**Supplementary file 3. All identified functional single nucleotide variants (SNVs) in the H1N1 virus with annotations.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pig ID** | **Treatment** | **Coding region** | **Site** | **Reference** | **Variant** | **Frequency (%)** | **Amino acid change** | **Mutation type** | **Functional description** | **Functional type** |
| 4473 | SINGLE LAIV | M1 | 598 | T | G | 88.5 | S200A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin, Petit, Weissenhorn, & Ruigrok, 2001) | Virus assembly, budding and release |
| 4486 | PRIME BOOST | M1 | 463 | G | A | 3.1 | A155T | Non\_Synonymous | Associated with the virulence of H9 subtype virus in mice (Hui, Smee, Wong, & Nayak, 2006; Z. Ye, Liu, Offringa, McInnis, & Levandowski, 1999) | Determinant of pathogenicity, virulence and disease progression |
| 4486 | PRIME BOOST | M1 | 695 | A | G | 2 | D232G | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4492 | SINGLE LAIV | M1 | 92 | T | C | 2 | V31A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4492 | SINGLE LAIV | M1 | 431 | T | C | 1.1 | F144S | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4492 | SINGLE LAIV | M1 | 598 | T | G | 100 | S200A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4493 | NO VAC | M1 | 598 | T | G | 22.9 | S200A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4937 | SINGLE LAIV | M1 | 598 | T | G | 2.9 | S200A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4938 | NO VAC | M1 | 598 | T | G | 96.1 | S200A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4938 | NO VAC | M1 | 601 | G | A | 3.1 | E201K | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 5166 | SINGLE LAIV | M1 | 655 | A | G | 2.3 | I219V | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 5175 | PRIME BOOST | M1 | 587 | G | A | 7.7 | S196N | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 5175 | PRIME BOOST | M1 | 737 | T | C | 2.1 | V246A | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 5185 | PRIME BOOST | M1 | 383 | T | C | 1.2 | M128T | Non\_Synonymous | M1 lipid/membrane binding region (Gregoriades & Frangione, 1981) | Virus assembly, budding and release |
| 5185 | PRIME BOOST | M1 | 732 | G | T | 1.2 | M244I | Non\_Synonymous | M1 (C-terminal) vRNP binding region (Baudin et al., 2001) | Virus assembly, budding and release |
| 4479 | SINGLE LAIV | NA | 445 | G | A | 2.1 | V149I | Non\_Synonymous | V149I is associated with support the NA active-site structure and decreased zanamivir sensitivity in a H5N1 virus (Naughtin et al., 2011; Yen et al., 2006) | Antiviral drug resistance |
| 4493 | NO VAC | NA | 1031 | A | G | 1.2 | N344S | Non\_Synonymous | Binding site for zanamivir and oseltamivir, also associated with NA stability (Collins et al., 2008; Gupta et al., 2011; Van Der Vries et al., 2012) | Antiviral drug resistance |
| 4938 | NO VAC | NA | 169 | G | A | 1.5 | V57I | Non\_Synonymous | Associated with the virulence of H5N1 in mice and chicken (Matsuoka et al., 2009; Zhou et al., 2009) | Determinant of pathogenicity, virulence and disease progression |
| 5175 | PRIME BOOST | NA | 626 | A | G | 1.5 | N209S | Non\_Synonymous | Support the NA active-site structure (Yen et al., 2006) | Virus assembly, budding and release |
| 4479 | SINGLE LAIV | NP | 1490 | A | G | 1.2 | D497G | Non\_Synonymous | Associated with PB2 interaction (Biswas, Boutz, & Nayak, 1998) | Viral genome/protein interaction |
| 4493 | NO VAC | NP | 183 | A | G | 5.7 | I61M | Non\_Synonymous | Associated with RNA and PB2 interaction (Albo, Valencia, & Portela, 1995; Biswas et al., 1998; Elton, Medcalf, Bishop, Harrison, & Digard, 1999) | Viral genome/protein interaction |
| 4493 | NO VAC | NP | 845 | G | A | 1.8 | G282E | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 4938 | NO VAC | NP | 878 | G | A | 1.4 | R293K | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 4938 | NO VAC | NP | 992 | T | G | 1.1 | M331R | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 4938 | NO VAC | NP | 1278 | G | A | 1.7 | M426I | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999; Q. Ye, Krug, & Tao, 2006) | Viral genome/protein interaction |
| 5174 | NO VAC | NP | 1066 | G | A | 15.6 | G356R | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 5175 | PRIME BOOST | NP | 425 | A | G | 1.4 | N142S | Non\_Synonymous | Associated with RNA and PB2 interaction (Albo et al., 1995; Biswas et al., 1998; Elton, Medcalf, Bishop, Harrison, et al., 1999) | Viral genome/protein interaction |
| 5175 | PRIME BOOST | NP | 1112 | T | C | 2.2 | V371A | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 5185 | PRIME BOOST | NP | 886 | T | C | 44.4 | Y296H | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999) | Viral genome/protein interaction |
| 5185 | PRIME BOOST | NP | 1256 | C | T | 91.7 | P419L | Non\_Synonymous | Associated with PB2 interaction and NP oligomerization (Biswas et al., 1998; Elton, Medcalf, Bishop, & Digard, 1999; Q. Ye et al., 2006) | Viral genome/protein interaction |
| 4473 | SINGLE LAIV | NS1 | 374 | A | G | 1 | E125G | Non\_Synonymous | A Gly at 125 confers high pathogenicity of H3N2 virus in mice and enhanced binding property to α-2,3 to α-2,6 sialic acid receptors. Also involved in multiple interactions with host proteins to meditate the host antiviral response (Bornholdt & Prasad, 2006; Das et al., 2008; Hale, Barclay, Randall, & Russell, 2008; Hale, Randall, Ortín, & Jackson, 2008; Narasaraju et al., 2009) | Determinant of pathogenicity, virulence and disease progression |
| 4473 | SINGLE LAIV | NS1 | 496 | C | A | 1.2 | L166I | Non\_Synonymous | Associated with multiple host proteins interactions to meditate the host antiviral response (Bornholdt & Prasad, 2006; Das et al., 2008; Hale, Barclay, et al., 2008; Hale, Randall, et al., 2008) | Host-virus interaction machinery |
| 4479 | SINGLE LAIV | NS1 | 7 | T | C | 3.2 | S3P | Non\_Synonymous | Associated with host proteins and dsRNA interactions to meditate the host antiviral response and IAV genome transportation (Cheng, Wong, & Yuan, 2009; Hale, Randall, et al., 2008; Yin et al., 2007) | Host-virus interaction machinery |
| 4479 | SINGLE LAIV | NS1 | 643 | C | T | 1.5 | P215S | Non\_Synonymous | Associated with Crk/CrkL SH3 binding and CDK/ERK phosphorylation to meditate the host cell signaling (Hale, Barclay, et al., 2008; Hale et al., 2009; Heikkinen et al., 2008) | Host-virus interaction machinery |
| 4492 | SINGLE LAIV | NS1 | 619 | A | G | 1.5 | N207D | Non\_Synonymous | Associated with Crk/CrkL SH3 binding and CDK/ERK phosphorylation to meditate the host cell signaling (Hale, Barclay, et al., 2008; Hale et al., 2009; Heikkinen et al., 2008) | Host-virus interaction machinery |
| 4493 | NO VAC | NS1 | 494 | C | A | 3.9 | S165Y | Non\_Synonymous | Associated with multiple host protein interactions to meditate the host antiviral response (Bornholdt & Prasad, 2006; Das et al., 2008; Hale, Barclay, et al., 2008; Hale, Randall, et al., 2008) | Host-virus interaction machinery |
| 4934 | SINGLE LAIV | NS1 | 443 | G | A | 6.1 | R148K | Non\_Synonymous | R148 is required for masking the nuclear export signal activity. Also involved in inhibiting the PI3K/Akt pathway and delay the host antiviral response (Bornholdt & Prasad, 2006; Das et al., 2008; Ehrhardt et al., 2007; Gallacher et al., 2009; Hale, Barclay, et al., 2008; Hale, Kerry, et al., 2010; Hale, Randall, et al., 2008; Y. Li, Yamakita, & Krug, 1998; Shin et al., 2007) | Viral genome transportation, transcription and replication |
| 4938 | NO VAC | NS1 | 100 | G | A | 1.3 | D34N | Non\_Synonymous | Locate in RNA binding site and associated with host proteins and dsRNA interactions to meditate the host antiviral response and IAV genome transportation (Cheng et al., 2009; Hale, Randall, et al., 2008; Wang et al., 1999; Yin et al., 2007) | Host-virus interaction machinery |
| 5179 | NO VAC | NS1 | 196 | G | A | 1.2 | E66K | Non\_Synonymous | Associated with multiple host proteins and dsRNA interactions to meditate the host antiviral response and IAV genome transportation (Cheng et al., 2009; Hale, Randall, et al., 2008; Yin et al., 2007) | Host-virus interaction machinery |
| 5179 | NO VAC | NS1 | 566 | G | A | 1.2 | G189D | Non\_Synonymous | Associated with multiple host protein interactions to inhibit the processing the pre-mRNAs and host antiviral response (Bornholdt & Prasad, 2006; Das et al., 2008; Hale, Barclay, et al., 2008; Hale, Randall, et al., 2008; Hale, Steel, et al., 2010; Noah, Twu, & Krug, 2003; Twu, Kuo, Marklund, & Krug, 2007) | Host-virus interaction machinery |
| 4486 | PRIME BOOST | PA | 1034 | T | C | 1.7 | L345P | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4486 | PRIME BOOST | PA | 1255 | G | A | 4.3 | D419N | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4486 | PRIME BOOST | PA | 1780 | A | G | 1 | S594G | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4492 | SINGLE LAIV | PA | 906 | A | G | 1.3 | I302M | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4492 | SINGLE LAIV | PA | 2014 | C | T | 1.9 | L672F | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4492 | SINGLE LAIV | PA | 2137 | C | T | 3.5 | H713Y | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4493 | NO VAC | PA | 806 | G | A | 1.5 | R269K | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4493 | NO VAC | PA | 1949 | A | T | 7.5 | Y650F | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4495 | NO VAC | PA | 1051 | G | A | 32.7 | E351K | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4495 | NO VAC | PA | 1853 | C | T | 1.5 | T618I | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4499 | PRIME BOOST | PA | 1025 | T | C | 1 | L342P | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4938 | NO VAC | PA | 298 | G | A | 2.3 | V100I | Non\_Synonymous | Inhibit the host protein synthesis and enhance the viral protein production (Desmet, Bussey, Stone, & Takimoto, 2013) | Host-virus interaction machinery |
| 5167 | NO VAC | PA | 1847 | C | T | 3 | S616L | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 5174 | NO VAC | PA | 2121 | C | A | 1.1 | F707L | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 5175 | PRIME BOOST | PA | 1388 | T | C | 1.1 | V463A | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 5175 | PRIME BOOST | PA | 1834 | T | A | 6 | F612I | Non\_Synonymous | PA (C-terminal) - PB1(N-terminal) binding region (He et al., 2008) | Viral genome/protein interaction |
| 4490 | NO VAC | PB1 | 2220 | C | A | 1.8 | F740L | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole, Medcalf, Elton, & Digard, 2007; Sugiyama et al., 2009; Toyoda, Adyshev, Kobayashi, Iwata, & Ishihama, 1996) | Viral genome/protein interaction |
| 4492 | SINGLE LAIV | PB1 | 2087 | T | A | 1 | F696Y | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole et al., 2007; Sugiyama et al., 2009; Toyoda et al., 1996) | Viral genome/protein interaction |
| 4493 | NO VAC | PB1 | 2168 | G | A | 30.8 | R723Q | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole et al., 2007; Sugiyama et al., 2009; Toyoda et al., 1996) | Viral genome/protein interaction |
| 4495 | NO VAC | PB1 | 8 | T | C | 1.8 | V3A | Non\_Synonymous | The introduction of V3A increased the virulence of a H5N1 virus in mice. Also locate in PB1 (N-terminal) – PA (C-terminal) interaction region (He et al., 2008; Salomon et al., 2006; Toyoda et al., 1996) | Determinant of pathogenicity, virulence and disease progression |
| 4495 | NO VAC | PB1 | 2110 | T | A | 2.2 | S704T | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole et al., 2007; Sugiyama et al., 2009; Toyoda et al., 1996) | Viral genome/protein interaction |
| 4938 | NO VAC | PB1 | 2168 | G | A | 2.9 | R723Q | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole et al., 2007; Sugiyama et al., 2009; Toyoda et al., 1996) | Viral genome/protein interaction |
| 5175 | PRIME BOOST | PB1 | 2098 | T | C | 2.7 | F700L | Non\_Synonymous | PB1 (C-terminal) - PB2 (N-terminal) binding region (Poole et al., 2007; Sugiyama et al., 2009; Toyoda et al., 1996) | Viral genome/protein interaction |
| 4479 | SINGLE LAIV | PB2 | 1268 | G | A | 1.1 | R423K | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 4486 | PRIME BOOST | PB2 | 1267 | A | G | 1.4 | R423G | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 4486 | PRIME BOOST | PB2 | 1291 | A | G | 4.7 | M431V | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 4492 | SINGLE LAIV | PB2 | 1076 | G | A | 1.4 | G359E | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 4492 | SINGLE LAIV | PB2 | 1189 | G | A | 1.7 | A397T | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 4492 | SINGLE LAIV | PB2 | 2216 | G | T | 1.6 | R739L | Non\_Synonymous | PB2 nuclear localization region (Mukaigawa & Nayak, 1991) | Viral genome transportation, transcription and replication |
| 4493 | NO VAC | PB2 | 1402 | G | A | 1.1 | A468T | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 5166 | SINGLE LAIV | PB2 | 2102 | A | G | 1.2 | D701G | Non\_Synonymous | Essential mammal adapted site for avian influenza virus (Gao et al., 2009; Le, Sakai-Tagawa, Ozawa, Ito, & Kawaoka, 2009; Z. Li et al., 2005; Steel, Lowen, Mubareka, & Palese, 2009) | Cross-species transmission and adaption |
| 5167 | NO VAC | PB2 | 1396 | G | A | 47.1 | D466N | Non\_Synonymous | PB2 nuclear localization region and cap-binding region with m7GTP (Guilligay et al., 2008; Mukaigawa & Nayak, 1991) | Viral genome transportation, transcription and replication |
| 5175 | PRIME BOOST | PB2 | 1138 | A | G | 2.1 | R380G | Non\_Synonymous | PB2 cap-binding region with m7GTP (Guilligay et al., 2008) | Viral genome transportation, transcription and replication |
| 5175 | PRIME BOOST | PB2 | 2221 | T | C | 1.1 | S741P | Non\_Synonymous | PB2 nuclear localization region (Mukaigawa & Nayak, 1991) | Viral genome transportation, transcription and replication |
| 5175 | PRIME BOOST | PB2 | 2257 | A | G | 1.2 | R753G | Non\_Synonymous | PB2 nuclear localization region (Mukaigawa & Nayak, 1991) | Viral genome transportation, transcription and replication |

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