Auckland Zoo has already ceased using AR for pest management (S. Buley, pers. comm., Auckland Zoo), a decision which is independently reinforced by our results. In contrast, despite a history of AR use on the more recently urbanely intensified Waiheke Island, very little AR resistance was detected. This is possibly due to a founder effect that did not introduce any mutation to be selected upon. To support this, recurrent invasion is uncommon in Aotearoa/New Zealand (Russell & Clout, 2005) and there is genetic evidence for mice not to establish on islands even after recolonization occurs (Hardouin et al. 2010).

Overall, it is reassuring that at the sites where introduced mammal eradication has taken place using AR (Rotoroa, Tāwharanui and Shakespear), but mice are still present due to a combination of eradication survivors and/or reinvaders (Pichlmueller et al. 2020), AR resistance is not widespread in these populations. The results from these three sites supports the current best-practice by Department of Conservation toward use of AR (especially the potent 2AR brodifacoum) for eradication-only purposes (Broome et al. 2019). On Rotoroa Island, nearby to Waiheke Island, where mice survived a 2010 rodent eradication attempt, no AR resistance was detected in the surviving population, that was subsequently eradicated in 2013. This is fortunate as had AR resistance been present and selected for following the first failed mouse eradication, it may have elevated the risk of failure in the subsequent mouse eradication (Holmes et al. 2015, Samaniego et al. 2021).

The clear landscape partitioning of VKORC1 mutations may reflect different origins of the mice populations included in this paper (Searle et al. 2009; MacKay et al 2013; King et al. 2016; Veale et al. 2018). Although, despite the presence of different mtDNA haplotypes in the study area, they all belong to clade E described by Jones et al. (2011) and so the different AR history rather than ancestral inheritance may cause the patterns we found. Indeed, it needs to be considered that VKORC1 mutations can arise independently and vary rapidly in frequency especially on islands and in AR-dense environments (Rost et al. 2009; Goulois et al. 2017; Gallozzi et al. 2024).

Although mice are a widespread human nuisance and biodiversity pest in Aotearoa/New Zealand, there is currently no single efficient tool for their landscape management at sites where eradication is not currently possible. Because AR are the most efficient current tool, there is a temptation to use them for long-term suppression. However, this entails an elevated risk of selection for AR resistance. Where mutations were not purged during foundational events, such AR resistance can be selected for rapidly, particularly where mice are not the primary target of AR. This does not mean that AR should not be used for long-term suppression at sites of high biodiversity or other value, but our results emphasise that such use of AR should be done with the knowledge that the timespan for such use may very much be finite.

Our survey revealed that even across a moderate geographic region such as the greater boundaries of one city, there can be important site-specific genetic diversity in AR resistance related to the history of AR use (whether mutations were selected for) and potentially also to the level of founder effect they experienced (whether mutations were purged) and the origin of mouse populations (which mutations could be introduced). For this reason, we urge land managers to be mindful of their use of AR for rodent management and consider integrated pest management strategies and alternative tools. Where eradication of a mouse population is planned, we recommend mice be screened for the genetic pre-cursors to AR resistance, lest it contribute to the risk of eradication failure (e.g., Lord Howe Island; Harper et al. 2020). As supported by previous studies (Rached et al. 2022; Yiğit et al. 2023; Carromeu-Santos et al. 2023; Gallozzi et al. 2024) and based on the average frequency of individuals with missense SNPs found here (0.25), we suggest a sample size of 15 covering multiple sites across a given area should be sufficient for this purpose (with 25% prevalence there is 99% probability of detection from 15 individuals) – a sample size that is typically collected prior to eradications anyway for the purpose of diagnosing causes of eradication failure (Russell et al. 2007, Pichlmueller et al. 2020). Given the increased understanding of mouse impacts on native biota, we recommend investment into landscape control tools for mice that are not reliant on AR.

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Data and code availability: detailed information about the genotypes of each sample is available in Supplementary Materials. Any further information will be available upon request.

Ethics: all mice were collected as part of standard pest control management and as such no ethics approvals were required to undertake this work.

Conflicts of interest: the authors declare no conflicts of interest.

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Supplementary material

Additional supporting information may be found in the supplementary material file for this article:

Appendix S1: New Zealand mice genotypes.xlsx

The New Zealand Journal of Ecology provides supporting information supplied by the authors where this may assist readers. Such materials are peer-reviewed but any issues relating to this information (other than missing files) should be addressed to the authors.