

Table S1: Listing of *S. pyogenes* Strains Examined in this Study

Strain Name	Country of Origin	Year of Isolation	Disease ^a	<i>emm</i> -type ^b	<i>emm</i> pattern ^c	<i>spn</i> Bayesian Cluster ^d	IFS ^e	House-keeping ST ^f
MGAS2096	Trinidad	1960	AGN	12	A-C	1 (NADase active)	Full length	36
D306	Trinidad	1968	AGN	57	A-C	4 (NADase inactive)	Truncated 1	33
SS53	USA	1942	ARF	37	A-C	3 (NADase inactive)	Truncated 2	155
22RS72	USA	1941	ARF	24	A-C	4 (NADase inactive)	Truncated 1	66
AA476	Australia	1994	carriage	st3765	A-C	3 (NADase inactive)	Truncated 1	108
25RS84	USA	1942	carriage	14	A-C	3 (NADase inactive)	Truncated 2	85
AA401	Australia	1996	carriage	stCK401	A-C	3 (NADase inactive)	Truncated 1	116
11RS100	USA	1942	carriage	26	A-C	4 (NADase inactive)	Truncated 1	67
MGAS2110	Trinidad	1960	eczema	1d4	A-C	3 (NADase inactive)	Truncated 1	91
SS1676	Australia	2000	impetigo	stNS90	A-C	3 (NADase inactive)	Truncated 1	206
D488	Trinidad	1971	impetigo	55	A-C	3 (NADase inactive)	Truncated 1	100
SS725	unknown	1967	impetigo	54	A-C	3 (NADase inactive)	Truncated 1	159
MGAS5005	Canada	1996	invasive	1	A-C	1 (NADase active)	Full length	28
2RSC3	USA	1942	pharyngitis	38/40	A-C	4 (NADase inactive)	Truncated 1	81
1GL217	USA	1946	pharyngitis	17	A-C	4 (NADase inactive)	Truncated 3	83
SS116	unknown	1934	scarlet	47	A-C	4 (NADase inactive)	Truncated 3	83
MGAS2109	New Zealand	unknown	tonsillitis	1d2	A-C	3 (NADase inactive)	Truncated 1	93
SS1681	China	unknown	unknown	st980584	A-C	3 (NADase inactive)	Truncated 1	300
3RP70	USA	1949	unknown	29	A-C	4 (NADase inactive)	Truncated 1	65
SS580	unknown	unknown	unknown	23	A-C	4 (NADase inactive)	Truncated 1	160
2911-97	Brazil	1997	abscess	st2911	D	3 (NADase inactive)	Truncated 1	174
SS1447	unknown	unknown	ARF	85	D	1 (NADase active)	Full length	109
C142	USA	1942	ARF	34	D	4 (NADase inactive)	Truncated 1	64
1RS79	USA	1941	ARF	42	D	4 (NADase inactive)	Full length	80
SS1443	Brazil	1997	bacteremia	st809	D	3 (NADase inactive)	Truncated 2	143
4756-01	unknown	2001	bacteremia	59	D	1 (NADase active)	Full length	172
SS1373	Papua New Guinea	1992	bacteremia	st2037	D	3 (NADase inactive)	Truncated 2	301
4770-01	USA	2000	bacteremia	st369	D	4 (NADase inactive)	Truncated 1	208
5282-00	USA	2000	bacteremia	st5282	D	3 (NADase inactive)	Truncated 2	182
3850-01	USA	2001	bacteremia	st3850	D	3 (NADase inactive)	Truncated 1	174
10RS101	USA	1942	carriage	32	D	4 (NADase inactive)	Truncated 2	1
Alab49	USA	1986	impetigo	53	D	3 (NADase inactive)	Truncated 2	11
A946	Trinidad	1971	impetigo	52	D	3 (NADase inactive)	Truncated 1	43
29486	Czech Republic	1987	impetigo	116	D	1 (NADase active)	Full length	6
29655	Czech Republic	1988	impetigo	81	D	2 (NADase active)	Full length	57
29689	Czech Republic	1988	impetigo	83	D	1 (NADase active)	Full length	5
D821	Trinidad	1975	impetigo	91	D	3 (NADase inactive)	Truncated 2	13
1165-99	Egypt	1997-1998	impetigo	st854	D	3 (NADase inactive)	Truncated 1	292
SS1098	Egypt	1971	impetigo	71	D	4 (NADase inactive)	Truncated 1	130
SS1096	Egypt	1971	impetigo	65/69	D	4 (NADase inactive)	Full length	129

D502	Trinidad	1971	impetigo	93	D	3 (NADase inactive)	Truncated 2	17
SS1497	Brazil	1998	impetigo	st3757	D	3 (NADase inactive)	Truncated 1	153
AA249	Australia	1995	impetigo	stCK249	D	3 (NADase inactive)	Truncated 2	113
SS1434	Australia	unknown	impetigo	98	D	3 (NADase inactive)	Truncated 2	10
D633	Trinidad	1972	impetigo	stD633	D	1 (NADase active)	Full length	48
AA472	Australia	1994	impetigo	56	D	3 (NADase inactive)	Truncated 1	115
AA216	Australia	1995	impetigo	74	D	4 (NADase inactive)	Truncated 1	120
AA416	Australia	1996	impetigo	101	D	3 (NADase inactive)	Truncated 2	182
SS1433	Australia	unknown	impetigo	99	D	3 (NADase inactive)	Truncated 1	141
MGAS308	USA	1986-1990	Invasive	105	D	3 (NADase inactive)	Truncated 1	72
MGAS341	USA	1986-1990	invasive	119	D	3 (NADase inactive)	Truncated 1	97
SS1369	Ethiopia	1992	invasive	st1967	D	3 (NADase inactive)	Truncated 1	136
SS1378	Brazil	1996	invasive	st204	D	4 (NADase inactive)	Full length	139
6949-99	Argentina	1999	invasive	123	D	3 (NADase inactive)	Truncated 2	123
SS1469	Chile	1997	tonsillitis	st2940	D	3 (NADase inactive)	Truncated 1	147
MGAS2111	USA	unknown	unknown	95	D	3 (NADase inactive)	Truncated 2	14
D997	Japan	1976	unknown	111	D	3 (NADase inactive)	Truncated 1	98
A457	Yugoslavia	1961	unknown	36	D	4 (NADase inactive)	Truncated 1	47
D432	Egypt	1971	unknown	stD432	D	3 (NADase inactive)	Truncated 1	71
SS795	unknown	1968	unknown	41	D	3 (NADase inactive)	Truncated 2	162
SS1472	Brazil	1997	unknown	st2917	D	3 (NADase inactive)	Truncated 1	149
2907-97	Brazil	1997	unknown	115	D	3 (NADase inactive)	Truncated 1	123
D795	USA	1975	unknown	67	D	4 (NADase inactive)	Truncated 1	61
1RP278	USA	1964	ARF	9	E	1 (NADase active)	Full length	74
86-809	USA	1986	ARF	75	E	2 (NADase active)	Full length	49
3360-01	USA	2001	bacteremia	118	E	1 (NADase active)	Full length	167
SS1416	Malaysia	1996	bacteremia	106	E	2 (NADase active)	Full length	140
SS1371	Papua New Guinea	1992	bacteremia	104	E	1 (NADase active)	Full length	137
1269-98	USA	1998	bacteremia	15	E	3 (NADase inactive)	Truncated 1	121
SS1376	The Gambia	1993	bacteremia	st2460	E	2 (NADase active)	Full length	138
3018-01	USA	1995	bacteremia	114	E	1 (NADase active)	Full length	188
AA348	Australia	1996	carriage	25	E	1 (NADase active)	Full length	192
ACTH81	Australia	1997-1999	carriage	st11014	E	1 (NADase active)	Full length	112
D691	Trinidad	1972	carriage	11	E	2 (NADase active)	Full length	23
1RP18RN	USA	1946	carriage	44/61	E	2 (NADase active)	Full length	31
29454	Czech Republic	1987	impetigo	58	E	1 (NADase active)	Full length	19
SS1468	Malaysia	1997	impetigo	109	E	1 (NADase active)	Full length	198
4426-S	USA	1970	impetigo	92	E	1 (NADase active)	Full length	82
29740	Czech Republic	1988	impetigo	8	E	2 (NADase active)	Full length	59
SS1541	Egypt	1999	impetigo	st2147	E	1 (NADase active)	Full length	169
AA188	Australia	1995	impetigo	stNS554	E	1 (NADase active)	Full length	110
SS1536	Egypt	1999	impetigo	124	E	2 (NADase active)	Full length	199
4500-S	USA	1960	impetigo	60	E	2 (NADase active)	Full length	53
Alab53	USA	1986	impetigo	66	E	2 (NADase active)	Full length	44

NS292	Australia	1990-1999	impetigo	stNS292	E	1 (NADase active)	Full length	114
5552-S	USA	1971	impetigo	68	E	1 (NADase active)	Full length	86
6250-S	USA	1972	impetigo	110	E	2 (NADase active)	Full length	27
D316	USA	1969	invasive	25	E	1 (NADase active)	Full length	54
MGAS261	USA	1986-1990	Invasive	77	E	2 (NADase active)	Full length	35
SS1485	USA	1998	invasive	st1389	E	2 (NADase active)	Full length	152
SS1551	Malaysia	1999	invasive	107	E	1 (NADase active)	Full length	173
SS1363	USA	unknown	invasive	117	E	2 (NADase active)	Full length	134
CT95-169	USA	1995	invasive	102	E	1 (NADase active)	Full length	60
CT95-122	USA	1995	invasive	94	E	3 (NADase inactive)	Truncated 2	89
CT95-121	USA	1995	invasive	73	E	3 (NADase inactive)	Truncated 2	7
MGAS6180	USA	1998	invasive	28	E	1 (NADase active)	Full length	52
CT95-189	USA	1995	invasive	28	E	1 (NADase active)	Full length	52
TW128	Taiwan	1992	invasive	103	E	2 (NADase active)	Full length	392
SS1377	The Gambia	1993	invasive	st2463	E	1 (NADase active)	Full length	166
MGAS2017	USA	1991	pharyngitis	89	E	2 (NADase active)	Full length	77
SS951	USA	1970	pharyngitis	50/62	E	2 (NADase active)	Full length	2
SS1402	United Kingdom	1972	skin sepsis	82	E	1 (NADase active)	Full length	26
6735-99	Brazil	1999	unknown	st6735	E	2 (NADase active)	Full length	165
SS1470	New Zealand	1997	unknown	113	E	2 (NADase active)	Full length	148
SS1550	Thailand	unknown	unknown	112	E	1 (NADase active)	Full length	194
SS636	United Kingdom	1935	unknown	13L	E	1 (NADase active)	Full length	157
SS582	United Kingdom	unknown	unknown	27G	E	1 (NADase active)	Full length	156
CS110	USA	Pre-1990	unknown	76	E	1 (NADase active)	Full length	51
SS737	unknown	1967	unknown	48	E	2 (NADase active)	Full length	161
A956	unknown	1967	unknown	63	E	2 (NADase active)	Full length	88
MGAS2140	Ethiopia	unknown	unknown	66	E	1 (NADase active)	Full length	95
10RS57	USA	1941	wound	87	E	1 (NADase active)	Full length	62
SS1151	unknown	unknown	wound	79	E	1 (NADase active)	Full length	132

^a Disease caused by the bacterial isolate. ARF is acute rheumatic fever and AGN is acute glomerulonephritis.

^b *emm*-type based on sequence analysis of the *emm* gene using primers 1 and 2 according to the standard CDC protocol (http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm)

^c *emm* pattern is defined by the # of *emm* genes, the *emm* gene subfamily content, and the relative arrangement of these genes on the chromosome (6).

^d Bayesian clusters were identified through the frequencies of single nucleotide polymorphisms using Bayesian Analysis of Population Structure (BAPS). Clusters are described in the text. NADase active *spn* encodes for a glycine at amino acid position 330, while NADase inactive *spn* encodes for a aspartic acid at amino acid position 330.

^e Full length IFS is 161 amino acids in length (See Fig. 3, strain JRS4). Truncated 1 contains a substitution of an adenine for a thymine at bp 71 that causes a nonsense mutation at codon 24 (See Fig. 3, strains MGAS2109 and 22RS72). Truncated 2 contains a deletion of a thymine at bp 71 and results in a nonsense mutation at codon 24 (See Fig. 3, strain MGAS2111). Truncated 3 contains a deletion of an adenine at bp 40 that triggers a frame shift resulting in a stop codon at amino acid position 19 (See Fig. 3, strain SS116).

^f Housekeeping Sequence Type (ST) is based on the internal fragments of 7 housekeeping genes used for multilocus sequence typing of *S. pyogenes* (see methods).