

## REVIEW ARTICLE:

# DOGS SERVE AS A RESERVOIR AND TRANSMIT RABIES IN ISRAEL. IS HISTORY REPEATING ITSELF?

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There are two known epidemic forms of rabies: the urban form in which the dog serves as the reservoir of the virus and the sylvatic form in which wild animals serve as a reservoir. In Israel the urban form of the disease was the most prevalent between 1930 and 1960. But this form faded with the introduction, in the 1960's, of the law enforcing vaccination of dogs and poisoning of jackals (*Canis aurus*) adjacent to urban areas. In the 1970's the source of the virus changed, and the fox (*Vulpes vulpes*) became the main source, a situation which continued until 2004. From 2004 and until today we have been confronted by a new strain of the rabies virus for which the dog (*Canis familiaris*) serves as the reservoir.

Because of an increase in the incidence rabies in the 1990's, and the occurrence of three cases in humans between 1996 and 1997 (1, 2), the Veterinary Services decided to vaccinate foxes and jackals in the wild by using an oral vaccine.

The rabies virus is a Rhabdovirus of the Lyssavirus group comprising of eleven genotypes that are classified according to the sequence of the nucleoprotein (N) gene of the virus (Figure 1).



The genotypes are:

**Figure 1.** The single stranded negative sense non segmented RNA rabies virus. It is about 11 kb in length and codes for five proteins the Nucleoprotein (N), Phosphoprotein (NS), Matrix protein (M), Glycoprotein (G), and RNA dependent RNA polymerase (L). Between the G and L there is a region referred to as the G-L non coding region that does not encode any known protein and is used for molecular epidemiology studies.

Genotype 1- RABV

Genotype 2 - Lagos bat virus

Genotype 3 – Mokola virus

Genotype 4 – Duvenhage virus

Genotype 5 – European Bat Lyssavirus type 1 (EBL-1)

Genotype 6 - European Bat Lyssavirus type 2 (EBL-2)

Genotype 7 – Australian Bat Lyssavirus

Genotype 8- Aravan Lyssavirus

Genotype 9- Khujand Lyssavirus

Genotype 10- Irkut Lyssavirus

Genotype 11- West Caucasian Lyssavirus

Almost 99% of human rabies cases (about 55,000 cases are reported annually worldwide) result from dog bites and are caused by genotype 1 (RABV). Furthermore, genotype 1 has been found among wild animals and bats in the United States and South America. In Israel the local rabies virus among animals also has been classified as genotype 1. Commercial vaccines protect against all viruses of genotype 1.

Before administration of the oral vaccine, a wide ranging survey was conducted by means molecular epidemiological methods, to map the distributions of the rabies strains in Israel. A total of 226 isolates collected between 1993 and 1998 from different parts of Israel, were surveyed according to nucleotide sequence analysis of 328 base pairs from the C terminus of the N coding region and the non-coding region between the nucleoprotein and the phosphoprotein (NS gene) (Figure 2) (3). A computerized comparison was made among the sequences obtained from the samples and five variants were identified which were distributed among four geographical regions (Figure 3). In each region, rabies virus was isolated from more than one animal species. The variants were distributed among the geographic regions as follows:

**Region 1:** (Golan Heights and the Galilee Panhandle):

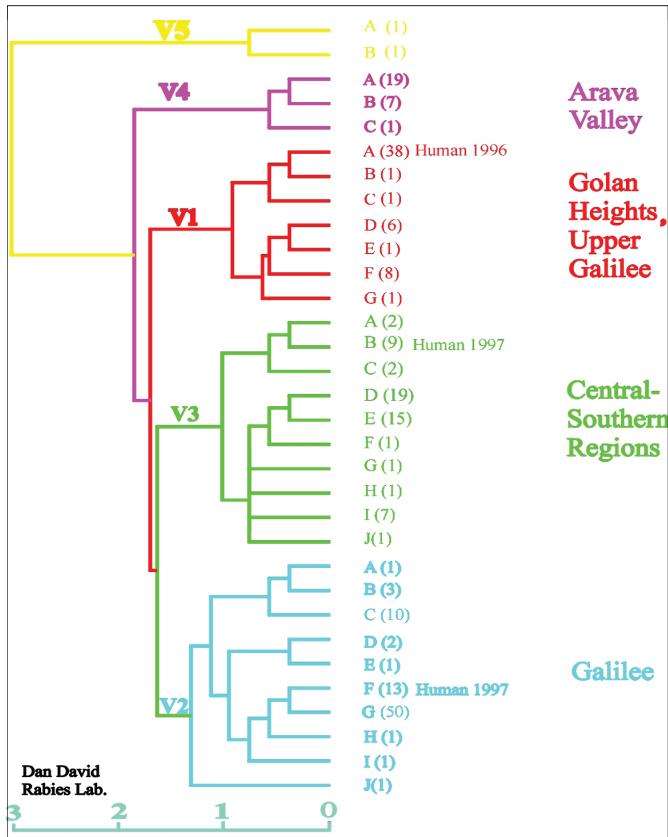
Variant V1

**Region 2:** (Upper and Lower Galilee): Variant V2

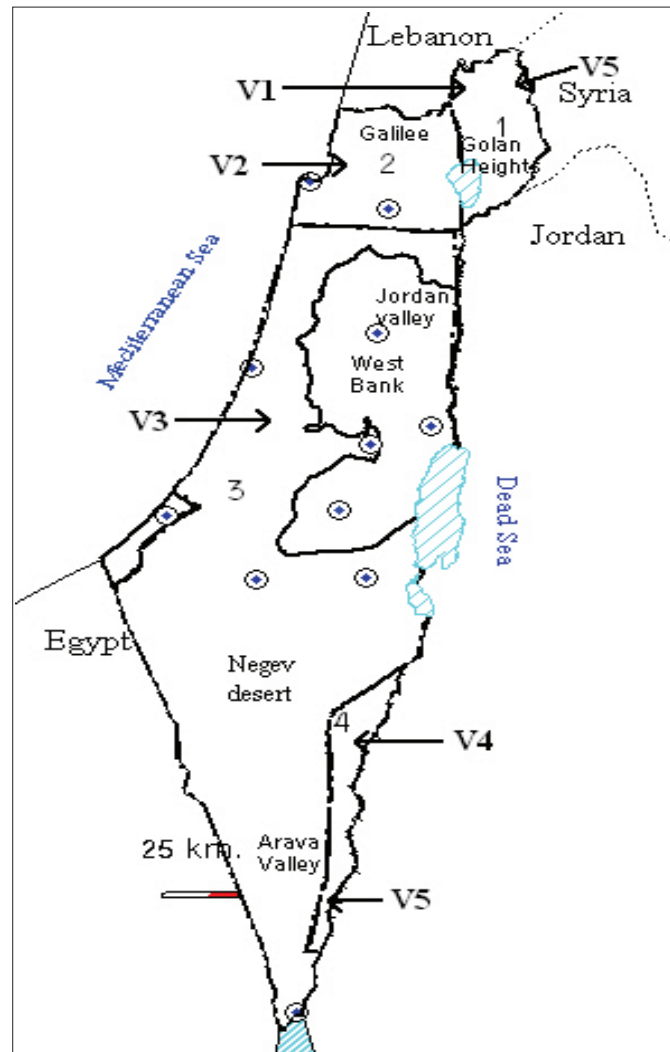
**Region 3:** (Between the Carmel Mountain range and Neot Smadar in the Negev): Variant V3

**Region 4:** (Arava on the border with Jordan): Variant V4

Variant V5 was found in two closely related genetically but widely separated geographical areas: one dog from Kibbutz Katura and a cow from Kibbutz Marom Golan. The discovery of this variant in 1997 roused the suspicion that infected animals might be crossing the borders from adjacent countries and infecting local animals. Later in the investigation it was found that rabies variant V5 was in fact prevalent in adjacent countries. Rabies virus strains isolated in Israel until 2004 originated from foxes, which served as both a reservoir and transmitter of the virus.

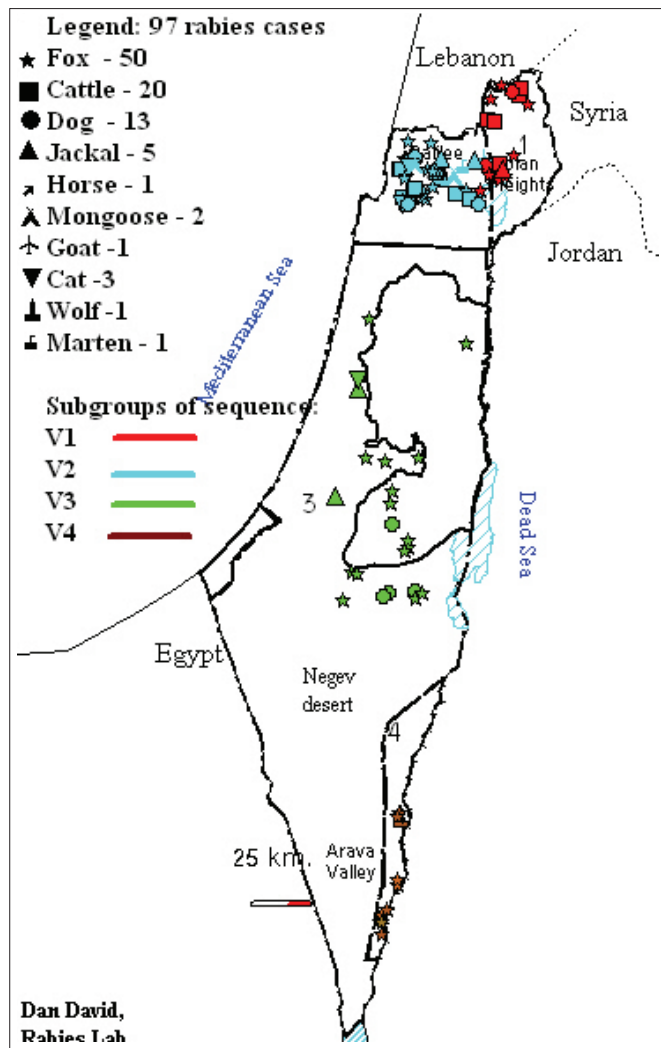


**Figure 2:** Phylogenetic analysis of the Israeli rabies isolates between 1993-1998 revealed five genetic variants V1-V5. The analysis was performed on a 328 bp fragment belonging to the nucleoprotein gene. The numbers in parentheses are numbers of isolates tested.



**Figure 3:** Map of Israel showing the geographical distribution of the rabies genetic variants V1-V5.

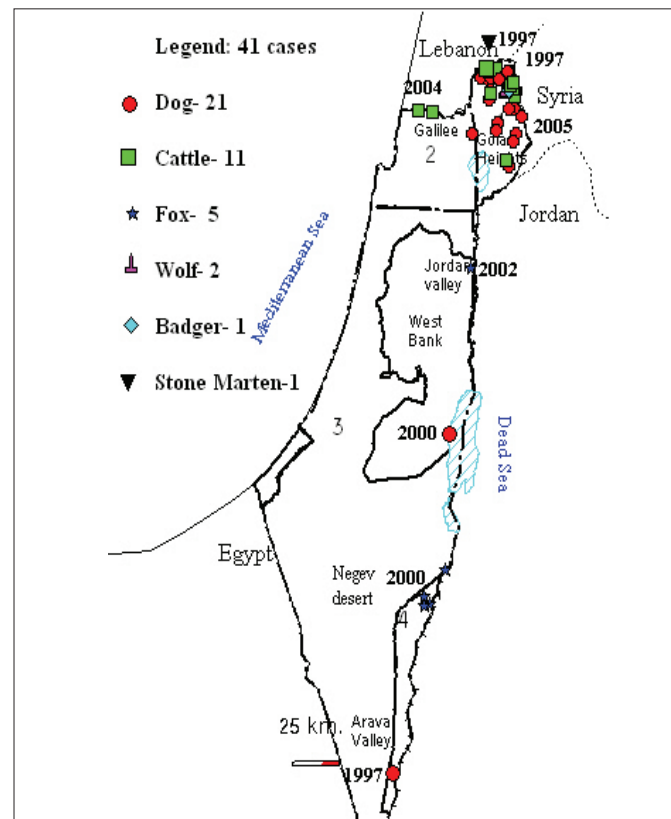
Rabies virus variants are distributed in various geographic areas and are restricted to each region by the topography of the terrain. In each geographic area the rabies virus was isolated from a range of animals, including humans. Rabies viruses isolated from humans between 1996 and 1997 were identical to those isolated from animals in the same region (Figure 2). Knowledge of the virus type in each geographic area enabled the Veterinary Services to vaccinate animals in the north of the country during 1998. In 1998 the greatest number of isolates were obtained, 97 in all, including those from 50 infected foxes (Figure 4).



**Figure 4:** Rabies cases in 1998 when the oral program of wild life vaccination was implemented in northern Israel. Genetic variant V1, distributed in the Golan Heights and Upper Galilee is colored red; variant V2, distributed in Galilee is light blue; variant V3, distributed in the central southern part of Israel is green; and variant V4, distributed in the Arava Valley is brown.

In 1998 the Veterinary Services started oral vaccination of wild animals in Israel (4). Gradually this vaccination program was extended to cover all areas of Israel, including the Palestinian administered territories. Israel is the only country in the Middle East which vaccinates animals with this oral vaccine. Unfortunately, in contrast to Europe where adjacent countries vaccinate against rabies at the same time, in the Middle East, only Israel carries out a vaccination program. It is therefore susceptible to introduction of the virus from adjacent countries by incursion of infected animals. For this reason, in addition to the vaccination program, Israel also carries out continuous monitoring along all of its borders.

From 1997 through 2005, 41 cases of rabies were detected on the borders of Israel; seven cases were detected on the Jordanian border, two cases on the Lebanese border and 32 cases of rabies on the Syrian border (Figure 5). Computer molecular analyses of the isolated rabies viruses that were found on the borders of Israel were based on comparison of 1,350 bases of the nucleoprotein gene (Figure 6). In light of the comparison among the sequences of the isolates, genetic strains V5, V6 and V7 were found. These new strains indicated that the incursions by infected animals with rabies from neighboring countries caused and continue to cause outbreaks of rabies in Israel (5) (Figures 6 and 7).



**Figure 5:** Map of Israel showing rabies cases isolated along the borders between Israel and neighboring countries during 1997-2005.

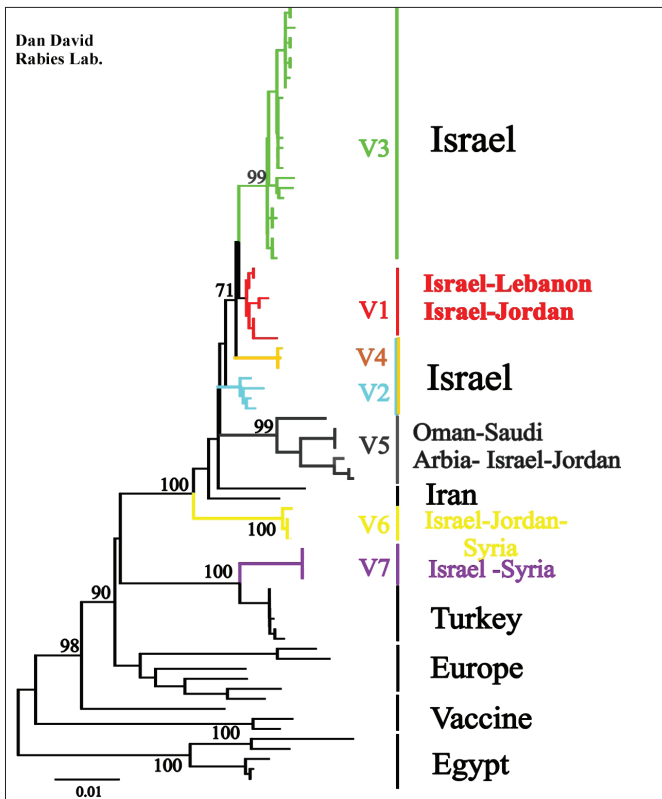


Figure 6: Phylogenetic tree describing the new rabies virus clades discovered in Israel during 1997-2005.

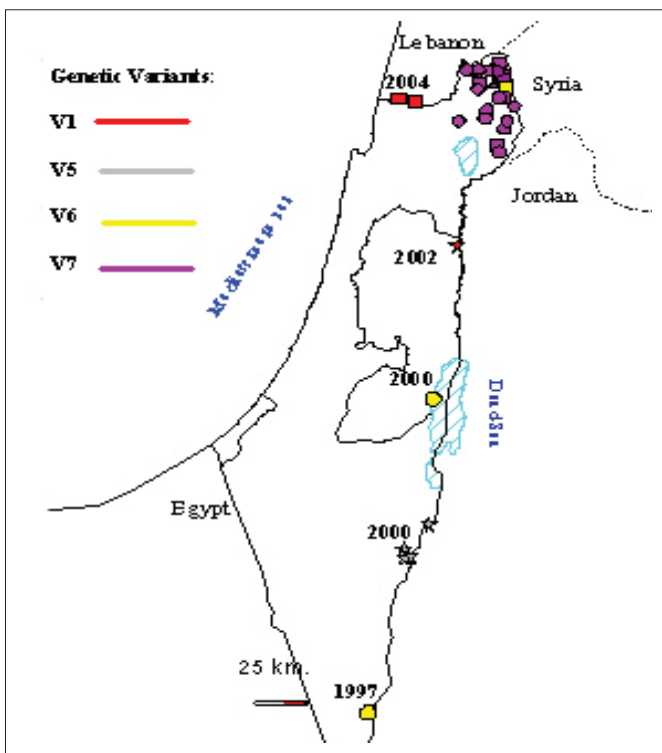


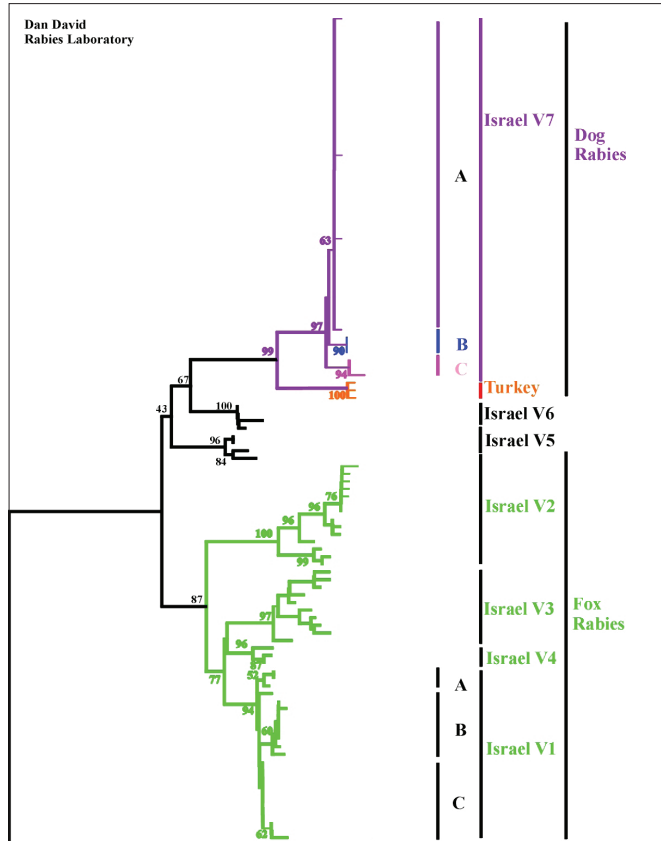
Figure 7: Map of Israel showed the geographical distribution of the new rabies clades V5-V7 on the borders between Israel and neighboring countries.

In the last few years no infected animals have been found carrying the genetic strains V5 and V6. Since 2004 through 2010, the State of Israel has been forced to cope with a rabies strain new to the country, designated V7. The importance of this strain is that dogs can both serve as a reservoir and also transmit the disease. This is in contrast to the fox strain (V1-V4), which were the major reservoir strains before introduction of the oral vaccination. The genetic strain V7 includes isolates from the Golan Heights, Upper Galilee and the Galilee Panhandle and is genetically closely related to isolates obtained in 2007 in Turkey (6), where the dog is considered to be a reservoir of rabies. In light of the facts that dogs are more closely in contact with humans than foxes, this new strain of dog rabies, poses a serious health threat to humans.

Four years after initiation of the oral vaccination program in the north of Israel, its efficacy was proven by the fact that not been a single case of rabies has been found among wild animals or dogs.

In October 2004, the first case of rabies caused by the new strain dog V7 was detected in a cow. The cow from Kibbutz Natur in the Golan Heights was bitten by an unknown animal. Later in 2005, 31 cases of rabies involving the V7 strain (20 of them from dogs) were detected in the north of Israel. During 2006 through 2008, 21 additional cases were diagnosed of which 19 were from dogs. Because of the increased incidence of rabies in infected dogs in the Golan Heights, an experiment was carried out using oral vaccine; it was found that only 28% of the dogs consumed the oral vaccine (7). In 2009, 51 cases of rabies related to the new dog V7 strain that were found in the northern Israel, 32 cases presented in dogs. Because these dogs were in contact with numerous people, more than 600 humans were vaccinated. In 2009 rabies spread throughout the Galilee and caused an outbreak in the town Zefat where four dogs were found to be infected, two of which previously had been vaccinated.

Phylogenetic analyses that were applied to sequences from rabies isolates in the north of Israel from 2004 through 2010 showed that there were differences among sequences of the isolates which resembled those of virus strains that had been present in wild animals in Israel (Figure 8) before the introduction of the oral vaccination program (8). Until 2010 there had been 106 cases of rabies of the dog strain V7 found in the northern Israel (Figure 9). Among the isolates in the north, 70 cases, that is, 66.03% were from dogs infected with this strain. This strain was found to contain substrains, V7A, V7B, and V7C. The V7A strain appeared on the border with Syria and V7B and V7C appeared on the Lebanese border.

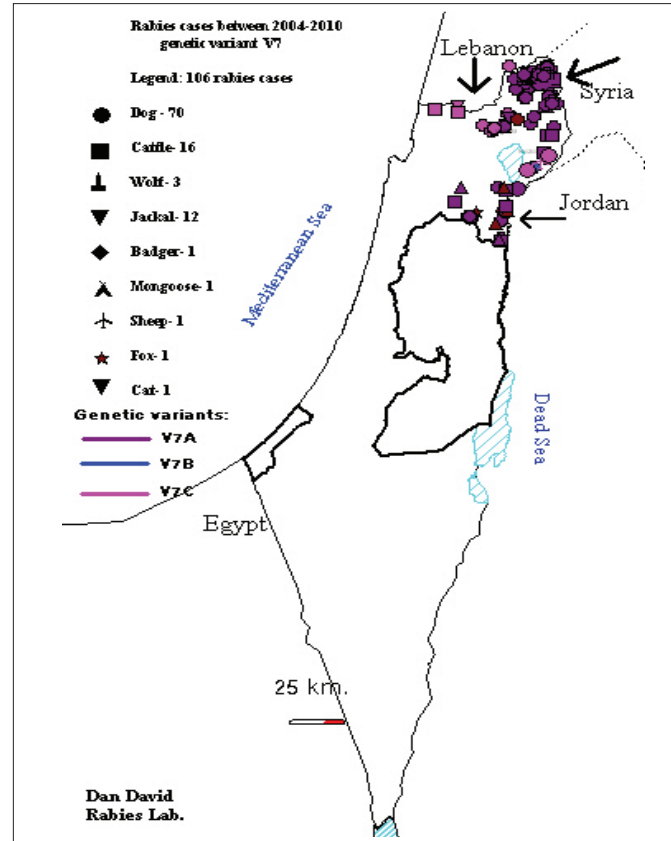


**Figure 8:** Phylogenetic analysis showing the difference between the dog rabies V7 clade transmitted by stray dogs, on the one hand, and the foxes clades V1-V4 transmitted by foxes, on the other hand, when the oral vaccination of wild life was implemented.

The origin of the outbreak in the north of Israel was attributed to the movement of infected dogs from across Israel's borders and the subsequent infection of stray dogs in Israel. The disease is liable to be spread rapidly from place to place over the entire country by humans who transport infected animals during the incubation period. For example a case of rabies was found in a dog in Moshav Micmoret 2 weeks after the dog had been adopted in Beer Sheva by a family visiting the area (9).

## CONCLUSIONS

1. The reservoir of rabies virus in wild animals was eliminated by administration of the oral vaccine.
2. A new strain of rabies (V7) which originated from Turkey and of which the dog is the reservoir has penetrated into the north of Israel from neighboring countries.
3. In spite of the large number of dogs infected with rabies over the last 5 years, only one fox was found to be infected with the new dog strain.
4. Dog rabies is of great concern to public health.
5. Control of stray dogs from the community is essential for continued control of rabies along with universal rabies vaccination of dogs by owners.



**Figure 9:** Map of Israel showing the geographical distribution of the Israeli rabies virus isolates belonging to the V7 genetic variant during 2004 to 2010.

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