# Marfan Database (third edition): new mutations and new routines for the software

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## ABSTRACT

The Marfan database is a software that contains routines for the analysis of mutations identified in the FBN1 gene that encodes fibrillin-1. Mutations in this gene are associated not only with Marfan syndrome but also with a spectrum of overlapping disorders. The third version of the Marfan database contains 137 entries. The software has been modified to accommodate four new routines and is now accessible on the World Wide Web at http://www.umd.necker.fr

# FIBRILLIN, MARFAN SYNDROME AND TYPE 1 FIBRILLINOPATHIES

Fibrillin-1 is the principal structural element of a class of connective tissue microfibrils that have a widespread distribution (1). In elastic tissues, fibrillin microfibrils play a key role in elastic fibrillogenesis and are components of elastic fibers which

generate elastic recoil (2,3). In non-elastic tissues, they are proposed to play an anchoring role (4). Fibrillin-1 is encoded by a relatively large and fragmented gene (65 exons distributed over ~110 kb) located at 15q15–q21.1 (5–8). It has a complex multi-domain structure comprising 47 epidermal growth factor (EGF)-like modules (43 of which have a calcium-binding consensus sequence) interspersed with seven '8-cysteine' repeats with homology to the TGF- $\beta$ 1 binding protein and two 'hybrid' modules.

Marfan syndrome (MFS) is an autosomal dominant disorder affecting mainly the cardiovascular, skeletal and ocular systems (9). The reported incidence is at least 1 per 10 000 with >25% of cases being the result of new mutations. The disease is associated with mutations in the gene encoding fibrillin-1 (FBN1). More recently, defects in this gene have been shown to cause a wide spectrum of microfibrilopathies, called 'type-1 fibrillinopaties', ranging from isolated skeletal features of Marfan syndrome or familial ectopia lentis to neonatal Marfan syndrome at the most severe end.

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Table 1. Each line represents a single FBN1 mutation report

| A  | в   | с   | D  | E  | F  | G  | Н   | I  | J   | к  | L   | М   | N  | 0   | P   | Q                                       | R   |
|--|---|---|--|--|--|--|---|--|---|--|---|---|--|---|---|---|---|
| 10   | 2   | 165   | 55   | GGA  | del83c   | Stop at 100  | 248 +1 G->A   | Gly  | Frameshift  | NH2 unique region  | ?   | ?   | +  | ?   | ?   | ?                                       | 19  |
| 111  | 3   | 331   | 111  | TGT  | CGT  | T->C   | C111R   | Cys  | Arg   | EGF-like #1  | +   | +   | -  | -   | -   | -                                       | NP3   |
| 37   | 4   | 364   | 122  | œ  | TGC  | C->T   | R122C (1)   | Arg  | Cys   | EGF-like #2  | +   | +   | -  | ?   | +   | ?                                       | 32  |
| 85   | 4   | 364   | 1  | 1  | TGC  | C->T   | R122C (2)   | Arg  | Cys   | EGF-like #2  | +   | +   | +  | -   | +   | -                                       | NP2   |
| 40   |   | 386   |  | 1  | TAC  | G->A   | C129Y   | Cys  | Tyr   | EGF-like #2  | +   | +   | +  | +   | +   | ?                                       | 13  |
| 41   | 5   | 497   |  | TGT  | 1  | G->T   | C166F   | Cys  | Phe   | EGF-like #3  | ?   | ?   | +  | ?   | ?   | ?                                       | 13  |
| 63   | 1   | 497   |  | TGT  | 1  | G->C   | C166S   | Cys  | Ser   | EGF-like #3  | ?   | ?   | ?  | ?   | ?   | ?                                       | 38  |
| 20   | 1   | 649   |  |  | GGG  | T->G   | W217G   | Trp  | Gly   | Hybrid motif #1  | +   | +   | +  | ?   | ?   | ?                                       | 24  |
| 133  | 1   | 718   |  |  |  | C->T   | R240C   | Arg  | Cys   | Hybrid motif #1<br>EGF-like #4   | +   | +   | +  | -   |   | -                                       | NP4<br>NP8  |
| 128  | 1   | 1421<br>1426  |  | TGT<br>TGC   | del48b<br>GGC  | dei<br>T->G  | G1468T<br>C476G   | Cys<br>Cys   | Frameshift<br>Gly   | EGF-like #4  | +++++++++++++++++++++++++++++++++++++++             | +++   | +++  | ?   | + ?   | ?                                       | 25  |
| 51   |   | 1604  |  |  | del1b  | Stop at 578  | 1604delT  | Leu  | Frameshift  | cb EGF-like #04  | ?   | ?   | +<br>?   | ?   | ?   | ?                                       | 13  |
| 112  |   | 1633  |  | œ  |  | C->T   | R545C (1)   | Arg  | Cys   | cb EGF-like #04  | +   | +   | +  |   |   | · .                                     | NP3   |
| 135  |   | 1633  |  |  | TGC  | C->T   | R545C (2)   | Arg  | Cys   | cb EGF-like #04  | +   | +   | +  | +   | +   | -                                       | NP4   |
| 6  |   | 1643  |  | 1  | ATC  | A->T   | N548I   | Asn  | lle   | cb EGF-like #04  | +   | +   | +  | ?   | +   | ?                                       | 19  |
| 74   |   | 1693  |  |  | TGA  | C->T   | R565X   | Arg  | Stop  | cb EGF-like #04  | ?   | ?   | ?  | ?   | ?   | ?                                       | 43  |
| 76   | 14  | 1760  | 587  | TGT  | TAT  | G->A   | C587Y   | Cys  | Tyr   | cb EGF-like #05  | +   | +   | -  | ?   | ?   | ?                                       | 44  |
| 134  | 14  | 1794  | 598  | TGC  | TGG  | C->G   | C598W   | Cys  | Trp   | cb EGF-like #05  | +   | +   | +  | -   | +   | +                                       | NP4   |
| 102  | 14  | 1836  | 612  | AAA  | del1c  | Stop at 624  | 1836delA  | Lys  | Frameshift  | cb EGF-like #05  | +   | +   | +  | -   | -   | -                                       | NP7   |
| 12   | 15  | 1879  | 627  | CGT  | TGT  | C->T   | R627C (1)   | Arg  | Cys   | cb EGF-like #06  | +   | +   | +  | -   | -   | -                                       | 21  |
| 75   | 15  | 1879  | 627  | CGT  | TGT  | C->T   | R627C (2)   | Arg  | Cys   | cb EGF-like #06  | ?   | ?   | ?  | ?   | ?   | ?                                       | 43  |
| 56   |   | 1981  |  | TGC  | CGC  | T->C   | C661R   | Cys  | Arg   | 8-Cys #2   | ?   | ?   | ?  | ?   | ?   | ?                                       | 35  |
| 87   | 17  | 2113  |  | GCG  |  | G->A   | A705T   | Ala  | Thr   | 8-Cys #2   | +   | +   | +  | -   | +   | -                                       | 48  |
| 86   |   | 2132  |  |  | 1  | G->A   | C711Y   | Cys  | Tyr   | 8-Cys #2   | +   | +   | +  | -   | +   | <u> </u>                                | 48  |
| 8  | 18  | 2168  |  | GAT  |  | A->C   | D723A   | Asp  | Ala   | cb EGF-like #07  | +   | +   | +  | ?   | ?   | ?                                       | 19  |
| 42   | 18  | 2237  | 746<br>748   | TAT  |  | A->G   | Y746C   | Tyr  | Cys   | cb EGF-like #07<br>cb EGF-like #07   | ?   | ?   | ?  | ?<br>?                                      | ?<br>?  | ?                                       | 13<br>41  |
| 90   | 18<br>18  | 2243<br>2248  |  |  | del51b<br>GGC  | del<br>T->G  | 2293 +2 T->C<br>C750G   | Cys<br>Cys   | Frameshift<br>Gly   | cb EGF-like #07  | ++  | +   | +++++  | <u>_</u>                                    | 1   | [                                       | 41<br>21  |
| 105  |   | 2447  |  |  |  | G->C   | C816S   | Cys  | Ser   | cb EGF-like #09  | +   | +   | +  |   |   |   | NP1   |
| 27   | 21  | 2584  |  | TGT  |  | T->C   | C862R   | Cys  | Arg   | Hybrid motif #2  | +   | +   | +  | ?   | ?   | ?                                       | 26  |
| 124  |   | 2668  |  |  | 1  | T->C   | C890R   | Cys  | Arg   | Hybrid motif #2  | +   | +   | +  |   | :   |   | 50  |
| 43   |   | 2776  | 926  |  | CGT  | T->C   | C926R   | Cys  | Arg   | cb EGF-like #10  | ?   | ?   | ?  | ?   | ?   | ?                                       | 13  |
| 150  |   | 2950  |  | GTC  |  | G->A   | V984I   | Val  | lle   | 8-Cys #3   | +   | +   | +  | -   | +   | +                                       | 15, NP6   |
| 84   |   | 2986  | 996  |  | CGT  | T->C   | C996R   | Cys  | Arg   | 8-Cys #3   | +   | +   | +  | -   | +   | -                                       | NP2   |
| 44   | 24  | 3037  | 1013   | GGA  | AGA  | G->A   | G1013R (1)  | Gly  | Arg   | 8-Cys #3   | +   | +   | +  | ?   | ?   | ?                                       | 13  |
| 70   | 24  | 3037  | 1013   | GGA  | AGA  | G->A   | G1013R (2)  | Gly  | Arg   | 8-Cys #3   | ?   | ?   | ?  | ?   | ?   | ?                                       | 40  |
| 104  | 24  | 3037  | 1013   | GGA  | CGA  | G->C   | G1013R (3)  | Gly  | Arg   | 8-Cys #3   | +   | +   | +  | .   | -   | -                                       | NP1   |
|  |   |   |  |  | 0.001  |  |   | 10.9   | <u>v</u>  |  | _   | الشمي   | . T I  |   |   |   |   |
|  |   |   |  |  |  | -  |   | 10.19  | L V   |  |   |   | <u> </u>   |   |   |   |   |
| A  | в   | с   | D  | E  | F  | G  | Н   | 1  | J   | к  | L   | M   |  | 0   | P   | Q                                       | R   |
| 18   | 24  | 3069  | <b>D</b><br>1023   | E<br>AAG   | F<br>AAC   | G->C   | H<br>K1023N   | I<br>Lys   | J<br>Asn  | 8-Cys #3   | L<br>+  | M<br>+  | N<br>+   | ?   | +   | ?                                       | 24  |
| 18<br>19   | 24<br>25  | 3069<br>3083  | D<br>1023<br>1028  | E<br>AAG<br>GAT  | F<br>AAC<br>del126b  | G->C<br>del  | H<br>K1023N<br>3208 +5 G->T   | I<br>Lys<br>Asp  | J<br>Asn<br>Frameshift  | 8-Cys #3<br>cb EGF-like #11  |   |   | N<br>+   | -+  |   |   | 24<br>24  |
| 18<br>19<br>141  | 24<br>25<br>25  | 3069<br>3083<br>3095  | D<br>1023<br>1028<br>1032  | E<br>AAG<br>GAT<br>TGC   | F<br>AAC<br>del126b<br>TAC   | G->C<br>del<br>G->A  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y   | I<br>Lys<br>Asp<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11   | +<br>+<br>+   | +   | N<br>+<br>+<br>+   | ?<br>?<br>-                                 | +<br>?<br>+                                       | ?<br>?<br>-                             | 2 4<br>2 4<br>NP2   |
| 18<br>19<br>141<br>81  | 24<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128  | D<br>1023<br>1028<br>1032<br>1043  | E<br>AAG<br>GAT<br>TGC<br>AAG  | F<br>AAC<br>del126b<br>TAC<br>AGG  | G->C<br>del<br>G->A<br>A->G  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R   | I<br>Lys<br>Asp<br>Cys<br>Lys  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11  | +<br>+<br>+<br>+                                    | +<br>+<br>-   | N<br>+<br>+<br>+<br>+  | ?<br>?<br>-<br>+                            | +<br>?<br>+<br>+                                  | ?<br>?<br>-                             | 2 4<br>2 4<br>NP2<br>4 7  |
| 18<br>19<br>141<br>81<br>67  | 24<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142  | D<br>1023<br>1028<br>1032<br>1043<br>1048  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a   | G->C<br>del<br>G->A<br>A->G<br>del   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11   | +<br>+<br>+<br>+<br>+                               | +   | N<br>+<br>+<br>+<br>+<br>+<br>+<br>+                               | ?<br>?<br>-                                 | +<br>?<br>+<br>+                                  | ?<br>?<br>-                             | 24<br>24<br>NP2<br>47<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78  | 24<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142deJATT<br>I1048T   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11  | + + + + + + +                                       | +<br>+<br>-<br>+<br>-   | N<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+                     | ?<br>?<br>+<br>?                            | +<br>?<br>+<br>+<br>+<br>+                        | ? ? -                                   | 24<br>24<br>NP2<br>47<br>39<br>45   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157  | D<br>1023<br>1028<br>1032<br>1043<br>1043<br>1048<br>1048<br>1053  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1053R   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11   | +<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+ | +<br>+<br>-<br>+<br>+<br>+  | N<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+ | ?<br>?<br>-<br>+                            | + ?<br>+ + + + ?                                  | ?<br>?<br>-                             | 24<br>24<br>NP2<br>47<br>39<br>45<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC<br>TGT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1053R<br>C1055G   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Cys  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Giy   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11  | + + + + + + + +                                     | +<br>+<br>-<br>+<br>+<br>+<br>+   | N + + + + + + + + + + + + + + + + + + +                            | ? - +? -? -                                 | +<br>+<br>+<br>+<br>+<br>+<br>+<br>+              | ? ? -                                   | 2 4<br>2 4<br>NP2<br>4 7<br>3 9<br>4 5<br>3 9<br>4 8  |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC<br>TGT<br>GGC   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>ins  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>11048T<br>C1053R<br>C1055G<br>3174insTGC   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Cys<br>Gly   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11  | + + + + + + + + +                                   | +<br>+<br>-<br>+<br>+<br>+  | N + + + + + + + + + + + + + + + + + + +                            | ? - + ? - ? - +                             | + ?<br>+ + + + + ?<br>+ +                         | ? ? - ?                                 | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC<br>TGT<br>GGC<br>GAA  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>11048T<br>C1053R<br>C1055G<br>3174insTGC   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Cys<br>Gly<br>Glu  | J<br>Asn<br>Framøshift<br>Tyr<br>Arg<br>Framøshift<br>Thr<br>Arg<br>Gly<br>Framøshift<br>Framøshift   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11<br>cb EGF-like #11  | + + + + + + + + + +                                 | +<br>+<br>-<br>+<br>+<br>+<br>+   | N + + + + + + + + + + + + + + + + + + +                            | ? - + ? - ? - + ?                           | +<br>+<br>+<br>+<br>+<br>+<br>+<br>+              | ? ? -                                   | 2 4<br>2 4<br>NP2<br>4 7<br>3 9<br>4 5<br>3 9<br>4 8  |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAC  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GCC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>ins<br>Stop at 1087  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA   | I<br>Lys<br>Asp<br>Cys<br>Ile<br>Ile<br>Cys<br>Cys<br>Gly<br>Glu<br>Asp  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #11   | + + + + + + + + +                                   | +<br>-<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+  | N + + + + + + + + + + + + + + + + + + +                            | ? - + ? - ? - +                             | + ? + + + + + + + + + ?                           | ? ? - ? ? - ? ? ? ? ? ? ? ? ? ? ? ? ? ? | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAC<br>GAA   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>QGC<br>QGC<br>GGT<br>ins3c<br>del1b<br>QGC<br>AAA   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->G<br>ins<br>Stop at 1087<br>A->G  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1053R<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G   | I<br>Lys<br>Asp<br>Cys<br>Ile<br>Ile<br>Cys<br>Cys<br>Gly<br>Glu<br>Asp<br>Glu   | J<br>Asn<br>Framoshift<br>Tyr<br>Arg<br>Framoshift<br>Thr<br>Arg<br>Gly<br>Framoshift<br>Framoshift<br>Gly  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12  | +             | + + - + + + + + + + + + + + + + + + + +   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ?                       | + ?<br>+ + + + + ?<br>?                           | ????                                    | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>48<br>29<br>47<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>26<br>26<br>26<br>26  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>TGT<br>GAA<br>GAA<br>GAA<br>GAA  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->G<br>ins<br>Stop at 1087<br>A->G<br>G->A  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)   | I<br>Lys<br>Asp<br>Cys<br>Ile<br>Ile<br>Cys<br>Cys<br>Gly<br>Glu<br>Asp<br>Glu   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12   | +             | +++-+++++++++++++++++++++++++++++++++++   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ?                     | + ? + + + + + ? ? ?                               | ????????                                | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217<br>3220  | D<br>1023<br>1028<br>1032<br>1043<br>1043<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>ins<br>Stop at 1087<br>A->G<br>G->A<br>G->A<br>G->A<br>T->C  | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (3)<br>C1074R   | I<br>Lys<br>Asp<br>Cys<br>Ile<br>Ile<br>Cys<br>Gly<br>Gly<br>Glu<br>Glu<br>Glu   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12   | +             | +++-+++++++++++++++++++++++++++++++++++   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ? ?                   | + ? + + + + + ? ? ?                               | ?????????                               | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>71  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217<br>3220<br>3258  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073<br>1074<br>1086  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>Stop at 1087<br>A->G<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12   | +             | +++-+++++++++++++++++++++++++++++++++++   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ??-+?-+?????-?                              | + ? + + + + ? + + ? ? ? ? ? + ?                   | ??-???????????????????????????????????? | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>48<br>29<br>47<br>39<br>13<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>71<br>65  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>26<br>26<br>26<br>26<br>26<br>26<br>26<br>26<br>27  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349  | D<br>1023<br>1028<br>1043<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073<br>1074<br>1086<br>1117  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TCC<br>TGT<br>TGT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Giy<br>Frameshift<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12   | +             | + + + - + + - + ? + - +   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ??-+?-+????????????????????????????????     | + ? + + + + + + + ? ? ? ? + ? ?                   | ??-???????????????????????????????????? | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>48<br>29<br>47<br>39<br>13<br>39<br>39<br>24<br>40<br>39   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>5<br>68<br>69<br>17<br>71<br>65<br>28   | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>26<br>26<br>26<br>26<br>26<br>26<br>26<br>27<br>27  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217  | D<br>1023<br>1028<br>1032<br>1043<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073<br>1074<br>1086<br>1117  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>TGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>AACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1053R<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13   | +             | + + + + - + + + + - + ? + + + + + ? + + + ? + + + ? + + + ? + + + ? + + + ? + + + + ? + + + + ? + + + ? + + + ? + + + ? + ? + + ? + ? + + ? + + ? + ? + + ? + ? + + ? + ? + ? + ? + ? + + ? + | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ??-+?-+?????-?                              | + ? + + + + ? + + ? ? ? ? ? + ?                   | ??-???????????????????????????????????? | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>48<br>29<br>26   |
| 18<br>19<br>141<br>81<br>67<br>78<br>68<br>9<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>71<br>65<br>28<br>106  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350  | <b>D</b><br>1023<br>1028<br>1032<br>1043<br>1048<br>1055<br>1055<br>1055<br>1058<br>1058<br>1073<br>1073<br>1073<br>1074<br>1074<br>1117   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>TGT<br>GCC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>TGT<br>TAT<br>TAT   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>ins<br>Stop at 1087<br>A->G<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A                          | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Gly<br>Gly<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13   | +             | + + + - + + + - + ? + - + ? + + + + +   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ? ? ? ? ? - ? ? ? -   | + ? + + + + ? + + ? ? ? ? + ? ? ? -               | · · · · · · · · · · · · · · · · · · ·   | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1  |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>7<br>71<br>65<br>28<br>106<br>83  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3191<br>3215<br>3217<br>3217<br>3217<br>3220<br>3258<br>3849<br>3350<br>3350<br>3391  | <b>D</b><br>1023<br>1028<br>1032<br>1043<br>1048<br>1053<br>1055<br>1058<br>1064<br>1073<br>1073<br>1073<br>1073<br>1073<br>1074<br>1107<br>1117<br>1117   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>TGT<br>GCC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->G<br>Stop at 1087<br>A->G<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>A<br>A->T                    | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3172G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13  | +             | + + + - + + + - + ? + - + ? + + + + ?   | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? - ? - +????????????????????????     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ?           | ??-???????????????????????????????????? | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>68<br>69<br>17<br>71<br>65<br>28<br>106<br>83<br>106  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217  | <b>D</b><br>1023<br>1028<br>1032<br>1043<br>1043<br>1053<br>1055<br>1058<br>1064<br>1073<br>1073<br>1073<br>1073<br>1073<br>1074<br>1117<br>1117<br>1117<br>1117   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC<br>TGT<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>AACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAC<br>TAC<br>CCC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A                 | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)  | I<br>Lys<br>Asp<br>Cys<br>Lys<br>IIe<br>IIe<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asn<br>Arg  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13  | +             | + + + - + + + - + ? + - + ? + + + ? +   | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? -? - +?????????????????????????     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ?         | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47  |
| 18<br>19<br>141<br>81<br>67<br>86<br>68<br>9<br>33<br>82<br>64<br>45<br>68<br>83<br>82<br>64<br>45<br>77<br>71<br>65<br>28<br>106<br>83<br>31<br>2   | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>26<br>26<br>26<br>26<br>26<br>26<br>27<br>27<br>27<br>27<br>27<br>27  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3351<br>3410  | D<br>1023<br>1028<br>1032<br>1048<br>1053<br>1055<br>1058<br>1055<br>1058<br>1073<br>1073<br>1073<br>1073<br>1073<br>1073<br>1177<br>1117<br>111   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AAT<br>TGC<br>TGT<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>CGC<br>CCC                                   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>AACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAC<br>COC<br>COC  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->G<br>Stop at 1087<br>A->G<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>A<br>A->T<br>G->A<br>A<br>A->T<br>G->C       | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)  | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asn<br>Arg  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13  | +             | + + + - + + + - + ? + - + ? + + ? + + ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? ? + ?   | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? - ? - +????????????????????????     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ?           | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>39<br>13<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16  |
| 18<br>19<br>141<br>81<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>75<br>28<br>106<br>83<br>106<br>83<br>12<br>28<br>88  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>26<br>26<br>26<br>26<br>26<br>27<br>27<br>27<br>27<br>27<br>27<br>27  | 3069<br>3083<br>3128<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3215<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3227<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3391<br>3410<br>3410<br>3410  | D<br>1023<br>1028<br>1032<br>1048<br>1055<br>1058<br>1055<br>1058<br>1072<br>1073<br>1073<br>1073<br>1073<br>1073<br>1073<br>1074<br>1177<br>1117<br>1117<br>1137<br>1137<br>1153  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AAT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>AACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAC<br>COC<br>COC<br>COC<br>TAT  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H<br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1053R<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)<br>C1153Y   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asn<br>Arg<br>Arg<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like # | +             | + + + - + + + - + ? + - + ? + + + ? +   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ? ? ? ? ? ? ? ? ? ?     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ?         | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16  |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>89<br>17<br>71<br>65<br>28<br>106<br>83<br>106<br>83<br>11<br>28<br>83<br>79  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3128<br>3142<br>3143<br>3143<br>3143<br>3157<br>3215<br>3215<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3359<br>3359<br>3359<br>3359<br>3359<br>3359<br>335   | D<br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1058<br>1058<br>1058<br>1073<br>1073<br>1073<br>1073<br>1073<br>1074<br>11073<br>1117<br>1117<br>1117<br>1131,<br>1153  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>ATT<br>TGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>GAC<br>CQC<br>CGC<br>TGT<br>GAC                                   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>CGT<br>TGG<br>CGT<br>TAT<br>TAT<br>TAC<br>CCC<br>TAT<br>AAC  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->G<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A                 | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)<br>C1153Y<br>D1155N  | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp<br>Arg<br>Asp   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Giy<br>Frameshift<br>Frameshift<br>Giy<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Asn  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14  | +             | + + + - + + + - + ? + - + ? + + ? + + ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? + ? ? ? + ?   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ? ? ? ? - ? ? ? ? ? ? | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + +   | · · · · · · · · · · · · · · · · · · ·   | 24<br>24<br>NP2<br>45<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>399<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>9<br>17<br>71<br>65<br>28<br>106<br>83<br>11<br>2<br>88<br>8<br>79<br>29  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3128<br>3142<br>3142<br>3142<br>3143<br>3157<br>3163<br>3174<br>3217<br>3217<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3350<br>3350<br>3410<br>3410<br>3410<br>3458<br>3463<br>3464  | D<br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1074<br>1086<br>1117<br>1117<br>1117<br>1117<br>1131<br>1137<br>1155  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>TGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>GAC<br>GAC<br>GAA   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>CGT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>AAC<br>del17b  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | <u>H</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)<br>C1153Y<br>D1155N<br>3464del17   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Asn<br>Frameshift   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14  | +             | + + + - + + + - + ? + - + ? + + + ? + + +   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ? ? ? ? - ? ? ? ? ? ? | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ?         | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>71<br>65<br>28<br>106<br>8<br>3<br>1<br>2<br>8<br>8<br>7<br>9<br>9<br>7<br>9<br>9<br>7<br>9<br>9<br>7<br>7<br>8<br>8<br>8<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3128<br>3142<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217  | D<br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073<br>1074<br>1074<br>1074<br>1107<br>1117<br>1117<br>1131<br>1131<br>1135<br>1155<br>1166  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>GAA<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>GAC<br>GAC<br>GAC                     | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAC<br>CCC<br>CCC<br>TAT<br>TAC<br>AAC<br>del17b<br>TAC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A         | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)<br>C1153Y<br>D1155N<br>3464del17<br>C1166Y   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Glu<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Asp<br>Asp<br>Asp<br>Cys  | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Frameshift<br>Frameshift   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #14  | +             | + + + - + + + - + ? + - + ? + + + ? + +   | <b>N</b> + + + + + + + + + + + + + + + + + + +                     | ? ? - + ? - ? - + ? ? ? ? ? ? - ? ? ? ? ? ? | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + +   | · · · · · · · · · · · · · · · · · · ·   | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>48<br>46<br>26<br>NP7   |
| 18<br>19<br>141<br>81<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>33<br>83<br>83<br>106<br>83<br>106<br>83<br>11<br>2<br>88<br>87<br>9<br>79<br>29<br>97<br>58  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217  | D<br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1074<br>1086<br>1117<br>1117<br>1117<br>1117<br>1131<br>1137<br>1155  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>GAA<br>GAC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT                                   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAC<br>CCC<br>CCC<br>TAT<br>AAC<br>del17b<br>TAC<br>CAT   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A | <u>H</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117G<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (2)<br>C1153Y<br>D1155N<br>3464del17   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Gly<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift<br>Uys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Frameshift<br>Tyr<br>His  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14  | +             | +++-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-  | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? - ? - +????? - ??? - ?????          | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + +   | · · · · · · · · · · · · · · · · · · ·   | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26   |
| 18<br>19<br>141<br>81<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>33<br>83<br>83<br>106<br>83<br>106<br>83<br>11<br>2<br>88<br>87<br>9<br>79<br>29<br>97<br>58  | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3128<br>3142<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3220<br>3258<br>3349<br>3250<br>3350<br>3350<br>3350<br>3350<br>3410<br>3410<br>3458<br>3468<br>3468<br>3468<br>3468<br>3468<br>3468<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>345                                 | D<br>1023<br>1028<br>1032<br>1048<br>1055<br>1055<br>1058<br>1064<br>1072<br>1073<br>1073<br>1073<br>1073<br>1073<br>1073<br>1177<br>1117<br>111   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>ATT<br>TGC<br>TGT<br>GCC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>AAC<br>CGC<br>GAC<br>TGT<br>TGT<br>CGC<br>CGT<br>CCT                     | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>CGT<br>TAT<br>TAT<br>TAT<br>TAC<br>CCC<br>TAT<br>TAT<br>TAT<br>TAT<br>CAT<br>C   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | <u>H</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1117G<br>C1117Y (1)<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (1)<br>R1137P (1)<br>R1137P (2)<br>C1153Y<br>D1155N<br>3464del17<br>C1166Y<br>R1170H (1)   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Ile<br>Ile<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp<br>Arg<br>Asp<br>Cys<br>Asp   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Tyr<br>Frameshift<br>Tyr<br>His<br>His   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14  | +             | +++-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-  | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? - ? - +????? - ??? - ?????          | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + + ? | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>39<br>13<br>39<br>39<br>24<br>40<br>39<br>26<br>NP1<br>16<br>16<br>48<br>46<br>26<br>NP7<br>36   |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>89<br>17<br>71<br>65<br>28<br>83<br>106<br>83<br>11<br>2<br>9<br>97<br>78<br>88<br>87<br>9<br>17<br>106<br>107<br>107<br>107<br>107<br>107<br>107<br>107<br>107   | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3177<br>3215<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>33463<br>3463<br>3464<br>3497<br>3509<br>3509   | <b>D</b><br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1054<br>1072<br>1073<br>1074<br>1074<br>1074<br>11177<br>11177<br>1137,<br>1155<br>1155<br>1155<br>1155<br>1170<br>11770   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>T  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>T  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C1074R           C1086W           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153Y           D1155N           3464del17           C1166Y           R1170H (1)           R1170H (2)  | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Asn<br>Frameshift<br>Tyr<br>His<br>His  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14   | +             | +++-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-+-  | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? - ? - +????? - ??? - ?????          | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + + ? | ······································  | 24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>48<br>46<br>26<br>NP7<br>36<br>NP2  |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>9<br>17<br>71<br>65<br>28<br>8<br>106<br>83<br>1<br>2<br>8<br>8<br>106<br>83<br>1<br>2<br>8<br>8<br>106<br>9<br>9<br>9<br>17<br>7<br>8<br>8<br>107<br>17<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1   | $\begin{array}{c} 24\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25$   | 3069<br>3083<br>3128<br>3142<br>3142<br>3142<br>3143<br>3157<br>3163<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3410<br>3410<br>3410<br>3410<br>3458<br>3468<br>3468<br>3468<br>3468<br>3458<br>3468<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>345 | <b>D</b><br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1064<br>1072<br>1073<br>1074<br>1074<br>1074<br>1073<br>1073<br>1074<br>1117<br>1117<br>1117<br>1155<br>1155<br>1156<br>11700<br>1170  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>ATT<br>CT<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>GAC<br>GAC<br>GAC<br>CC<br>GAC<br>GAA<br>GAA | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT<br>TAC<br>CCC<br>CCC<br>CCC<br>CCC<br>CCC<br>CC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | <u>н</u><br>K1023N<br>3208 +5 G->T<br>C1032Y<br>K1043R<br>3142delATT<br>I1048T<br>C1055G<br>3174insTGC<br>3174insTGC<br>3192delA<br>D1072G<br>E1073K (1)<br>E1073K (2)<br>E1073K (2)<br>E1073K (3)<br>C1074R<br>C1086W<br>C1117Y (1)<br>C1117Y (2)<br>N1131Y<br>R1137P (1)<br>R1137P (1)<br>R1137P (2)<br>C1155N<br>3464del17<br>C1166Y<br>R1170H (1)<br>R1170H (2)<br>C1171W   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asn<br>Asp<br>Asp<br>Asp<br>Cys<br>Asp<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Gly<br>Frameshift<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Pro<br>Tyr<br>Tyr<br>Frameshift<br>Tyr<br>His<br>Frameshift<br>Tyr<br>His   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14<br>cb EGF-like #14  | +             | +++-+++++++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ? ? ? ? ? ? ? ? ? ?     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? - ? ? ? + + ? | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>48<br>26<br>NP7<br>36<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2<br>NP2           |
| 18<br>19<br>1411<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>9<br>17<br>71<br>68<br>83<br>108<br>83<br>108<br>83<br>112<br>28<br>88<br>79<br>29<br>99<br>29<br>99<br>29<br>95<br>81<br>142<br>113<br>1142<br>142<br>142<br>142<br>142<br>142<br>142<br>14   | 24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3340<br>3463<br>3463<br>3463<br>3463<br>3463<br>3463<br>3458<br>3463<br>3458<br>3463<br>3457<br>3509<br>3509<br>3513<br>3519  | D           1023           1028           1032           1048           1053           1055           1056           1072           1073           1074           1073           1073           1074           1073           1074           1177           1117           1137           1155           1166           1170           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1177           1175 | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>AATT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT                          | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAC<br>CGC<br>TAT<br>TAC<br>CGC<br>TAT<br>TAC<br>CGC<br>TAT<br>TAC<br>CGC<br>TAT<br>TAC<br>CAT<br>CAT<br>CAT<br>CAT<br>CAT<br>CAT<br>CAT<br>CA | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C1056G           S192delA           D1072G           E1073K (2)           E1073K (3)           C1074R           C1117G           C1117G           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153Y           D155N           3464del17           C1166Y           R1170H (1)           R1170H (2)           C1171W           N1173K           I1175T           C1182S | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asn<br>Asp<br>Asp<br>Asp<br>Cys<br>Asp<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Trp<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Pro<br>Frameshift<br>Tyr<br>His<br>His<br>Trp<br>Lys  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #14   | +             | +++-+++++++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ? ? ? ? ? ? ? ? ? ?     | +?++++?++?????+?????++??                          | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>16<br>16<br>48<br>46<br>26<br>NP7<br>36<br>NP7<br>36<br>NP3<br>NP3  |
| 18<br>19<br>1411<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>89<br>17<br>71<br>65<br>29<br>106<br>83<br>106<br>83<br>106<br>83<br>106<br>83<br>11<br>29<br>97<br>75<br>88<br>142<br>113<br>114<br>125<br>18<br>106<br>106<br>106<br>106<br>106<br>106<br>106<br>106   | $\begin{array}{c} 24\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25\\ 25$   | 3069<br>3083<br>3128<br>3142<br>3143<br>3142<br>3143<br>3157<br>3163<br>3174<br>3215<br>3217<br>3220<br>3258<br>3247<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>3458<br>3509<br>3509  | <b>D</b><br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1058<br>1058<br>1072<br>1073<br>1074<br>1073<br>1074<br>1086<br>1117<br>1117<br>1117<br>1117<br>1155<br>1155<br>1155<br>115  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>ATT<br>TGC<br>GAA<br>GAC<br>GAA<br>GAC<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>T  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1053R           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C1074R           C1086W           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153S           3464del17           C1155N           3464del17           C1171W           N1173K           R1170H (1)           R1170H (2)           C1171W           N1173K           E1200G   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Asp<br>Arg<br>Cys<br>Asp<br>Asp<br>Asp<br>Cys<br>Asp<br>Cys<br>Glu<br>Cys<br>Glu<br>Cys<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Giy<br>Cly<br>Cly<br>Cly<br>Cly<br>Cly<br>Cly<br>Cly<br>Cly<br>Cly<br>Cl  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like # | +             | +++-++++-++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ? ? ? ? ? ? ? ? ? ?     | +?++++?++?????+?????++??                          | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>16<br>16<br>16<br>8<br>48<br>46<br>26<br>NP7<br>36<br>0<br>NP3<br>NP3<br>NP3<br>NP7<br>NP8  |
| 18<br>19<br>141<br>8<br>167<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>9<br>17<br>71<br>65<br>28<br>8<br>106<br>83<br>1<br>2<br>8<br>8<br>3<br>1<br>2<br>8<br>8<br>106<br>107<br>7<br>106<br>107<br>107<br>107<br>107<br>107<br>107<br>107<br>107  | 24<br>255<br>255<br>255<br>255<br>255<br>255<br>255<br>266<br>226<br>226<br>226<br>226<br>226<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>225<br>226<br>226<br>226<br>227<br>227<br>227<br>227<br>227<br>227<br>227<br>227<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>226<br>226<br>227<br>227<br>227<br>227<br>227<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>228<br>229<br>229 | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3142<br>3143<br>3157<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3448<br>3458<br>3468<br>3458<br>3468<br>3458<br>3458<br>3458<br>3458<br>3459<br>3524<br>3559<br>3623  | D           1023           1028           1032           1048           1055           1058           1058           1072           1073           1074           1073           1074           1073           1074           1107           1117           1131           1155           1155           1155           1166           1170           1171           1175           1182           1170           1177           1200           12008  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>ATT<br>TGC<br>TGT<br>GGA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>TAT<br>T  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1053R           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C1074R           C1086W           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153Y           D1155N           3464del17           C1171W           N1173K           R1170H (2)           C1171W           N1173K           E1200G           3623 del G   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys                      | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Thr<br>Arg<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Pro<br>Pro<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift  | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #15  | +             | +++-+++++++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ? ? - + ? - ? - + ? ? ? ? ? ? ? ? ? ? ?     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? ? ?           | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>8<br>46<br>26<br>NP7<br>362<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP4 |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>9<br>17<br>71<br>65<br>28<br>8<br>106<br>83<br>12<br>8<br>8<br>106<br>83<br>12<br>28<br>8<br>106<br>83<br>12<br>12<br>58<br>141<br>141<br>141<br>157<br>178<br>107<br>178<br>107<br>107<br>107<br>107<br>107<br>107<br>107<br>107   | $\begin{array}{c} 24\\ 225\\ 255\\ 225\\ 255\\ 255\\ 255\\ 255\\ 255\\ 255\\ 256\\ 266\\ 226\\ 226\\ 227\\ 77\\ 227\\ 227\\ 228\\ 88\\ 228\\ 88\\ 228\\ 28\\ 2$   | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3142<br>3143<br>3147<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>321   | <b>D</b><br>1023<br>1028<br>1032<br>1048<br>1048<br>1053<br>1055<br>1058<br>1054<br>1074<br>1073<br>1073<br>1073<br>1073<br>1074<br>1086<br>1177<br>1117<br>1117<br>1155<br>1155<br>1155<br>1155<br>115  | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>ATT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>TGC<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT<br>TGT                                  | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>CGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>CGC<br>TGG<br>CGT<br>TAT<br>TAT<br>TAT<br>TAC<br>CCC<br>CCC<br>CCC<br>CCC<br>CCC<br>CC   | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C10174R           C1086W           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153Y           D1155N           3464del17           C1166Y           R1170H (1)           R1170H (2)           C11171W           N1173K           E1200G           3623 del G           C1223Y (1)   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Gly<br>Frameshift<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Tyr<br>Tyr<br>Tyr<br>Frameshift<br>Tyr<br>His<br>Frameshift<br>Tyr<br>His<br>Frameshift<br>Tyr<br>Frameshift<br>Tyr<br>Frameshift<br>Tyr<br>Frameshift<br>Tyr   | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #15<br>cb EGF-like # | +             | +++-+++++++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? -? - +?????????????????????????     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? ? ?           | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>45<br>39<br>45<br>39<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>48<br>46<br>26<br>NP7<br>36<br>NP7<br>36<br>NP3<br>NP3<br>NP3<br>NP3<br>NP4<br>34                           |
| 18<br>19<br>141<br>81<br>67<br>78<br>66<br>89<br>33<br>82<br>64<br>45<br>68<br>69<br>17<br>71<br>65<br>28<br>106<br>83<br>1<br>2<br>83<br>11<br>2<br>83<br>11<br>2<br>83<br>11<br>2<br>83<br>11<br>2<br>83<br>11<br>2<br>83<br>11<br>12<br>13<br>7<br>11<br>12<br>13<br>13<br>11<br>12<br>11<br>13<br>14<br>11<br>15<br>15<br>15<br>15<br>15<br>15<br>15<br>15<br>15 | $\begin{array}{c} 24\\ 225\\ 255\\ 2222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 222\\ 2222\\ 2222\\ 2222\\ 2222\\ 2222\\ 2222\\ 2222\\ 2222$  | 3069<br>3083<br>3095<br>3128<br>3142<br>3143<br>3142<br>3143<br>3157<br>3217<br>3217<br>3217<br>3217<br>3217<br>3217<br>3220<br>3258<br>3349<br>3350<br>3350<br>3350<br>3350<br>3448<br>3458<br>3468<br>3458<br>3468<br>3458<br>3458<br>3458<br>3458<br>3459<br>3524<br>3559<br>3623  | D           1023           1028           1032           1048           1053           1055           1056           1073           1074           1073           1074           1073           1074           1074           1074           1177           1117           1137           1137           1155           1166           1170           1175           1166           1170           1171           1175           1162           12000           1208           1223           1223   | E<br>AAG<br>GAT<br>TGC<br>AAG<br>AATT<br>ATT<br>TGC<br>TGT<br>GGC<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA<br>GAA   | F<br>AAC<br>del126b<br>TAC<br>AGG<br>del3a<br>ACT<br>OGC<br>GGT<br>ins3c<br>del1b<br>GGC<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA<br>AAA  | G->C<br>del<br>G->A<br>A->G<br>del<br>T->C<br>T->C<br>T->C<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A<br>G->A   | H           K1023N           3208 +5 G->T           C1032Y           K1043R           3142delATT           I1048T           C1053R           C1055G           3174insTGC           3192delA           D1072G           E1073K (1)           E1073K (2)           E1073K (3)           C1074R           C1086W           C1117Y (1)           C1117Y (2)           N1131Y           R1137P (1)           R1137P (2)           C1153Y           D1155N           3464del17           C1171W           N1173K           R1170H (2)           C1171W           N1173K           E1200G           3623 del G   | I<br>Lys<br>Asp<br>Cys<br>Lys<br>Cys<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys                      | J<br>Asn<br>Frameshift<br>Tyr<br>Arg<br>Frameshift<br>Frameshift<br>Gly<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Lys<br>Arg<br>Trp<br>Arg<br>Tyr<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Pro<br>Tyr<br>Tyr<br>Pro<br>Pro<br>Frameshift<br>Tyr<br>His<br>His<br>Trp<br>Lys<br>Trp<br>Lys<br>Trp<br>Asn<br>Frameshift<br>Tyr<br>His<br>Frameshift<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr<br>Tyr | 8-Cys #3<br>cb EGF-like #11<br>cb EGF-like #12<br>cb EGF-like #13<br>cb EGF-like #14<br>cb EGF-like #15  | +             | +++-+++++++++++++++++++++++++++++++++   | N + + + + + + + + + + + + + + + + + + +                            | ?? - +? -? - +?????????????????????????     | + ? + + + + ? + + ? ? ? ? ? + ? ? ? ? ?           | ······································  | 24<br>24<br>24<br>NP2<br>47<br>39<br>45<br>39<br>48<br>29<br>47<br>39<br>13<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>24<br>40<br>39<br>26<br>NP1<br>47<br>16<br>16<br>16<br>8<br>46<br>26<br>NP7<br>362<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP3<br>NP4 |

| Table 1 | <ol> <li>conti</li> </ol> | inued |
|---------|---------------------------|-------|
|---------|---------------------------|-------|

| A   | -  | -  |   | -   |  |  |  |   |  |  | 1.  |  |  |   |  |   |   |
|---|--|--|---|---|--|--|--|---|--|--|---|--|--|---|--|---|---|
| 1 0   | B  | C  | D   | E   | F  | G  | H  | 1   | J  | K  | 1   | M  | N  | 0   | P  | Q   | R   |
| 3   |  | 3746   |   |   | TCT  | G->C   | C1249S   | Cys   | Ser  | cb EGF-like #16  | +   | +  | +  | ?   | ?  | ?   | 17  |
| 91  |  | 3839   |   |   | del126b  | del  | 3839 -1 G->T   | Asp   | 1  | cb EGF-like #17  | +   | ?  | +  | ?   | ?  | ?   | 41  |
| 35  |  | 3965   |   |   | del123b  | dei  | 3965 -2 A->T   | Asp   | Frameshift   | cb EGF-like #18  | +   | -  | +  | ?   | ?  | ?   | 31  |
| 36  |  |  |   |   | del123b  | del  | 4087 +1 G->A   | Asp   | Frameshift   | cb EGF-like #18  | +   | +  | +  | ?   | ?  | ?   | 31  |
| 151   | 32   | 4009   | 1337  | 1   | CCT  | G->C   | A1337P   | Ala   | Pro  | cb EGF-like #18  | +   | +  | +  | -   | -  | -   | NP4   |
| 103   | 32   | 4011   | 1337  | GCT   | del1c  | Stop at 1412   | 4011delT   | Ala   | Frameshift   | cb EGF-like #18  | +   | -  | +  | -   | -  | -   | NP7   |
| 52  | 32   | 4020   | 1340  | ACC   | del1c  | Stop at 1412   | 4020delC   | Thr   | Frameshift   | cb EGF-like #18  | 2   | ?  | ?  | ?   | ?  | ?   | 13  |
| 46  | 33   | 4145   | 1382  | AAT   | AGT  | A->G   | N1382S   | Asn   | Ser  | cb EGF-like #19  | ?   | ?  | ?  | ?   | ?  | ?   | 13  |
| 115   | 34   | 4210   | 1404  | GAC   | TAC  | G->T   | D1404Y   | Asp   | Tyr  | cb EGF-like #20  | +   | +  | +  | -   | -  | -   | NP3   |
| 107   | 34   | 4270   | 1424  | CCA   | GCA  | C->G   | P1424A   | Pro   | Ala  | cb EGF-like #20  | +   | +  | -  | -   | -  | -   | NP1   |
| 130   | 34   | 4285   | 1429  | TGT   | AGT  | T->A   | C1429S   | Cys   | Ser  | cb EGF-like #20  | +   | +  | +  | -   | +  | -   | NP4   |
| 98  | 36   | 4490   | 1497  | TGC   | TCC  | G->C   | C1497S   | Cys   | Ser  | cb EGF-like #22  | +   | +  | +  | -   | -  | -   | NP7   |
| 22  | 36   | 4537   | 1513  | TGC   | CGC  | T->C   | C1513R   | Cys   | Arg  | cb EGF-like #22  | +   | +  | +  | ?   | ?  | ?   | 24  |
| 30  | 38   | 4766   | 1589  | TGT   | TTT  | G->T   | C1589F   | Cys   | Phe  | 8-Cys #4   | +   | +  | +  | ?   | ?  | ?   | 26  |
| 116   | 39   | 4828   | 1610  | TGC   | GGC  | T->G   | C1610G   | Cys   | Gly  | cb EGF-like #23  | +   | +  | +  | -   | -  | -   | NP3   |
| 49  | 1 1  | 4857   | 1619  |   | del1c  | Stop at 1639   |  | Gly   | Frameshift   | cb EGF-like #23  | +   | +  | +  | ?   | +  | ?   | 13  |
| 4   | I i  | 4987   | 1663  |   | CGT  | T->C   | C1663R   | Cys   | Arg  | cb EGF-like #24  | +   | +  | +  | ?   | ?  | ?   | 17  |
| 9   | 41   | 5137   | 1713  |   |  | Stop at 1735   |  | Asn   | Frameshift   | 8-Cys #5   | +   | +  | +  | ?   | +  | ?   | 19  |
| 148   |  | 5162   | 1721  |   |  | G->A   | C1721Y   | Cys   | ⊤yr  | 8-Cys #5   |   |  | +  |   | +  |   | NP2   |
| 100   | 1 1  | 5453   | 1818  |   |  | G->A   | C1818Y   | Cys   | Tyr  | cb EGF-like #26  | +++   | +  | +  |   | +  |   | NP7   |
| 99  |  | 5467   | 1823  |   |  | G->T   | E1823X   | Glu   | Stop   | cb EGF-like #26  |   | 1  |  |   |  |   | NP7   |
| 143   |  | 5494   | 1832  |   |  | G->T   | R1832C   |   |  | cb EGF-like #26  | + ?   | +<br>?   | + ?  | - ?   | ?  | ?   | NP7<br>NP2  |
|   |  |  |   |   |  |  |  | Arg   | Cys  |  |   | ?  |  | 1   |  | ſ   |   |
| 80  |  | 5509   | 1837  |   |  | C->T   | P1837S   | Pro   | Ser  | cb EGF-like #26  | +   | -  | +  | _   | +  |   | 46  |
| 92  | 1 1  | 5672   |   |   | del117b  | del  | 5788 +5 G->A   | Asp   | Frameshift   | cb EGF-like #28  | +   | +  | +  | ?   | ?  | ?   | 41  |
| 117   | 1 1  | 5679   | 1893  |   | AAA  | T->A   | N1893K   | Asn   | Lys  | cb EGF-like #28  | +   | +  | +  | - 1   | -  | -   | NP3   |
| 101   |  | 5729   | 1910  |   | GTT  | G->T   | G1910V   | Gly   | Val  | cb EGF-like #28  | +   | +  | +  | -   | +  | -   | NP7   |
| 47  |  | 5782   | 1928  |   |  | T->C   | C1928R   | -   | Arg  | cb EGF-like #28  | ?   | ?  | ?  | ?   | ?  | ?   | 13  |
| 53  |  | 5789   |   |   | del129b  | del  | 5788 +5 G->A (1)   | Asp   | Frameshift   | cb EGF-like #29  | ?   | ?  | ?  | ?   | ?  | ?   | 13  |
| 54  | 1 1  | 5789   |   |   | del129b  | del  | 5788 +5 G->A (2)   | Asp   | Frameshift   | cb EGF-like #29  | ?   | ?  | ?  | ?   | ?  | ?   | 13  |
| 55  | 47   | 5789   | 1930  | GAT   | del129b  | del  | 5788 +5 G->A (3)   | Asp   | Frameshift   | cb EGF-like #29  | ?   | ?  | ?  | ?   | ?  | ?   | 13  |
| 138   | r 1  | 5898   | 1966  |   |  | Stop at 1979   |  | Pro   | Frameshift   | cb EGF-like #29  | +   | -  | +  | -   | +  | -   | NP4   |
| 136   | 48   | 5930   | 1977  |   |  | G->A   | C1977Y   | Cys   | ⊤yr  | cb EGF-like #30  | +   | +  | +  | -   | -  | -   | NP4   |
| 144   | 48   | 5989   | 1997  | AGA   | TGA  | A->T   | R1997X   | Arg   | Stop   | cb EGF-like #30  | +   | -  | +  | -   | +  | -   | NP2   |
| 93  | 50   | 6164   | 2055  | GAT   | del126b  | del  | 6163 +2 del16pb  | Asp   | Frameshift   | 8-Cys #6   | +   | +  | +  | ?   | ?  | ?   | 4 1   |
| 118   | 50   | 6297   | 2099  | TGC   | TGG  | C->G   | C2099W   | Cys   | Trp  | 8-Cys #6   | +   | +  | +  | -   | -  | -   | NP3   |
| 145   | 51   | 6314   | 2105  | GAG   | del66b   | del  | 6314del66  | Glu   | Frameshift   | 8-Cys #6   | +   |  | . I  | -   | +  | -   | 49, NP5   |
| 119   | 51   | 6332   |   |   |  |  |  | 0.0   | 1 anoonine   |  |   | +  | +  |   |  |   | 1100  |
|   |  | 0002   | 2111  | TGT   | TAT  | G->A   | C2111Y   |   | Tyr  | 8-Cys #6   | +   | ++   | ++   | -   | -  | -   | NP3   |
| A   | - 1  |  |   |   |  |  |  | Cys   | Tyr  | 8-Cys #6   | +   | +  | +  | -   | -  | -   |   |
|   | в  | с  | D   | E   | F  | G  | Н  | Cys<br>I  | ⊤yr<br>J   | 8-Cys #6   | +<br>L  | +<br>M   | +<br>N   |   | -<br>P   | Q   | R   |
| 57  | 51   | <u>с</u><br>6339   | D<br>2113   | E<br>TAT  | F<br>TAA   | <b>G</b><br>T->A   | <mark>н</mark><br>Ү2113Х   | Cys<br>I<br>Tyr   | Tyr<br>J<br>Stop   | 8-Cys #6<br>K<br>8-Cys #6  | +   | +  | +  | -<br>0<br>?   | -<br>P<br>?  | Q<br>?  | <b>R</b><br>35  |
| 57<br>23  | 51<br>52   | <b>C</b><br>6339<br>6381   | D<br>2113<br>2127   | E<br>TAT<br>GAT   | F<br>TAA<br>GAA  | <b>G</b><br>T->A<br>T->A   | <mark>н</mark><br>Y2113X<br>D2127Е   | Cys<br>I<br>Tyr<br>Asp  | Tyr<br>J<br>Stop<br>Glu  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32   | +<br>L  | +<br>M   | +<br>N   | ?   | ?  | ?<br>-  | R<br>35<br>24   |
| 57  | 51<br>52   | <b>C</b><br>6339<br>6381<br>6431   | D<br>2113<br>2127<br>2144   | E<br>TAT<br>GAT<br>AAT  | F<br>TAA<br>GAA<br>AGT   | <b>G</b><br>T->A   | <mark>н</mark><br>Ү2113Х   | Cys<br>I<br>Tyr   | Tyr<br>J<br>Stop<br>Glu  | 8-Cys #6<br>K<br>8-Cys #6  | +<br>L<br>?   | +<br>M   | +<br>N<br>?  | ?<br>-<br>?   |  |   | <b>R</b><br>35  |
| 57<br>23  | 51<br>52<br>52<br>52   | <b>C</b><br>6339<br>6381   | D<br>2113<br>2127   | E<br>TAT<br>GAT<br>AAT  | F<br>TAA<br>GAA<br>AGT   | <b>G</b><br>T->A<br>T->A   | <mark>н</mark><br>Y2113X<br>D2127Е   | Cys<br>I<br>Tyr<br>Asp<br>Asn   | Tyr<br>J<br>Stop<br>Glu  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32   | +<br><b>L</b><br>?<br>+   | +<br>M   | +<br>N<br>?<br>+                                   | ?   | ?  | ?<br>-  | R<br>35<br>24   |
| 57<br>23<br>14<br>24<br>11  | 51<br>52<br>52<br>52<br>52<br>54   | C<br>6339<br>6381<br>6431<br>6453<br>6617  | D<br>2113<br>2127<br>2144<br>2151<br>2206   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b   | <b>G</b><br>T->A<br>T->A<br>A->G<br>C->G<br>del  | <u>н</u><br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C   | Cys<br>I<br>Tyr<br>Asp<br>Asn   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32  | +<br>2<br>+<br>+<br>+   | +<br>M<br>?<br>-                                   | +<br>N<br>?<br>+<br>+                              | ?<br>-<br>?<br>?<br>+                               | ?<br>-<br>?<br>?<br>?  | ? - ? ? ?   | R<br>35<br>24<br>22   |
| 57<br>23<br>14<br>24<br>11<br>7   | 51<br>52<br>52<br>52<br>52<br>54<br>54   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT   | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT  | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C   | <u>н</u><br>Y2113X<br>D2127E<br>N2144S<br>C2151W   | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32   | +<br><b>L</b><br>?<br>+<br>+<br>+   | +<br><b>M</b><br>?<br>-<br>+                       | +<br>N<br>?<br>+<br>+<br>+                         | ?<br>-<br>?<br>?                                    | ?<br>-<br>?<br>?   | ?<br>-<br>?<br>?  | <b>R</b><br>35<br>24<br>22<br>24  |
| 57<br>23<br>14<br>24<br>11  | 51<br>52<br>52<br>52<br>52<br>54   | C<br>6339<br>6381<br>6431<br>6453<br>6617  | D<br>2113<br>2127<br>2144<br>2151<br>2206   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT   | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT   | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C   | <u>н</u><br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C   | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Asp<br>Cys  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34  | +<br>?<br>+<br>+<br>+<br>+  | +<br>?<br>- +<br>+                                 | + N ? + + + +                                      | ?<br>-<br>?<br>?<br>+                               | ?<br>-<br>?<br>?<br>?  | ? - ? ? ?   | <b>R</b><br>35<br>24<br>22<br>24<br>20  |
| 57<br>23<br>14<br>24<br>11<br>7   | 51<br>52<br>52<br>52<br>52<br>54<br>54   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT   | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Asp<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34   | +<br><b>L</b><br>?<br>+<br>+<br>+<br>+<br>+   | +<br>? • • + + +                                   | +<br><b>N</b><br>?<br>+<br>+<br>+<br>+<br>+<br>+   | ?<br>-<br>?<br>?<br>+                               | ?<br>-<br>?<br>?<br>?  | ? - ? ? ?   | <b>R</b><br>35<br>24<br>22<br>24<br>20<br>17  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120  | 51<br>52<br>52<br>52<br>54<br>54<br>55   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA  | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Gln   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35  | +<br>?<br>+<br>+<br>+<br>+<br>+<br>+  | +<br>? + + + +                                     | +<br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+     | ?<br>- ?<br>?<br>+ ?<br>-                           | ?<br>-<br>?<br>?<br>?  | ? - ? ? ? -   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48  | 51<br>52<br>52<br>52<br>54<br>54<br>55<br>55<br>55   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>03G  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG   | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C<br>C->T   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2282X<br>R2282W (1)  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35   | +<br><b>L</b><br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>?  | + <b>M</b> ? + + + + ?                             | + <b>N</b> ? + + + + ?                             | ?<br>- ?<br>?<br>+ ?<br>-                           | ?<br>-<br>?<br>?<br>?  | ? - ? ? ? -   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121   | 51<br>52<br>52<br>52<br>54<br>54<br>55<br>55<br>55   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>OGG<br>OGG  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG  | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>del<br>de-<br>C->C<br>T->C<br>C->T<br>C->T   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>O2262X<br>R2282W (1)<br>R2282W (2)  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35   | +<br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>?   | + <b>M</b> ? - + + + + + + + + + + + + + + + + + + | + N ? + + + + + + + + + + + + + + + + +            | ?<br>- ?<br>?<br>+ ?<br>-                           | ?<br>- ?<br>?<br>?<br>- ?  | ? - ? ? ? -   | <b>R</b><br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132  | 51<br>52<br>52<br>52<br>54<br>54<br>55<br>55<br>55<br>55   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>OGG<br>OGG<br>TGC  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG  | G<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C<br>C->T<br>C->T<br>C->T   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>O2262X<br>R2282W (1)<br>R2282W (2)  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Trp<br>Ser  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35   | +<br><b>L</b><br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+   | +<br>?<br>- + +<br>+ +<br>?<br>+ +                 | + N ? + + + + + + + + + + + + + + + + +            | ? - ? ? + ? - ?                                     | ?<br>?<br>?<br>?<br>?<br>?<br>+  | ? - ? ? ? - ?<br>? - ?  | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP4  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94   | 51<br>52<br>52<br>54<br>54<br>55<br>55<br>55<br>55<br>55<br>56   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307<br>2333   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>CAA<br>CAA<br>CAA<br>CAA<br>CAA<br>CAG<br>TGC<br>GAC   | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>TGG<br>TCC<br>del126b   | G<br>T->A<br>A->G<br>C>G<br>C>G<br>del<br>G>C<br>T->C<br>C->T<br>C->T<br>C->T<br>C->T<br>G->C  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Arg<br>Cys<br>Asp  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Trp<br>Ser  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35   | +<br><b>L</b><br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+   | + <b>M</b> ? - + + + + ? + + + + + + + + + + + + + | + N ? + + + + + + + + + + + + + + + + +            | ?<br>- ?<br>?<br>+ ?<br>- ?<br>- ?                  | ?<br>- ?<br>?<br>?<br>?<br>- +<br>?  | ? - ? ? ? - ? · ?<br>? - ?  | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP4<br>18  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94   | 51<br>52<br>52<br>54<br>54<br>55<br>55<br>55<br>55<br>55<br>56<br>57   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307<br>2333   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>CAA<br>CAA<br>CAA<br>CAA<br>CAG<br>GAC<br>GAT  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>TCC<br>del126b<br>del126b   | G<br>T→A<br>T→A<br>A→G<br>C→G<br>del<br>G→C<br>T→C<br>C→T<br>C→T<br>C→T<br>C→T<br>G→C<br>del   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Arg<br>Cys<br>Asp<br>Asp   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #36<br>cb EGF-like #36     | +<br><b>L</b><br><b>?</b><br><b>+</b><br><b>+</b><br><b>+</b><br><b>+</b><br><b>+</b><br><b>+</b><br><b>+</b><br><b>+</b> | + <b>M</b> ? - + + + + + + + + + + + + + + + + + + | + <b>N</b> ? + + + + + + + + + + + + + + + + + +   | ? - ? ? + ? - ? ? ?                                 | ?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>?<br>? | ;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;                     | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>NP4<br>18<br>41   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31   | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>55<br>55<br>55<br>57<br>58<br>59   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>CAA<br>CGG<br>CGG<br>GAC<br>GAC<br>GAC<br>GAG  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>TCC<br>del126b<br>del126b<br>AAG  | G<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>del<br>del<br>del<br>G->A  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K  | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Asp<br>Cys<br>Asp<br>Glu  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Frameshift<br>Lys  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37  | +<br><b>L</b><br>?<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+<br>+                                       | + <b>M</b> ? - + + + + + + + + + + + + + + + + + + | + <b>N</b> ? + + + + + + + + + + + + + + + + + +   | \$<br>- ? ; + ? - ? ; ? ;<br>\$                     | ?<br>- ?<br>?<br>?<br>?<br>- ?<br>?<br>?<br>?<br>?<br>?                                | ;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>; | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>NP4<br>18<br>41<br>41<br>27   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15   | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6772<br>6772<br>6784<br>6844<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339<br>7456  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>CGG<br>CGG<br>GAC<br>GAC<br>GAG<br>CTT  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>TCC<br>del126b<br>del126b<br>del126b<br>AAG<br>del366a  | G<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>del<br>del<br>del<br>del<br>del<br>del<br>del<br>de->A   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>O2262X<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Asp<br>Asp<br>Glu<br>Leu  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Frameshift<br>Frameshift<br>Lys<br>Frameshift   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #38<br>cb EGF-like #39   | + L ? + + + + + + + + + + + + + + + + +   | + ? - + + + + + + + + + + + + + + + + +            | + <b>N</b> ? + + + + + + + + + + + + + + + + + + + | \$<br>- ? ; + ? - ? ; ? ;<br>\$                     | ?<br>- ?<br>?<br>?<br>?<br>- ?<br>?<br>?<br>?<br>?<br>?                                | ;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>; | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>NP3<br>NP3<br>NP4<br>18<br>41<br>41<br>27<br>23   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122  | 51<br>52<br>52<br>52<br>54<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60   | C<br>6339<br>6381<br>6431<br>6453<br>6617<br>6662<br>6784<br>6844<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339<br>7456<br>7465  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2282<br>2282<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>02G<br>GAG<br>GAC<br>GAC<br>GAG<br>CTT<br>TGT   | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>TGG<br>TCC<br>del126b<br>del126b<br>AAG<br>del366a<br>CGT   | G<br>T→>A<br>T→>A<br>A→>G<br>C→SG<br>del<br>G→C<br>T→>C<br>C→T<br>C→T<br>C→T<br>C→T<br>C→T<br>C→T<br>del<br>del<br>del<br>del<br>T→>C  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366<br>C2489R  | Cys<br>I<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Lys<br>Frameshift<br>Arg  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #37<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39   | + <b>L</b> ? + + + + + + + + + + + + + + + + + +  | + <b>M</b> ? - + + + + + + + + + + + + + + + + + + | + <b>N</b> ? + + + + + + + + + + + + + + + + + + + | ? - ? ? + ? - ? ? ? ? ?                             | ? - ? ? ? - ? ? + ? ? +  | · · · · · · · · · · · · · · · · · · ·   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>NP3<br>18<br>41<br>41<br>27<br>23<br>NP3  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126   | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>60   | C<br>6339<br>6381<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339<br>7456<br>7465<br>7531  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489<br>2511   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>CGA<br>CAA<br>GAG<br>GAC<br>GAC<br>GAC<br>GAG<br>CTT<br>TGT<br>TGT  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CCGT<br>TAA<br>TGG<br>TGG<br>TCC<br>del126b<br>del126b<br>del366a<br>CGT<br>CGT   | G<br>T→>A<br>T→>A<br>A→>G<br>C→>G<br>del<br>G→>C<br>C→>T<br>C→>T<br>C→>T<br>C→T<br>C→T<br>C→T<br>del<br>del<br>del<br>T→>C<br>T→>C   | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C22258R<br>Q2262X<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366<br>C2489R<br>C2511R   | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Asp<br>Asp<br>Glu<br>Leu<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Frameshift<br>Arg<br>Arg  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #38<br>cb EGF-like #39<br>cb EGF-like #39  | + + L ? + + + + + + + + + + + + + + + +   | + <b>M</b> ? - + + + + + + + + + + + + + + + + + + | + N ? + + + + + + + + + + + + + + + + +            | \$<br>- ? ; + ? - ? ; ? ;<br>\$                     | ?<br>- ?<br>?<br>?<br>?<br>- ?<br>?<br>?<br>?<br>?<br>?                                | ;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>;<br>; | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>13<br>NP3<br>NP3<br>41<br>41<br>41<br>27<br>23<br>NP3<br>24  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>108  | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>60<br>63   | C<br>6339<br>6381<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339<br>7456<br>7465<br>7531<br>7868  | D<br>2113<br>2127<br>2144<br>2151<br>2206<br>2221<br>2258<br>2262<br>2282<br>2307<br>2333<br>2402<br>2446<br>2489<br>2511<br>2623   | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>GAG<br>GAC<br>GAC<br>GAC<br>TGC<br>GAC<br>TGT<br>TGT<br>TGT<br>CAC  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>CGT<br>TAA<br>TGG<br>TGG<br>CGT<br>TCC<br>del126b<br>del126b<br>AAG<br>del366a<br>CGT<br>CGT<br>CGT   | G           T ->A           T ->A           A ->G           C->G           del           G->C           C->T           C->T           C->T           G->C           del           del           del           T->C           T->C           T->C           T->C           T->C           T->C           T->C           A->C  | H<br>22127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C22258R<br>Q2262X<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366<br>C2489R<br>C2511R<br>H2623P   | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Glov<br>Cys<br>Glov<br>Cys<br>Asp<br>Glu<br>Leu<br>Cys<br>Cys<br>His  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Lys<br>Frameshift<br>Arg<br>Arg<br>Pro   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #38<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42  | + + L ? + + + + + + + + + + + + + + + +   | + 2 ? + + + + + + + + + + + + + + + + +            | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? ? ? ? ? - · ? - ? ? ? ? - · ? - ? - | ? - ? ? ? - + ? ? + ? +  |   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>41<br>41<br>41<br>27<br>23<br>NP3<br>24<br>37   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>108<br>32                                      | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>60<br>63<br>63   | C<br>6339<br>6381<br>6453<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6844<br>6849<br>20<br>6998<br>7205<br>7339<br>7456<br>7465<br>7531<br>7868<br>7879                                    | D<br>2113<br>2127<br>2144<br>2258<br>2262<br>2282<br>2282<br>2282<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489<br>2511<br>2623<br>2627   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>03G<br>03G<br>TGC<br>GAC<br>GAC<br>GAC<br>GAG<br>CTT<br>TGT<br>TGT<br>CAC<br>Q3G   | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>del126b<br>del126b<br>del126b<br>AAG<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>CCC<br>AGG   | G<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>G->C<br>del<br>del<br>del<br>G->A<br>del<br>G->A<br>del<br>G->A  | H           Y2113X           D2127E           N2144S           C2151W           6739 +1 G->C           C2258R           Q2262X           R2282W (1)           R2282W (2)           C2307S           6997 +1 G->A           7205 -2 A->G           E2447K           7456del366           C24511R           H2623P           G2627R  | Cys<br>Tyr<br>Asp<br>Asn<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Asp<br>Cys<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Trp<br>Trp<br>Trp<br>Frameshift<br>Frameshift<br>Frameshift<br>Arg<br>Pro<br>Arg   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #42   | + <b>L</b> ? + + + + + + + + + + + + + + + + + +  | + • • • • • • • • • • • • • • • • • • •            | + N ? + + + + + + + + + + + + + + + + +            | ? - ? ? + ? - ? ? ? ? ?                             | ? - ? ? ? - ? ? + ? ? +  | · · · · · · · · · · · · · · · · · · ·   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>18<br>41<br>41<br>41<br>27<br>23<br>NP3<br>24<br>37<br>28   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>31<br>15<br>122<br>126<br>108<br>32<br>59                                      | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>63<br>63<br>63<br>63   | C<br>6339<br>6381<br>6453<br>66453<br>66453<br>66453<br>6672<br>6784<br>6844<br>6844<br>6844<br>6844<br>6844<br>6844<br>6844   | D<br>2113<br>2127<br>2144<br>2258<br>2262<br>2282<br>2282<br>2282<br>2282<br>2282<br>2282   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>03G<br>03G<br>TGC<br>GAC<br>GAC<br>GAC<br>GAG<br>CTT<br>TGT<br>TGT<br>CAC<br>Q3G<br>C3C                                    | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TCC<br>del126b<br>del126b<br>del126b<br>AAG<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT  | G<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>T->C<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>del<br>del<br>G->A<br>del<br>T->C<br>A->C<br>A->C<br>A->C<br>A->C<br>A->C<br>C->T  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366<br>C2489R<br>C2511R<br>H2623P<br>G2627R<br>R2680C   | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Gln<br>Arg<br>Cys<br>Asp<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Cys<br>Gln<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Lys<br>Frameshift<br>Arg<br>Arg<br>Pro<br>Arg<br>Cys   | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #37<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #43   | + L ? + + + + + + + + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? ? ? ? ? - · ? - ? ? ? ? - · ? - ? - | ? - ? ? ? - + ? ? + ? +  |   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP4<br>18<br>41<br>41<br>27<br>23<br>NP3<br>24<br>37<br>28<br>37   |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>31<br>15<br>122<br>126<br>108<br>32<br>59<br>60                                | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>57<br>58<br>59<br>60<br>60<br>63<br>63<br>63<br>64                                     | C<br>6339<br>6431<br>6453<br>6617<br>6662<br>6772<br>6772<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7205<br>7465<br>7531<br>7456<br>7531<br>7868<br>98038<br>8052   | D<br>2113<br>2127<br>22144<br>2151<br>2256<br>2282<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2447<br>2448<br>2511<br>2623<br>2627<br>2680<br>2680  | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>GAG<br>GAC<br>GAC<br>CTT<br>TGT<br>TGT<br>TGT<br>CAC<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG        | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CCT<br>CGT<br>TAA<br>TGG<br>TCC<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGC<br>del175c  | G           T ->A           T ->A           A ->G           C>G           G ->C           T ->C           C>T           C->T           G->C           del           del           del           del           G->A           G->A           C->T           Stop at 2693  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R2282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456dol366<br>C2489R<br>C2511R<br>H2623P<br>G2627R<br>R2680C<br>8052 -2 A->G  | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Glu<br>Cys<br>Cys<br>Glu<br>Cys<br>Cys<br>Glu<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Arg<br>Arg<br>Arg<br>Cys<br>Frameshift  | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #43<br>cb EGF-like #43<br>cb EGF-like #43  | + L ? + + + + + + + + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? ? ? ? ? - · ? - ? ? ? ? - · ? - ? - | ? - ? ? ? - + ? ? + ? +  |   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>7<br>NP3<br>13<br>NP3<br>13<br>NP3<br>NP3<br>13<br>NP4<br>18<br>41<br>41<br>41<br>27<br>23<br>24<br>37<br>28<br>37<br>37             |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>108<br>32<br>59<br>60<br>61                    | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>60<br>63<br>63<br>63<br>64<br>64                         | C<br>6339<br>6431<br>6453<br>6642<br>6772<br>6784<br>6844<br>6844<br>6844<br>6920<br>6998<br>7205<br>7339<br>7456<br>7531<br>7868<br>7879<br>8038<br>8052  | D<br>2113<br>2127<br>2214<br>2256<br>2262<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489<br>2511<br>2623<br>2627<br>2680<br>2684<br>2680   | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>GAG<br>GAC<br>GAC<br>GAC<br>CTT<br>TGT<br>TGT<br>CAC<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG        | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>del126b<br>del126b<br>del126b<br>del126b<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGC<br>del175c<br>del175c  | G           T ->A           T ->A           A ->G           C->G           del           G->C           C->T           C->T           G->C           del           del           G->C           del           C->T           C->C           T->C           T->C           T->C           Stop at 2693           Stop at 2693   | H           Y2113X           D2127E           N2144S           C2151W           6739 +1 G->C           C22258R           Q2262X           R2282W (1)           R2282W (2)           C2307S           6997 +1 G->A           7205 -2 A->G           E2447K           7456dol366           C2499R           C2511R           H2623P           G2627R           R2680C           8052 -2 A->G           8052 +2 A->G           8051 +5 G->A                   | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Arg<br>Cys<br>Asp<br>Cys<br>Cys<br>Glu<br>Leus<br>Cys<br>Gly<br>Cys<br>Gly<br>Gly<br>Cys<br>Gly<br>Cys<br>Gly<br>Cys<br>Gly<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cy  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Arg<br>Arg<br>Arg<br>Cys<br>Frameshift<br>Frameshift<br>Frameshift                             | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #38<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #43<br>cb EGF-like #43<br>cb EGF-like #43<br>cb EGF-like #43  | + L ? + + + + + + + + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? ? ? ? ? - · ? - ? ? ? ? - · ? - ? - | ? - ? ? ? - ? + ? +  |   | R<br>3 35<br>2 4<br>2 2<br>2 4<br>2 0<br>1 7<br>NP3<br>1 3<br>NP3<br>NP3<br>NP4<br>1 8<br>4 1<br>4 1<br>2 7<br>2 3<br>NP4<br>3 7<br>2 8<br>3 7<br>2 8<br>3 7<br>3 7<br>3 7    |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>108<br>32<br>59<br>60<br>61<br>123             | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>63<br>63<br>63<br>64<br>64<br>64                         | C<br>6339<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6998<br>7205<br>7339<br>7456<br>7465<br>7465<br>7465<br>7465<br>7879<br>8038<br>8052<br>8052<br>8176                          | D<br>2113<br>2127<br>2144<br>2151<br>2208<br>2258<br>2282<br>2282<br>2307<br>2486<br>2489<br>2489<br>2489<br>2623<br>2623<br>2623<br>2623<br>2623<br>2624<br>2684<br>2726                                 | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>QGG<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>G  | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>del126b<br>del126b<br>del126b<br>del126b<br>CGT<br>CC<br>del126b<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>TGC<br>del175c<br>del175c<br>TGG  | G<br>T->A<br>T->A<br>A->G<br>C->G<br>del<br>G->C<br>C->T<br>C->T<br>C->T<br>C->T<br>C->T<br>G->C<br>del<br>del<br>del<br>G->A<br>del<br>C->C<br>C->T<br>C->T<br>Stop at 2693<br>C->T   | H           Y2113X           D2127E           N2144S           C2151W           6739 +1 G->C           C2221S           C2221S           C2262X           R2282W (2)           C2307S           6997 +1 G->A           7205 -2 A->G           E2447K           7456del366           C2511R           H2623P           G2627R           R2680C           8052 -2 A->G           8052 -2 A->G           8052 -5 A->G           8051 +5 G->A           R2726W | Cys<br>I<br>Tyr<br>Asp<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Arg<br>Cys<br>Arg<br>Cys<br>Asp<br>Cys<br>Cys<br>Glu<br>Leu<br>Cys<br>Gly<br>His<br>Gly<br>Gly<br>Arg<br>Gly<br>Arg<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys   | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Lys<br>Frameshift<br>Arg<br>Arg<br>Cys<br>Frameshift<br>Frameshift<br>Frameshift<br>Trp | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #43<br>cb EGF- | + L ? + + + + + + + + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? - ? ? ? ? ? +                       | ? - ? ? ? - ? + ? ? ? + ? + ?  | · · · · · · · · · · · · · · · · · · ·   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>13<br>NP3<br>13<br>NP3<br>41<br>41<br>41<br>27<br>23<br>NP3<br>24<br>43<br>7<br>28<br>37<br>37<br>37<br>37<br>30 |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>108<br>32<br>59<br>60<br>60<br>61<br>123<br>50 | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>55<br>56<br>57<br>58<br>59<br>60<br>60<br>60<br>63<br>63<br>64<br>64<br>64<br>64<br>65 | C<br>6339<br>6431<br>6453<br>6617<br>6662<br>6772<br>6772<br>6772<br>67784<br>6844<br>6844<br>6844<br>6920<br>6790<br>6792<br>7339<br>7456<br>7465<br>7465<br>7465<br>7465<br>8753<br>8052<br>8052<br>8176<br>8236 | D<br>2113<br>2127<br>2144<br>2151<br>2226<br>22282<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489<br>2511<br>2623<br>2623<br>2623<br>2624<br>2684<br>2684<br>2726<br>2684<br>2726        | E<br>TAT<br>GAT<br>AAT<br>TGC<br>GAT<br>TGT<br>CAA<br>CGG<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>GAC<br>CTT<br>TGT<br>TGT<br>CAC<br>CGG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG        | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TGG<br>del126b<br>del126b<br>del126b<br>AAG<br>del366a<br>CGT<br>CGT<br>CGT<br>CC<br>del175c<br>del175c<br>del175c<br>del175c<br>del12a  | G           T->A           T->A           A->G           C->G           del           G->C           C->T           C->T           C->T           G->C           del           del           G->A           del           G->A           del           G->A           Ge->A           Go->A           Stop at 2693           C->T           Stop at 2693           C->T           Stop at 2758 | H           Y2113X           D2127E           N2144S           C2151W           6739 +1 G->C           C2221S           C2258R           Q2262X           R2282W (1)           R2282W (2)           C2307S           6997 +1 G->A           7205 -2 A->G           E2447K           7456del366           C2451IR           H2623P           G2627R           R2880C           8051 +5 G->A           R2726W           8236delGA                            | Cys<br>I<br>Tyr<br>Asp<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys  | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Trp<br>Frameshift<br>Frameshift<br>Arg<br>Arg<br>Arg<br>Cys<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift                      | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #42<br>cb EGF-like #43<br>cb EGF- | + L ? + + + + + + ? + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + <b>N</b> ?++++++++++++++++++++++++++++++++++++   | ? - ? ? + ? - ? - ? ? ? ? ? + ?                     | ? - ? ? ? - ? - + ? ? ? + ? + ? +  | · · · · · · · · · · · · · · · · · · ·   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>NP3<br>NP4<br>18<br>41<br>41<br>27<br>23<br>NP3<br>24<br>37<br>37<br>37<br>37<br>37<br>30<br>13                  |
| 57<br>23<br>14<br>24<br>11<br>7<br>120<br>48<br>121<br>132<br>5<br>94<br>95<br>31<br>15<br>122<br>126<br>32<br>59<br>60<br>61<br>123<br>50<br>60<br>16  | 51<br>52<br>52<br>52<br>54<br>55<br>55<br>55<br>55<br>55<br>55<br>57<br>58<br>59<br>60<br>60<br>60<br>63<br>63<br>64<br>64<br>64<br>65<br>65             | C<br>6339<br>6431<br>6453<br>6617<br>6662<br>6772<br>6784<br>6844<br>6844<br>6844<br>6998<br>7205<br>7339<br>7456<br>7465<br>7465<br>7465<br>7465<br>7879<br>8038<br>8052<br>8052<br>8176                          | D<br>2113<br>2127<br>2144<br>2151<br>2226<br>2282<br>2282<br>2282<br>2307<br>2333<br>2402<br>2447<br>2486<br>2489<br>2511<br>2623<br>2627<br>2680<br>2684<br>2684<br>2684<br>2726<br>2746<br>2746<br>2746 | E<br>TAT<br>GAT<br>TGC<br>GAT<br>TGT<br>TGT<br>CAA<br>CGA<br>GAC<br>GAC<br>GAC<br>GAC<br>CTT<br>TGT<br>TGT<br>TGT<br>CAC<br>GGG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG<br>GAG | F<br>TAA<br>GAA<br>AGT<br>TGG<br>del123b<br>TCT<br>CGT<br>TAA<br>TGG<br>TCC<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del126b<br>del366a<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT<br>CGT | G           T->A           T->A           A->G           C>>G           del           G->C           C->T           C->T           G->C           del           del           G->C           del           del           del           G->A           G->A           C->T           Stop at 2693           Stop at 2693           Stop at 2758           G->A                                  | H<br>Y2113X<br>D2127E<br>N2144S<br>C2151W<br>6739 +1 G->C<br>C2221S<br>C2258R<br>Q2262X<br>R2282W (1)<br>R282W (2)<br>C2307S<br>6997 +1 G->A<br>7205 -2 A->G<br>E2447K<br>7456del366<br>C2489R<br>C2511R<br>H2623P<br>G2627R<br>R2680C<br>8052 -2 A->G<br>8051 +5 G->A<br>R2726W<br>8286delGA<br>W2756X  | Cys<br>I<br>Tyr<br>Asp<br>Cys<br>Asp<br>Cys<br>Cys<br>Gln<br>Arg<br>Cys<br>Cys<br>Gln<br>Cys<br>Arg<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Gln<br>Cys<br>Cys<br>Gln<br>Cys<br>Cys<br>Gln<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys<br>Cys | Tyr<br>J<br>Stop<br>Glu<br>Ser<br>Trp<br>Frameshift<br>Ser<br>Arg<br>Stop<br>Trp<br>Ser<br>Frameshift<br>Frameshift<br>Arg<br>Arg<br>Cys<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift<br>Frameshift<br>Stop       | 8-Cys #6<br>K<br>8-Cys #6<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #32<br>cb EGF-like #34<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #35<br>cb EGF-like #36<br>8-Cys #7<br>cb EGF-like #37<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #39<br>cb EGF-like #42<br>cb EGF-like #43<br>cb EGF- | + L ? + + + + + + + + + + + + + + + + +   | + M? + + + + ? + + + + + + + + + + + +             | + N?+++++++++++++++++++++++++++++++++++            | ? - ? ? + ? - ? - ? ? ? ? ? +                       | ? - ? ? ? - ? + ? ? ? + ? + ?  | · · · · · · · · · · · · · · · · · · ·   | R<br>35<br>24<br>22<br>24<br>20<br>17<br>NP3<br>13<br>NP3<br>13<br>NP3<br>13<br>NP3<br>41<br>41<br>27<br>23<br>NP3<br>24<br>37<br>28<br>37<br>37<br>37<br>30                  |

The columns contain the following information and abbreviations:

A: Report number.

**B**: Exon number at which the mutation is located.

C: Nucleotide position at which the mutation is located, numbered with respect to the FBN1 gene cDNA sequence obtained from GenBank (GenBank accession number L13923; complete coding sequence of HUM-FIBRILLIN *Homo sapiens* fibrillin mRNA).

**D**: Codon number at which the mutation is located.

**E**: Normal base sequence of the codon in which the mutation occured.

**F**: Mutated base sequence of the codon in which the mutation occured.

G: Concerns base substitutions. It gives the base change, by convention, read from the coding strand. If the mutation predicts a premature protein-termination, the novel stop codon position is given, e.g. Stop at 2115.

H: Mutation name according to Beaudet et al. (51).

I: Wild type amino acid.

J: Mutant amino acid. Deletion and insertion mutations which result in a frameshift are designated by Frameshift. Nonsense mutations are designated by Stop.

K: Protein domain in which the mutation occured. Each module group is numbered separately and according to the position of the module with respect to the N-terminal end of the protein, e.g. cb EGF-like (for calcium-binding EGF-like modules) #1-43, EGF-like (for non calcium-binding EGF-like modules) #1-4, 8-cys (for 8-cysteine modules) #1-7, Hybrid modules #1-2 (6–8). L–Q: Diagnostic manifestations in the systems entered with respect to the nosology proposals of Beighton *et al.* (52) recently revised by de Paepe *et al.* (53). In all these columns, '?' indicates either lack of or unspecified data until more precise information is available. L: Presence (+) or absence (–) of skeletal manifestations.

M: Presence (+) or absence (-) of ocular manifestations.

N: Presence (+) or absence (-) of cardiovascular manifestations.

O: Presence (+) or absence (-) of pulmonary manifestations.

P: Presence (+) or absence (-) of manifestations in skin and integument.

Q: Presence (+) or absence (-) of manifestations in central nervous system.

**R**: Reference number indicating the publication in which the mutation is described. NP indicates unpublished mutations contributed by NP1 (Lesley Ades and Katherine J. Holman), NP2 (M. Boxer and C. Black), NP3 (Caroline Hayward and David J. H. Brock), NP4 (Anne de Paepe and Lieve Nuytinck), NP5 (Uta Francke and Wanguo Liu), NP6 (Ulrich Grau and Hanns-

Georg Klein), NP7 (Ana Beatriz Alvarez Perez) (54) and NP8 (Leena Peltonen and Terhi Rantamäki).

### THE MARFAN DATABASE

The mutations file of the database lists point mutations, deletions or insertions, and splice mutations in the FBN1 gene (Table 1). It contains in a standarized, easily accessible and summary form the molecular and the clinical data on the causative mutations of Marfan syndrome and type 1 fibrillinopathies. For each mutation, information is provided at several levels: at the gene level (exon and codon number, wild type and mutant codon, mutational event, mutation name), at the protein level (wild type and mutant amino acid, affected domain) and at the clinical level (absence or presence of skeletal, ocular, cardiovascular, central nervous system and other various manifestations). The present version of the database contains 137 entries corresponding to mutations either recently published or only reported in meeting proceedings or contributed by the co-authors of this paper. It is not intented to replace primary publications, although it does contain unpublished data. Forty eight new entries appear, as compared to the last update.

# ANALYSIS AND LIMIT OF THE DATABASE

The global molecular analysis of the mutations file reveals that nonsense mutations (7/137), splicing errors (18/137) and small deletions (12/137) predicted to result in truncated fibrillin-1 molecules have been identified but represent a small proportion of the mutations. Insertions are surprisingly under-represented (2/137). The majority of mutations identified are missense mutations (99/137 or 72.3%) affecting primarily (73/99) the numerous calcium binding (EGF)-like modules found throughout the protein. The fibrillin gene has been identified and sequenced in two mammalian species. The identity at the amino acid level is so high (97.8% human-mouse and 96.2% human-bovine) that very often phylogenic conservation should be observed at the amino acid position affected by a given missense mutation. In effect, in all the mutations thus far reported in the FBN1 gene, the mutational event affects a conserved amino acid with respect to the mouse and bovine sequences. It is interesting to note that the only exception is the Y2113X mutation (which affects a non-conserved amino acid) leads to a truncated protein. The mutations file contains 11 recurrent mutations that have been reported either twice (R122C, R545C, R627C, C1117Y, R1137P, R1170H, C1223Y and R2282W) or thrice (G1013R, E1073K and 5788+5G $\rightarrow$ A). Until haplotype analysis is available it is unclear whether these are truly recurrent mutations or if they are carried by the same chromosome.

There is an excess of mutations in exons 25, 27 and 28 (P < 0.001) when comparing observed to expected mutations. This clustering is explained by the fact that almost all the mutations identified in neonatal cases of MFS1 are located within this area.

Since the present version of the software cannot accomodate two mutational events in a given individual, three mutations are not included in the current version of the mutations file: the double mutant Splice exon 51 and X2113X reported by Dietz *et al.* (12), the compound deletion del3901-4; 3908-9 reported by Nijbroek *et al.* (13), and the double mutant I1071S and E1073D reported by Wang *et al.* (14). Three other mutations are not included in the Marfan database [1588+21G $\rightarrow$ A (15), 2294–1G $\rightarrow$ C and 1837+5G $\rightarrow$ A (NP1)] until more precise information is available on mRNA splicing or stability. All things considered, 143 mutations have been described to date in the FBN1 gene.

# NEW WEB VERSION OF THE SOFTWARE AND ITS NEWLY DEVELOPED ROUTINES

Four new routines now appear in the Marfan database as follows. (i) Amino acid changes: lists for each of the 20 amino acids the observed substitutions throughout the protein. (ii) Base modification: lists the observed mutations with respect to their position within the codon for each of the four bases. (iii) CpG: studies the distribution of mutations occuring at CpG sites throughout the coding sequence. The result is displayed in a graphic representation. (iv) Distribution of mutation: lists the proportion of each of the mutational events observed in a selected group of mutation records.

The software is now accessible through the World Wide Web and analyses with the various routines can be performed by users on-line. The investigation of genotype/phenotype correlations with these tools is currently difficult since clinical data is often sparse in mutation records. To facilitate the input of high quality clinical data, we are currently developing a Mutation Report Entry in the web site.

#### DATABASE UPDATE, SOFTWARE AVAILABILITY AND ONLINE ANALYSIS

The current database and subsequent updated versions are available on request to G.C-B. or C.Boileau on floppy disc using Apple format and Microsoft Excel®, or by Email (collod@ ceylan.necker.fr). Notification of omissions and errors in the current version as well as specific phenotypic data would be gratefully received by the corresponding author. The software package is available on a collaborative basis. The software will be expanded as the database grows and according to the requirements of its users. New functions could be implemented. New web version of the Marfan Database permitting on-line analysis is accessible at http://www.umd.necker.fr . Users of the database must cite this article.

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