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Distribution of superantigens in group A streptococcal isolates from Salvador, Brazil

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Abstract

Background: Group A streptococcus (GAS) causes invasive disease, superficial disease, and can asymptptomatically colonize humans. Superantigens are one virulence factor found in GAS. Previous studies found associations between the genes that encode superantigens and emm type of GAS. It is unknown if these associations are due to underlying biological factors that limit the distribution of superantigens or, alternatively, if these associations are due to the expansion of local GAS lineages where these studies took place. To further address this question we screened GAS isolates collected from Salvador, Brazil for 11 known superantigen genes.

Methods: Seventy-seven GAS isolates were screened by PCR for superantigen genes. These superantigen genes were speA, speC, speG, speH, speI, speJ, speK, speL, speM, ssa, and smeZ. We used Fisher’s two-sided exact test to identify associations between superantigens and GAS emm type. We then compared our results to previous reports of superantigen prevalence and superantigen association with emm type.

Results: In our collection we found several emm type and superantigen genotype combinations that have previously been reported in isolates from Europe and Australia. We also found that speA was significantly associated with emm type 1, and that speC was significantly associated with emm type 12.

Conclusions: Our study reports superantigen genotypes of GAS from a region of the world that is lacking this information. We found evidence of common GAS superantigen genotypes that are spread worldwide as well as novel superantigen genotypes that, so far, are unique to Brazil.

Keywords: Streptococcus pyogenes, Streptococcal superantigens, Group A streptococcus, Emm types

Background

Streptococcus pyogenes (Group A Streptococcus, or GAS) is a Gram positive bacterium that causes a wide spectrum of clinical manifestations including pharyngitis, skin infections, necrotizing fasciitis, and streptococcal toxic shock syndrome [1]. GAS harbors many virulence factors including superantigens [1].

Superantigens are bacterial exotoxins that are able to activate large numbers of T cells [1-3]. There are eleven known superantigens found in S. pyogenes: SpeA, SpeC, SpeG, SpeH, SpeI, SpeJ, SpeK, SpeL, SpeM, SSA, and SmE [4]. Superantigen genotype varies by emm type and the region of the world in which the isolate was collected [5,6]. An area of active research is whether these associations are due to factors that limit the distribution

of superantigens or are due to the expansion of local GAS lineages [7]. To further address this question we studied a collection of GAS isolates from Brazil. Previous studies of superantigens in GAS isolates from this region of the world are limited and none of these studies have reported the genotypes of all eleven superantigens [8].

Some superantigens are encoded by genes located in the prophage region of the GAS genome. Others are encoded by genes located outside of this region and are considered to be chromosomally encoded [7,9,10]. The SpeA, speC, SpeH, speI, speK, speL, spM and ssa genes have been found within prophages in streptococcal isolates [4,7,11]. The speG, SpeJ, and smeZ genes are considered to be encoded chromosomally [9,12].

The aim of this project was to determine if associations between superantigens, superantigen genotypes, and emm types that have been reported elsewhere were also found in our collection of Group A streptococcus

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isolates collected from Salvador, Brazil. These isolates were collected as part of a previous study of Group A Streptococcus in children with and without pharyngitis [13,14]. From this previously published study we selected all isolates of the two most common emm types (emm 1 and emm 12) and the emm type with the strongest association with pharyngitis (emm 66) to genotype [13].

Methods
Isolate collection and emm typing
S. pyogenes isolates were collected and emm typing was conducted as part of a separate cross-sectional study detailed elsewhere [13,14]. Briefly, isolates were collected from three hospital clinics in Salvador, Brazil. Patients between the ages of three and fifteen were recruited from the middle of April 2007 to end of October 2008 [13,14]. As described in previous publications, Institutional Review Board (IRB) approval was obtained from all hospitals, the Comissão Nacional de Ética em Pesquisa (Conep) (National Bioethics Commission of Brazil), the Comitê de Ética em Pesquisa-Centro de Pesquisa Gonçalo Moniz-Fiocruz (Ethics Committee for Research - Fiocruz), and the University of California, Berkeley Committee for the Protection of Human Subjects [13,14]. As previously described consent was obtained from parents or guardians and verbal consent was obtained from children [13,14]. Isolates were collected from children who had pharyngitis (strept throat) and those who were asymptomatic carriers of GAS. Emm typing of all isolates was performed as described by the Center for Disease Control and Prevention (CDC) protocol http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm.

We selected the two most common emm types (emm 1; n = 25 and emm 12; n = 40) as well as the emm type with strongest association with pharyngitis (emm 66; n = 12) to analyze for superantigen genes. For the purposes of this analysis the emm 1.25 isolate (n = 1) was included with emm 1.

Superantigen identification by PCR
Superantigen genes were identified by PCR using primers previously published by Maripuu et al. or Commons et al. [6,15] (Table 1). The Commons et al. primers were used to identify speB (a positive control for DNA quality), speF, speK, speH, speL, and speM. The Maripuu et al. primers were used to identify speA, speC, speG, speS, and smeZ. Each 20 μl PCR mixture contained 1 U of taq DNA polymerase (New England Biolabs, Ipswich, MA), 0.25 mM dNTPs (New England Biolabs, Ipswich, MA), 1X ThermoPol buffer (New England Biolabs, Ipswich, MA), 1 μl template DNA, and 1 nanomole of the forward and reverse primer. Template DNA was extracted with the Qiagen DNaseasy kit as previously described [13]. The cycling program for the Commons et al. primers was as follows: 2 minutes at 95°C, 35 cycles of 30 seconds at 94°C, 30 seconds at 50°C, 60 seconds at 72°C, and a final extension of 2 minutes at 72°C. The cycling program used for Maripuu et al. was as follows: 5 minutes at 94°C, 25 cycles of 30 seconds at 94°C, 30 seconds at primer specific annealing temperature, 60 seconds at 72°C, and a final extension of 7 minutes at 72°C. As a positive control for each superantigen gene PCR, we used the DNA of an isolate known to contain the relevant superantigen gene. We were unable to amplify

Table 1 Primers used

| Gene   | Forward primer (5′ to 3′) | Reverse primer (5′ to 3′) | Annealing temp. °C | Product size (bp) |
|--------|--------------------------|---------------------------|-------------------|------------------|
| speA1-36 [15] | 5′-GGACTACAACATCTGCCAGAGG-3′ | 5′-TTACTTGGTTAGGATGACTTC-3′ | 54 | 696 |
| speA5 [15]  | 5′-GCTAACAACCTCAACAGAAG-3′ | 5′-TGCTTGAGACCGCTTCTC-3′ | 53 | 659 |
| speC [15]   | 5′-GATTCCACTTATTTACACC-3′ | 5′-AAATATCTGATCTAGTCCTC-3′ | 44 | 584 |
| speG [15]   | 5′-CTTATGCAGATGAAATTTAAAGG-3′ | 5′-AAAGCAAGGGGAGAATAG-3′ | 53.2 | 664 |
| speI [15]   | 5′-ATGAGTAGTGCGAGGTATTAA-3′ | 5′-ATGAAGTTGATCAGAAATAG-3′ | 55 | 645 |
| speJ [15]   | 5′-ATCTTATTAGCAGAATAGTAAT-3′ | 5′-GTGACGGAGGAGGATAGA-3′ | 55.5 | 718 |
| smeZ [15]   | 5′-TTGTTGAAAGAAGTATAA-3′ | 5′-TTGATAAAGGGATCTTTCTATCT-3′ | 52 | 638 |
| ssa [15]    | 5′-AGTCAGAGCCCTGACCTTACAACC-3′ | 5′-TAAGTGGAACCTCTATAGCTATAG-3′ | 59.1 | 691 |
| speH [6]    | 5′-TTGATCCGCTTATTATATAACACC-3′ | 5′-CCACTTTCCTGACGGGTATTTTCG-3′ | 50 | 399 |
| speI [6]    | 5′-CTTTTGGAGAATGAAACC-3′ | 5′-CAGTTTATGGTGCATATGTCG-3′ | 50 | 247 |
| speK [6]    | 5′-GGGATCCATTGACATGGCACTTTAAACACGA-3′ | 5′-GCGAATTCAATAGGCATTACCA-3′ | 50 | 798 |
| speL [6]    | 5′-GACACGATATGGAAGAAGAATCTCCTGCTGAGATATACAC-3′ | 5′-GGGGATCTTACATTTATTTTATTTTGATGAAATAATAGC-3′ | 50 | 703 |
| speM [6]    | 5′-GGAGCGCTATGTGTTCGAGATCAGTGTGACG-3′ | 5′-GGGGATCCTTAAATTTTATTTTTTGGATGAAATAATAGC-3′ | 50 | 661 |
| speN [6]    | 5′-GATCCACAGCTTGTGAGAATACCTCTC-3′ | 5′-AAAGCTTCAAGGTTGATCCTACAA-3′ | 50 | 774 |

All primer sequences shown here have previously been published by Maripuu et al. or Commons et al.
from any isolate and therefore were unable to generate a positive control for speL.

Literature review
To the best of our knowledge, we included all studies in our literature review that tested for the presence or absence of the GAS superantigen genes that showed variability in our study. These superantigens are speA, speC, speG, speH, speJ, speM, ssa, and smeZ. We excluded any studies in which superantigen genotypes of individual isolates could not be determined.

Data analysis
The associations between superantigens and categorical variables were analyzed by Fisher’s two-sided exact test. STATA (StataCorp, Version 10) was used for all analyses.

Results and discussion
Distribution of superantigen genes
We identified speA, speC, speG, speH, speJ, speM, ssa, and smeZ gene sequences from at least one isolate. We did not find any isolates with speK or speL in the collection (Table 2). The most common gene, speG, was present in all isolates. The smeZ gene was present in 99% of 77 isolates. The least common superantigen genes that were identified in at least one strain were speM, found in 5% isolates, and ssa, found in 8% isolates.

The speA genes in emm 1 strains were identified by the Maripuu et al. speA1–3, 6 primers. The speA genes in emm 12 and emm 66 strains were identified by the Maripuu et al. speA-4, 5 primers, indicating they were different alleles. The prevalence of superantigen genes varied across emm type (Table 2). The speA gene was

| Genotype | speA | speC | speG | speH | speJ | speM | ssa | smeZ | emm12 (N = 40) | emm1 (N = 25) | emm66 (N = 12) | p-value |
|----------|------|------|------|------|------|------|-----|------|----------------|---------------|---------------|---------|
| A (n = 1) | X    | X    | X    | X    |    |     |     |     | 1 (4%)         |               |               | .001    |
| B (n = 17)| X    | X    |      |      |    |     |     |     | 13 (52%)       | 4 (33.3%)     |               | <.001   |
| C (n = 1) | X    | X    | X    |      |    |     |     |     | 1 (4%)         |               |               | .001    |
| D (n = 7) | X    | X    |      |      |    |     |     |     | 7 (28%)        |               |               | <.001   |
| E (n = 3) | X    | X    | X    |      |    |     |     |     | 2 (8%)         | 1 (8.3%)      |               |         |
| F (n = 1) | X    | X    | X    | X    |    |     |     |     | 1 (4%)         |               |               | .001    |
| G (n = 1) | X    | X    | X    | X    |    |     | X   |     | 1 (2.5%)       |               |               | .001    |
| H (n = 2) | X    | X    | X    | X    |    |     |     | X   | 2 (5%)         |               |               | .001    |
| J (n = 19)| X    | X    | X    | X    |    |     | X   | 19 | 47.5%)        | 0             |               | <.001   |
| K (n = 3) | X    | X    |      |      |    |     |     |     | 3 (7.5%)       |               |               | .001    |
| M (n = 2) | X    | X    | X    | X    |    |     | X   | 2 | 5%)           |               |               | .001    |
| N (n = 8) | X    | X    | X    | X    |    |     | X   | 5 (12.5%)     | 0             | 3 (25%)       | .001    |
| O (n = 1) | X    | X    | X    | X    |    |     | X   | 1 (2.5%)     |               |               | .001    |
| P (n = 1) | X    |      |      |      |    |     |     |     | 0             | 1 (8.3%)     |               |         |
| Q (n = 4) | X    | X    | X    |      |    |     |     |     | 4 (10%)        |               |               | .001    |
| R (n = 1) | X    | X    | X    | X    |    |     | X   | 1 (2.5%)     |               |               | .001    |
| S (n = 1) | X    | X    | X    |      |    |     | X   | 1 (2.5%)     |               |               | .001    |
| T (n = 1) | X    | X    | X    |      |    |     |     |     | 0             | 1 (8.3%)     |               | .001    |
| U (n = 2) | X    | X    | X    |      |    |     | X   | 1 (2.5%)     |               |               | .001    |
| V (n = 1) | X    | X    | X    |      |    |     |     |     | 0             | 1 (8.3%)     |               | .001    |

Superantigen genotypes B and D were found significantly more often in emm type 1 isolates. Superantigen genotype J was found significantly more often in emm type 12 isolates. P-values were generated with the two-sided Fisher’s exact test.
found in 100% of emm 1 isolates, 50% of emm 66 isolates, and in only 3% of emm 12 isolates (p < .001). SpeC was found in 83% of emm 12 isolates and in no emm 1 or emm 66 isolates (p < .001). The speH gene was found in 55% of emm 12 isolates, 50% of emm 66 isolates, and in no emm 1 isolates (p < .001). The speI gene was found in 93% of emm 12 isolates, 58% of emm 66 isolates, and in 16% of emm 1 isolates (p < .001). The speJ gene was found in 3% of emm 12 isolates, 8% of emm 66 isolates, and in 36% of emm 1 isolates (p < .001).

Table 4 Previously reported superantigen genotypes

| Genotype | speA | speC | speG | speH | speI | speJ | speK | speL | speM | ssa | smeZ | Othername | Countries | emm | Year          |
|----------|------|------|------|------|------|------|------|------|------|-----|------|------------|-----------|-----|--------------|
| A (n = 1) | X    | X    | X    | X    |      |      |      |      |      |     |     | None       |           |     | 2001-2002    |
| B (n = 17)| X    | X    |      |      | X    |      |      |      |      |     |     | R          | Australia  | 1   | 2001-2002    | 6    |
| C (n = 1) | X    | X    | X    |      |      | X    |      |      |      |     |     | F          | Australia  | 1   | 2001-2001    | 6    |
| D (n = 7) | X    | X    | X    |      |      |      |      |      |      |     |     | D          | Australia  | 1   | 2001-2002    | 6    |
|           |      |      |      |      |      |      |      |      |      |     |     |            |           |     |              |      |
| E (n = 3) | X    | X    |      |      |      |      |      |      |      |     |     | None       |           |     | 2005-2006    | 21   |
| F (n = 1) | X    | X    | X    |      |      |      |      |      |      |     |     |            |           |     | 1993-1994, 2005-2006 | 21   |
| G (n = 1) | X    | X    |      |      |      |      |      |      |      |     |     |            |           |     | 2001-2002    | 6    |
| H (n = 2) |      |      |      |      |      |      |      |      |      |     |     |            |           |     | 1989-1993    | 15   |
| J (n = 19)| X    | X    | X    |      |      |      |      |      |      |     |     |            |           |     | 2001-2002    | 6    |
|           |      |      |      |      |      |      |      |      |      |     |     |            |           |     | 1989-1993    | 15   |
|           |      |      |      |      |      |      |      |      |      |     |     |            |           |     | 1989-1993    | 15   |
| K (n = 3) | X    | X    |      |      |      |      |      |      |      |     |     | None       |           |     | 2001-2002    | 6    |
| M (n = 2) | X    | X    | X    |      |      |      |      |      |      |     |     | None       |           |     | 2001-2002    | 6    |
| N (n = 8) | X    | X    | X    |      |      |      |      |      |      |     |     | J          | Australia  | 1   | 2001-2002    | 6    |
|           |      |      |      |      |      |      |      |      |      |     |     |            |           |     | 2001-2002    | 6    |
| O (n = 1) | X    | X    | X    |      |      |      |      |      |      |     |     | None       |           |     | 2001-2002    | 6    |
| P (n = 1) | X    |      |      |      |      |      |      |      |      |     |     | None       |           |     |              |      |
| Q (n = 4) | X    | X    |      |      |      |      |      |      |      |     |     |            |           |     | 2006-2007    | 16   |
| R (n = 1) | X    | X    | X    |      |      |      |      |      |      |     |     | Not Given  | Norway     | 1   | 1988-2003    | 19   |
| S (n = 1) | X    | X    |      |      |      |      |      |      |      |     |     | Not Given  | Spain      | 1   | 1999-2003    | 18   |
| T (n = 1) | X    | X    | X    |      |      |      |      |      |      |     |     | Not Given  | Spain      | 1   | 1999-2003    | 18   |
| U (n = 2) | X    | X    | X    |      |      |      |      |      |      |     |     | T          | Australia  | 1   | 2001-2002    | 6    |
| V (n = 1) | X    | X    | X    |      |      |      |      |      |      |     |     | None       |           |     | 1988-1990    | 15   |

Previously published emm 1, 12 and 66 superantigen genotypes were reviewed and compared to our collection. "Genotype" refers to designations given in this paper. "Other name" refers to pattern name given in previously published work. Citations refer to the reference section.
Superantigen-emm genotyping

We examined the diversity of superantigen genotypes within the same emm type. We were able to distinguish 20 distinct strains of GAS using superantigen genotypes alone (Table 3). The three emm types we examined in this study were further divided into 24 distinct genotypes by the combination of emm typing and superantigen genotype. We reviewed previously reported emm 1, 12, and 66 superantigen genotypes and found many genotypes have been given multiple names. For further reference, we have included the original citation and superantigen genotype name from all studies included in our literature review (Table 4). For the subsequent analysis all the genotypes names used are from Table 3.

The most common superantigen genotype, J, contained 19 isolates. The second most common genotype, B, contained 17 isolates. Genotype J was exclusively found in emm 12, and represented 48% of all emm 12 isolates (p < .001). Genotype B was significantly associated with emm 1 (p < .001) but was also found in 4 emm 66 isolates. Genotype D was exclusively found in emm 1 isolates (p < .001).

Discussion

In this study speA and speI were significantly associated with emm 1. speH and speI were significantly less likely to be found in emm 1 isolates as compared to the rest of the collection (Table 2). Previous studies also found that speA is frequently found in emm type 1 GAS isolates [6,15,22,23]. We found that superantigen genotype B and superantigen genotype D comprised the majority of emm 1 isolates. Genotype B and genotype D differ only by the presence of speI in genotype D. Genotype B has previously been reported in emm 1 isolates from Australia between 1989 and 2002 [6]. Genotype D has previously been reported exclusively in emm 1 isolates. These isolates were collected in Norway, Spain, New Zealand, and Australia between 1988 and 2003 [6,15,16,18,19].

In this study speC was significantly associated with emm 12 and was not found in either emm 1 or emm 66 isolates. Previous studies found speC is often found in emm 12 isolates including isolates from China and Japan [23,24]. However, in contrast to the results of the current study, the studies of isolates from China and Japan have found that speC is also present in the emm1 isolates from these same collections [23,24].

In the current study, the majority of emm 12 isolates had superantigen genotype J. Genotype J has previously been reported in emm 12 and 66 from Norway, Spain, and Australia between 1989 and 2007, indicating that this particular genotype is very common and has spread worldwide [6,15,16,18,19]. There were no statistically significant associations of superantigens with emm 66. Only 12 emm 66 isolates were included in this study and the sample size may have been too small to produce meaningful results.

Conclusions

Previous studies found superantigens are not randomly distributed across emm types [6,15,22]. However, associations between specific superantigens and emm types often vary by study. Previous studies have suggested numerous hypotheses to explain this variation. It is unknown if this variation is due to underlying biological factors that limit the distribution of superantigens, the selective advantage due to carrying particular superantigens, or the chance expansion of local GAS clones at the time these studies took place. This is an area of active research [7,11]. The current study helps to address this question by reporting the superantigen genotypes of GAS isolated from a region of the world from which information on superantigen genotypes is lacking. This is the first study to report the prevalence of all 11 superantigens in a collection of isolates from South America or Brazil. Similar to other previously published work we found some common genotypes of GAS which are spread world wide as well as novel genotypes of GAS which have only been reported in this study.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

HB and ST carried out the lab work and statistical analysis required for the study. HB drafted the manuscript. LW, JR, and MR provided critical review of the manuscript and participated in the study designed. All authors read and approved the final manuscript.

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