NGS CF Control Panel G211 v1.1 Package Insert

BACKGROUND:

Cystic fibrosis (CF) is the most common inherited disease in the United States today. CF is an autosomal recessive disorder, caused by the presence of mutations in both copies of the gene for the protein, cystic fibrosis transmembrane conductance regulator (CFTR). CF has a disease occurrence of approximately one out of 2,000 – 4,000 live births[1]. Although CF does not affect all people the same way, it is generally recognized as causing persistent lung infections. CF also affects other organs, including the pancreas, liver, kidneys and intestine. It is characterized by the buildup of thick, sticky mucus in the lungs, pancreas and other organs, resulting in a complex multi-organ, multisystem disease[1]. There is no cure for CF but some therapies may prolong life, therefore, a key focus of current interventional efforts is early diagnosis through newborn screening[2].

CFTR protein is involved in production of sweat, digestive fluids and mucus. The gene was first identified in 1989 on human chromosome 7 and contains 27 coding exons[3,4]. When CFTR is not functional, these secretions which are usually thin and watery instead become thick and mucus-like and ultimately lead to nutritional decline and progression of lung disease associated with morbidity and mortality[1]. Over 2,000 variants have been reported in the CFTR coding and flanking sequence, in all ethnic and racial populations at various frequencies. However, less than 10% of these reported variants have been interpreted to be clinically-relevant variants. The 188 CFTR variants listed in Table 1 are contained in the 6 tubes of **NGS CF Control Panel G211 v1.1.** The 143 asterisked (*) variants have been identified as CF-causing by The Clinical and Functional Translation of CFTR (CFTR2) international project and are listed in the CFTR2 database at http://cftr2.org (August 13, 2015 version)[5,6]. Included in Table 1 are the 23 mutations recommended in 2004 by the American College of Medical Genetic (ACMG) and in 2011 by the American College of Obstetricians and Gynecologists (ACOG)[7,8,9]. These mutations have been bolded and asterisked in Table 1. Legacy nomenclature is used throughout this Package Insert.

INTENDED USE:

The **NGS CF Control Panel G211 v1.1** is intended for *in vitro* use as a quality control to monitor the analytical performance of library preparation, sequencing and data analysis associated with Next Generation Sequencing for identifying variants within the CFTR gene. Additionally, because the **NGS CF Control Panel G211 v1.1** carries multiple insertions, deletions and homopolymers of varying lengths and composition, this control panel can also serve as a method control to monitor the ability of any NGS test system to correctly identify these types of variants. Appropriate primers are required to amplify the areas of interest.

NGS CF Control Panel G211 v1.1 is provided for Research Use Only (RUO). It cannot be cloned, sold, or transferred without the explicit written consent of MMQCI.

PRODUCT SUMMARY AND PRINCIPLE:

Next Generation Sequencing (NGS) technology, also known as massively parallel sequencing, involves sequencing of spatially separated, clonally amplified DNA templates to generate simultaneous sequencing of thousands to millions of relatively short nucleic acid sequences in parallel. This technology allows for targeted, sequencing of the CFTR gene and includes a complex multistep procedure for library preparation, target enrichment and sequencing analysis.

NGS CF Control Panel G211 v1.1 is designed as a multiplex reference material to monitor the simultaneous detection of the CFTR mutations and variants associated with cystic fibrosis listed in Table 1, including the 23 mutations recommended by ACMG and ACOG. The **NGS CF Control Panel G211 v1.1** product is intended to be analyzed routinely with each cystic fibrosis test run and provide a quality control for all aspects of library preparation, sequencing, and data analysis.

Controls should be tested routinely as a matter of Good Laboratory Practice and according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations. Best practice is to establish a quality control program for every assay performed by the laboratory. Routine use of quality controls that are consistent lot to lot assists the laboratory in identifying shifts, trends, and increased frequency of random errors caused by variations in the test system. Early investigation can prevent failed assay runs.

COMPOSITION:

NGS CF Control Panel G211 v1.1 consists of synthetic CFTR DNA suspended in a non-infectious buffer with stabilizers. The synthetic DNA is composed of all 27 CFTR gene exons plus intronic borders, and contains CF associated mutations and variants divided among 6 tubes (G211Av1.1, G211Bv1.1, G211Cv1.1, G211Dv1.1, G211Ev1.1 and G211Fv1.1). The mutations and variants present in **NGS CF Control Panel G211 v1.1** are described in Table 1. This control panel is provided as a non-extractable control with copy numbers of target sequence that are similar to that of extracted human whole blood samples.

INSTRUCTIONS FOR USE:

Controls are ready to use; no extraction is needed.

1. Thaw all controls completely.
2. Allow the controls to be tested to come to room temperature (18° – 25°C).
3. Mix well by flicking the control tubes and vortex immediately before using.
4. Quick spin to remove droplets from the tube cap before opening.
5. Pipette the same volume (usually 5-10µL) pipetted for patient sample DNA for each control tube, and treat just as you would extracted genomic DNA.
6. Follow all other procedures as described by test manufacturer's product insert.
7. Opened material should be tightly capped and returned to freezer (≤ -20°C) immediately after use.

Note: NGS CF Control Panel G211 v1.1 cannot be quantified or measured by standard methods such as spectrophotometry (A260nm/A280nm) because synthetic DNA has significantly less mass than genomic DNA. However, the controls are manufactured to have approximately equivalent copy numbers of the target gene as genomic DNA. Please contact MMQCI if guidance on volume to add to assay is desired.

STORAGE and STABILITY:

Upon receipt and after opening, the material should be stored at ≤ -20°C. Unopened **NGS CF Control Panel G211 v1.1** is stable through the expiration date printed on each tube when stored frozen (≤ -20°C). Opened material should be tightly capped and returned to the freezer (≤ -20°C) immediately after use. The material is stable for five freeze/thaw cycles.

PRECAUTIONS and WARNINGS:

- Do not dilute.
- Do not transfer control material to a new tube.
- Do not quantify by spectrophotometry or other standard methods.
- Do not freeze/thaw more than 5 times.
- This product does not contain any biological material of human origin and is not infectious. Universal Precautions are not required when handling this product.

EXPECTED VALUES:

The genotype for each CFTR variant found in tubes A-F of **NGS CF Control Panel G211 v1.1** is listed in Table 1. The sequence of **NGS CF Control Panel G211 v1.1** has been confirmed by bi-directional Sanger sequencing. In order for an NGS assay to detect all genotypes listed, the NGS assay primers must have sufficient control sequence on either side of the variant to anneal and amplify the area of interest. If unexpected calls are reported, or variants not detected, your laboratory's NGS primers may require sequence not present in **NGS CF Control Panel G211 v1.1**, or they may anneal poorly due to the presence of a mutation. Please contact MMQCI for interpretation assistance as needed.

The laboratory should follow Good Laboratory Practice (GLP) and establish its own performance characteristics for **NGS CF Control Panel G211 v1.1** in demonstrating adequate system performance.

ORDERING INFORMATION:

NGS CF Control Panel G211 v1.1
Part Number: G211v1.1
Kit Contains: 6 tubes x 50 µL
Order and Customer Support: Email: info@mmqci.com, Phone: 207-885-1072 ext1

Maine Molecular Quality Controls, Inc.
23 Mill Brook Road
Saco, ME 04072 USA
Phone: 207-885-1072, FAX: 207-885-1079, Web: www.mmqci.com

References:

1. Moskowitz SM, Chmiel JF, Sternan DL, Cheng E, Gibson RL et al. Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders. Genet Med. 2008;10:851–868
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7. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. [published errata appear in Genet Med 2005;7:286; Genet Med 2004;6:548]. Genet Med 2004;6:387-91
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9. Bobadilla JL, Macek M, Fine JP, and Farrell PM. Cystic fibrosis: A worldwide analysis of CFTR mutations correlation with incidence data and application to screening. Human Mutation 2002;19(6):575-606

Table 1. NGS CF Control Panel G211 v1.1. Variants are listed in genomic coordinate order. **Bold** = ACMG recommended panel of 23 variants. Asterisk* = clinically relevant CFTR2 variants.

CFTR Mutation Legacy Name	cDNA Name (HGVS)	Tube A	Tube B	Tube C	Tube D	Tube E	Tube F
1. M1V	c.1A>G	WT	WT	WT	WT	WT	HET
2. R31C	c.91C>T	WT	WT	HET	WT	WT	WT
3. CFTRdele2,3	c.54-5940_273+10250 del21kb	HET	WT	WT	WT	WT	WT
4. Q39X*	c.115C>T	WT	WT	WT	WT	WT	HET
5. 296+2T>A	c.164+2T>A	WT	WT	WT	WT	HET	WT
6. E60X*	c.178G>T	WT	HET	WT	WT	WT	WT
7. P67L*	c.200C>T	WT	WT	WT	WT	HET	WT
8. R74W	c.220C>T	WT	WT	WT	WT	WT	HET
9. R75X*	c.223C>T	WT	WT	WT	HET	WT	WT
10. **G85E***	c.254G>A	WT	HET	WT	WT	WT	WT
11. 394delTT*	c.262_263delTT	WT	WT	HET	WT	WT	WT
12. 405+1 G>A*	c.273+1G>A	WT	WT	WT	WT	HET	WT
13. 405+3A>C*	c.273+3A>C	WT	WT	WT	HET	WT	WT
14. 406-1 G>A*	c.274-1G>A	WT	WT	WT	HET	WT	WT
15. E92K*	c.274G>A	WT	WT	WT	WT	WT	HET
16. E92XG>T*	c.274G>T	WT	WT	WT	WT	HET	WT
17. Q98X*	c.292C>T	WT	WT	HET	WT	WT	WT
18. 444delA*	c.313delA	WT	WT	WT	HET	WT	WT
19. 457TAT>G*	c.325_327delTATinsG	WT	WT	WT	WT	HET	WT
20. D110H*	c.328G>C	WT	WT	WT	WT	WT	HET
21. R117C*	c.349C>T	WT	WT	WT	HET	WT	WT
22. **R117H**	c.350G>A	WT	WT	HET	WT	WT	WT
23. Y122X*	c.366T>A	HET	WT	WT	WT	WT	WT
24. 574delA*	c.442delA	WT	WT	WT	WT	HET	WT
25. I148T	c.443T>C	WT	HET	WT	WT	WT	WT
26. **621+1 G>T***	c.489+1G>T	WT	HET	WT	WT	WT	HET
27. 663delT*	c.531delT	WT	WT	WT	WT	HET	WT
28. G178R*	c.532G>A	WT	WT	WT	HET	WT	WT
29. **711+1 G>T***	c.579+1G>T	WT	HET	WT	WT	WT	WT
30. 711+3 A>G*	c.579+3A>G	WT	WT	WT	WT	WT	HET
31. 711+5 G>A*	c.579+5G>A	WT	WT	HET	WT	WT	WT
32. 712-1 G>T*	c.580-1G>T	WT	WT	WT	WT	HET	WT
33. H199Y	c.595C>T	WT	HET	WT	WT	WT	WT
34. P205S C>T*	c.613C>T	WT	WT	HET	WT	WT	WT
35. L206W*	c.617T>G	WT	WT	WT	HET	WT	WT
36. Q220X*	c.658C>T	WT	WT	WT	WT	WT	HET
37. L227R*	c.680T>G	WT	WT	HET	WT	WT	WT
38. 852del22*	c.720_741 delAGGGAGAATGATGA TGAAGTAC	WT	WT	HET	WT	WT	WT
39. 935delA*	c.803delA	WT	WT	WT	HET	WT	WT
40. 936delTA	c.805_806 delAT	WT	WT	WT	HET	HET	WT
41. delF311	c.933_935 delCTT	WT	WT	WT	HET	WT	WT
42. 1078delT*	c.948delT	WT	HET	WT	WT	WT	WT
43. G330X*	c.988G>T	WT	WT	WT	HET	WT	WT
44. **R334W***	c.1000C>T	WT	HET	WT	WT	WT	WT
45. I336K*	c.1007T>A	WT	WT	WT	WT	WT	HET
46. T338IC>T*	c.1013C>T	WT	WT	WT	WT	HET	WT
47. S341P*	c.1021T>C	WT	WT	HET	WT	WT	WT
48. 1154insTC*	c.1022_1023 insTC	HET	WT	WT	WT	WT	WT
49. R347H*	c.1040G>A	WT	WT	HET	WT	WT	WT
50. **R347P***	c.1040G>C	WT	HET	WT	WT	WT	WT
51. R352Q*	c.1055G>A	WT	WT	WT	HET	WT	WT
52. 1213delT*	c.1081delT	WT	WT	WT	WT	WT	HET
53. S364P	c.1090T>C	WT	WT	WT	HET	WT	WT
54. 1248+1G>A*	c.1116+1G>A	HET	WT	WT	WT	WT	WT
55. 1259insA*	c.1127_1128 insA	WT	WT	WT	WT	WT	HET
56. 1288insTA*	c.1153_1154 insAT	WT	WT	WT	WT	HET	WT
57. W401X (TAG)*	c.1202G>A	HET	WT	WT	WT	WT	WT
58. W401X (TGA)*	c.1203G>A	WT	WT	WT	HET	WT	WT
59. 1341+1G>A*	c.1209+1G>A	WT	WT	HET	WT	WT	WT
60. PolyT	PolyT	7T/7T	9T/9T	7T/5T	5T/9T	9T	9T/9T
61. 1461ins4*	c.1329_1330 insAGAT	WT	WT	WT	WT	WT	HET
62. **A455E***	c.1364C>A	WT	HET	WT	WT	WT	WT
63. 1525-1G>A*	c.1393-1G>A	WT	WT	WT	WT	WT	HET
64. S466X (C>A)	c.1397C>A	WT	WT	WT	WT	HET	WT
65. S466X (C>G)*	c.1397C>G	HET	WT	WT	WT	WT	WT
66. L467P*	c.1400T>C	WT	WT	HET	WT	WT	WT
67. M470V	c.1408G>A	HET	HOM	HET	HOM	HOM	HET
68. 1548delG*	c.1418delG	WT	WT	WT	HET	WT	WT
69. G480C	c.1438G>T	WT	WT	WT	HET	WT	WT
70. S489X*	c.1466C>A	WT	WT	HET	WT	WT	WT
71. S492F*	c.1475C>T	HET	WT	WT	WT	WT	WT
72. Q493X*	c.1477C>T	HET	WT	WT	WT	WT	WT
73. I506V	c.1516A>G	WT	WT	HET	WT	WT	WT
74. I506T (T>C)	c.1517T>C	WT	WT	WT	WT	HET	WT
75. I507V	c.1519A>G	HET	WT	WT	WT	WT	WT
76. **I507del***	c.1519_1521delATC	WT	WT	HET	HET	WT	WT
77. **F508del***	c.1521_1523delCTT	WT	HET	WT	WT	WT	WT
78. F508C	c.1523T>G	HET	WT	WT	WT	WT	WT
79. 1677delTA*	c.1545_1546delTA	WT	WT	HET	HET	WT	WT
80. V520F*	c.1558G>T	WT	HET	WT	WT	WT	WT
81. Q525X*	c.1573C>T	WT	WT	WT	WT	WT	HET
82. **1717-1G>A***	c.1585-1G>A	WT	HET	WT	WT	WT	WT
83. 1717-8G>A*	c.1585-8G>A	WT	WT	WT	WT	WT	HET
84. **G542X***	c.1624G>T	WT	HET	WT	WT	WT	WT
85. S549R*	c.1645A>C	WT	WT	HET	WT	WT	WT
86. S549R*	c.1647T>G	HET	WT	WT	WT	WT	WT
87. S549N*	c.1646G>A	WT	WT	WT	HET	WT	WT
88. **G551D***	c.1652G>A	WT	HET	WT	WT	WT	WT
89. Q552XC>T*	c.1654C>T	WT	WT	WT	WT	HET	WT
90. **R553X***	c.1657C>T	WT	WT	HET	WT	WT	WT
91. L558S	c.1673T>C	WT	WT	WT	WT	WT	HET
92. A559T*	c.1675G>A	HET	WT	WT	WT	WT	WT
93. **R560T***	c.1679G>C	WT	HET	WT	WT	WT	WT
94. R560K*	c.1679G>A	WT	WT	WT	HET	WT	WT
95. 1811+1.6 kb	c.1679+1.6kbA>G	WT	WT	WT	WT	WT	HET

CFTR Mutation Legacy Name	cDNA Name (HGVS)	Tube A	Tube B	Tube C	Tube D	Tube E	Tube F
96. 1812-1 G>A*	c.1680-1G>A	WT	WT	WT	HET	WT	WT
97. Y569D*	c.1705T>G	WT	WT	WT	WT	WT	HET
98. G576A	c.1727G>C	WT	WT	WT	HET	WT	WT
99. D579G	c.1736A>G	WT	WT	WT	WT	HET	WT
100. E585X*	c.1753G>T	WT	WT	HET	WT	WT	WT
101. **1898+1 G>A***	c.1766+1G>A	WT	HET	WT	WT	WT	WT
102. 1898+3 A>G*	c.1766+3A>G	WT	WT	WT	WT	HET	WT
103. 1898+5G>T	c.1766+5G>T	HET	WT	WT	WT	WT	WT
104. 1949del84	c.1820_1903del84	HET	WT	WT	WT	WT	WT
105. D614G*	c.1841A>G	WT	WT	WT	WT	WT	HET
106. G622D	c.1865G>A	WT	WT	WT	HET	WT	WT
107. 2055del9>A*	c.1923_1931del9insA	WT	WT	WT	HET	WT	WT
108. 2108delA	c.1976delA	WT	WT	WT	WT	HET	WT
109. R668C	c.2002C>T	WT	WT	WT	WT	WT	HET
110. 2143delT*	c.2012delT	WT	HET	WT	WT	WT	WT
111. 2183AA>G*	c.2051_2052delAAinsG	WT	WT	HET	WT	WT	WT
112. 2184insA*	c.2052_2053insA	WT	WT	WT	WT	HET	WT
113. **2184delA***	c.2052delA	WT	HET	WT	WT	WT	WT
114. R709XC>T*	c.2125C>T	WT	WT	WT	WT	HET	WT
115. K710X*	c.2128A>T	WT	WT	WT	HET	WT	WT
116. 2307insA*	c.2175_2176insA	HET	WT	WT	WT	WT	WT
117. L732X*	c.2195T>G	WT	WT	WT	WT	WT	HET
118. 2347delG*	c.2215delG	WT	WT	WT	HET	WT	WT
119. V754M	c.2260G>A	WT	WT	WT	WT	WT	HET
120. R764XC>T*	c.2290C>T	WT	WT	WT	WT	HET	WT
121. 2585delT*	c.2453delT	WT	WT	WT	WT	WT	HET
122. E822X*	c.2464G>T	WT	WT	WT	HET	WT	WT
123. 2622+1G>A*	c.2490+1G>A	WT	HET	WT	WT	WT	WT
124. E831X*	c.2491G>T	WT	WT	WT	WT	WT	HET
125. W846X*	c.2537G>A	HET	WT	WT	WT	WT	WT
126. W846X(2670)	c.2538G>A	WT	HET	WT	WT	WT	WT
127. R851X*	c.2551C>T	WT	WT	WT	WT	WT	HET
128. 2711delT*	c.2583delT	WT	WT	WT	HET	WT	WT
129. 2789+2insA	c.2657+2_2657+3insA	WT	WT	WT	WT	WT	HET
130. **2789+5G>A***	c.2657+5G>A	WT	HET	WT	WT	WT	WT
131. Q890X*	c.2668C>T	WT	WT	WT	HET	WT	HET
132. 2869insG*	c.2737_2738insG	WT	WT	WT	HET	WT	WT
133. L927P*	c.2780T>C	WT	WT	WT	WT	WT	HET
134. S945L*	c.2834C>T	WT	WT	WT	WT	WT	HET
135. 3007delG*	c.2875delG	WT	HET	WT	WT	WT	WT
136. G970R*	c.2908G>C	WT	WT	WT	WT	WT	HET
137. S977F	c.2930C>T	WT	WT	WT	WT	WT	HET
138. 3120G>A*	c.2988G>A	WT	WT	WT	HET	WT	WT
139. **3120+1G>A***	c.2988+1G>A	WT	HET	WT	WT	WT	WT
140. 3121-1G>A*	c.2989-1G>A	WT	WT	WT	WT	WT	HET
141. L997F (G>C)	c.2991G>C	WT	WT	WT	WT	HET	WT
142. 3171delC*	c.3039delC	WT	WT	WT	WT	HET	WT
143. 3199del6	c.3067_3072delATAGTG	WT	HET	WT	WT	WT	WT
144. I1027T	c.3080T>C	WT	WT	WT	WT	WT	HET
145. 3272-26A>G*	c.3140-26A>G	WT	WT	HET	WT	WT	WT
146. F1052V	c.3154T>G	WT	WT	WT	WT	WT	HET
147. L1065P*	c.3194T>C	WT	WT	WT	WT	HET	WT
148. R1066C*	c.3196C>T	WT	WT	WT	HET	WT	WT
149. R1066H*	c.3197G>A	WT	WT	HET	WT	WT	WT
150. G1069R	c.3205G>A	WT	WT	WT	WT	WT	HET
151. R1070W	c.3208C>T	WT	HET	WT	WT	WT	WT
152. R1070Q	c.3209G>A	HET	WT	WT	WT	WT	WT
153. L1077P*	c.3230T>C	WT	HET	WT	WT	HET	WT
154. W1089X*	c.3266G>A	WT	WT	WT	HET	WT	WT
155. Y1092X (C>A)*	c.3276C>A	HET	WT	WT	WT	WT	WT
156. Y1092X (C>G)*	c.3276C>G	WT	WT	HET	WT	WT	WT
157. M1101K*	c.3302T>A	HET	WT	WT	WT	WT	WT
158. E1104X*	c.3310G>T	WT	WT	WT	WT	WT	HET
159. D1152H	c.3454G>C	WT	HET	WT	WT	WT	WT
160. R1158X*	c.3472C>T	WT	WT	WT	HET	WT	WT
161. **R1162X***	c.3484C>T	WT	HET	WT	WT	WT	WT
162. R1162L	c.3485G>T	WT	WT	WT	WT	WT	HET
163. **3659delC***	c.3528delC	WT	HET	WT	WT	WT	WT
164. 3667del4	c.3535_3538delACCA	WT	WT	WT	WT	HET	WT
165. S1196X*	c.3587C>G	WT	WT	WT	HET	WT	WT
166. W1204X (3743G>A)*	c.3611G>A	WT	WT	WT	WT	HET	WT
167. W1204X (3744G>A)*	c.3612G>A	WT	WT	WT	WT	WT	HET
168. 3791delC	c.3659delC	WT	WT	WT	HET	WT	WT
169. I1234V*	c.3700A>G	WT	WT	WT	WT	WT	HET
170. S1235R	c.3705T>G	WT	HET	WT	WT	WT	WT
171. Q1238XC>T	c.3712C>T	WT	WT	WT	WT	HET	WT
172. **3849+10kb C>T***	c.3717+12191C>T	WT	HET	WT	WT	WT	WT
173. 3849+4A>G*	c.3717+4A>G	HET	WT	WT	WT	WT	WT
174. G1244E*	c.3731G>A	WT	WT	WT	WT	HET	HET
175. 3876delA*	c.3744delA	WT	HET	WT	WT	WT	WT
176. S1251N*	c.3752G>A	HET	WT	WT	WT	HET	WT
177. S1255XA>G	c.3607A>G	WT	WT	HET	WT	WT	WT
178. S1255XC>A*	c.3764C>A	WT	WT	HET	WT	WT	WT
179. 3905insT*	c.3773_3774insT	WT	HET	WT	WT	WT	WT
180. D1270N	c.3808G>A	WT	WT	WT	HET	WT	WT
181. **W1282X***	c.3846G>A	WT	HET	WT	WT	WT	WT
182. 4005+1G>A*	c.3873+1G>A	WT	WT	WT	WT	WT	HET
183. 4016insT*	c.3884_3885insT	WT	WT	WT	WT	HET	WT
184. **N1303K***	c.3909C>G	WT	HET	WT	WT	WT	HET
185. Q1313X*	c.3937C>T	HET	WT	WT	WT	WT	WT
186. CFTRdel22,23*	c.3964-78_4242+577del	WT	WT	WT	WT	WT	HET
187. 4209TGTT>AA*	c.4077_4080delTGTT insAA	HET	WT	WT	WT	WT	WT
188. 4382delA*	c.4251delA	HET	WT	WT	WT	WT	WT