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Insights from Genomics on Post-Infectious Streptococcal Glomerulonephritis

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1. Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is one of the nonsuppurative sequelae that can occur following a group A streptococcal infection, the other common post-infection sequelae being rheumatic heart disease. Worldwide, it is estimated that approximately 470,000 cases of APSGN occur annually. Children and young adults most commonly are affected with males having twice the incidence as females. By the middle of the twentieth century, evidence was found that streptococcal skin infections were associated with APSGN, and these infections usually did not cause rheumatic fever, leading to the hypothesis that certain GAS strains were "rheumatogenic" while others were "nephritogenic." In contrast to the molecular and immunological details that have brought considerable insight into the pathogenesis of rheumatic heart disease, the bacterial and host factors that contribute to ASPGN remain poorly defined and at times controversial. Modern bacterial genome sequencing projects have now provided a rich genetic resource that includes complete sequences of nephritogenic group A streptococcus strain NZ131 (McShan et al., 2008) and nephritogenic group C streptococcus strain MGCS10565 (Beres et al., 2008) as well as other group A and C strains associated with rheumatic heart disease and other syndromes. A metagenomic analysis is presented and considers the contribution of genes previously associated with APSGN strains (such as streptokinase, protease SpeB, and M protein) as well as other potential genetic factors that may be found uniquely in these genomes including genes acquired by horizontal transfer and via mobile genetic elements. This analysis provides complementary information to the many published studies using nephritogenic *S. pyogenes* strain NZ131 and places them in a broader context, shedding light upon the genetic basis for the human disease caused by this and related streptococci.

2. Acute post-streptococcal glomerulonephritis

Streptococcus pyogenes (group A streptococcus) is a common bacterial pathogen of humans, causing a wide range of disease from uncomplicated pharyngitis to severe life-threatening infections like toxic shock syndrome or necrotizing fasciitis. Acute post-streptococcal glomerulonephritis (APSGN) is one of the two major post-infection sequelae that can follow acute streptococcal infections, the other being rheumatic heart disease. The typical causative agent of APSGN is the group A streptococcus although other Lancefield groups may occasionally trigger this disease. Worldwide, it is estimated that approximately 470,000

cases of APSGN occur annually (Carapetis et al., 2005). Children and young adults are the group that is most commonly presents with APSGN, and males have twice the incidence as females (Silva, 1998).

The link between group A streptococcal infections and the onset of nephritis was considered as early as 1917 by Ophuls (Ophuls, 1917). By the 1940s, a link had been found between streptococcal skin infections and the onset of APSGN, and since the associated strains usually did not cause rheumatic fever, the hypothesis was developed that certain *S. pyogenes* strains were "rheumatogenic" while others were "nephritogenic" (Futcher, 1940; Osman et al., 1933; Seegal and Earle, 1941). Additionally, it was observed that there were divergent seasonal patterns of peak incidence separating nephritogenic and rheumatogenic GAS, with skin infections and APSGN cases peaking in the late summer while throat infections and rheumatic fever had the highest incidence in October (Bisno et al., 1970). Cases of rheumatic fever were rare during the summer APSGN outbreaks, peaking instead during the autumn season. These observations lead to the development of the hypothesis that subpopulations of GAS exist that were adapted for colonization and infection of either the throat or the skin. These "throat specialists" and "skin specialists" were proposed to have specific sets of virulence factors that lead to the post-streptococcal sequelae of rheumatic heart disease or APSGN, respectively. This hypothesis has been refined over time to now define throat specialists, skin specialists and generalists using a classification scheme that relates the Mga regulon, the gene complement surrounding the major antiphagocytic protein M gene (*emm*), to preferred anatomical site of infection (Bessen et al., 1997; Enright et al., 2001; McGregor et al., 2004).

3. Comparative genomics of nephritogenic streptococcal strains

3.1 The nephritogenic streptococcal genomes

The role of streptococcal induced autoimmunity as the basis for the development of rheumatic heart disease has been supported by a number of detailed studies (Cunningham, 2000a; Cunningham et al., 1989; Ellis et al., 2010; Krisher and Cunningham, 1985). It is reasonable therefore to expect that a similar underlying source of antigenic cross-reactivity might be responsible for the development of APSGN, especially since the time of onset roughly follows the time required for the adaptive immune response. However, to date no definitive link has been found although a number of candidate streptococcal proteins have been proposed over the years, including streptokinase, protease SpeB, and the antiphagocytic M protein (reviewed by Cunningham (Cunningham, 2000b)). One of the goal's for genome sequencing of multiple streptococcal strains associated with different diseases was to use comparative genomics to gain insight into the genetic variations that underlie virulence. Several nephritogenic streptococcal isolates now have had their genome sequences determined, and this information will be crucial in understanding the pathogenic mechanisms underlying APSGN.

3.2 Physical chromosome characteristics

The genomes of nephritis-associated streptococcal isolates *S. pyogenes* NZ131 (group A) and *S. equi* subsp. *zooepidemicus* MGCS10565 (group C) were completely sequenced in independent efforts in 2008 (Beres et al., 2008; McShan et al., 2008). Both of these isolates were originally isolated from cases of human glomerulonephritis (Beres et al., 2008; McShan et al., 2008); additionally, NZ131 has been also studied intensively in over thirty published studies (McShan et al., 2008). Both genomes are single circular molecules of 1,815,783 bp and 2,024,171 bp for NZ131 and MGCS10565, respectively. Neither strain has been found to have naturally

occurring plasmids or other episomes. Strain NZ131 has 1,699 predicted open reading frames (ORFs) that use 1,548,919 bases so that 85.3% of the genomic DNA is used as coding sequences. The base composition of the ORFs is 39.18% G+C while the composition of the total genome is 38.57%; both values are similar to the composition seen in the other completed GAS genomes (McShan et al., 2008). The MGCS10565 genome has a 42.59% G+C content, and its genome has 1,961 predicted ORFs, which require 85% of the genome (Beres et al., 2008). The physical parameters of both genomes are typical for the family streptococcaceae.

3.3 Prophages and mobile genetic elements

Strikingly, strain NZ131 carries three prophages in its genome while MGCS10565 carries none. Prophages are always prominent features in the group A streptococcal genomes, sometimes accounting for 10% of the total DNA, and are well-known as vectors for carrying virulence genes such as superantigens or other bioactive proteins. While MGCS10565 has genes that are homologous to prophage integrases or regulatory proteins as well as virulence factors that are often associated with prophages (two DNases and a phospholipase A2), no organized prophage genome exists (Beres et al., 2008). This lack of prophages is in contrast to the *S. equi* subsp. *zooepidemicus* animal pathogen strain NC_012470 that was recently described as having four endogenous prophages (Holden et al., 2009).

The naturally competent streptococci have the *com*CDE operon that is thought to be essential in genetic transformation (Cvitkovitch, 2001). Although a previous study had not found this operon in *S. equi* subsp. *zooepidemicus* strain NCTC 4676 (Havarstein et al., 1997), it is present in MGSA10565 (Beres et al., 2008). The genomes of the naturally competent streptococci (including *S. pneumoniae* and *S. mutans* (Ajdic et al., 2002; Hoskins et al., 2001; Tettelin et al., 2001)) contain *com*CDE and lack prophages, and it is often suggested that frequent DNA transformation events may disrupt the genomes of prophages; thus, their typical absence. The presence of *com*CDE in MGCS10565 suggests that this isolate also may be naturally competent for DNA transformation, and this phenotype may be responsible for the absence of prophages (Beres et al., 2008). Balancing that viewpoint is the fact that these genes appear in the genome of *S. equi* subsp. *zooepidemicus* strain NC_120470, which does carry prophages. Thus, there may be other factors controlling competence in this species.

The prophages of NZ131 carry the virulence genes streptococcal pyrogenic exotoxin H (*spe*H), a streptodornase (*spd*3) and the paratox gene (McShan et al., 2008). Prophage-associated virulence factors have not been linked to APSGN in the literature, and comparison of these two genomes would tend to confirm that non-association. Rather, it would seem that if a common genetic trait exists that leads to APSGN, it would be found among the bacterial genes. Further, the absence of prophages in MGCS10565 and its potential to be competent suggests that if it has acquired genetic material from group A streptococci, it may have occurred via uptake of DNA from the environment rather by bacteriophage mediated transduction. This scenario suggests that genetic transfer may be somewhat of a one-way street, flowing from *S. pyogenes* to this and similar *S. zooepidemicus* strains since group A streptococci have not been demonstrated to be naturally competent. Therefore, the lack of prophages in MGCS10565 argues that group A streptococci, which probably use transduction as a means for horizontal transfer, would be somewhat genetically isolated from these group C streptococcal strains.

3.4 The nephritogenic strains and diversity

The NZ131 and MGCS10565 genomes are not collinear with respect to gene order, but a great number of genes are shared between the two. The genome map of NZ131 is shown in

Fig. 1 with gene homology comparisons to strains MGCS10565 (circle 6) and MGAS2096 (circle 5). Strain MGAS2096 is a group A streptococcus M12 serotype strain that was also isolated from a case of APSGN (Beres et al., 2006) and provides an inter-species reference.

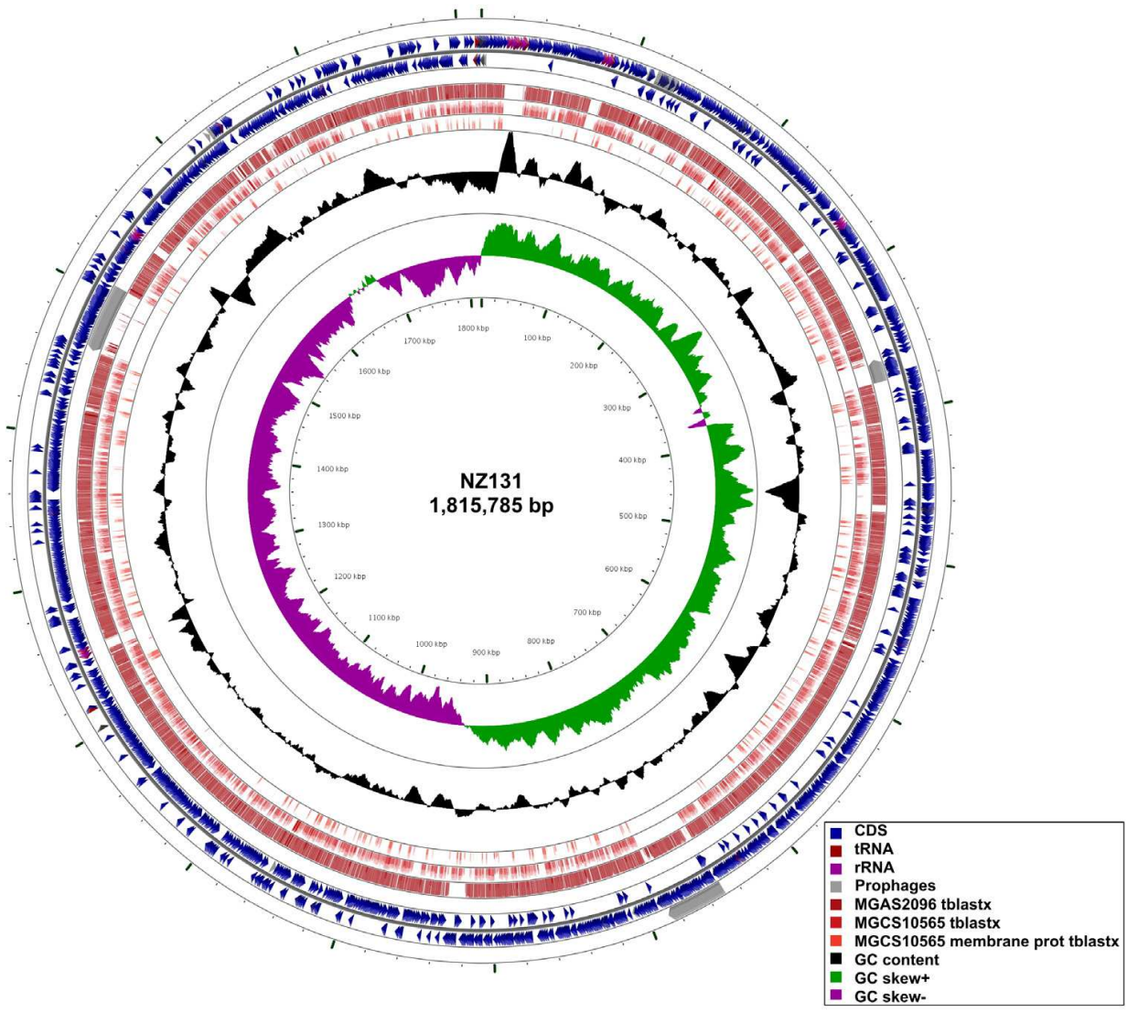

Fig. 1. **The genome map of M49 *S. pyogenes* strain NZ131.** The NZ131 genome map is shown with comparisons to the other two sequenced nephritogenic streptococcal genomes, *S. pyogenes* strain MGAS2096 and *S. equi* subsp. *zooepidemicus* strain MGCS10565. The outer circle and circle 4 indicate the positions of the three endogenous prophages in strain NZ131. The two circles they enclose (circles 2 and 3) show the location of the predicted NZ131 ORFs encoded by the two strands of DNA. The open reading frames were extracted from *S. pyogenes* strain MGAS2096 and *S. equi* subsp. *zooepidemicus* strain MGCS10565 and were compared to the genome of NZ131 using tblastx (circles 5 and 6). Circle 7 shows the specific tblastx hits of surface exposed proteins from MGCS10565. The innermost circles show the total G+C percentage of the NZ131 genomic DNA and the %G+C skew. The ribosomal RNA (rRNA) and tRNA (tRNA) genes were not included in the tblastx comparison. The figure was created using the online tools available at http://stothard.afns.ualberta.ca/cgview_server/index.html.

Overall, the main regions of divergence between the two *S. pyogenes* strains are in the endogenous prophages and other mobile genetic elements (MGE) carried by each (Fig. 1, circles 1 and 4), the genetic structures of the M protein gene region (Mga regulon) and streptococcal pilus region (circle 5), and by the presence the novel M49 and M82 specific NUDIX hydrolase operon in NZ131 (circle 5 (McShan et al., 2008)). NZ131 prophage NZ131.2 shares significant homology with a prophage from MGAS2096 (circle 5) but not including the crucial lysogeny module or virulence genes. Additionally, MGAS2096 has a deletion of a cluster of genes required for citrate metabolism (circle 5, about 925 kb on the map). To date, little evidence has been found to suggest that genes found on prophages or other MGE play a role in APSGN, and the lack of homology in these elements from the two group A streptococcal strains strengthens this idea. Thus, if a common mechanism for triggering APSGN exists, one would predict that bacterially encoded genes would be responsible, either in the form of unique nephritis-associated genes or gene alleles. A number of streptococcal proteins have been investigated as potential triggers of APSGN, and many of targets remain still largely unexplored. For example, circles 6 and 7 show the homology of MGCS10565 total genes and predicted membrane associated genes, respectively, to NZ131. While the homology is not as complete as was for the inter-species strain, many genes and particularly genes encoding cell-surface proteins are present in this intra-species streptococcus. Most of these proteins have not had their function or their potential immunogenicity identified. Thus, if genome comparisons tell us anything, it is that that many targets for future investigations remain. However, several genes have been considered to play a role in APSGN in previous work, and it is worthwhile to examine the variants found in each of these nephritogenic strains for possible shared features.

4. Genes associated with post-streptococcal glomerulonephritis

4.1 Streptokinase

Streptokinase is a plasminogen activator that is released as an extracellular protein by groups A, C, and G streptococci. It generates plasmin, which may promote bacterial spread through fibrinolysis and degradation of the extracellular matrix as well as induce inflammation via complement activation. This latter event may play a role in post-infection sequelae like APSGN (Nordstrand et al., 1999). It has been proposed that structural differences between alleles of streptokinase may be associated with diverse pathogenic outcomes, particularly in the variable βeta-domain (Lizano and Johnston, 2005). The role of streptokinase in the pathogenesis of APSGN has been supported by the use of a mouse model and derivatives of strain NZ131 with either nephritis- or non-nephritis-associated alleles of streptokinase (Nordstrand et al., 2000; Nordstrand et al., 1998).

The streptococcal streptokinase is composed of three domains, which are the highly conserved alpha and gamma domains and the variable βeta domain (Wang et al., 1998). The alpha and βeta domains are associated with plasminogen activation while the variable βeta domain is not required for this enzymatic activity (Lizano and Johnston, 2005). However, in the mouse model used by Nordstrand and her co-workers, the alleles that caused the onset of nephritis mapped their variations to the βeta domain (Nordstrand et al., 2000; Nordstrand et al., 1998). These studies, along with clinical observations (Johnston et al., 1992), have lead to a proposed role for streptokinase in APSGN, possibly in mediating complement deposition in the kidney.

One of the striking observations from the genome of the nephritis-associated group C MGCS10565 strain is the divergence of the encoded streptokinase when compared to those encoded by other group C and group A strains, whether nephritis-associated or not. Figure 2 shows a clustalw alignment of the amino acids from the streptokinase βeta regions from the group A genome strains M1, M2, M3, M4, M6, M12, M18, M28, and M49 as well as the group C strains H46 and GGS 124 (*S. dysgalactiae* subsp. *equisimilis*) and H70 and MGCS10565 (*S. equi* subsp. *zooepidemicus*). The βeta region from the two *zooepidemicus* strains is quite divergent from the other streptokinase proteins from both groups A and C subsp. *equisimilis* strains. Considerable divergence is also observed in the alpha and gamma domains (not shown). The βeta domain is required for docking to plasminogen via a kringle binding hairpin loop (Dhar et al., 2002; Wang et al., 1998), and the variation seen in this region suggests that a number of primary sequences are able to generate the needed secondary and tertiary protein structures.

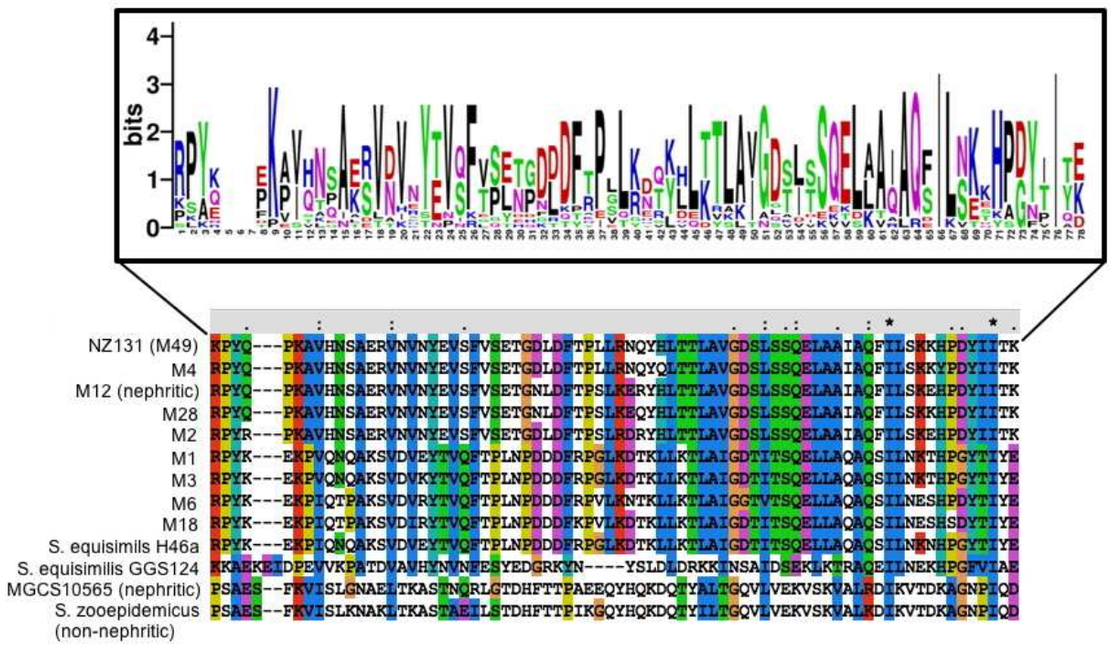

Fig. 2. **Analysis of the streptokinase gene *ska* βeta-region.** The variable βeta-region from the *ska* genes from GAS genome strains (NZ131 (M49, APSGN), MGAS10750 (M4), MGAS2096 (M12, APSGN), MGAS6180 (M28), MGAS10270 (M2), SF370 (M1), MGAS315 (M3), MGAS10394 (M6), and MGAS8232 (M18)) and GCS strains (*S. equisimilis* H46a, *S. equisimilis* GGS124, MGCS10565 (APSGN), and the non-nephritogenic *S. zooepidemicus* H70) was aligned using CLUSTALW (Thompson et al., 1994) and the resulting consensus analyzed using WebLogo (Crooks et al., 2004). The non-nephritogenic M12 *S. pyogenes* strain MGAS9429 was omitted from this analysis since its sequence is 100% identical to that of the nephritis-associated M12 strain MGAS2096. The primary descriptions of each of these genomes are found in the literature (Banks et al., 2004; Beres et al., 2006; Beres et al., 2008; Beres et al., 2002; Ferretti et al., 2001; Green et al., 2005; Holden et al., 2009; Holden et al., 2007; McShan et al., 2008; Shimomura et al., 2011; Smoot et al., 2002)

Further, it should be noted that a number of conserved neutral amino acid residues are positioned in the βeta domain, suggesting an essential contribution to function. Inspection of the primary sequence of the streptokinase proteins in this group shows additional conserved sequences in the two nephritogenic group A streptococcal isolates (NZ131 and MGAS2096) but not found in the nephritogenic group C strain. Protein folding of this domain may create similar structures in both groups that might contribute to APSGN, but such information is not available yet. Interestingly, the streptokinase gene from the non-nephritis M12 serotype strain MGAS9429 is 100% identical to the nephritogenic M12 strain. It is also possible that the mechanisms of pathogenesis that trigger nephritis following group A or group C infection may be different. Clearly, more detailed studies need to be done to address the possible role of streptokinase in APSGN.

4.2 Protease SpeB

Zabriskie and co-workers first observed that strains were associated with APSGN produced an extracellular protein not seen in non-nephritis strains, which was subsequently found to be bound to plasmin (Poon-King et al., 1993; Villarreal et al., 1979). This plasmin binding protein was discovered to be the major extracellular protease SpeB, and analysis of patient sera showed significantly higher levers of anti-SpeB antibodies in APSGN patients as compared to rheumatic fever patients or controls (Cu et al., 1998; Poon-King et al., 1993). Recent studies using a mouse tissue cage model have demonstrated that SpeB expression is inhibited in *S. pyogenes* strains that are maintained in the animal for extended periods, and this inhibition is inversely related to the increased expression of phage-encoded pyogenic exotoxins and DNases (Aziz et al., 2004). The strains studied were not associated with nephritis, suggesting that group A streptococci which cause APSGN may differentially express this protein when compared to non-nephritogenic strains. The lack of an identifiable homolog to SpeB in the group C strain MGCS10565 argues against the necessity of it in either the onset or progression of APSGN. However, the molecular mechanisms that underlie APSGN in the group C species may be different in some aspects from group A nephritogenic strains, and thus the absence of this protein in MGCS10565 may not be informative about group A APSGN disease. Further studies on this problem are clearly warranted.

4.3 Surface associated proteins

4.3.1 The Mga regulon genes

The molecular mimicry that underlies the onset of rheumatic heart disease results from the immune response to a prominent surface antigen of group A streptococci, the M protein. Therefore, such immunological cross-reactivity may be expected to contribute to APSGN, especially considering the time course of onset of symptoms. Particular M protein serotypes have been associated with APSGN, with M types 2, 49, 42, 56, 57, and 60 being associated with skin infections and APSGN while M types 1, 4, 12, and 25 being associated with throat infections and APSGN (Bessen et al., 1997; Bessen et al., 1996; Bisno, 1995; Enright et al., 2001; Kalia et al., 2002; Silva, 1998). As reported in the original description of the MGCS10565 genome, this group C contains a major deletion in much of the Mga regulon, including the genes for protease SpeB and the serum opacity factor (*sof*), although orthologs of many of these proteins including the M protein gene (*emm*) are found elsewhere in this genome (Beres et al., 2008). The genome of MGCS10565 revealed a large number of predicted extracellular collagen-like proteins, but none of these provided direct evidence of linkage to the nephritis-associated group A streptococcal serotypes. The linkage of serotype

and disease in the streptococcal, while clearly observed, remains somewhat unclear from the genetic level in terms of gene linkage or evolutionary co-selection.

4.3.2 Glyceraldehyde phosphate dehydrogenase (GAPDH)

Surface associated glyceraldehyde phosphate dehydrogenase (GAPDH) from nephritogenic strains of group A streptococci have been implicated in APSGN, with the molecule often detected in renal biopsies and patient sera having elevated anti-GAPDH antibody titers (Lange et al., 1976; Yamakami et al., 2000; Yoshizawa et al., 1992; Yoshizawa et al., 2004). This protein, which also has been referred to in the literature as the nephritis associated plasmin receptor, shows >85% homology between *S. zooepidemicus* MGCS10565 and the group A genome strains, which are virtually identical in amino acid sequence (Beres et al., 2008). Thus, it seems that if GAPDH plays a role in APSGN it is not a specific trigger for the disease. Indeed, other investigators have failed to find an association between GAPDH and APSGN (Batsford et al., 2005), so its role remains somewhat in question.

4.3.3 Enolase

Another *S. pyogenes* surface associated protein that has been implicated in APSGN is enolase, which is a major plasminogen binding protein and may be involved in triggering APSGN (Fontan et al., 2000). The phylogenetic analysis of the enolase genes from the *S. pyogenes*, *S. zooepidemicus*, *S. equisimilis* subsp. *dysgalactiae*, *S. pneumoniae*, and *S. mutans* genomes is presented in Fig. 3. The two *S. zooepidemicus* genes form a separate branch that is quite distinct from the *S. pyogenes* genes and encode proteins that are 100% identical.

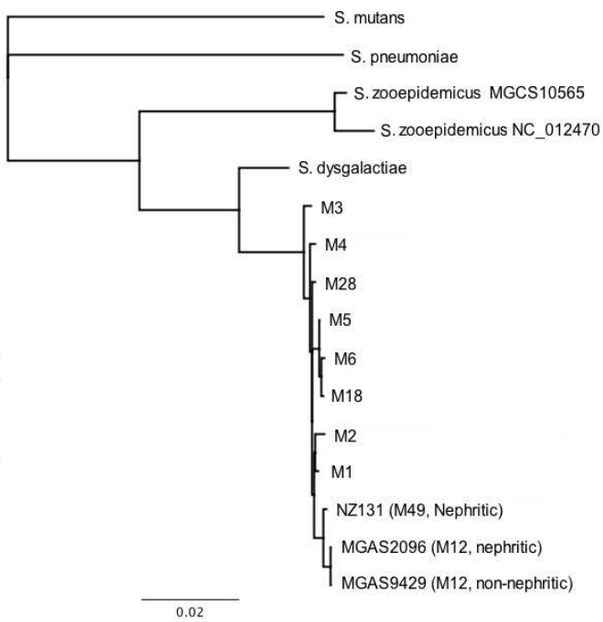

Fig. 3. **Phylogenetic analysis of streptococcal enolase genes.** The enolase genes from the group A streptococcal genomes (see Fig. 2 legend), now including the non-nephritogenic M12 strain MGAS2096, along with the genes from *S. zooepidemicus* strains MGCS10565 (nephritogenic) and NC_012470 (non-nephritogenic), *S. dysgalactiae* subsp. *equisimilis* GGS_124, *S. pneumoniae* TIGR4, and *S. mutans* UA159 were compared and a phylogenetic tree constructed using Geneious (Drummond et al., 2010).

Interestingly, the two nephritogenic group A streptococcal strains, NZ131 and MGAS2096, occupy a separate branch from the other *S. pyogenes* strains. However, this branch also includes the other M12 genome strain (MGAS9429) that was not nephritis associated. It may be that these closely related alleles of enolase play a role in the onset or development of APSGN in *S. pyogenes*, but the presence a non-nephritogenic strain argues that other factors must be required. Further, it would seem that enolase is probably not a common factor between groups A and C streptococci in the onset of APSGN.

4.3.4 Streptococcal pilus genes

Recent studies have demonstrated that group A streptococci and other Gram positive bacteria produce long, pili-like appendages that mediate binding to human fibronectin or collagen (Kang et al., 2007; Mora et al., 2005). These regions are identified by the presence of the genes encoding the pilus subunit proteins and their associated C sortases. A transcriptional regulator is included in the gene cluster of group A streptococci, and strains may be subdivided into two groups based upon whether the pilus region carries *rof*A or *nra* regulator genes. A recent classification scheme has described this region in *S. pyogenes* as belonging to one of six FCT groups (Kratovac et al., 2007). Strain NZ131 is a member of the *nra* group (FCT-3) that also includes the M3, M5, and M18 genome strains.

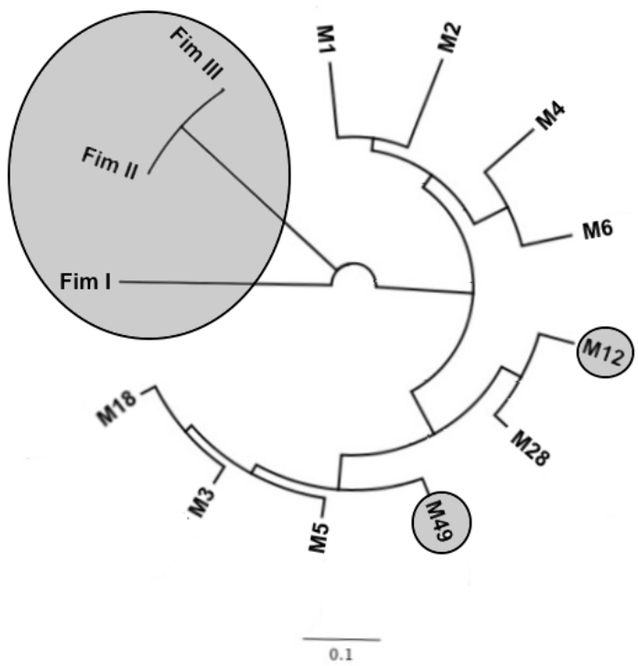

Fig. 4. **Phylogeny of the streptococcus pili regions.** The phylogenetic tree of the streptococcal pilus (fibronectin binding) regions from the *S. pyogenes* genome strains (see Fig. 2 legend) and from MGCS10565 is shown. The regions from the *S. pyogenes* genomes are indicated by the M protein serotype, and the nephritogenic group A streptococcal strains (NZ131 and MGCS2096) and group C strain (MGCS10565) are shaded.

Group C strain has three potential pilus (fibronectin binding protein) regions (Beres et al., 2008), which is in contrast to the one pilus (T antigen) cluster found in the group A

streptococci (McShan et al., 2008). Two of the group C pilus regions have homology to the pilus regions from the M2 and M6 genomes but little match that genome location in either the NZ131 or MGAS2096 chromosomes. Sortases are Gram-positive transpeptidases that anchor pili and other surface proteins to the cell wall (Hae Joo Kang and Baker, 2011; Janulczyk and Rasmussen, 2001). Strain NZ131 encodes an alternate sortase in this region (*src*C2, Spy49_0116). Interestingly, the *rof*A gene in MGCS10565 is not included in this gene cluster, being encoded elsewhere on the genome. When a phylogenetic tree of the pilus regions from the *S. pyogenes* and *S. equi* subsp. *zooepidemicus* genomes is constructed (Figure 4), the three pili regions (FimI – FimIII) form a distinct out-group from the *S. pyogenes* regions. The regions from the two nephritogenic group A streptococcal strains, NZ131 and MGAS2096, also are not closely related to each other, and the diversity of this region again argues that this is not the genetic location where are located unique factors that define nephritogenic strains of streptococci.

5. Conclusions

Comparison of the genomes of nephritogenic strain NZ131 and MGCS10565 reveals many similarities and differences that reflect related genera but distinct species. It is difficult, however, to make a convincing argument that an obvious shared trait is responsible for APSGN in both strains; rather, it is the differences that seem the most obvious when comparing potential virulence mechanisms.

One striking finding from genome comparison is the level of diversity between the group A streptococcal genomes and the genome of MGCS10565. Indeed, no common link to APSGN is immediately evident from the examination of the potential genetic sources from previous studies to the genomes. Beres et al. (Beres et al., 2008), after considering the diversity between the group A and group C genomes, tended to discount potential roles for streptokinase and protease SpeB in APSGN. Indeed, these proteins may not be key in the onset or progression of the disease although there are a number of studies supporting both. However, this conclusion presumes that the mechanism of pathogenesis of APSGN is the same in both species, which it well may not be. Many diarrheal diseases present with similar symptoms even though the underlying bacterial infection may be quite different, and it is possible that streptococcal nephritis caused by different species may result from a different series of molecular events. Further, even if there is a common molecular trigger for APSGN, it may be also true that for some bacterial factors that may amplify or promote the disease the phenotype may be more important through their enzymatic activity than their antigenicity. Thus, the important message from genomics at this time is that many aspects of APSGN remain to be explored so to uncover the roles played by virulence factors both known and yet to be characterized. Additional genome sequences from nephritogenic streptococci would help increase our understanding. The genomic information that is already available provides a rich resource for future studies as well as providing a framework for understanding the previous efforts in this field of investigation.

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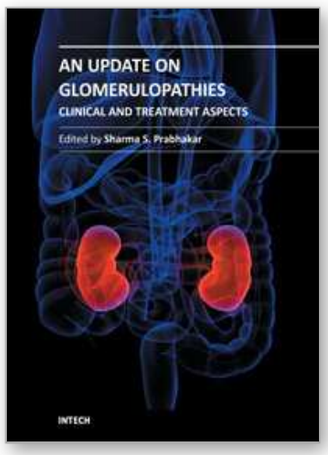

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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