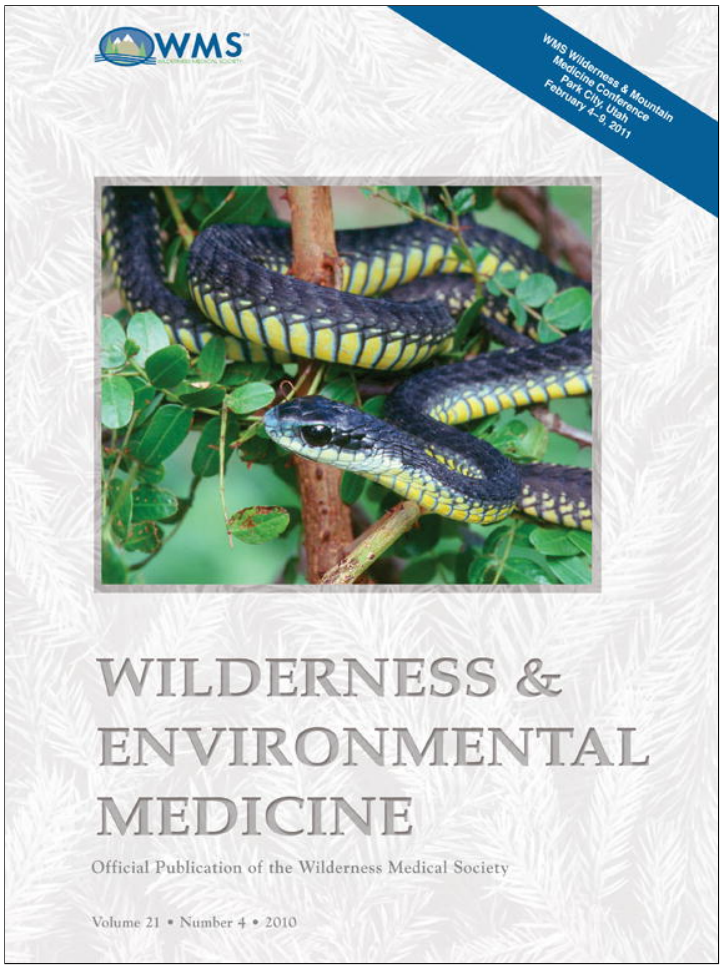

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ORIGINAL RESEARCH

Envenomation by the Scorpion *Tityus breweri* in the Guayana Shield, Venezuela: Report of a Case, Efficacy and Reactivity of Antivenom, and Proposal for a Toxinological Partitioning of the Venezuelan Scorpion Fauna

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Objectives.—Scorpion envenomation is a common public health problem in Venezuela. We report an envenoming case by *Tityus breweri*, endemic to the Guayana Shield, southeast Venezuela, and the outcome of its treatment with antivenom anti–*Tityus discrepans*. Toxin composition and antigenic reactivity of *T breweri* venom were also explored. *T breweri* distribution range was re-evaluated.

Methods.—Clinical signs and symptoms in an adult male were recorded after envenoming and treatment with antivenom. Toxin composition and antigenicity of *T breweri* venom were investigated by polyacrylamide gel electrophoresis, immunoblotting, and mass spectrometry. *T breweri* distribution range was reassessed by mapping new records of the species.

Results.—The moderately severe case (a 21-year-old man) presented autonomic manifestations, including cardiopulmonary and gastrointestinal effects. Full recovery was achieved after anti–*T discrepans* antivenom administration. *T breweri* venom contains toxins in the 6–8 kd range that affect voltage-sensitive sodium channels. Based on new records, *T breweri* distribution area reaches 12 155 km.^{2} Inclusion of southeast Venezuela as an endemic area of scorpionism prompted the examination of clinical, immunological, and phylogenetic evidence for suggesting a partitioning of the Venezuelan *Tityus* fauna into toxinological provinces.

Conclusions.—The severity of the case reinforces categorization of the Guayana Shield region as a macroendemic area of scorpionism in Venezuela and allows classification of *T breweri* as a species of medical importance, with toxins immunologically related to central-eastern Venezuelan *Tityus*. Partitioning of the territory incorporating multiple criteria may help health authorities establish and implement preventive and therapeutic measures for scorpion envenoming in this region.

Key words: scorpionism, *Tityus*, *Tityus breweri*, scorpion venom, scorpion toxin, Guayana, Venezuela

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Conflict of Interest statement: The authors declare that there are no conflicts of interest.

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Introduction

Distinction between proven and presumptive reports of envenoming by toxic fauna is crucial in order to provide a more accurate basis for the information appearing in the literature.[1] Appropriate therapeutic measures should ideally be based on the systematic identification of the offending animal as the ensuing envenoming syndrome is very likely to depend on the species implicated. Amply documented for snakes,[2] differential clinical manifestations also have been recorded in the case of scorpions, depending on the species involved. Scorpion envenomation is an important public health problem in tropical and subtropical areas of the world due to its frequent incidence and potential severity. Management of some of these cases can be difficult especially in regions with limited medical facilities.[3] For example, envenoming by *Tityus cambridgei* in Pará, northeastern Brazil, typically presents with central neurotoxicity (eg, myoclonia, dysmetria, dysarthria, and ataxia) as opposed to envenoming by *Tityus serrulatus* in the southeast, which mainly involves autonomic manifestations, with few or no neurological effects.[4] In Venezuela, envenoming by *Tityus zulianus* (Zulia, Mérida, and Táchira States, western range) often produces respiratory arrest and death by pulmonary edema,[5–7] whereas that of *Tityus discrepans* (north-central Venezuela) mainly causes pancreatic and gastrointestinal disorders.[8,9] Additionally, envenoming by *Tityus neoespartanus* from Margarita Island (northeastern Venezuela) produces a combination of cardiac and gastrointestinal effects.[10] The relevance of a proper taxonomic identification of the offending scorpion is also warranted taking into account that allopatric species can be imported into areas where they do not occur and/or are occasionally extralimital.[11,12] Given the diversity in antigenic terms among scorpion toxins targeting ion channels in excitable cells (responsible for >90% of the lethality of scorpion venoms), the effective use of antivenoms is restricted to the neutralization of venoms that are cross-reactive, which complicates clinical management using heterologous antivenom.[13,14]

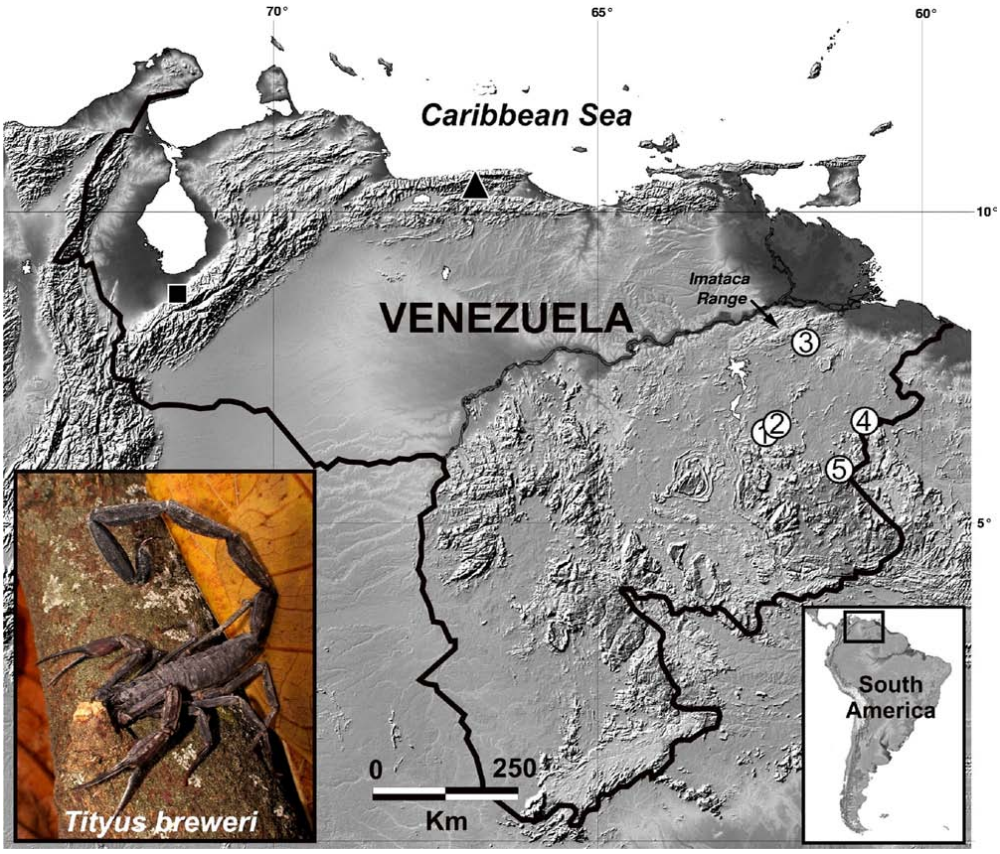

Figure 1. *Tityus breweri* distribution in southeast Venezuela, Guayana Shield. Collection sites within the original distribution area defined by González-Sponga (1997): 1. Salto Parapapoy (type locality); 2. El Triunfo Mine; 3. Village of El Palmar. New records for the species reported in this work: 4. Anacoco Island; 5. Low Wey River (envenomation case is reported from this location). Filled square, collection site of *T. zulianus* (Mérida State, western range); Filled triangle, collection site of *T discrepans* (Miranda State, central range). The arrow points to the Imataca range, northern Bolívar State, southeast Venezuela, where severe scorpion envenomations have been recorded in the past. Inset: Male specimen of *T breweri* collected in Anacoco Island.

As part of a current survey of the fauna inhabiting the lower Cuyuní River, in the Guayana Highlands (northeast Bolívar State, Venezuela) (Figure 1), this work reports on the association of a clinical case with a scorpion species identified taxonomically as *Tityus breweri*. Scorpion envenoming in Venezuela is endemic to 7 geographical areas, 5 of which overlap with the densely populated northern section of the country. Envenoming is mostly due to species belonging to the genus *Tityus* (family Buthidae), with 70 referred species, 11 of which have been incriminated in severe and lethal cases.[15–18] Several reports have documented clinical cases following scorpion stings in the north-central, northeastern, and Andean regions,[10,19–23] but information from the also endemic Deltaic (Delta of the Orinoco River) and the Guayano-Amazonian (Venezuela′s southeast) regions is scarce. Marín and et al[24] reported for the Orinoco Delta the first sting case with neurological complications in Venezuela, including aphasia and hemiparesia (for details of the case, see De Sousa et al[20]). The present work is the first to positively associate *T breweri* with an envenoming case from the Guayano-Amazonian region. We also show that *T breweri* produces toxins immunologically related to *Tityus* species inhabiting the Venezuelan central/northeastern regions. This suggests that commercial anti–*T discrepans* antivenom might be effective for treating stings by *T breweri*.

The Guayana Shield region (Figure 1) extends between the Amazon and the Orinoco basins, comprising the states of Bolívar in Venezuela and Roraima in Brazil, and is one of the most diverse centers of floral and faunal endemism of northern South America.[25] The area has been subjected to intensive biological exploration and industrialization due to its biodiversity and natural resources, which involves a higher risk of envenoming by local endemic fauna.

In the 1920s, Oxford noted that large-sized (14–16 cm long) scorpions inhabited the area of the Imataca range (northeast of the current Bolívar State) (see Figure 1) and were responsible for sting cases presenting with high fever, cephalalgia, and vomiting.[26] In 1974, toxic myocarditis was associated to a scorpion envenomation from the area of El Pao, very close to the Imataca range.[27] This mountain range is part of the distribution area of the species *T breweri*, identified in 1997 by González-Sponga from its type locality, Parapapoy Falls[28] (Figure 1). To our knowledge, no reports associating this species with known clinical cases had been published. We also wish to report on the extension of *T breweri* distribution range by providing additional collection localities. A proposal for a partitioning of the Venezuelan territory into provinces according to the toxinology of its scorpion fauna is suggested.

Materials and Methods

SCORPIONS, VENOMS AND ANTIVENOM

Scorpions were collected at night using ultraviolet lamps.[29] Adult *T breweri* scorpions (n = 4) were collected at Anacoco Island (6°45′N; 61°10′W), northeast Bolívar state, Venezuela (Figure 1). Adult *T zulianus* scorpions (n = 10) were collected around Santa Cruz de Mora (8°22′N, 71°43′W), western Mérida State, Venezuela. Adult *T discrepans* scorpions (n = 10) were collected near San Antonio de Los Altos (10°20′N, 67°45′W), Miranda State, central Venezuela. *T zulianus* and *T discrepans* collection sites are also indicated in Figure 1. The arachnids were kept in captivity at the Institute of Experimental Medicine, Caracas, with water ad libitum and fed *Tenebrio molitor* (Coleoptera, Tenebrionidae) larvae or *Acheta domesticus* (Orthoptera, Gryllidae) every week.

Taxonomical diagnosis of the *T breweri* specimen involved in the envenomation case reported herein was performed using a 700 Mitutoyo calibrated, digital caliper (Mitutoyo America Corp, Aurora, IL) under an Olympus SZH10 stereoscopic microscope (KS Olympus Co, Shinjuku-ku, Tokyo, Japan). Morphometric data (recorded in millimeters) are available upon request. Diagnosis of *T breweri,* as well as *T discrepans* and *T zulianus,* specimens was performed by one of the authors (L.D.S.) at the Laboratory of Toxinology, School of Health Sciences, Universidad de Oriente, Anzoátegui Campus, Venezuela, home of one of the largest Venezuelan arachnid collections,[16] based on this center′s previous research on *Tityus* taxonomy.[12,16,30]

Venom from *T zulianus* and *T discrepans* was pooled from 10 scorpions and from 4 scorpions in the case of *T breweri*. Venom was obtained by manual stimulation of the telson (the last caudal segment) by forcing the animals to sting repeatedly onto Parafilm (Sigma Chemicals, St Louis, MO) sheets[31] and subsequently lyophilized at −50°C and 80 mBar of pressure. Anti–*T discrepans* antivenom (lot no. 043) derived from immunized horses was obtained from Centro de Biotecnología, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela.

GEL ELECTROPHORESIS AND IMMUNOBLOTTING

Lyophilized venom samples were solubilized in doubly distilled water (0.5 mL/mg), centrifuged at 5000*g* for 20 minutes to eliminate particulate matter, and aliquots taken from the supernatant for protein determination according to the Lowry method.[32] Samples (15 μg pro-

tein) were fractionated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) on 20% gels and subsequently transferred to nitrocellulose paper and reacted against anti–*T discrepans* antivenom at a 1:1000 dilution as previously reported.[33]

MASS SPECTROMETRY ANALYSES

Mass spectra of positively charged ions from *T breweri* venom (prepared as indicated earlier) were analyzed by matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI–TOF MS) in a Biflex III MALDI–TOF MS (Bruker, Germany) essentially as described previously.[35] Mass spectra of positively charged ions were recorded on the Biflex III instrument operated in the linear mode. The total acceleration voltage and the detector voltage were 19 kV and 0.55 kV, respectively. A total of 100 to 150 single shots were accumulated for each sample. Masses were calculated from at least 3 independent analyses.

Results

CASE REPORT

A 21-year-old man was stung by a scorpion on January 30, 2008 at 20:05 hours on the right foot while checking the electric plant of the base camp during a biological survey near Las Claritas Mine (06°05′11.4″N, 61°29′48.2″W, 154 m above sea level), lower river Wey (tributary to the Cuyuní River), southwest of Bolívar State, Venezuela (Figure 1). He presented immediate, intense pain in the lower section of the right leg that later referred to the inguinal-scrotal area with concomitant erythema around the sting site. Diaphoresis, rhinorrhea, and sialorrhea started 15 minutes after the accident, together with odinophagy and tremors. Generalized muscle fasciculation (in superior and inferior limbs) and fever appeared 25 minutes later, together with persistent cough, thick and abundant sialorrhea, piloerection, bilateral myosis, and epiphora. Upon physical examination, the patient demonstrated tachycardia (115 beats per minute), tachypnea (26 beats per minute) and irregular pulse. The abdomen was painful on deep palpation at the epigastrium and left hypochondrium. The patient was hydrated with saline solution and given intravenously 2 anti–*T discrepans* antivenom ampoules (Centro de Biotecnología, Universidad Central de Venezuela, Caracas; 5 mL each diluted in 25 mL of saline) approximately 40 minutes after the envenomation; hydrocortisone was also administered. Clinical signs (both cholinergic and adrenergic) subsided 10 minutes after antivenom administration. The patient was taken by river to a rural clinic in Las Claritas and later to the Tumeremo General Hospital. The patient′s condition improved considerably during the trip and complete recovery occurred 2 hours after the accident. It should be noted that the patient was envenomed by *Lachesis muta muta* (Serpentes, Viperidae) a year before the scorpion accident and received the antivenom manufactured at the Universidad Central de Venezuela against the venoms of *Bothrops colombiensis* and *Crotalus durissus cumanensis*.

The scorpion specimen involved in the accident was deposited at La Salle Museum of Natural History, Caracas, Venezuela, under the catalog no. MHNLS 1385. Taxonomical diagnosis was performed at the Laboratory of Toxinology, School of Health Sciences, Universidad de Oriente, Anzoátegui Campus, Venezuela, which allowed its classification as a male *T breweri*.[28]

Two additional *T breweri* specimens from Bolívar State were examined and deposited at the Scorpion Collection, Laboratory of Toxinology (CELT), Universidad de Oriente, with catalog no. CELT 534 (♂) and no. CELT 1107 (♂). The first scorpion was collected inside a human dwelling (bathroom) at El Palmar (Padre Pedro Chien Municipality), within the distribution range of *T breweri*[28] (Figure 1). The second specimen was from a peridomicile area in Anacoco Island, Sifontes Municipality (6°45′N, 61°10′W), Bolívar State, around 143 km from the type locality of *T breweri* (Parapapoy Falls, Meseta de Santa Rosa, 06°37′12”N; 62°27′17”),[28] on the border with the Esequibo territory (Figure 1). Morphometric data corresponding to these specimens are available upon request. It is noteworthy that specimen CELT 1107 is the largest Venezuelan example of *Tityus* sp (110.55 mm) collected to this date.

T BREWERI VENOM COMPOSITION AND IMMUNOREACTIVITY

Composition of *T breweri*, *T discrepans*, and *T zulianus* venoms evaluated by SDS-PAGE is shown in Figure 2A. Low molecular mass proteins migrating around 6–8 kd are the main components in all 3 venoms. Figure 2B shows a representative immunoblot indicating venom reactivity against anti–*T discrepans* antivenom. Using this panel, intensity of the areas corresponding to signals in the 6–8 kd range (right arrow) was evaluated for *T discrepans*, *T breweri*, and *T. zulianus* venoms by densitometry analysis using the software ImageJ (http://rsbweb.nih.gov/ij/). While there was no difference in the intensity of recognition between the control (*T discrepans*) and *T breweri* low molecular mass venom components, the intensity of recognition of *T zulianus* components was approximately 54% of the intensity recorded for *T discrepans*.

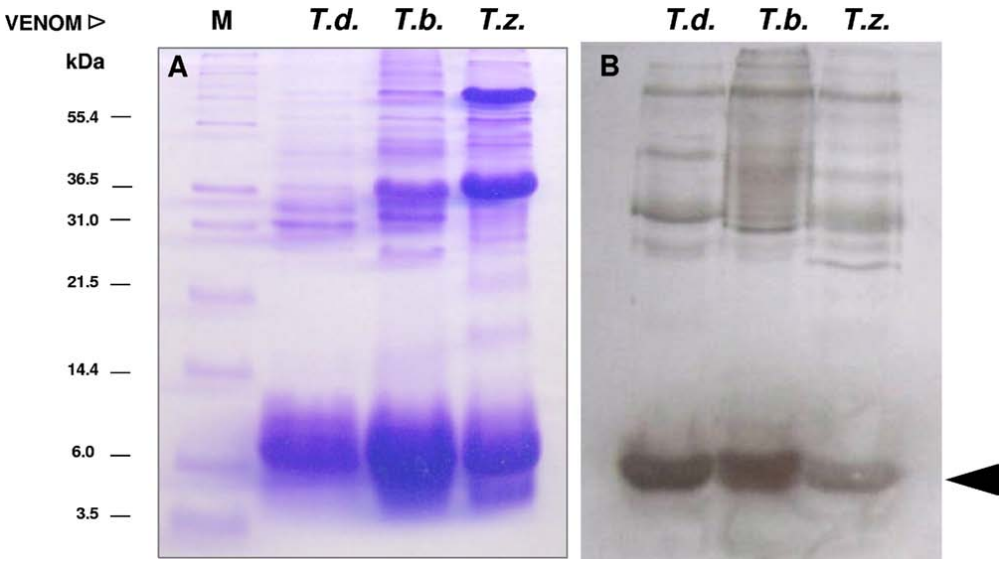

Figure 2. Antigenic reactivity of *T breweri* venom components as evaluated by inmunoblotting. (A) SDS-PAGE (20% polyacrylamide gel) of *T discrepans* (T.d.), *T breweri* (T.b.), and *T zulianus* (T.z.) venoms using equal amounts of protein (15 μg). (B) Venom reactivity towards anti–*T discrepans* antibodies using 15 μg of venom protein per well. Arrow indicates migration of the neurotoxic, low molecular mass components (~6–7 kd) as shown previously.[33]

Figure 3 shows the spectrum obtained by MALDI-TOF MS of *T breweri* venom indicating the presence of components in the 5500–8500 d mol mass range.

Discussion

TITYUS BREWERI ENVENOMATION AND TOXIN COMPOSITION

Regardless of the Venezuelan *Tityus* species involved in the envenomation, there are common clinical manifestations characteristic of excitatory neurotoxicity, including excessive discharge of cholinergic and cathecolaminergic neurotransmitters. However, the severity and nature of signs and symptoms are dependent on the species involved, as has been documented in several regions of Venezuela.[5,6,10,44] In addition, other factors can influence the extent of envenoming, such as the amount of venom injected and patient characteristics. The envenomation case by *T breweri* reported herein presented on the whole the clinical manifestations previously seen in victims stung by *T discrepans*,[8,9] *T caripitensis*,[34] and *T neoespartanus*[10] from north-central and northeastern Venezuela. However, the tremors and muscle fasciculations observed in this case are reminiscent of the envenomation by North American *Centruroides* species, particularly *C sculpturatus*.[36,37] In this regard, neuromuscular hyperactivity has been rarely seen after accidents by Venezuelan *Tityus* (L.D.S., personal observations, May 2009). Such differential activity of *Tityus* venoms could be due to the fact that neurotoxins affecting voltage-sensitive sodium channels distinguish between tissue-specific isoforms of the channel.[38,39] For example, toxin Tz1 from *T zulianus* specifically modifies the gating of the $Na_v1.6$ isoform, predominantly expressed in skeletal muscle.[38] Scorpion peptides (mol mass 6–8 kd) affecting the gating mechanism of voltage-gated sodium channels in excitable cells produce a sustained entrance of sodium and, in turn, the massive release of neurotransmitters from presynaptic terminals.[38,39] Therefore, differences in the composition of the venome (the venom gland proteome)[2] across the genus could be responsible, at least in part, for the differential clinical manifestations.

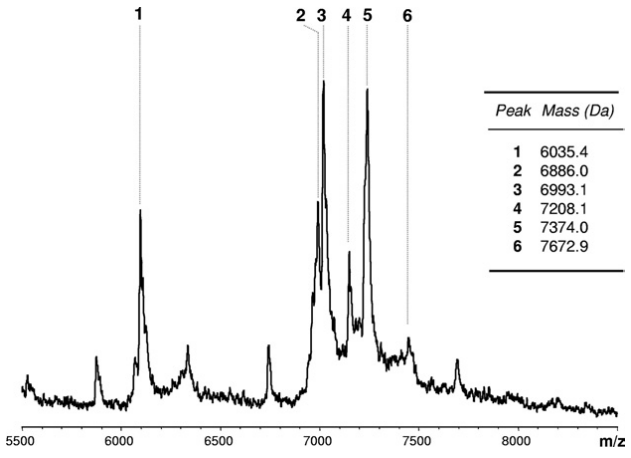

Figure 3. Mass spectral analysis of *T breweri* venom peptide composition using MALDI-TOF MS. The area corresponding to the 5500–8500 d range has been selected. The spectrum is representative of at least 3 analyses of independent venom pools.

As such manifestations in the envenomed patient by *T breweri* were rapidly neutralized by the anti–*T discrepans* antivenom, we compared the peptide fingerprint of *T breweri* venom with that of *T discrepans* (the species prevalent in north-central Venezuela) by mass spectrometry and also evaluated the in vitro reactivity of *T breweri* towards the commercial anti–*T discrepans* antivenom. The *T breweri* MALDI-TOF MS toxin spectrum (Figure 3) was species-specific, as the molecular masses in the 5–8 kd range, albeit close, are different from those reported previously within the same range for *T discrepans* and *T zulianus* venoms by Borges et al.[35] The anti–*T discrepans* antivenom recognized in *T breweri* venom the 6–8 kd bands associated with neurotoxic activity in *Tityus* venoms[33,35] (Figure 2). This result is consistent with previous observations reporting that a rabbit anti–*T discrepans* antivenom fully recognized *T breweri* venom in enzyme-linked immunosorbent assay (ELISA) experiments[40] and confirm the observed efficacy of this antivenom in the management of the clinical case reported in this work. Notably, intensity of the recognition of *T zulianus* 6–8 kd mass components were significantly less than that recorded for *T discrepans*, in agreement with the lower efficacy of this antiserum in neutralizing the in vivo toxicity of *T zulianus* venom in comparison with *T discrepans*,[35] and reinforcing the notion of antigenic diversity among *Tityus* toxins in Venezuela.[40] Borges et al[40] have suggested that differences in immunological reactivity among Venezuelan *Tityus* toxins can arise from sequence variations within antigenic epitopes (ie, presence of antigenically unique, species-specific components) and/or differences in abundance of related components. According to our data, *T breweri* toxins may share antigenic epitopes with toxins from the north-central species, *T discrepans*. On the other hand, ongoing fauna surveys (eg, snakes in the Colubridae family) have suggested that the Guayano-Amazonian region is related biogeographically to the Venezuelan northeastern mountain range,[41,42] which could explain the relationship between *T breweri* and central-eastern *Tityus*, particularly with *T discrepans*. Phylogenetic studies are warranted to confirm this hypothesis.

T breweri is endemic to northeast Bolívar State, originally comprising an estimated distribution area of 1071 km.[2] With the new collection localities reported here, which include Anacoco Island and low Wey River (where the envenoming took place) (Figure 1), this area now reaches 12 155 km,[2] making *T breweri* an amply distributed scorpion species in Venezuela, together with *T norientalis*, *T quirogae*, *T discrepans,* and *T perijanensis*.[15–18,35] The presence of *T breweri* in Anacoco Island should be taken into account by health authorities from the neighboring Esequibo Territory and also the Republic of Guyana in the design of appropriate prevention measures against scorpionism in this area, particularly considering the efficacy of the available Venezuelan scorpion antivenom for treating *T breweri* envenoming.

A PROPOSAL FOR THE TOXINOLOGICAL PARTITIONING OF THE VENEZUELAN *TITYUS* FAUNA

Of all referred Venezuelan *Tityus* (n = 70), the species responsible for severe/lethal accidents are *T valerae, T zulianus, T valerae* (Andean region and south of Lake Maracaibo, respectively), *T perijanensis* (Perijá range, western Zulia State), *T falconensis* (Coro Massif, northwestern Venezuela), *T pittieri, T isabelceciliae, T discrepans* (north-central coastal range), *T quirogae*, *T norientalis*, *T caripitensis*, and *T neoespartanus* (northeastern and insular regions).[10,34,35,43,44] Inclusion of the Guayana Shield as an endemic area of scorpionism and of *T breweri* as a medically important species prompted us to examine available evidence for suggesting a partitioning of the Venezuelan *Tityus* fauna into toxinological provinces in order to guide health authorities in the design of appropriate preventive and therapeutic measures.

Figure 4 presents a proposal for the grouping of the scorpion species responsible for severe/lethal sting cases in Venezuela into toxinological provinces, based on (1) the clinical consequences of the envenomation,[15] and (2) the immunological cross-reactivity of their venoms[40] and their phylogenetic affinity.[13] Province I includes *Tityus* species inhabiting the Venezuelan north-central and eastern ranges (including the mountainous areas of Margarita Island), the Guayana Shield, and the island of Trinidad. The Venezuelan species harbored within this province are *T discrepans*, *T nororientalis*, *T neoespartanus*, *T caripitensis,* and *T breweri,* whose envenomations are effectively neutralized by the commercial antivenom available in Venezuela.[9,10,40] We have also included the Trinidadian *T trinitatis*, endemic to Trinidad and Tobago, whose venom contains a neurotoxic low molecular mass venom fraction that exhibits immunoreactivity with anti–*T discrepans* antibodies.[33] Clinical manifestations associated with envenomation by these species are predominantly neuroexcitatory with notable parasympathomimetic effects.[9,10,20,34] In the case of northeastern *Tityus*, cardiac effects have been observed,[10] that have also been recorded after stings by *T trinitatis* in Trinidad.[45] As a result of a recent phylogeographic study of Venezuelan *Tityus*, phylogenetic analyses using nucleotide sequences derived from two mitochondrial DNA (mtDNA) markers (subunit I of cytochrome oxidase and the 16S subunit of ribosomal RNA) resulted in mtDNA

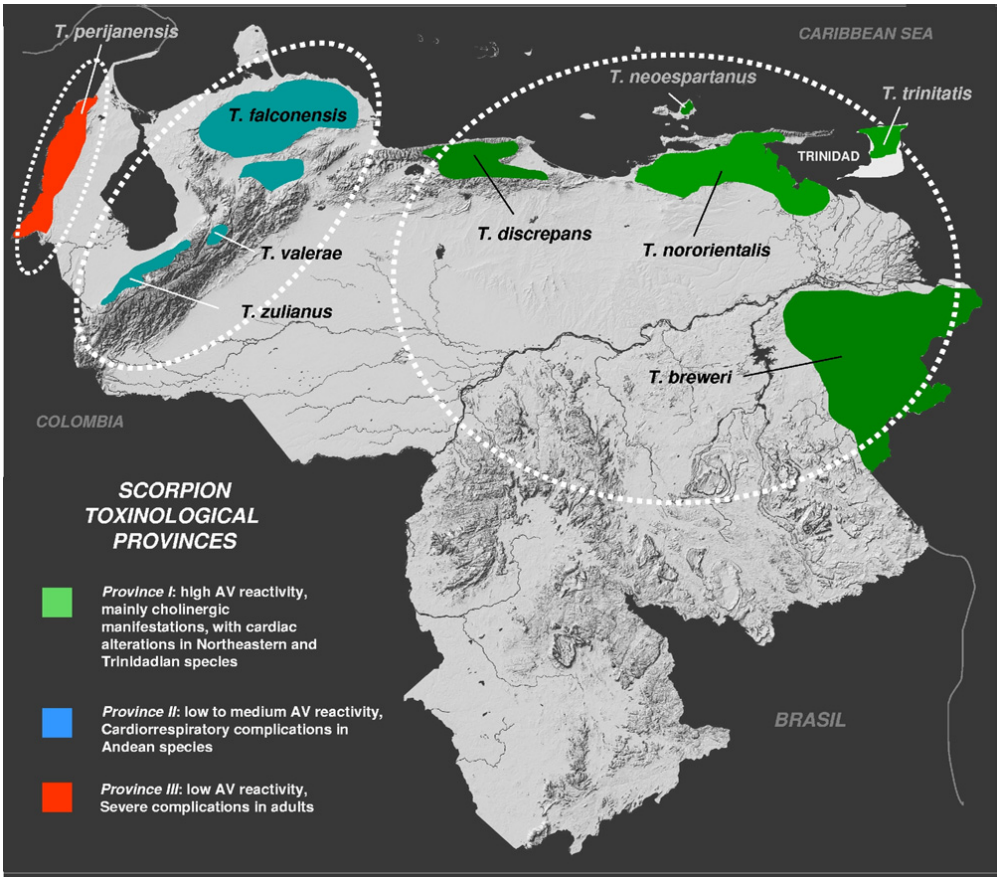

Figure 4. A proposal for a toxinological partitioning of the Venezuelan scorpion fauna of medical importance, considering phylogenetic, immunological (reactivity towards anti–*T discrepans* antivenom, AV) and clinical data. Shaded areas represent approximate distribution ranges for the indicated *Tityus* species according to Rojas-Runjaic and De Sousa[16] and this report.

haplotypes clearly representing groupings associated with the main mountainous ranges of Venezuela.[13] The north-central, north-eastern, and the Trinidadian species all fall within a statistically supported single mtDNA clade. Therefore, Province I is suggested to group species with high phylogenetic affinity and whose venomes probably contain toxins that are antigenically and functionally related.

Province II includes species endemic to the Andean and central-western ranges, including *T zulianus*, *T valerae,* and *T falconensis*. Reactivity of venoms from these species towards the available antivenom ranges from medium to low[35] (Adolfo Borges, unpublished results, May 2010). The envenomation syndrome taking place after stings by some of these species, particularly in the case of *T zulianus*, comprises severe cardiorespiratory effects, including lung edema,[6,34] a complication not frequently seen in the case of Province I. Pancreatic pathology, including hyperamilasemia and edema, has been recorded after experimental envenoming by *T zulianus* at significantly higher rates than those produced by the north-central species, *T discrepans*.[7] *Tityus* species belonging to Province II have been assigned to a statistically supported mtDNA clade in the aforementioned phylogeographic analyses.[13]

Province III includes thus far only the species *T perijanensis*, endemic to the Perijá range in western Venezuela (Figure 4), which also inhabits the Department of Cesar in Colombia.[17] Venom reactivity of this species towards the commercial antivenom is low in both in vivo and in vitro assays[40,46] and its lethality ranks highest among Venezuelan *Tityus*.[17] Clinical manifestations associated with *T perijanensis* envenoming indicate the presence of very potent neurotoxins capable of exerting systemic complications even in adults.[22] *T perijanensis* is phylogenetically related to *T asthenes* and *T nematochirus* from Colombia and Panamá,[13] species also responsible for severe envenomations.[47] With the ongoing analysis of new *Tityus* of medical importance in Venezuela, particularly from the western areas,[30] we expect to assess whether this proposal can be applied to the remaining species inhabiting the country. Although the delimitation of toxinological provinces is necessarily restricted by the potential for intra-species venom variabil-

ity across distribution ranges (as shown for the scorpions *T nororientalis*[40] and *Scorpio maurus palmatus*[48]), it should be possible after enough cases are examined from each region that clinical manifestations associated with envenoming by different species may become more homogeneous.

Available evidence suggests that in parallel to the strong biogeographic structuring of *Tityus* species, toxinological partitioning exists, which may have important epidemiological as well as clinical consequences. In this respect, our data suggest there could be an association between clinical manifestations of *Tityus* envenoming and species/distribution range. Such potential diversity in venom action and composition should constitute a warning for clinicians confronted with *Tityus* envenomations from different endemic areas. On the other hand, health authorities in Venezuela and probably other countries inhabited by *Tityus* species should consider the possibility of improving the quality of available antivenoms through the inclusion of representative species from various toxinological provinces and thus broaden their spectrum of reactivity.

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