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Polymorphic sites in the 5´-region of the porcine *C8A* gene

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Abstract

The membrane attack complex (MAC) of the complement system is known as a natural immune mechanism of hosts against invading pathogens. This study was undertaken to structurally characterize and computationally analyzed the 5´-region, i.e. the downstream promoter region and the 5´-UTR nucleotide sequence of the porcine *C8A*, one of the components of the MAC. Sequencing approximately 950 bp of the 5´-region and analyzing in silico revealed the transcription start site, the TATA-box, the CAAAT-box, and the GATAA-box. High identity was found in range of 37-74 % among the sequences of pig, human, cattle, and mouse. Transcription factor binding sites, such as NFκB, Oct-1, HNF1, CDP, and C/EBP, showed high conservation between vertebrate animal species, especially between human and mouse, or pig and cattle. Seven single nucleotide polymorphisms were detected in the breeds Hampshire, Duroc, German Landrace, Large White, Pietrain, Berlin Miniature Pig, and Muong Khuong. Nucleotide exchanges could cause the generation of new binding motifs, which may affect the expression of the porcine *C8A*, particularly the C/EBP regulation of the porcine *C8A* gene - as described in the human *C6* and *C7* promoter.

Keywords: porcine *C8A*, 5´-UTR, motifs, polymorphism

Zusammenfassung

Polymorphismen in der 5´-Region des porcinen *C8A* Gens

Der Membranangriffskomplex (membrane attack complex, MAC) des Komplementsystems ist ein angeborenener Immunmechanismus gegen Pathogene. Die Untersuchung zielte auf die Analyse der 5´flankierenden und 5´-UTR Sequenz des porcinen *C8A* Gens, das die *C8A*-Komponente des MAC kodiert. Die *in silico* Analyse von ca. 950 bp der 5´-Region des *C8A* Gens weist den Transkriptinsstart sowie regulatorische Elemente (TATA-Box, CAAAt-Box, GATAA-Box, Transkriptionsfaktorbindungsstellen für NFκB, Oct-1, HNF1, CDP, und C/EBP) aus. Die Identität zwischen der porcinen Sequenz und den Sequenzen von Mensch, Rind und Maus liegt zwischen 37 und 74 %. Die vergleichende Sequenzierung bei Tieren der Rassen Hampshire, Duroc, Deutscher Landrasse, Deutsches Edelschwein, Pietrain, Berliner Miniaturschwein und Muong Khuong führte zur Identifizierung von sieben polymorphen Stellen (single nucleotide polymorphisms, SNPs). Die SNPs können neue Bindungsmotive bilden und so die Expression des porcinen *C8A* beeinflussen – dies gilt insbesondere für die C/EBP-Regulation der Expression von *C8A*.

Schlüsselwörter: Schweine *C8A*, 5'-UTR, Motive, Polymorphismus

Introduction

The complement system is a part of the innate immune system, which protects the host body from bacterial infections. Complement activation from three different pathways leads to the formation of the membrane attack complex including the components *C5b-9*. This complex functions in lysis of bacterial cells. Particularly, the *C8* oligomeric serum protein is assembled from products of three non-identical polypeptide chains, which are encoded by three separate genes *C8A*, *C8B* and *C8G* (Plumb & Sodetz 2000). The *C8A* and *C8G* subunits are bound covalently through a disulfide linkage, where as the *C8B* is associated via weaker, non-covalent bonds (Alper *et al.* 1983). *C8A* directly binds to *C9* via its MACPF module in the formation of the MAC (Slade *et al.* 2006). Both, the coding region of the human (Rao *et al.* 1987) and porcine (Nakajima *et al.* 1998) *C8A*, have been characterized. However it is known that gene expression is finely regulated at the post-transcriptional level. Features of the untranslated regions of mRNAs that control their translation, degradation and localization include stem-loop structures, upstream initiation codons and open reading frames, internal ribosome entry sites and various cis-acting elements that are bound by RNA-binding proteins (Mignone *et al.* 2002). So far, the 5´-region, including the 5´-UTR and downstream promoter sequences, of the human and porcine *C8A* has not been analyzed yet. In the present study an in silico analysis was made to detect potential regulatory elements in this region and comparative sequencing was conducted to identify genetic variation which may contribute to the regulation of the transcription of the *C8A* gene in pigs.

Materials and methods

Animals

For the detection of polymorphisms by comparative sequencing a SNP discovery panel of animals of the breeds Hampshire, Duroc, German Landrace, Pietrain, Large White, as well as Berlin Miniature Pig and Muong Khuong was used. Allele and genotype frequencies were determined by genotyping 30 unrelated individuals of the commercial breeds German Landrace, Large White, and Pietrain.

Primer design

To identify the 5´-UTR nucleotide sequence and the promoter sequence of the porcine *C8A*, two primer pairs were designed for polymerase chain reaction (PCR) as follows (1) C8A_01 forward 5´-TGC TTC TGG AGG TGT TCA TTT-3´ and reverse 3´-CGG TTC ACC TTC TCC TGT ATG-5´, and (2) C8A_02 forward 5´-TTG ATA AGG CCA ATC CTG CT-3´, and reverse 3´-AAC ACC TGG AGC CTG AGA AG-5´ which can amplify DNA fragments of 707bp and 455bp, respectively. The first reverse-primer sequence belongs to the exon segment. The primers were designed upon the nucleotide sequence of the clone XX-1C1 (GenBank acc. no. CT025761, nt 319616-320568) (Sims 2005). The clone located on porcine chromosome 16 where the porcine *C8A* was assigned using in-situ hybridisation (Nakajima *et al.* 1998).

DNA extraction, sequencing and genotyping

Preparation of genomic DNA from tail or ear sample of experimental animals was performed by standard procedures involving Proteinase K digestion followed by phenol-chloroform extraction and ethanol precipitation.

A standard PCR mixture for sequencing and genotyping contained 100 ng of genomic DNA, 0.2 µM of each primer (forward and reverse primer), 50 µM of each dNTP, 0.5 U of Taq polymerase and 1×PCR buffer containing 1.5 mM of $MgCl_2$ in a final volume of 20 µl. Standard PCR thermal cycling program was set up with an initial denaturation step of 94 °C for 4 min, followed by 40 cycles at 94 °C for 30 s, annealing at 60 °C for 30 s, elongation at 72 °C for 1 min and a final extension at 72 °C for 5 min. Three µl of PCR products were analyzed on 1 % agarose gel stained with ethidium bromide in 1 × TAE buffer and electrophoresed to evaluate specifity and efficiency of the amplification and the remainder was retained for sequencing after purification based on the Sanger dideoxy nucleotide triphosphate (ddNTP) terminator method.

In silico analysis software

The Neural Network Promoter Prediction http://www.fruitfly.org/seq_ tools/promoter.html and the FPROM software http://www.softberry.com were used to identify the transcription start site (TSS) and TATA-box, respectively. Detection of the transcription factor binding site motifs was done by the AliBaba 2.1 http://www.gene-regulation.com/pub/programs/alibaba2/index .html and the multiTF http://rvista.dcode.org/ tools.

Results and discussion

The 950 bp nucleotide sequence of the 5´-UTR and downstream promoter of the porcine *C8A* was obtained and analysed. High similarity was found in the 5´-region among various animal species, which was 74, 62, or 49 % between pig and human, mouse, or cattle, respectively; between human and mouse or cattle 69 or 45 %, and between mouse and cattle 37 %. At the protein level, the porcine *C8A* showed 80, 78, and 72 % identity with cattle, human, and mouse orthologue. Together the genetic distance was close between human and mouse or between the domestic animal species pig and cattle (Figure 1, 2).

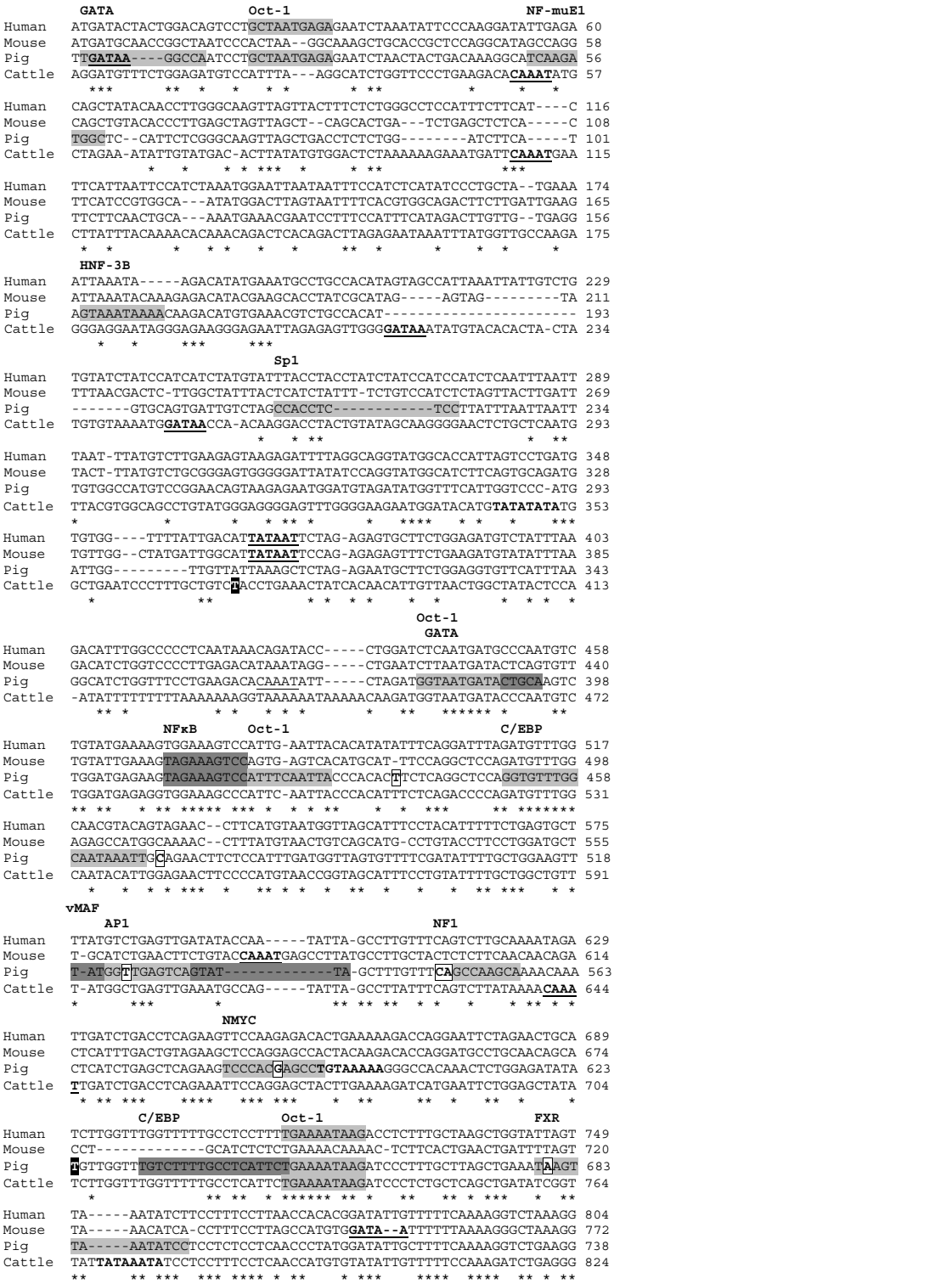
It is interesting to note the presence of the transcription start site at nucleotide nt 624, the TAT A-box sequence TGT AAA AA (nt. 593-600) the CAA AT box (nt. 366-370), and GAT AA box (nt. 3-7) in the pig. The TATA-box was also determined in two different motifs TAT ATA TA (nt. 344-351) and TAT AAA TA (nt. 768-775) in cattle. In the human (nt. 366-371) and the mouse (nt. 348-353) sequence the motif TAT AAT was highly conserved. The *C8A* promoter regions of human, mouse or pig only contain one CAA AT-box and/or one GAT AA-box, whereas a two of these boxes is presenting in that of cattle. Additionally, putative transcription factor binding site motifs were identified, namely AP1, Oct-1, NF-muE1, HNF-3B, Sp1, NFκB, NF1, and C/EBP. The NFκB motif (TAG AAA GTC C) was found in the pig (nt. 410-419) and mouse sequence (nt. 452-461). The Oct-1 motif correspondingly appeared in pig (GCT AAT GAGA nt. 18-27) and human (GCT AAT GAG A nt. 22-31).

Most of the transcription factor binding site motifs analyzed in the 5´-region of the porcine *C8A* have previously been identified in other complement components such as the human

C3 (Vik *et al.* 1991), human *C6* (González & López-Larrea 1996), human *C7* (González *et al.* 2003), murine *C5* (Haviland *et al.* 1991) or grass carp *C9* (Li *et al.* 2007). In particular, C/EBPs are basic region leucine zipper transcription factors that regulate cell differentiation, growth, survival, and inflammation (Miller *et al.* 2003). Therefore, C/EBP is essential for the human *C6* and *C7* expression (González & López-Larrea 1996, González *et al.* 2003). C/EBP delta is also the major protein responsible for regulating the acute-phase expression of the human *C3* gene (Juan *et al.* 1993). Oct-1 binding sites are ubiquitous in some immune gene promoters such as granulocyte/macrophage colony stimulating factor and IL-3 promoters (Wu *et al.* 1997). Furthermore, Oct-1 and C/EBP may cooperate with promoter elements to mediate the *C9* transcription in grass carp (Li *et al.* 2007). According to Pontoglio *et al.* (2001), HNF1 plays a key role in the expression of *C5* and *C8A* for hemolytic complement activity, which has indirect effect on the expression of the other terminal complement components *C8B*, *C8G* and *C9*. HNF1 and C/EBP are the hepatopancreas-enriched transcription factors (Dogra & May 1997). The NFκB binding motif has an effect on the integrity of the intestine and therefore contributes to the pathophysiology of inflammatory bowel (Moehle *et al.* 2006). The NFκB element was over-represented in the inflamed mucosa regulatory network (Saban *et al.* 2006). Terminal complement components *C5b-9* may increase the inflammatory response of vascular smooth-muscle cells through activation of transcription factors NFκB and AP-1, which in turn can induce expression of the proinflammatory cytokine IL-6 (Viedt *et al.* 2000).

The liver is the main site of synthesis of most of the complement components circulating in blood, as indicated by allotypic changes in recipients of liver transplants (Alper *et al.* 1980). The homologous complement components *C6-9* of the MAC complex are acute phase proteins, which derive from an ancestral gene. Therefore, the porcine *C8A* shares 30, 28, 28, and 27 % identity with the porcine *C6* (GenBank acc. no. DQ333199), *C7* (GenBank acc. no. AF162274), *C8B* (GenBank acc. no. DQ333201), and *C9* (GenBank acc. no. DQ333198) at protein level, respectively. Accumulation of these proteins during the formation of the MAC complex synergistically promotes cell lysis causing the death of target cells. The existence of common transcription factor binding sites in the promoter regions of several complement component genes reflects their common responsiveness to immune stimulation and contributes to the coordinated simultaneous regulation of the functionally linked genes.

In a short segment of approximately 600 bp of the porcine *C8A* 5´-region, seven single nucleotide polymorphisms (SNPs) 680A>G, 588A>G, 548A>G, 547C>T, 524A>T, 469C>T, 437C>T were detected by comparative sequencing (Figure 1). Genotype and allele frequencies of three European pig breeds, German Landrace, Large White and Pietrain are given in Table 1. There was no deviation from Hardy Weinberg equilibrium. It is also interesting to point out that the replacement of the vMAF/AP1 (TAT GG**A** TGA GTC AGT ATT A, nt. 519-537) or BACH2 (G**A**T GAG TCA GT, nt. 523-533) motif into the ATF4 (GG**T** TGA GTC AGT, nt. 522-533) motif is observed for polymorphism at nt. 524A→T whereas SNP at nt. 588A→G causes exchange from HES1 (AGT CCC AC**A** AGC CTG, nt. 580-594) to DEAF1 (GAG CTC AGA AGT CCC AC**G** AGC CTG T, nt. 571-595), NMYC (TCC CAC **G**AG CCT, nt. 582-593), or MYCMAX (CCC AC**G** AGC C, nt. 583-592). These motif substitutions have not been tested for expression of the complement components yet. However, function of the motifs, which concern host response, has been studied. For instance, MAF family transcription factors are important regulators in various differentiation systems (Muto *et al.* 1998). They have been implicated in a number of


GATA
Oct-1
NF-muE1
HNF-3B
Sp1
Oct-1
GATA
NFκB
Oct-1
C/EBP
vMAF
AP1
NF1
NMYC
C/EBP
Oct-1
FXR
Human
Mouse
Pig
Cattle

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                                                HNF1
                                                 CDP
Human   GCAGTGGCCTTTGGTGCCTGGAACACTTTTAGAGTATTTAGGTAATCAATACCCTGGTTA 864
Mouse   GC--------TTGGGGCC------ATATTTGAAGGCGTTTGGCTAATCAATACCTTGGTTA 818
Pig     ACAGTGGCCTTTGGTGTCTAG---AATTTTAGGGTGTTTGGCTAATCAATATCCTAGTAA 795
Cattle  GCAGTAGCCTTTGGTGTGTAG---GATTTTAGGGAAGTTGGCTAATCAATACCCTAGTAA 881
         *        **** *          *** *  *   ** * ********* * * ** *
          C/EBP                C/EBP
Human   CTATTTAACCATATTTGAAAGAGAATCAAGTGAGTTCTGTGCAAATCAATGTGTATCTGG 924
Mouse   CTAGTTAATCACATT-GAATGGGAACTGGGGGACTTTTGACCA---------------- 860
Pig     GTAATTAACCACATCTGAATGAGAATCAAACAAGTTCTGTTAG---------------- 838
Cattle  GTAATTAACCATATTTGAATGAGAATCAAGTGAGTTGTCTTTTTTTTTTT---------- 931
         ** **** ** **  *** * ***       * ** *
Human   GTGAGTTTCCAACATCAGATAGATCTTACAGGTCCCAGCCTGTAGACATCTTTTACTCCA 984
Mouse   -----TTTTAAACATCCGGTAGACAATTTGGGTCCCAGCCTGGATATATCTAT------G 909
Pig     -----TTTCAAACATTAGATAGATCTTCTAGGTCCTGGTCTGTAGACACCTCTTACTTCA 893
Cattle  -----TTTTTAGTTTCAAACA--TTAGATAGATCCCAGACTGTAGATGTCTTTTATTCCA 984
             ***  *   *     *          * ***  * *** * *   ** *
Human   ATTTCCTGAATAGATAGCTTTATT-CCTTCAAGGTAATATAGTGCGGTGGCTTCTGGCTG 1043
Mouse   GCTTCTAAGGTAGGCTCTTCTCGT-CTTTTACATAGACACTAGTTGGTGACTTCTGGATG 968
Pig     ACTCCCTAAGTAG----TTTTAGT-CCTTCTTTGTAATATAGGGTAGTGGCTTCTGGATG 948
Cattle  ACTCCCTGAGTAG----TTTTATTACTTTCTAGGTAATACAGGTTGGTAGCTCCTGGATG 1040
         * *     ***     * *  * * **       * *       **  ** **** **
Human   AGATG 1048
Mouse   AGATG 973
Pig     AGATG 953
Cattle  AGATG 1045
        *****
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Figure 1
Alignment of the 5´-UTR sequences among various species. The nucleotides are enumerated at each line on the right side. Identical and missing nucleotides are indicated with asterisks (*) and dashes (-), respectively. The CAAAT-box, the GATAA-box, and the TATAAT-box are in bold and underlined. The transcription start site is in black shade blocks with white font. Single nucleotide polymorphisms are in boxes. The transcription factor binding sites are in grey shade blocks. Names of motifs locate at the first nucleotide. The start codon is in outline font.

physiological processes, including development, differentiation, haematopoiesis and stress response but may be regulated via different mechanisms (Blank & Andrews 1997, Moran *et al.* 2002). BACH2 is abundantly expressed in the early stages of B-cell differentiation and might be involved in the repression of immunoglobulin genes (Muto *et al.* 1998). ATF4 binding motif is a factor also upregulated during cellular stress responses (Passe *et al.* 2006). The NMYC transcription factor is critically involved in neuronal development and tumorigenesis (Knoepfler *et al.* 2002, Strieder & Lutz 2002).

Although liver is the main production source of plasma complement, many other cell types such as astrocytes and astrocytoma cell lines also synthesize the terminal complement components (Gasque *et al.* 1995, Morgan & Gasque 1996, Alker *et al.* 1998).

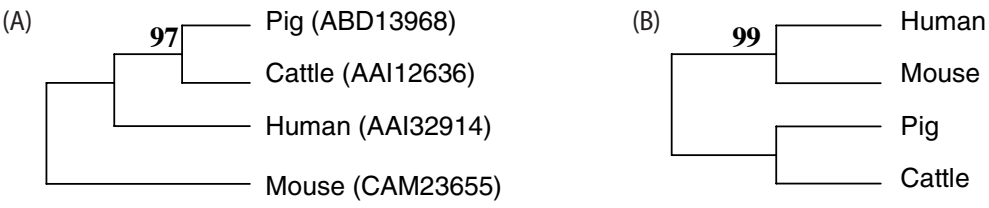

Figure 2
Unrooted phylogenic trees constructed by the neighbour-joining method based on the alignment of (A) protein sequences obtained from by GenBank, and (B) the 5´-region,of various mammalian animal species. Bootstrap indices were used to verify the reliability of the branches with 500 replications. The tree for evaluating evolutionary distance was computed using the MEGA3 software (Kumar *et al.* 2004).

In summary, approximately 950bp of the 5´-region of the porcine *C8A* were sequenced and analyzed. Functional motifs as well as transcription factor binding site are conserved among pig, mouse, cattle and human as well as among the evolutionary related complement genes. Polymorphims in this region generate new motifs, which may affect synthesis and expression of the porcine *C8A* protein. It is suspected and there is evidence that the Vietnamese local breeds are a source of promising alleles of unpredictable economic value (Lemke *et al*. 2005). Correspondingly, Muong Khuong owns valuable alleles associated with increased hemolytic complement activity (Do *et al*. 2007). Therefore, polymorphisms found in the 5´-region have also a great potential representing genetic sources for developing markers in efforts to improve animal health and animal welfare.

Table 1
Genotypic and allelic frequency

SNP (position in sequence Genbank acc no. CT025761)	Genotype/ allele	Landrace n, %	Large White n, %	Pietrain n, %
Genotypic frequency				
680A>G (320295)	AA	15 (0.49)	24 (0.75)	9 (0.28)
	AG	12 (0.42)	4 (0.23)	14 (0.50)
	GG	3 (0.09)	2 (0.02)	7 (0.22)
588A>G (320203)	AA	0 (0.00)	0 (0.00)	0 (0.00)
	AG	0 (0.00)	2 (0.06)	2 (0.06)
	GG	30 (1.00)	28 (0.93)	28 (0.93)
548A>G (320163)	AA	15 (0.49)	24 (0.78)	9 (0.32)
	AG	12 (0.42)	5 (0.21)	16 (0.49)
	GG	3 (0.09)	1 (0.01)	5 (0.19)
547C>T (320162)	CC	15 (0.49)	24 (0.78)	9 (0.32)
	CT	12 (0.42)	5 (0.21)	16 (0.49)
	TT	3 (0.09)	1 (0.01)	5 (0.19)
524A>T (320139)	AA	4 (0.10)	1 (0.01)	6 (0.20)
	AT	11 (0.43)	4 (0.18)	15 (0.50)
	TT	15 (0.47)	25 (0.81)	9 (0.30)
469C>T (320084)	CC	3 (0.09)	25 (0.84)	9 (0.32)
	CT	12 (0.42)	5 (0.15)	16 (0.49)
	TT	15 (0.49)	0 (0.01)	5 (0.19)
437C>T (320052)	CC	3 (0.09)	2 (0.02)	8 (0.23)
	CT	12 (0.42)	4 (0.23)	13 (0.50)
	TT	15 (0.49)	24 (0.75)	9 (0.27)
Alellic frequency				
680A>G	A	42 (0.70)	52 (0.90)	32 (0.53)
	G	18 (0.30)	8 (0.10)	28 (0.47)
588A>G	A	0 (0.00)	2 (0.03)	2 (0.03)
	G	60 (1.00)	58 (0.97)	58 (0.97)
548A>G	A	42 (0.70)	53 (0.88)	34 (0.57)
	G	18 (0.30)	7 (0.12)	26 (0.43)
547C>T	C	42 (0.70)	53 (0.88)	34 (0.57)
	T	18 (0.30)	7 (0.12)	26 (0.43)
524A>T	A	19 (0.32)	6 (0.10)	27 (0.45)
	T	41 (0.68)	54 (0.90)	33 (0.55)
469C>T	C	18 (0.30)	55 (0.92)	34 (0.57)
	T	42 (0.70)	5 (0.08)	26 (0.43)
437C>T	C	18 (0.30)	8 (0.13)	29 (0.48)
	T	42 (0.70)	52 (0.87)	31 (0.52)

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