**The Validation of Pharmacogenetics for the Identification of Fabry Patients for Treatment with Migalastat**

**Supplementary Information**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Benjamin et al., 2016

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*Transient Transfection and Migalastat Incubation*

HEK-293 cells were plated in 96-well plates at 7500 cells in 100 μL cell culture media per well and incubated overnight at 37°C with 5% CO2. To transfect the cells, plasmid DNA was incubated with the FuGENE lipid-based transfection reagent as previously described 1, and then 5 µL of transfection reaction 1 was added to each well of cells in the 96-well plate. Each plate contained three controls: WT-*GLA* in Column 1, pcDNA vector control in Column 2, and R301Q, a mutant that is known to be responsive to migalastat, in Column 12. Up to nine different α-Gal A mutant-expressing plasmids were added to Columns 3-11 of the plate, with a different plasmid in each column. One hour following transfection, migalastat was diluted to 200 μM in cell culture media and then 5.5 μL of 200 μM AT1001 was added to rows E-H of the 96-well plate for a final concentration of 10 µM migalastat in a final volume of 110.5 μL. 5.5 μL of cell culture media alone was added to rows A-D of the plate. Cells were then incubated for five days at 37°C with 5% CO2. To prevent evaporation over the extended incubation time, all incubations were performed at greater than 95% relative humidity in a humidity chamber. The concentration of 10 µM migalastat is used in this assay because it is the approximate maximum concentration of migalastat in the plasma of patients with Fabry disease following a single oral dose of 150 mg 2.

*α-Gal A Enzyme Activity Measurement*

After five days, excess migalastat was removed by washing cells twice with phosphate-buffered saline (PBS) and then incubating in migalastat-free cell culture media for two hours at 37°C with 5% CO2. Cells were washed again twice with PBS and then lysed by adding lysis buffer (27 mM sodium citrate, 46 mM sodium phosphate dibasic, 0.5% Triton X-100, pH 4.6). A volume of 65 µL of lysis buffer was added per well, and plates were incubated on a plate shaker at 150 rpm for 30 minutes at room temperature.

After the 30-minute lysis, cell lysate containing solubilized α-Gal A was transferred to a new 96-well plate. α-Gal A activity was measured in 10 µL cell lysate, both undiluted and diluted 1:30 in 0.1 µg/µL untransfected HEK-293 cell lysate, by incubation with 4-methylumbelliferone-α-D-galactopyranoside and *N*-acetyl-D-galactosamine as previously described 1 for one hour at 37°C. Stop buffer was then added to the reaction and fluorescence was read using 355 nm excitation and 460 nm emission wavelengths on a SpectraMax Plus 5e spectrophotometer (Molecular Devices Corp., Sunnyvale, CA). The amount of 4-MU generated in the assay was calculated based on a 4-methylumbelliferone (4-MU) standard curve (ranging from 29 nM to 30 µM) run on a separate plate. If results from either the undiluted or the 1:30-diluted cell lysate were above the lower limit of quantification (29 nM) but neither result was within the range of the 4-MU standard curve, then the enzyme assay was repeated within three hours of lysis using a higher dilution.

To normalize for the total cellular protein, a protein assay (Pierce Bicinchoninic Acid

Protein Assay, Thermo Fisher Scientific Inc.) was performed according to the manufacturer’s instructions on 25 µL of cell lysate from each well.

α-Gal A activity from every well was expressed as nmoles of 4-MU/mg protein/hour. The endogenous HEK-293 cellular α-Gal A activity was measured in lysates from pcDNA-transfected wells that were incubated either in the absence or presence of 10 µM migalastat. The final α-Gal A activity in each well of transfected mutant *GLA*, WT-*GLA*, and R301Q was calculated after subtracting the average activity of pcDNA-transfected wells that were incubated either in the absence or presence of 10 µM migalastat in parallel from the same plate.

*Quantitative Polymerase Chain Reaction Test*

After the 30-minute lysis (described above), the layer of cells that remained on the bottom of each well in the cell culture plate was analyzed by quantitative polymerase chain reaction (qPCR) for the presence of plasmid DNA as a transfection control. To access plasmid DNA within the layer of cells that remained on the bottom of the cell culture plate, cells were further lysed using an SDS-based lysis buffer in a final volume of 65 µL, and then the lysate was diluted 1:30 in nuclease-free water and used directly in the qPCR reaction. qPCR was performed on a 384-well plate, with lysate from up to three different 96-well plates in three quadrants and standards and quality controls in the fourth quadrant.

The qPCR reaction utilized a FAM-labeled Taqman probe with an MGB non-fluorescent quencher, with primers that amplified a 73-basepair region of the plasmid that spanned the junction between the 3’ end of the *GLA* cDNA and the pcDNA vector. The qPCR reaction was run on a ViiA-7 Real-Time PCR System using “fast” chemistry, with 40 cycles consisting of 95°C for one second and 60°C for 20 seconds per cycle. Data were collected at the end of each cycle.

Cycle threshold values for each well were compared to a standard curve of WT-*GLA* plasmid DNA diluted in nuclease-free water to calculate the final reported value of pg DNA per well. Assay acceptance criteria: 1) reportable pg DNA per well values were required to be between 6.25 and 480 pg DNA per well (the lower and upper limits of quantification, respectively), 2) pg DNA values per well in each column of the transfection plate containing pcDNA with the *GLA* insert (regardless of treatment group, n=8) were required to have a %CV≤10, 3) the result for the pcDNA-transfected control was required to be below the lower limit of quantification (6.25 pg DNA per well), 4) for each plasmid tested in a transfection plate (each column, n=8), the average pg DNA per well value was required to be at least 40% of the average pg DNA per well value of WT-*GLA* in Column 1 of the same transfection plate. For example, if the average value for WT-*GLA* was measured as 100 pg DNA per well, the average value of R301Q must be ≥40 pg DNA per well. The final GLP HEK assay result for transfected *GLA* mutants without a sufficient quantity of *GLA* cDNA recovered was pre-specified to be “no conclusion.”

*Determination of the Mutant α-Gal A Response to Migalastat*

Twenty separate determinations of α-Gal A activity from five different assays with n=4 per assay for each condition (with or without migalastat) for each mutant form were obtained. The results were then used to calculate the average ± SEM α-Gal A activity in nmol/mg/hour for the twenty data points for each treatment. If this value was below the limit of detection (142 nmol/mg/hour), then the average value was reported as below the limit of detection.

The % wild-type activity value for each mutant α-Gal A was calculated based on the average (n=4) baseline wild-type value on the same plate on the same day (plate acceptance criteria for the average baseline wild-type α-Gal A activity was 18000 to 60000 nmol/mg/hour with a precision (CV%) ≤30%). The average ± SEM of the mutant α-Gal A % wild-type values for the twenty data points for each condition was then calculated. To calculate the absolute increase, the average mutant α-Gal A % wild-type baseline value was subtracted from the average mutant α-Gal A % wild-type from migalastat-incubated wells. The α-Gal A activity –fold over baseline was calculated by dividing the average nmol/mg/hour value from migalastat-incubated wells by the average nmol/mg/hour baseline value.

Differences in α-Gal A activity measured in migalastat-incubated versus baseline were determined using a one-tailed Mann-Whitney U non-parametric test (GraphPad Prism, version 4.02). The difference was considered significant if incubation with migalastat resulted in an increase in activity with p<0.05.

*Statistical Analyses*

The degree of consistency between pairs of datasets was evaluated by calculating the sensitivity, specificity, positive predictive value, negative predictive value, and each of the 95% confidence intervals, using Microsoft Office Excel 2007 (Redmond, WA) and the Center for Clinical Research and Biostatistics website.

Analyses to determine *p*-values for statistically significant increases in mutant α-Gal A activity of transfected HEK-293 cells incubated with and without migalastat by one-tailed Mann Whitney-U test were carried out using GraphPad Prism, version 4.02 (San Diego, CA). Absolute change from baseline in Fabry substrate (i.e., kidney interstitial capillary GL-3 or plasma lyso-Gb3) is calculated as the value after 6 months of migalastat treatment minus the value prior to treatment. The mean baseline (minimum, maximum), mean changes from baseline (95% confidence interval), and mean difference (95% confidence interval) in the change from baseline after 6 months were calculated using SAS, version 9.4 (Cary, NC). The GLP HEK assay α-Gal A activity –fold over baseline and absolute increase at 10 μM migalastat were calculated using Microsoft Office Excel 2007 according to Equations 1 and 2 (see below). The α-Gal A activity –fold over baseline and absolute increase at 10 μM migalastat mean, standard error of the mean, and 95% confidence intervals were calculated using GraphPad prism, version 4.02.

Equation 1:

Equation 2:

Absolute Increase (% WT)

RESULTS

*Sensitivity and Specificity Calculations for Mutant α-Gal A Responses to Migalastat in the GLP HEK Assay and 74 Male Fabry Patient-Derived Lymphoblast Cell Lines*

27/74 mutant forms met the amenability criteria in male Fabry patient-derived lymphoblasts. 25/ 27 mutant forms met the amenability criteria in the GLP HEK assay. Therefore, the sensitivity was calculated to be 0.92 (25 ÷ 27). Forty-seven of the 74 mutant forms did not meet the amenability criteria in male Fabry patient-derived lymphoblasts; Forty-two of these 47 mutant forms did not meet the criteria in the GLP HEK assay. Therefore, the specificity was calculated to be 0.89 (42 ÷ 47).

*Comparison of Mutant α-Gal A Responses to Migalastat in the GLP HEK Assay and PBMCs in 51 Male Fabry Patients from Phase 2 and 3 Clinical Studies*

Calculations for all male patients receiving 150 mg migalastat HCl QOD are provided below (Data are provided in Tables 3S-6S):

1. Sensitivity: Thirty-five male patients showed positive PBMC α‑Gal A responses to migalastat (defined as an increase in α-Gal A levels of at least 2.0% of normal in PBMCs). The mutant forms of 35 of those patients consistently had responses to 10 µM migalastat in the GLP HEK assay that met the amenable mutation criteria. The sensitivity was calculated to be 1.0 (35 ÷ 35); 95% confidence intervals, 1.0, 1.0.
2. Specificity: Sixteen male patients showed less than 2.0% of normal increases in α-Gal A levels in PBMCs in response to migalastat. Fourteen of the 16 patients did not meet the amenable mutation criteria in the GLP HEK assay. The specificity was calculated to be 0.875 (14 ÷ 16); 95% confidence intervals, 0.7130, 1.0371.
3. Positive predictive value: Amenable mutant forms were represented in 37 male patients. Thirty-five of the 37 patients showed positive PBMC α‑Gal A responses to oral administration of migalastat. The positive predictive value was calculated to be 0.9460 (35 ÷ 37); 95% confidence intervals, 0.8731, 1.0188.
4. Negative predictive value: Non-amenable mutant forms were represented in 14 male patients. All 14 patients showed less than 2.0% of normal increases in α-Gal A levels in PBMCs in response to migalastat. The negative predictive value was calculated to be 1.0 (14 ÷ 14); 95% confidence intervals (1.0, 1.0).

*Comparison of Mutant α-Gal A Responses to Migalastat in the GLP HEK Assay and Fabry Patient Substrate Responses*

*Kidney Interstitial Capillary GL-3*

Predictive calculations for male patients in Study 011 (Data are provided in Table 7S):

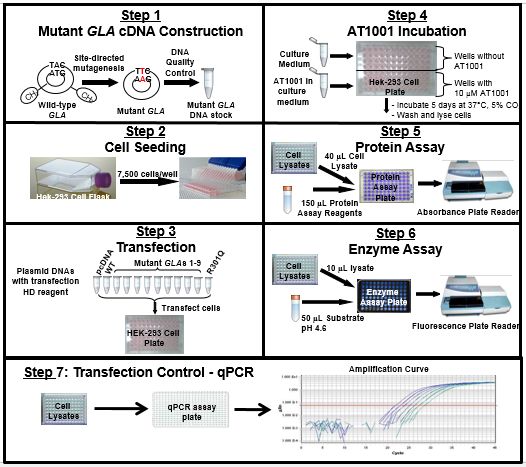
1. Sensitivity: Twelve of 12 male patients that met the amenable mutation criteria in the GLP HEK assay showed positive responses. The sensitivity was calculated to be 1.0 (12 ÷ 12); 95% confidence intervals, 1.0, 1.0.
2. Specificity: Six male patients did not have a positive response in disease substrate. None of the 6 patients met the amenable mutation criteria in the GLP HEK assay. The specificity was calculated to be 1.0 (6 ÷ 6); 95% confidence intervals, 1.0, 1.0.
3. Positive Predictive Value: Amenable mutant forms were represented in 12 male patients. All 12 patients showed a positive kidney interstitial capillary GL-3 response. The positive predictive value was calculated to be 1.0 (12 ÷ 12); 95% confidence intervals, 1.0, 1.0.
4. Negative Predictive Value: Non-amenable mutant forms were represented in 6 male patients. None of the 6 patients showed a positive response in kidney interstitial capillary GL-3. The negative predictive value in these patients was calculated to be 1.0 (6 ÷ 6 = 1.0); 95% confidence intervals, 1.0, 1.0.

*Plasma Lyso-Gb3*

Predictive calculations for male patients in Study 011 (Data are provided in Table 8S):

1. Sensitivity: Eleven of 11 male patients with mutant α-Gal A responses that met the amenable mutation criteria in the GLP HEK assay showed a positive lyso-Gb3 response. The sensitivity was calculated to be 1.0 (11 ÷ 11); 95% confidence intervals, 1.0, 1.0.
2. Specificity: Five male patients did not show a positive plasma lyso-Gb3 response. None of the 5 met the amenable mutation criteria in the GLP HEK assay. The specificity was calculated to be 1.0 (5 ÷ 5); 95% confidence intervals, 1.0, 1.0.
3. Positive Predictive Value: Amenable mutant forms were represented in 11 male patients. All 11 patients showed positive plasma lyso-Gb3 responses. The positive predictive value was calculated to be 1.0 (11 ÷ 11); 95% confidence intervals, 1.0, 1.0.
4. Negative Predictive Value: Non-amenable mutant forms were represented in 5 male patients. None of the 5 patients showed positive plasma lyso-Gb3 responses. The negative predictive value was calculated to be 1.0 (5 ÷ 5); 95% confidence intervals, 1.0, 1.0.

**Figure 1S: GLP HEK assay Procedure**



The GLP HEK assay includes: 1. Plasmid DNA quality control assessments and storage specifications; 2. Binary design in which *GLA* transfected HEK cells are incubated in the absence or presence of a 10 μM migalastat (AT1001); 3. Quantitative real-time PCR transfection efficiency control obtained from every sample; 4. Consistent assay acceptance criteria.

**Figure 2S: Mutant α-Gal A Responses in the GLP HEK Assay**



Migalastat increases the activity of different α-Gal A mutant forms. Six hundred (600) mutant forms were evaluated in the GLP HEK assay for increases in α-Gal A activity in response to incubation with 10 µM migalastat. The average baseline (orange bars) and average increased (blue bars) α-Gal A activity in the absence or presence of migalastat, respectively, are shown. The data have been normalized to the α-Gal A activity of untreated wild-type. Mutant forms with no associated bar did not have any quantifiable baseline α-Gal A activity nor response to migalastat.

Table 1S: Effect of Migalastat on Mutant α‑Gal A Activity Measured in HEK-293 Cell Lysates

| α‑Gal A Mutant Form | | -Migalastat | | +Migalastat | | Absolute Increase at 10 µM (%WT) | α-Gal A Activity at 10 µM –Fold Over Baseline | Meets Amenable Mutation Criteria? (Yes/No) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Amino Acid Change | Nucleotide Change | α‑Gal A Activity (nmol/mg/hr) | % WT | α‑Gal A Activity (nmol/mg/hr) | % WT |
| M1I | c.3 G>A | 159 ± 12 | 0.5 ± 0.0 | 186 ± 31 | 0.6 ± 0.1 | 0.1 | 1.17 | no |
| M1K | c.2 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M1L | c.1 A>C | 186 ± 16 | 0.6 ± 0.1 | 268 ± 35\* | 0.8 ± 0.1 | 0.3 | 1.44 | no |
| M1R | c.2 T>G | BLD | N/A | 219 ± 25\*\* | 0.6 ± 0.1 | 0.6 | NC | no |
| M1T | c.2 T>C | 187 ± 15 | 0.5 ± 0.0 | 234 ± 30\* | 0.7 ± 0.1 | 0.1 | 1.26 | no |
| M1V | c.1 A>G | BLD | N/A | 166 ± 29 | 0.5 ± 0.1 | 0.5 | NC | no |
| L3P | c.8 T>C | 24582 ± 1394 | 71.9 ± 4.5 | 31557 ± 1312\*\*\* | 92.2 ± 4.5 | 20.3 | 1.28 | yes |
| C12\_L14del-3aa or 12del3aa or 12del3 | c.34 del TGCGCGCTT | 934 ± 32 | 2.7 ± 0.1 | 1245 ± 47\*\*\* | 3.6 ± 0.1 | 0.9 | 1.33 | no |
| A13P | c.37 G>C | 1952 ± 136 | 5.6 ± 0.4 | 5102 ± 140\*\*\* | 14.9 ± 0.6 | 9.3 | 2.61 | yes |
| A13T | c.37G>A | 17810 ± 823 | 51.7 ± 2.5 | 21391 ± 849\*\* | 62.2 ± 2.6 | 10.4 | 1.20 | yes |
| L14P | c.41 T>C | BLD | N/A | 183 ± 29\* | 0.5 ± 0.1 | 0.5 | NC | no |
| A15G | c.44 C>G | 7293 ± 437 | 19 ± 0.7 | 10647 ± 594\*\*\* | 28 ± 1.2 | 9.0 | 1.46 | yes |
| A15P | c.43 G>C | 328 ± 22 | 0.9 ± 0 | 462 ± 37\*\* | 1.2 ± 0.1 | 0.3 | 1.41 | no |
| A15T | c.43 G>A | 12581 ± 757 | 39.1 ± 1.3 | 18353 ± 851\*\*\* | 57.5 ± 1.4 | 18.4 | 1.46 | yes |
| L16H | c.47 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L16P | c.47 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| F18S | c.53 T>C | 699 ± 29 | 2.0 ± 0.1 | 897 ± 44\*\*\* | 2.5 ± 0.1 | 0.5 | 1.28 | no |
| 19del-5aa | c.57 Del GCCCTCGTTTCCTGG | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L19P | c.56 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L19Q | c.56 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A20D | c.59 C>A | 1625 ± 68 | 4.3 ± 0.2 | 3864 ± 346\*\*\* | 10 ± 0.8 | 5.7 | 2.38 | yes |
| A20P | c.58 G>C | 3955 ± 238 | 11.5 ± 0.8 | 5483 ± 352\*\* | 15.9 ± 1.1 | 4.4 | 1.39 | yes |
| A20V | c.59 C>T | 29269 ± 1385 | 81.7 ± 3.7 | 30693 ± 1277 | 86.1 ± 3.6 | 4.4 | 1.05 | no |
| L21F | c.61C>T | 25529 ± 1105 | 71.4 ± 2.9 | 27062 ± 1039 | 75.9 ± 3.0 | 4.5 | 1.06 | no |
| L21P | c.62 T>C | 380 ± 28 | 1.1 ± 0.1 | 549 ± 36\*\*\* | 1.6 ± 0.1 | 0.5 | 1.44 | no |
| L21R | c.62 T>G | 419 ± 40 | 1.2 ± 0.1 | 640 ± 44\*\*\* | 1.8 ± 0.1 | 0.6 | 1.53 | no |
| W24C | c.72 G>C | 6711 ± 373 | 19.9 ± 1.2 | 11951 ± 534\*\*\* | 35.0 ± 1.3 | 15.1 | 1.78 | yes |
| W24G | c.70 T>G | 8723 ± 855 | 22.1 ± 1.1 | 15839 ± 950\*\*\* | 41 ± 1.1 | 19.0 | 1.82 | yes |
| W24R | c.70 T>A | 20250 ± 1395 | 52.6 ± 2.3 | 24519 ± 1565\*\* | 63.4 ± 1.7 | 10.9 | 1.21 | yes |
| A31V | c.92 C>T | 593 ± 35 | 1.7 ± 0.1 | 1030 ± 29\*\*\* | 3.0 ± 0.1 | 1.3 | 1.74 | no |
| L32P | c.95 T>C | 2529 ± 183 | 7.3 ± 0.4 | 12391 ± 735\*\*\* | 36.3 ± 2.0 | 29.0 | 4.90 | yes |
| D33G | c.98 A>G | 9913 ± 600 | 29.3 ± 1.8 | 24033 ± 865\*\*\* | 70.6 ± 2.4 | 41.3 | 2.42 | yes |
| D33Y | c.97 G>T | 6209 ± 465 | 18.0 ± 1.2 | 16998 ± 723\*\*\* | 49.6 ± 1.7 | 31.7 | 2.74 | yes |
| N34K | c.102 T>A | BLD | N/A | 2231 ± 196\*\*\* | 6.6 ± 0.6 | 6.6 | NC | yes |
| N34S | c.101 A>G | 195 ± 35 | 0.6 ± 0.1 | 5690 ± 239\*\*\* | 16.7 ± 0.6 | 16.1 | 29.23 | yes |
| G35R | c.103 G>A | 6400 ± 321 | 19.2 ± 1.0 | 22376 ± 1529\*\*\* | 66.1 ± 3.4 | 46.9 | 3.50 | yes |
| L36F | c.108 G>C | 1305 ± 75 | 4.0 ± 0.3 | 12093 ± 753\*\*\* | 35.9 ± 1.7 | 31.9 | 9.27 | yes |
| L36S | c.107 T>C | 10811 ± 481 | 32.5 ± 1.6 | 25401 ± 1000\*\*\* | 76.9 ± 3.8 | 44.3 | 2.35 | yes |
| L36W | c.107 T>G | 241 ± 19 | 0.7 ± 0.1 | 5182 ± 463\*\*\* | 16.6 ± 2.1 | 15.9 | 21.49 | yes |
| A37T | c.109 G>A | 16336 ± 625 | 48.9 ± 1.8 | 32066 ± 1226\*\*\* | 96.4 ± 3.9 | 47.5 | 1.96 | yes |
| A37V | c.110 C>T | 15709 ± 855 | 46.7 ± 2.0 | 24997 ± 1355\*\*\* | 75.1 ± 3.9 | 28.4 | 1.59 | yes |
| P40A | c.118 C>G | BLD | N/A | 775 ± 43\*\*\* | 2.1 ± 0.1 | 2.1 | NC | no |
| P40H | c.119 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P40L | c.119 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P40R | c.119 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P40S | c.118 C>T | BLD | N/A | 308 ± 26\*\*\* | 1.0 ± 0.1 | 1.0 | NC | no |
| T41I | c.122 C>T | 22348 ± 897 | 68.7 ± 3.1 | 37401 ± 1677\*\*\* | 116.7 ± 7.1 | 48.0 | 1.67 | yes |
| M42K | c.125 T>A | 1284 ± 39 | 3.9 ± 0.1 | 9851 ± 505\*\*\* | 29.7 ± 1.5 | 25.8 | 7.67 | yes |
| M42L | c.124 A>C | 12287 ± 726 | 38.8 ± 2.0 | 18812 ± 893\*\*\* | 60.2 ± 2.7 | 21.3 | 1.53 | yes |
| M42R | c.125 T>G | 2262 ± 231 | 6.9 ± 0.4 | 9236 ± 336\*\*\* | 29.5 ± 1.0 | 22.7 | 4.08 | yes |
| M42T | c.125 T>C | 788 ± 44 | 2.5 ± 0.1 | 6287 ± 328\*\*\* | 20.3 ± 1.2 | 17.8 | 7.98 | yes |
| M42V | c.124 A>G | 159 ± 20 | 0.5 ± 0.1 | 1338 ± 52\*\*\* | 4.3 ± 0.1 | 3.8 | 8.44 | yes |
| G43D | c.128 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G43R | c.127 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G43S | c.127 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G43V | c.128 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W44C | c.132 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L45P | c.134 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L45R | c.134 T>G | 224 ± 23 | 0.6 ± 0.1 | 194 ± 22 | 0.6 ± 0.1 | -0.1 | 0.87 | no |
| L45R/H46S | c.134\_138 del TGCAC; ins GCTCG | BLD | N/A | BLD | N/A | N/A | N/A | no |
| H46L | c.137 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| H46P | c.137 A>C | 10645 ± 580 | 31.0 ± 1.2 | 36121 ± 1306\*\*\* | 106.9 ± 4.4 | 75.9 | 3.39 | yes |
| H46R | c.137 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| H46Y | c.136 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W47C | c.141 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W47G | c.139 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W47L | c.140 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W47R | c.139 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E48D | c.144 G>T | 177 ± 17 | 0.5 ± 0.0 | 741 ± 40\*\*\* | 2.0 ± 0.1 | 1.5 | 4.17 | no |
| E48K | c.142 G>A | 260 ± 18 | 0.9 ± 0.1 | 402 ± 23\*\*\* | 1.3 ± 0.1 | 0.5 | 1.54 | no |
| E48Q | c.142 G>C | 844 ± 40 | 2.3 ± 0.1 | 4481 ± 151\*\*\* | 12.0 ± 0.4 | 9.7 | 5.31 | yes |
| 49insP-1aa or 49ins1 | c.147\_148 Ins CCC | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R49C | c.145 C>T | BLD | N/A | 1031 ± 71\*\*\* | 2.7 ± 0.2 | 2.7 | NC | no |
| R49G | c.145 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R49L | c.146 G>T | BLD | N/A | 332 ± 43\*\*\* | 0.9 ± 0.1 | 0.9 | NC | no |
| R49P | c.146 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R49S | c.145 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| F50C | c.149 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M51I | c.153 G>A | 9074 ± 557 | 22.3 ± 1.1 | 19030 ± 676\*\*\* | 47.1 ± 1.5 | 24.7 | 2.10 | yes |
| M51K | c.152 T>A | 2020 ± 137 | 6.3 ± 0.5 | 6950 ± 360\*\*\* | 22.1 ± 1.9 | 15.8 | 3.44 | yes |
| C52G | c.154 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C52R | c.154 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C52S | c.155 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C52W | c.156 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C52Y | c.155 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N53D | c.157 A>G | 17104 ± 863 | 42.2 ± 1.9 | 32019 ± 821\*\*\* | 79.4 ± 2.0 | 37.2 | 1.87 | yes |
| N53L | c.157 A>C; c.158 A>T | 7509 ± 460 | 18.5 ± 0.9 | 19650 ± 762\*\*\* | 48.6 ± 1.5 | 30.1 | 2.62 | yes |
| L54F | c.160 C>T | 1796 ± 87 | 5 ± 0.2 | 15077 ± 875\*\*\* | 41.4 ± 1.4 | 36.5 | 8.39 | yes |
| L54P | c.161 T>C | BLD | N/A | 4589 ± 296\*\*\* | 11.2 ± 0.5 | 11.2 | NC | yes |
| D55Vφ | c.164 A>T | 176 ± 27 | 0.5 ± 0.1 | 6566 ± 454\*\*\* | 19.1 ± 1.0 | 18.5 | 37.34 | yes |
| D55V/Q57L | c.164 A>T; c.170 A>T | BLD | N/A | 2526 ± 287\*\*\* | 8.0 ± 0.5 | 8.0 | NC | yes |
| C56F | c.167 G>T | BLD | N/A | 2195 ± 261\*\*\* | 6.4 ± 0.7 | 6.4 | NC | yes |
| C56G | c.166 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C56S | c.167 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C56Y | c.167 G>A | BLD | N/A | 2517 ± 271\*\*\* | 7.3 ± 0.7 | 7.3 | NC | yes |
| Q57Lφ | C170 A>T | 24215 ± 725 | 71.6 ± 2.0 | 31563 ± 1022\*\*\* | 93.3 ± 2.7 | 21.7 | 1.30 | yes |
| E59K | c.175 G>A | 2910 ± 192 | 8.6 ± 0.5 | 5861 ± 230\*\*\* | 17.5 ± 0.8 | 9.0 | 2.01 | yes |
| P60L | c.179 C>T | 7464 ± 483 | 21.7 ± 1.1 | 20863 ± 1170\*\*\* | 61.0 ± 2.4 | 39.2 | 2.80 | yes |
| P60S | c.178 C>T | 13236 ± 1201 | 35.1 ± 1.7 | 28850 ± 1909\*\*\* | 78.1 ± 2 | 43.0 | 2.18 | yes |
| P60T | c.178 C>A | 9459 ± 792 | 25.3 ± 1.3 | 28325 ± 1457\*\*\* | 77.7 ± 1.9 | 52.4 | 2.99 | yes |
| C63R | c.187 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C63S | c.188 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C63Y | c.188 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E66G | c.197 A>G | 12137 ± 377 | 34.2 ± 1.0 | 16474 ± 746\*\*\* | 46.2 ± 1.7 | 11.9 | 1.36 | yes |
| E66K | c.196 G>A | 1694 ± 51 | 4.8 ± 0.1 | 4462 ± 171\*\*\* | 12.9 ± 0.8 | 8.1 | 2.63 | yes |
| E66Q | c.196 G>C | 18508 ± 569 | 52.0 ± 1.3 | 19720 ± 1005 | 55.0 ± 2.1 | 3.0 | 1.07 | no |
| L68F | c.202 C>T | BLD | N/A | 278 ± 38\*\*\* | 0.8 ± 0.1 | 0.8 | NC | no |
| M72I | c.216 G>A | 19494 ± 758 | 54.7 ± 1.8 | 27499 ± 929\*\*\* | 77.6 ± 2.6 | 22.8 | 1.41 | yes |
| M72R | c.215 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M72V | c.214 A>G | 5090 ± 261 | 14.5 ± 0.9 | 26104 ± 831\*\*\* | 73.2 ± 1.3 | 58.7 | 5.13 | yes |
| A73E | c.218 C>A | 203 ± 26 | 0.5 ± 0 | 522 ± 47\*\*\* | 1.4 ± 0.1 | 0.9 | 2.57 | no |
| A73V | c.218 C>T | 18892 ± 383 | 53.6 ± 1.6 | 30798 ± 701\*\*\* | 86.9 ± 2.1 | 33.3 | 1.63 | yes |
| M76R | c.227 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M76T | c.227 T>C | 1047 ± 33 | 2.7 ± 0.1 | 4722 ± 187\*\*\* | 12.2 ± 0.7 | 9.6 | 4.51 | yes |
| W81C | c.243 G>T | BLD | N/A | 288 ± 15\*\*\* | 0.7 ± 0.0 | 0.7 | NC | no |
| W81R | c.241 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W81S | c.242 G>C | BLD | N/A | 179 ± 20\*\*\* | 0.6 ± 0.1 | 0.6 | NC | no |
| D83N | c.247G>A | 26837 ± 844 | 69.2 ± 3.3 | 36340 ± 1231\*\*\* | 93.0 ± 3.7 | 23.9 | 1.35 | yes |
| G85D | c.254 G>A | 888 ± 38 | 2.7 ± 0.1 | 4534 ± 135\*\*\* | 14.3 ± 0.9 | 11.6 | 5.10 | yes |
| G85M | c.253 G>A; c.254 G>T; c.255 T>G | 3148 ± 261 | 7.9 ± 0.5 | 4680 ± 338\*\* | 11.8 ± 0.7 | 4.0 | 1.49 | yes |
| G85S | c.253 G>A | 4914 ± 361 | 12.4 ± 0.8 | 7431 ± 217\*\*\* | 19.1 ± 0.8 | 6.7 | 1.51 | yes |
| 86del6 or 86del-6aa | c.258del18 GAG TAC CTC TGC ATT GAT | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y86C | c.257 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y86D | c.256 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y86H | c.256 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y88D | c.262 T>G | BLD | N/A | 399 ± 18\*\*\* | 1.0 ± 0.0 | 1.0 | NC | no |
| L89F | c.265 C>T | 6990 ± 491 | 18.9 ± 0.8 | 13716 ± 689\*\*\* | 37.8 ± 1.1 | 18.9 | 1.96 | yes |
| L89P | c.266 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L89R | c.266 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C90R | c.268 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C90Y | c.269 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I91T | c.272 T>C | 372 ± 19 | 0.9 ± 0.1 | 5227 ± 293\*\*\* | 12.6 ± 0.5 | 11.6 | 14.07 | yes |
| D92G | c.275 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D92H | c.274 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D92N | c.274 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D92V | c.275A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D92Y | c.274 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D93E | c.279 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D93G | c.278 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D93N | c.277 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D93V | c.278 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D93Y | c.277 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C94S | c.281 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C94Y | c.281 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W95L | c.284 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W95S | c.284 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M96I | c.288 G>A | 10088 ± 549 | 30.3 ± 1.2 | 19384 ± 1082\*\*\* | 58.2 ± 2.5 | 27.9 | 1.92 | yes |
| A97P | c.289 G>C | 245 ± 16 | 0.7 ± 0.0 | 1443 ± 62\*\*\* | 4.0 ± 0.1 | 3.3 | 5.88 | yes |
| A97V | c.290 C>T | 3854 ± 118 | 12.2 ± 0.8 | 12772 ± 548\*\*\* | 39.6 ± 2.3 | 27.4 | 3.31 | yes |
| R100K | c.299 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R100T | c.299 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S102L | c.305 C>T | 6645 ± 500 | 19.9 ± 1 | 20794 ± 1141\*\*\* | 62.8 ± 2.2 | 42.9 | 3.13 | yes |
| E103Q | c.307 G>C | 36955 ± 1623 | 102.9 ± 3.7 | 41654 ± 2285 | 114.6 ± 3.9 | 11.7 | 1.13 | no |
| G104V | c.311G>T | 7506 ± 378 | 20.9 ± 0.8 | 12067 ± 506\*\*\* | 33.6 ± 1.1 | 12.8 | 1.61 | yes |
| L106R | c.317 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q107L | c.320 A>T | 35023 ± 1291 | 98.4 ± 4.3 | 39620 ± 1540\* | 110.0 ± 2.7 | 11.6 | 1.13 | no |
| A108T | c.322 G>A | 20760 ± 1166 | 57.1 ± 2.2 | 29391 ± 1630\*\*\* | 80.8 ± 2.9 | 23.7 | 1.42 | yes |
| D109G | c.326 A>G | 863 ± 62 | 2.6 ± 0.1 | 3384 ± 188\*\*\* | 10.3 ± 0.5 | 7.7 | 3.92 | yes |
| R112C | c.334 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R112G | c.334 C>G | BLD | N/A | 1219 ± 41\*\*\* | 3.5 ± 0.2 | 3.5 | NC | yes |
| R112H | c.335 G>A | 845 ± 39 | 2.6 ± 0.1 | 5583 ± 215\*\*\* | 17.4 ± 0.8 | 14.8 | 6.61 | yes |
| R112S | c.334 C>A | BLD | N/A | 1109 ± 53\*\*\* | 2.8 ± 0.2 | 2.8 | NC | no |
| 113del6 or del113-6 | c.336 Del TTTCCTCATGGGATTCGC | BLD | N/A | BLD | N/A | N/A | N/A | no |
| F113L | c.337 T>C | 7327 ± 399 | 18.3 ± 0.8 | 16382 ± 637\*\*\* | 41.2 ± 1.5 | 22.9 | 2.24 | yes |
| F113S | c.338 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I117S | c.350 T>G | 288 ± 18 | 0.7 ± 0.0 | 598 ± 36\*\*\* | 1.5 ± 0.1 | 0.8 | 2.08 | no |
| R118C | c.352 C>T | 9544 ± 529 | 24.0 ± 1.3 | 11903 ± 555\*\* | 29.5 ± 0.7 | 5.5 | 1.25 | yes |
| L120H-del-2aa or L120H-del2 | c.358 Del6 ntd TAGCTA | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L120P | c.359 T>C | BLD | N/A | 199 ± 19\*\*\* | 0.5 ± 0.0 | 0.5 | NC | no |
| L120P/A121T | c.359 T>C; c.361 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L120S | c.358 C>T; c.359 T>C | BLD | N/A | 922 ± 39\*\*\* | 2.4 ± 0.1 | 2.4 | NC | no |
| L120V | c.358 C>G | 26234 ± 869 | 66.8 ± 3.1 | 29802 ± 1234\* | 74.7 ± 2.4 | 7.9 | 1.14 | no |
| A121P | c.361 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A121T | c.361 G>A | 5292 ± 184 | 18.9 ± 0.5 | 18850 ± 721\*\*\* | 67.9 ± 3.4 | 49.0 | 3.56 | yes |
| Y123C | c.368 A>G | 2932 ± 190 | 8.9 ± 0.4 | 5084 ± 335\*\*\* | 15.1 ± 0.5 | 6.3 | 1.73 | yes |
| V124D | c.371 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| H125L | c.374 A>T | 563 ± 27 | 1.4 ± 0.1 | 1947 ± 187\*\*\* | 4.7 ± 0.4 | 3.3 | 3.46 | yes |
| H125L/G128E | c.374 A>T; c.383 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| H125P | c.374 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S126G | c.376 A>G | 34476 ± 1611 | 83.7 ± 2.4 | 46491 ± 1720\*\*\* | 113.9 ± 3.2 | 30.2 | 1.35 | yes |
| G128E | c.383 G>A | 17297 ± 1047 | 45.2 ± 1.8 | 22334 ± 1057\*\* | 58.5 ± 1.7 | 13.4 | 1.29 | yes |
| L129P | c.386 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| K130R | c.389 A>G | 24226 ± 1579 | 63.0 ± 2.7 | 28327 ± 1972 | 73.7 ± 3.9 | 10.7 | 1.17 | no |
| L131P | c.392 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G132A | c.395 G>C | BLD | N/A | 774 ± 66\*\*\* | 2.5 ± 0.1 | 2.5 | NC | no |
| G132E | c.395 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G132R | c.394 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y134D | c.400 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y134H | c.400 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y134S | c.401 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A135V | c.404 C>T | BLD | N/A | 1397 ± 36\*\*\* | 3.7 ± 0.1 | 3.7 | NC | yes |
| D136E | c.408 T>A | 545 ± 21 | 1.4 ± 0.1 | 4958 ± 195\*\*\* | 12.9 ± 0.8 | 11.5 | 9.10 | yes |
| D136H | c.406 G>C | 628 ± 27 | 1.6 ± 0.1 | 1565 ± 56\*\*\* | 4.0 ± 0.2 | 2.4 | 2.49 | no |
| D136Y | c.406 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G138E | c.413 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G138R | c.412 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N139S | c.416 A>G | 25805 ± 1183 | 65.5 ± 2.0 | 31068 ± 1539\*\* | 79.1 ± 3.2 | 13.6 | 1.20 | yes |
| N139T | c.416 A>C | 27948 ± 1068 | 71.4 ± 2.2 | 31174 ± 1204\* | 79.4 ± 2.0 | 7.9 | 1.12 | no |
| K140T | c.419 A>C | 17228 ± 1211 | 51.4 ± 2.1 | 30034 ± 1847\*\*\* | 89.8 ± 2.7 | 38.4 | 1.74 | yes |
| T141I | c.422 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| T141N | c.422 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C142R | c.424 T>C | 182 ± 19 | 0.4 ± 0.0 | BLD | N/A | N/A | N/A | no |
| C142W | c.426 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C142Y | c.425 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A143P | c.427 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A143T | c.427 G>A | 6874 ± 248 | 21.4 ± 0.8 | 14038 ± 309\*\*\* | 43.8 ± 1.4 | 22.4 | 2.04 | yes |
| G144D | c.431 G>A | 16773 ± 1140 | 50.2 ± 2.2 | 25424 ± 1311\*\*\* | 76.5 ± 1.7 | 26.3 | 1.52 | yes |
| G144V | c.431 G>T | 253 ± 21 | 0.8 ± 0.1 | 2924 ± 335\*\*\* | 9.2 ± 1.2 | 8.4 | 11.58 | yes |
| P146S | c.436 C>T | 16859 ± 910 | 41.9 ± 1.9 | 25622 ± 1398\*\*\* | 64.1 ± 3.7 | 22.2 | 1.52 | yes |
| G147E | c.440 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G147R | c.439 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S148N | c.443 G>A | BLD | N/A | 273 ± 16\*\*\* | 0.7 ± 0.0 | 0.7 | NC | no |
| S148R | c.444 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| 152ins-D-aa or 152insD or 152ins | c.455\_456 CGA insertion | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y152C | c.455 A>G | 6934 ± 250 | 16.7 ± 0.6 | 13163 ± 696\*\*\* | 31.5 ± 1.4 | 14.8 | 1.90 | yes |
| 153del or del153aa | c.456 DelGAC | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D155H | c.463 G>C | BLD | N/A | 579 ± 30\*\*\* | 1.4 ± 0.1 | 1.4 | NC | no |
| A156D | c.467 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A156T | c.466 G>A | 907 ± 31 | 2.8 ± 0.1 | 7034 ± 289\*\*\* | 21.9 ± 0.9 | 19.1 | 7.75 | yes |
| A156V | c.467 C>T | 505 ± 25 | 1.2 ± 0.1 | 5340 ± 315\*\*\* | 12.8 ± 0.7 | 11.6 | 10.58 | yes |
| W162C | c.486 G>C | 188 ± 20 | 0.5 ± 0.1 | BLD | N/A | N/A | N/A | no |
| W162G | c.484 T>G | 338 ± 26 | 0.8 ± 0.1 | 2538 ± 222\*\*\* | 5.9 ± 0.4 | 5.1 | 7.50 | yes |
| W162L | c.485 G>T | BLD | N/A | BLD | N/A | N/A | N/A | No |
| W162R | c.484 T>C | BLD | N/A | 456 ± 22\*\*\* | 1.1 ± 0.1 | 1.1 | NC | no |
| G163V | c.488 G>T | 458 ± 30 | 1.4 ± 0.1 | 969 ± 45\*\*\* | 2.9 ± 0.1 | 1.5 | 2.12 | no |
| V164G | c.491 T>G | 558 ± 49 | 1.7 ± 0.1 | 1061 ± 64\*\*\* | 3.2 ± 0.1 | 1.5 | 1.90 | no |
| D165G | c.494 A>G | 808 ± 21 | 2.5 ± 0.1 | 4414 ± 275\*\*\* | 13 ± 0.4 | 10.5 | 5.46 | yes |
| D165H | c.493 G>C | 448 ± 34 | 1.3 ± 0.1 | 2869 ± 365\*\*\* | 8.3 ± 0.9 | 7.0 | 6.40 | yes |
| D165V | c.494 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D165Y | c.493 G>T | BLD | N/A | 428 ± 26\*\*\* | 1.3 ± 0.1 | 1.3 | NC | no |
| L166G | c.496 C>G; c.497 T>G | 3478 ± 279 | 10.2 ± 0.6 | 11075 ± 627\*\*\* | 33.0 ± 1.6 | 22.8 | 3.18 | yes |
| L166V | c.496 C>G | 1306 ± 100 | 3.8 ± 0.2 | 7069 ± 447\*\*\* | 20.9 ± 1.1 | 17.1 | 5.41 | yes |
| L167P | c.500 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L167Q | c.500 T>A | BLD | N/A | 186 ± 16\*\*\* | 0.6 ± 0.1 | 0.6 | NC | No |
| K168N | c.504 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| K168R | c.503 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| F169S | c.506 T>C | 4375 ± 594 | 12.8 ± 1.4 | 26078 ± 1758\*\*\* | 78.7 ± 3.8 | 65.9 | 5.96 | yes |
| D170G | c.509 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D170H | c.508 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D170N | c.508 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D170V | c.509 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G171C | c.511 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G171D | c.512 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G171R | c.511 G>C | 1628 ± 83 | 4.9 ± 0.2 | 2190 ± 246 | 6.4 ± 0.5 | 1.4 | 1.35 | no |
| C172F | c.515 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C172G | c.514 T>G | 349 ± 24 | 1.1 ± 0.1 | 881 ± 60\*\*\* | 2.7 ± 0.2 | 1.6 | 2.53 | no |
| C172R | c.514 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C172S | c.515 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C172W | c.516 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C172Y | c.515 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C174G | c.520 T>G | 10655 ± 475 | 29.6 ± 1.5 | 33198 ± 2150\*\*\* | 91.2 ± 5.2 | 61.6 | 3.12 | yes |
| C174R | c.520 T>C | 4671 ± 270 | 14.3 ± 0.6 | 16505 ± 393\*\*\* | 51.6 ± 2.0 | 37.4 | 3.53 | yes |
| D175E | c.525 C>G | 15726 ± 1126 | 44.3 ± 2.9 | 18946 ± 953\* | 53.4 ± 2 | 9.1 | 1.20 | yes |
| G183A | c.548 G>C | 8094 ± 665 | 22.4 ± 1.9 | 20538 ± 1068\*\*\* | 56.4 ± 2.7 | 34.0 | 2.54 | yes |
| G183D | c.548 G>A | 207 ± 15 | 0.7 ± 0.1 | 6074 ± 212\*\*\* | 19.1 ± 1.0 | 18.4 | 29.31 | yes |
| G183V | c.548 G>T | BLD | N/A | 796 ± 29\*\*\* | 2.5 ± 0.1 | 2.5 | NC | no |
| Y184C | c.551A>G | 609 ± 37 | 1.7 ± 0.1 | 2667 ± 318\*\*\* | 7.2 ± 0.8 | 5.6 | 4.38 | yes |
| Y184N | c.550 T>A | 831 ± 80 | 2.3 ± 0.2 | 3445 ± 380\*\*\* | 9.7 ± 1 | 7.4 | 4.15 | yes |
| K185E | c.553 A>G | 14363 ± 1097 | 39.6 ± 3.1 | 25849 ± 1110\*\*\* | 71.3 ± 2.9 | 31.8 | 1.80 | yes |
| H186P | c.557 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M187I | c.561 G>A | 1775 ± 57 | 5.1 ± 0.2 | 10824 ± 555\*\*\* | 30.7 ± 1.1 | 25.6 | 6.10 | yes |
| M187R | c.560 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M187S188ins or 187del2aa | c.565 Ins ATGTCC | 488 ± 53 | 1.2 ± 0.1 | 3434 ± 466\*\*\* | 8.6 ± 1.1 | 7.4 | 7.04 | yes |
| M187T | c.560 T>C | 3548 ± 354 | 9.8 ± 1.0 | 9900 ± 644\*\*\* | 27.4 ± 1.8 | 17.7 | 2.79 | yes |
| M187V | c.559 A>G | 7318 ± 565 | 20.1 ± 1.5 | 16628 ± 1075\*\*\* | 45.7 ± 2.8 | 25.6 | 2.27 | yes |
| L191P | c.572 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L191Q | c.572 T>A | 234 ± 16 | 0.6 ± 0.0 | 3616 ± 512\*\*\* | 9.0 ± 1.2 | 8.4 | 15.45 | yes |
| T194I | c.581 C>T | 908 ± 56 | 2.3 ± 0.1 | 7563 ± 578\*\*\* | 19.1 ± 1.2 | 16.8 | 8.33 | yes |
| G195V | c.584 G>T | 7154 ± 228 | 25.8 ± 1.3 | 13437 ± 383\*\*\* | 48.2 ± 1.5 | 22.3 | 1.88 | yes |
| I198T | c.593 T>C | 25662 ± 1774 | 64.7 ± 3.5 | 38048 ± 2670\*\*\* | 95.5 ± 4.8 | 30.8 | 1.48 | yes |
| V199G | c.596 T>G | 10219 ± 842 | 26.0 ± 1.9 | 24502 ± 1693\*\*\* | 62.7 ± 3.8 | 36.6 | 2.40 | yes |
| V199M | c.595 G>A | 23234 ± 1550 | 59.7 ± 3.8 | 42207 ± 1690\*\*\* | 108.4 ± 3.9 | 48.6 | 1.82 | yes |
| Y200C | c.599 A>G | 521 ± 24 | 1.3 ± 0.1 | 5910 ± 421\*\*\* | 14.9 ± 0.9 | 13.6 | 11.35 | yes |
| S201F | c.602 C>T | 911 ± 42 | 2.4 ± 0.1 | 11996 ± 876\*\*\* | 30.8 ± 1.8 | 28.4 | 13.16 | yes |
| S201Y | c.602 C>A | 2524 ± 148 | 6.5 ± 0.3 | 15727 ± 995\*\*\* | 40.2 ± 1.7 | 33.6 | 6.23 | yes |
| C202R | c.604 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C202R/N215S | c.604 T>C; c.644 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C202W | c.606 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C202Y | c.605 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E203D | c.609 G>C | 1271 ± 108 | 3.4 ± 0.1 | 3353 ± 336\*\*\* | 9 ± 0.6 | 5.6 | 2.64 | yes |
| E203K | c.607 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E203V | c.608 A>T | 16830 ± 1210 | 43.0 ± 2.4 | 24921 ± 1228\*\*\* | 64.5 ± 2.4 | 21.5 | 1.48 | yes |
| W204C | c.612 G>T | BLD | N/A | 427 ± 37\*\*\* | 1.1 ± 0.1 | 1.1 | NC | no |
| 205del3 or del205-7 or 205del3aa | c.612 Del9 CCTCTTTAT | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P205L | c.614 C>T | 258 ± 18 | 0.8 ± 0.1 | 1633 ± 252\*\*\* | 4.7 ± 0.7 | 3.9 | 6.34 | yes |
| P205R | c.614 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P205S | c.613 C>T | 12423 ± 1020 | 35.3 ± 2.2 | 32286 ± 2137\*\*\* | 93.2 ± 5.5 | 57.9 | 2.60 | yes |
| P205T | c.613 C>A | 4802 ± 230 | 14.4 ± 0.9 | 16371 ± 647\*\*\* | 48.8 ± 2.2 | 34.4 | 3.41 | yes |
| L206P | c.617 T>C | BLD | N/A | 230 ± 20\*\*\* | 0.7 ± 0.1 | 0.7 | NC | no |
| Y207C | c.620 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y207H | c.619 T>C | 11787 ± 617 | 34.4 ± 2.0 | 22407 ± 1029\*\*\* | 65.5 ± 3.2 | 31.1 | 1.90 | yes |
| Y207S | c.620 A>C | 766 ± 40 | 2.2 ± 0.1 | 2594 ± 315\*\*\* | 7.3 ± 0.8 | 5.1 | 3.39 | yes |
| P210L | c.629 C>T | 9895 ± 792 | 27.1 ± 1 | 21673 ± 1165\*\*\* | 60.5 ± 1.7 | 33.4 | 2.19 | yes |
| P210S | c.628 C>T | 27219 ± 1787 | 75.2 ± 2 | 40698 ± 2183\*\*\* | 113.3 ± 2.7 | 38.2 | 1.50 | yes |
| K213M | c.638 A>T | 15309 ± 722 | 43.2 ± 1.4 | 19904 ± 1061\*\*\* | 55.9 ± 1.8 | 12.7 | 1.30 | yes |
| P214L | c.641 C>T | 11857 ± 868 | 33 ± 1.3 | 32647 ± 1804\*\*\* | 91.6 ± 1.6 | 58.6 | 2.75 | yes |
| P214S | c.640 C>T | 7895 ± 555 | 22.4 ± 1.1 | 28745 ± 1688\*\*\* | 82.5 ± 3.8 | 60.1 | 3.64 | yes |
| N215D | c.643 A>G | 16980 ± 1644 | 43.8 ± 3.0 | 21987 ± 1391\*\* | 58.3 ± 3.1 | 14.5 | 1.29 | yes |
| N215S | c.644 A>G | 5154 ± 239 | 15.6 ± 1.0 | 11976 ± 334\*\*\* | 35.6 ± 1.2 | 20.0 | 2.32 | yes |
| N215S/D313Yφ | c.644 A>G; c.937 G>T | 569 ± 47 | 1.5 ± 0.1 | 3678 ± 381\*\*\* | 9.7 ± 1.0 | 8.2 | 6.46 | yes |
| N215S/G271Sφ | c.644 A>G; c.811 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N215S/G271S/D313Yφ | c.644 A>G; c.811 G>A; c.937 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Y216C | c.647 A>G | 673 ± 38 | 2.0 ± 0.1 | 7003 ± 305\*\*\* | 20.7 ± 0.8 | 18.7 | 10.40 | yes |
| Y216D | c.646 T>G | 516 ± 50 | 1.6 ± 0.1 | 4233 ± 372\*\*\* | 13.3 ± 0.7 | 11.7 | 8.21 | yes |
| I219N | c.656 T>A | 242 ± 18 | 0.6 ± 0.1 | 4806 ± 396\*\*\* | 12.9 ± 1.1 | 12.2 | 19.87 | yes |
| I219T | c.656 T>C | 21564 ± 1710 | 55.8 ± 2.9 | 34880 ± 1199\*\*\* | 93.6 ± 3.7 | 37.8 | 1.62 | yes |
| R220P | c.659 G>C | 11244 ± 1052 | 30.9 ± 1.8 | 22597 ± 1382\*\*\* | 63.5 ± 2.2 | 32.6 | 2.01 | yes |
| R220Q | c.660 G>A | 16215 ± 1135 | 45.2 ± 1.4 | 21913 ± 1115\*\*\* | 61.7 ± 0.8 | 16.5 | 1.35 | yes |
| C223G | c.667 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C223R | c.667 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C223Y | c.668 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N224D | c.670 A>G | BLD | N/A | 997 ± 31\*\*\* | 2.7 ± 0.1 | 2.7 | NC | no |
| N224S | c.671 A>G | 3918 ± 371 | 10.3 ± 1.0 | 11625 ± 1244\*\*\* | 29.7 ± 2.8 | 19.4 | 2.97 | yes |
| H225D | c.673 C>G | 16595 ± 932 | 43.8 ± 2.6 | 42058 ± 2750\*\*\* | 110.6 ± 7.2 | 66.9 | 2.53 | yes |
| H225R | c.674 A>G | BLD | N/A | 687 ± 33\*\*\* | 2.0 ± 0.1 | 2.0 | NC | no |
| W226C | c.678 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W226R | c.676 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R227P | c.680 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R227Q | c.680 G>A; | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N228S | c.683 A>G | 48389 ± 2790 | 124.5 ± 4.1 | 63268 ± 2078\*\*\* | 169.2 ± 8.2 | 44.7 | 1.31 | yes |
| F229L | c.687 T>G | 7760 ± 694 | 21.4 ± 1.1 | 13519 ± 885\*\*\* | 37.6 ± 0.8 | 16.2 | 1.74 | yes |
| A230T | c.688 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D231G | c.692 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D231N | c.691 G>A | 187 ± 12 | 0.5 ± 0.0 | BLD | N/A | N/A | N/A | no |
| D231V | c.692 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I232T | c.695 T>C | 6486 ± 826 | 15.0 ± 1.6 | 36389 ± 2899\*\*\* | 85.0 ± 4.1 | 69.9 | 5.61 | yes |
| D234E | c.702 T>G | 159 ± 19 | 0.4 ± 0.0 | 339 ± 28\*\*\* | 0.8 ± 0.1 | 0.4 | 2.13 | no |
| D234Y | c.700 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S235C | c.704 C>G | BLD | N/A | 306 ± 58\*\*\* | 0.7 ± 0.1 | 0.7 | NC | no |
| S235F | c.704 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S235Y | c.704 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W236C | c.708 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W236L | c.707 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W236R | c.706 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S238N | c.713 G>A | 9330 ± 395 | 37.1 ± 1.8 | 24510 ± 777\*\*\* | 96.4 ± 2.0 | 59.3 | 2.63 | yes |
| S238R | c.714 T>G | 13999 ± 688 | 55.3 ± 2.7 | 14781 ± 758 | 58.0 ± 2.5 | 2.7 | 1.06 | no |
| I239del or del-I239 or 239del or 239del1 | c.715 del ATA | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I239T | c.716 T>C | 9473 ± 448 | 37.7 ± 1.9 | 23430 ± 954\*\*\* | 92.8 ± 3.9 | 55.2 | 2.47 | yes |
| I242F | c.724 A>T | 270 ± 15 | 1.1 ± 0.1 | 2253 ± 185\*\*\* | 9.0 ± 0.8 | 7.9 | 8.36 | yes |
| I242N | c.725 T>A | 1909 ± 57 | 7.6 ± 0.3 | 16871 ± 859\*\*\* | 67.4 ± 4.2 | 59.7 | 8.84 | yes |
| L243F | c.729 G>C | 2694 ± 117 | 7.9 ± 0.3 | 14370 ± 618\*\*\* | 42.3 ± 1.4 | 34.4 | 5.33 | yes |
| L243W | c.728 T>G | 190 ± 24 | 0.6 ± 0.1 | 4729 ± 227\*\*\* | 14.3 ± 0.9 | 13.7 | 24.86 | yes |
| D244H | c.730 G>C | 6129 ± 366 | 18.1 ± 1.1 | 14873 ± 425\*\*\* | 44.0 ± 1.3 | 25.9 | 2.43 | yes |
| D244N | c.730 G>A | 10317 ± 386 | 30.9 ± 1.6 | 16321 ± 402\*\*\* | 48.7 ± 1.7 | 17.8 | 1.58 | yes |
| W245G | c.733 T>G | 15737 ± 1100 | 44.1 ± 1.6 | 22218 ± 1097\*\*\* | 63 ± 1.4 | 18.9 | 1.41 | yes |
| 247ins3 or ins247-3aa | c.741 Ins TGGACATCT | BLD | N/A | 476 ± 28\*\*\* | 1.8 ± 0.1 | 1.8 | NC | no |
| S247C | c.740 C>G | 7515 ± 308 | 28.0 ± 1.1 | 13828 ± 558\*\*\* | 51.5 ± 2.0 | 23.5 | 1.84 | yes |
| S247P | c.739 T>C | BLD | N/A | 351 ± 25\*\*\* | 1.3 ± 0.1 | 1.3 | NC | no |
| N249K | c.747 C>A | 6350 ± 649 | 17.9 ± 1.6 | 12325 ± 615\*\*\* | 35.2 ± 1.4 | 17.3 | 1.94 | yes |
| Q250P | c.749 A>C | 6647 ± 340 | 24.8 ± 1.3 | 15759 ± 786\*\*\* | 58.7 ± 2.9 | 33.9 | 2.37 | yes |
| R252T | c.755 G>C | 26643 ± 1720 | 74.8 ± 2.5 | 28168 ± 1724 | 79.1 ± 2.1 | 4.2 | 1.06 | no |
| I253S | c.758 T>G | 901 ± 55 | 3.3 ± 0.2 | 8374 ± 400\*\*\* | 31.2 ± 1.4 | 27.8 | 9.29 | yes |
| I253T | c.758 T>C | 11287 ± 506 | 38.9 ± 3.0 | 23417 ± 1077\*\*\* | 80.2 ± 5.9 | 41.3 | 2.07 | yes |
| 254del or del254aa or 254del1 | c.760-762 delGTT | 9950 ± 504 | 37.2 ± 1.9 | 21123 ± 716\*\*\* | 78.7 ± 2.5 | 41.5 | 2.12 | yes |
| A257D | c.770 C>A | BLD | N/A | 271 ± 23\*\*\* | 1.0 ± 0.1 | 1.0 | NC | no |
| A257G | c.770 C>G | 15820 ± 749 | 59.0 ± 2.8 | 27273 ± 779\*\*\* | 101.7 ± 2.8 | 42.6 | 1.72 | yes |
| A257P | c.769 G>C | 4467 ± 329 | 16.6 ± 1.2 | 14040 ± 474\*\*\* | 52.3 ± 1.6 | 35.7 | 3.14 | yes |
| G258R | c.772 G>C | 9558 ± 348 | 32.6 ± 2.1 | 22630 ± 801\*\*\* | 78.1 ± 5.8 | 45.5 | 2.37 | yes |
| G258V | c.773 G>T | 1957 ± 86 | 7.7 ± 0.3 | 10126 ± 457\*\*\* | 39.8 ± 1.7 | 32.1 | 5.17 | yes |
| P259L | c.776 C>T | 2799 ± 190 | 10.9 ± 0.6 | 11189 ± 451\*\*\* | 44.0 ± 1.8 | 33.1 | 4.00 | yes |
| P259R | c.776 C>G | 6681 ± 364 | 23.3 ± 2.3 | 17645 ± 515\*\*\* | 60.3 ± 3.8 | 37.0 | 2.64 | yes |
| G260A | c.779 G>C | 2221 ± 142 | 7.5 ± 0.6 | 10749 ± 403\*\*\* | 37.4 ± 3.1 | 29.9 | 4.84 | yes |
| G260E | c.779 G>A | 3828 ± 318 | 10.6 ± 0.6 | 14341 ± 595\*\*\* | 41.1 ± 1.3 | 30.4 | 3.75 | yes |
| G261D | c.782 G>A | BLD | N/A | 590 ± 19\*\*\* | 2.1 ± 0.2 | 2.1 | NC | no |
| G261V | c.782 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W262C | c.786 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W262L | c.785 G>T | BLD | N/A | 639 ± 35\*\*\* | 2.5 ± 0.1 | 2.5 | NC | no |
| N263S | c.788 A>G | 4010 ± 233 | 15.8 ± 0.9 | 20024 ± 998\*\*\* | 80.5 ± 6.2 | 64.8 | 4.99 | yes |
| D264A | c.791 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D264V | c.791 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D264Y | c.790 G>T | 143 ± 13 | 0.5 ± 0.0 | 1842 ± 100\*\*\* | 6.2 ± 0.3 | 5.7 | 12.89 | yes |
| D264Y/V269M | c.790 G>T; c.805 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P265L | c.794 C>T | 3510 ± 144 | 13.9 ± 0.7 | 19126 ± 837\*\*\* | 74.8 ± 2.9 | 60.9 | 5.45 | yes |
| P265R | c.794 C>G | BLD | N/A | 441 ± 18\*\*\* | 1.8 ± 0.1 | 1.8 | NC | no |
| P265S | c.793 C>T | 268 ± 16 | 1.0 ± 0.1 | 997 ± 38\*\*\* | 3.9 ± 0.2 | 2.8 | 3.73 | no |
| D266A | c.797 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D266E | c.798 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D266H | c.796 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D266N | c.796 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D266V | c.797 A>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| D266Y | c.796 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M267R | c.800 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M267T | c.800 T>C | 9325 ± 374 | 28.8 ± 0.9 | 14708 ± 735\*\*\* | 45.3 ± 1.7 | 16.4 | 1.58 | yes |
| L268S | c.803 T>C | BLD | N/A | 715 ± 24\*\*\* | 2.8 ± 0.1 | 2.8 | NC | no |
| V269A | c.806 T>C | BLD | N/A | 1966 ± 137\*\*\* | 7.8 ± 0.7 | 7.8 | NC | yes |
| V269E | c.806 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| V269M | c.805 G>A | 1213 ± 40 | 4.4 ± 0.2 | 7170 ± 223\*\*\* | 25.9 ± 1.2 | 21.5 | 5.91 | yes |
| I270T | c.809 T>C | 1846 ± 119 | 6.3 ± 0.5 | 12416 ± 377\*\*\* | 42.8 ± 3.0 | 36.5 | 6.73 | yes |
| G271C | c.811 G>T | BLD | N/A | 156 ± 12\*\*\* | 0.5 ± 0.0 | 0.5 | NC | no |
| G271D | c.812 G>A | 477 ± 25 | 1.5 ± 0.1 | 10511 ± 778\*\*\* | 32.2 ± 2 | 30.8 | 22.06 | yes |
| G271S | c.811 G>A | 1329 ± 44 | 3.8 ± 0.1 | 11177 ± 520\*\*\* | 31.9 ± 1.3 | 28.1 | 8.41 | yes |
| G271S/D313Yφ | c.811 G>A; c.937 G>T | BLD | N/A | 877 ± 18\*\*\* | 3.0 ± 0.2 | 3.0 | NC | yes |
| G271V | c.812 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N272K | c.816 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N272S | c.815 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| F273L | c.819 T>G | 348 ± 13 | 1.3 ± 0.1 | 493 ± 19\*\*\* | 1.8 ± 0.1 | 0.5 | 1.42 | no |
| G274S | c.820 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G274V | c.821 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L275F | c.823 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S276G | c.826 A>G | BLD | N/A | 694 ± 25\*\*\* | 2.0 ± 0.1 | 2.0 | NC | no |
| S276N | c.827 G>A | 638 ± 18 | 2.3 ± 0.1 | 2511 ± 190\*\*\* | 9.3 ± 0.9 | 7.0 | 3.93 | yes |
| W277C | c.831 G>C | 9174 ± 479 | 28.5 ± 1.4 | 17288 ± 588\*\*\* | 53.7 ± 1.5 | 25.3 | 1.88 | yes |
| W277G | c.829 T>G | 16576 ± 1205 | 50.3 ± 2.2 | 27884 ± 1783\*\*\* | 84.9 ± 2.8 | 34.6 | 1.68 | yes |
| Q279E | c.835 C>G | 4865 ± 298 | 16.7 ± 1.0 | 14893 ± 507\*\*\* | 51.7 ± 2.2 | 35.0 | 3.06 | yes |
| Q279H | c.837 G>C | BLD | N/A | 152 ± 15\*\*\* | 0.5 ± 0.1 | 0.5 | NC | no |
| Q279K | c.835 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q279R | c.836 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q280H | c.840 A>T | 2119 ± 98 | 7.3 ± 0.4 | 11351 ± 594\*\*\* | 39.2 ± 2.1 | 31.8 | 5.36 | yes |
| Q280K | c.838 C>A | 8019 ± 395 | 27.7 ± 1.4 | 14012 ± 476\*\*\* | 48.5 ± 1.9 | 20.8 | 1.75 | yes |
| V281A-del-1 | c.841 DelTAA | BLD | N/A | BLD | N/A | N/A | N/A | no |
| T282A | c.844 A>G | BLD | N/A | 1199 ± 38\*\*\* | 4.2 ± 0.2 | 4.2 | NC | yes |
| T282I | c.845 C>T | 1515 ± 57 | 5.2 ± 0.2 | 6918 ± 239\*\*\* | 23.7 ± 0.6 | 18.5 | 4.57 | yes |
| T282N | c.845 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q283P | c.848 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q283R | c.848 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| M284T | c.851 T>C | 606 ± 40 | 1.7 ± 0.1 | 5050 ± 268\*\*\* | 14.3 ± 0.6 | 12.6 | 8.33 | yes |
| M284V | c.850 A>G | 8003 ± 785 | 25.2 ± 1.6 | 19455 ± 970\*\*\* | 63.1 ± 2.4 | 37.9 | 2.43 | yes |
| A285D | c.854 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A285P | c.853 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W287C | c.861 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| W287G | c.859 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A288D | c.863 C>A | BLD | N/A | 626 ± 26\*\*\* | 2.1 ± 0.1 | 2.1 | NC | no |
| A288P | c.862 G>C | 366 ± 26 | 1.1 ± 0.1 | 3541 ± 277\*\*\* | 10.4 ± 0.7 | 9.3 | 9.69 | yes |
| I289F | c.865 A>T | BLD | N/A | 246 ± 19\*\*\* | 0.8 ± 0.1 | 0.8 | NC | no |
| I289S | c.866 T>G | BLD | N/A | 795 ± 28\*\*\* | 3.0 ± 0.2 | 3.0 | NC | yes |
| M290I | c.870 G>C | 18049 ± 690 | 68.0 ± 3.4 | 30322 ± 1225\*\*\* | 114.8 ± 6.3 | 46.7 | 1.68 | yes |
| M290L | c.868 A>C | 15488 ± 629 | 58.6 ± 3.2 | 29261 ± 1572\*\*\* | 111.4 ± 7.7 | 52.8 | 1.89 | yes |
| A291T | c.871 G>A | 4401 ± 380 | 16.5 ± 1.5 | 10511 ± 768\*\*\* | 40.5 ± 3.8 | 24.0 | 2.39 | yes |
| A292P | c.874 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A292T | c. 874 G>A | BLD | N/A | 803 ± 22\*\*\* | 2.3 ± 0.1 | 2.3 | NC | no |
| A292V | c.875 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P293A | c.877 C>G | BLD | N/A | 184 ± 18\*\*\* | 0.7 ± 0.1 | 0.7 | NC | no |
| P293H | c.878 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P293L | c.878 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P293S | c.877 C>T | BLD | N/A | 150 ± 15\*\*\* | 0.5 ± 0.0 | 0.5 | NC | no |
| P293T | c.877 C>A | 229 ± 20 | 0.7 ± 0.1 | 4488 ± 327\*\*\* | 13.3 ± 1.1 | 12.7 | 19.60 | yes |
| L294S | c.881 T>C | BLD | N/A | 1268 ± 37\*\*\* | 4.9 ± 0.1 | 4.9 | NC | yes |
| F295C | c.884 T>G | 1196 ± 38 | 3.4 ± 0.1 | 5051 ± 190\*\*\* | 14.5 ± 0.6 | 11.1 | 4.22 | yes |
| M296I | c.888 G>A | 4036 ± 141 | 15.7 ± 0.7 | 16247 ± 1022\*\*\* | 63.2 ± 4.2 | 47.4 | 4.03 | yes |
| M296L | c.886 A>C | 3594 ± 164 | 14.0 ± 0.8 | 16728 ± 992\*\*\* | 65.4 ± 4.3 | 51.4 | 4.65 | yes |
| M296T | c.887 T>C | 427 ± 26 | 1.6 ± 0.1 | 6911 ± 722\*\*\* | 26.9 ± 2.9 | 25.3 | 16.18 | yes |
| M296V | c.886 A>G | 2896 ± 136 | 11.3 ± 0.6 | 14022 ± 852\*\*\* | 55.4 ± 4.4 | 44.1 | 4.84 | yes |
| S297C | c.890 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S297F | c.890 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N298H | c.892 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N298K | c.894 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N298S | c.893 A>G | 1610 ± 107 | 5.0 ± 0.2 | 13414 ± 892\*\*\* | 41.4 ± 1.5 | 36.4 | 8.33 | yes |
| D299E | c.897 C>G | 11248 ± 786 | 34.2 ± 1.5 | 23786 ± 1332\*\*\* | 73 ± 2.8 | 38.7 | 2.11 | yes |
| D299G | c.896 A>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L300F | c.898 C>T | 4746 ± 363 | 14.8 ± 0.9 | 16129 ± 810\*\*\* | 50.5 ± 1.4 | 35.7 | 3.40 | yes |
| L300H | c.899 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L300P | c.899 T>C | 1277 ± 38 | 3.7 ± 0.1 | 13219 ± 412\*\*\* | 37.9 ± 1.2 | 34.2 | 10.35 | yes |
| R301G | c.901 C>G | 5974 ± 309 | 19.1 ± 1.2 | 20713 ± 1192\*\*\* | 64.7 ± 2.1 | 45.6 | 3.47 | yes |
| R301L | c.902 G>T | 1369 ± 94 | 4.3 ± 0.2 | 11612 ± 602\*\*\* | 36.1 ± 0.7 | 31.9 | 8.48 | yes |
| R301P | c.902 G>C | BLD | N/A | 1440 ± 236\*\*\* | 4.2 ± 0.5 | 4.2 | NC | yes |
| R301Q | c.902 G>A | 1914 ± 52 | 5.5 ± 0.2 | 15547 ± 353\*\*\* | 44.5 ± 1.0 | 39.0 | 8.12 | yes |
| I303N | c.908 T>A | BLD | N/A | 2070 ± 180\*\*\* | 6.2 ± 0.3 | 6.2 | NC | yes |
| S304N | c.911 G>A | 30563 ± 1196 | 94.1 ± 1.1 | 39629 ± 1765\*\*\* | 121.8 ± 2.2 | 27.7 | 1.30 | yes |
| S304T | c.911 G>C | 23174 ± 1016 | 76.4 ± 1.6 | 35071 ± 1111\*\*\* | 116.9 ± 3.3 | 40.5 | 1.51 | yes |
| A307T | c.919 G>A | 12581 ± 782 | 36.2 ± 1.2 | 30323 ± 1339\*\*\* | 87.7 ± 1.5 | 51.5 | 2.41 | yes |
| K308N | c.924 A>C | 1331 ± 123 | 3.7 ± 0.2 | 6219 ± 476\*\*\* | 17.6 ± 0.8 | 13.9 | 4.67 | yes |
| A309P | c.925 G>C | 313 ± 24 | 0.9 ± 0.1 | 3599 ± 352\*\*\* | 10.0 ± 0.6 | 9.1 | 11.51 | yes |
| L310F | c.928 C>T | 300 ± 41 | 0.8 ± 0.1 | 4270 ± 554\*\*\* | 11.6 ± 1.2 | 10.8 | 14.23 | yes |
| L310R | c.929 T>G | BLD | N/A | 242 ± 18\*\*\* | 0.7 ± 0.0 | 0.7 | NC | no |
| L311F | c.931 C>T | BLD | N/A | 596 ± 32\*\*\* | 2 ± 0.1 | 2.0 | NC | no |
| L311P | c.932 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L311R | c.932 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L311V | c.931 C>G | 598 ± 34 | 2 ± 0.1 | 5434 ± 286\*\*\* | 18 ± 0.8 | 16.0 | 9.09 | yes |
| Q312H | c.936 G>C | 2265 ± 353 | 6.1 ± 0.7 | 8244 ± 912\*\*\* | 23.1 ± 1.7 | 17.0 | 3.64 | yes |
| Q312R | c.935 A>G | 6594 ± 696 | 18.5 ± 1.3 | 11214 ± 795\*\*\* | 31.9 ± 1.4 | 13.4 | 1.70 | yes |
| D313G | c.938 A>G | 9017 ± 723 | 25.5 ± 1.0 | 14089 ± 851\*\*\* | 40.4 ± 1.4 | 14.9 | 1.56 | yes |
| D313Y | c.937 G>T | 19526 ± 1460 | 59.0 ± 3.1 | 26474 ± 1225\*\*\* | 80.9 ± 2.4 | 21.8 | 1.36 | yes |
| V316E | c.947 T>A | BLD | N/A | 256 ± 26\*\*\* | 0.8 ± 0.1 | 0.8 | NC | no |
| V316G | c.947 T>G | 211 ± 17 | 0.7 ± 0.1 | 1151 ± 57\*\*\* | 3.8 ± 0.1 | 3.1 | 5.47 | yes |
| V316I | c.946 G>A | 27748 ± 1279 | 92.1 ± 3.6 | 37859 ± 1752\*\*\* | 126.1 ± 5.5 | 34.0 | 1.36 | yes |
| I317N | c.950 T>A | BLD | N/A | 967 ± 68\*\*\* | 2.9 ± 0.2 | 2.9 | NC | no |
| I317S | c.950 T>G | BLD | N/A | 243 ± 16\*\*\* | 0.8 ± 0 | 0.8 | NC | no |
| I317T | c.950 T>C | 2298 ± 338 | 6.5 ± 0.6 | 7812 ± 530\*\*\* | 23.6 ± 1.0 | 17.0 | 3.40 | yes |
| I319F | c.955 A>T | 781 ± 38 | 2.6 ± 0.1 | 5879 ± 252\*\*\* | 19.6 ± 0.7 | 17.0 | 7.53 | yes |
| I319T | c.956 T>C | 3462 ± 303 | 10.3 ± 0.6 | 9297 ± 626\*\*\* | 28.0 ± 1.2 | 17.7 | 2.69 | yes |
| N320I | c.959 A>T | 459 ± 44 | 1.4 ± 0.1 | 5660 ± 340\*\*\* | 17.1 ± 0.5 | 15.7 | 12.34 | yes |
| N320K | c.960 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| N320Y | c.958 A>T | BLD | N/A | 188 ± 30\*\*\* | 0.6 ± 0.1 | 0.6 | NC | no |
| Q321E | c.961 C>G | BLD | N/A | 944 ± 61\*\*\* | 2.9 ± 0.1 | 2.9 | NC | no |
| Q321H | c.963 G>C | 620 ± 61 | 1.9 ± 0.1 | 6430 ± 466\*\*\* | 19.8 ± 0.9 | 17.9 | 10.38 | yes |
| Q321H/D322N | c.963-964 GG>CA | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q321L | c.962 A>T | 944 ± 78 | 2.9 ± 0.2 | 8091 ± 733\*\*\* | 24.6 ± 1.4 | 21.6 | 8.57 | yes |
| Q321R | c.962 A>G | 7398 ± 652 | 22.3 ± 1.3 | 21497 ± 1284\*\*\* | 66.1 ± 1.9 | 43.8 | 2.91 | yes |
| D322E | c.966 C>A | 2398 ± 141 | 6.7 ± 0.2 | 9554 ± 667\*\*\* | 26.8 ± 1.3 | 20.0 | 3.98 | yes |
| D322Nφ | c.964 G>A | 11843 ± 924 | 36.1 ± 1.8 | 15122 ± 976\* | 46.4 ± 1.6 | 10.3 | 1.28 | yes |
| G325D | c.974 G>A | BLD | N/A | 311 ± 26\*\*\* | 1.0 ± 0.1 | 1.0 | NC | no |
| G325R | c.973G>C | 909 ± 31 | 2.6 ± 0.1 | 9244 ± 417\*\*\* | 26.6 ± 1.4 | 24.0 | 10.17 | yes |
| G325S | c.973 G>A | 8102 ± 580 | 24.7 ± 1.1 | 20203 ± 1147\*\*\* | 62.5 ± 2.0 | 37.8 | 2.49 | yes |
| Q327E | c.979 C>G | 7436 ± 508 | 22.9 ± 1.1 | 16443 ± 1059\*\*\* | 50.4 ± 1.6 | 27.5 | 2.21 | yes |
| Q327K | c.979 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G328A | c.983 G>C | 2170 ± 69 | 6.9 ± 0.3 | 9054 ± 239\*\*\* | 28.7 ± 1.0 | 21.8 | 4.17 | yes |
| G328E | c.983 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G328R | c.982 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G328V | c.983 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G328W | c.982 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q333Rφ | c.998 A>G | 28914 ± 1765 | 93.5 ± 2.5 | 34401 ± 1520\* | 113.1 ± 3.2 | 19.6 | 1.19 | no |
| G334E | c.1001 G>A | 26216 ± 1395 | 86.7 ± 3.4 | 31679 ± 1244\*\* | 105.5 ± 3.7 | 18.8 | 1.21 | yes |
| E338K | c.1012 G>A | 2179 ± 232 | 6.8 ± 0.4 | 5691 ± 331\*\*\* | 18.6 ± 0.8 | 11.8 | 2.61 | yes |
| V339E | c.1016 T>A | 3805 ± 323 | 11.5 ± 0.6 | 6459 ± 488\*\*\* | 19.6 ± 0.6 | 8.1 | 1.70 | yes |
| V339G | c.1016 T>G | BLD | N/A | 471 ± 40\*\*\* | 1.5 ± 0.1 | 1.5 | NC | no |
| W340R | c.1018 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E341D | c.1023 A>C | BLD | N/A | 519 ± 48\*\*\* | 1.6 ± 0.1 | 1.6 | NC | no |
| E341K | c.1021 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R342L | c.1025 G>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R342P | c.1025 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R342Q | c.1025 G>A | BLD | N/A | 282 ± 23\*\*\* | 0.9 ± 0.1 | 0.9 | NC | no |
| P343L | c.1028 C>T | 11040 ± 397 | 36.6 ± 0.9 | 14919 ± 583\*\*\* | 49.6 ± 1.5 | 13.0 | 1.35 | yes |
| L344P | c.1031 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| S345P | c.1033 T>C | BLD | N/A | 1194 ± 92\*\*\* | 3.7 ± 0.2 | 3.7 | NC | yes |
| A348P | c.1042 G>C | 162 ± 24 | 0.5 ± 0.1 | 789 ± 73\*\*\* | 2.4 ± 0.2 | 1.9 | 4.88 | no |
| W349R | c.1045 T>C | BLD | N/A | 255 ± 31\*\*\* | 0.8 ± 0.1 | 0.8 | NC | no |
| W349S | c.1046 G>C | 5288 ± 337 | 16.5 ± 0.7 | 10035 ± 618\*\*\* | 31.4 ± 1.7 | 15.0 | 1.90 | yes |
| A350P | c.1048 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A352D | c.1055 C>A | BLD | N/A | 532 ± 46\*\*\* | 1.6 ± 0.1 | 1.6 | NC | no |
| A352P | c.1054 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| A352V | c.1055 C>T | 15153 ± 1083 | 44.5 ± 1.8 | 23791 ± 1662\*\*\* | 70.2 ± 3.2 | 25.7 | 1.57 | yes |
| 353insT, or 353ins1aa | c.1055\_57 dup CTA ; or, c.1054\_1055 ins CTA | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I354K | c.1061 T>A | 583 ± 66 | 1.7 ± 0.1 | 7398 ± 555\*\*\* | 21.6 ± 0.9 | 19.9 | 12.68 | yes |
| N355K | c.1065 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| R356G | c.1066 C>G | 4702 ± 213 | 15.4 ± 0.7 | 11329 ± 719\*\*\* | 36.2 ± 1.2 | 20.8 | 2.41 | yes |
| R356Q | c.1067G>A | 12084 ± 634 | 36.1 ± 1.5 | 25098 ± 1433\*\*\* | 75.1 ± 3.6 | 39.0 | 2.08 | yes |
| R356W | c.1066 C>T | 3526 ± 240 | 11.0 ± 0.7 | 15570 ± 830\*\*\* | 49.1 ± 2.6 | 38.1 | 4.42 | yes |
| Q357X | c.1069 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| 358del1 or 358del or del358aa | c.1072 DelGAG | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E358A | c.1073 A>C | 625 ± 31 | 1.9 ± 0.1 | 5625 ± 385\*\*\* | 16.6 ± 0.8 | 14.7 | 8.99 | yes |
| E358D | c.1074 G>T | 2142 ± 84 | 6.3 ± 0.2 | 10553 ± 268\*\*\* | 31.0 ± 0.7 | 24.7 | 4.93 | yes |
| E358G | c.1073 A>G | BLD | N/A | 1967 ± 274\*\*\* | 5.5 ± 0.5 | 5.5 | NC | yes |
| E358K | c.1072 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I359T | c.1076 T>C | 11337 ± 464 | 33.7 ± 1.7 | 21598 ± 466\*\*\* | 63.9 ± 2.0 | 30.3 | 1.91 | yes |
| G360C | c.1078 G>T | 2965 ± 152 | 8.7 ± 0.5 | 5668 ± 189\*\*\* | 16.8 ± 0.7 | 8.0 | 1.91 | yes |
| G360D | c.1079 G>A | 344 ± 23 | 1.0 ± 0.1 | 2457 ± 160\*\*\* | 7.2 ± 0.4 | 6.2 | 7.13 | yes |
| G360S | c.1078 G>A | 3350 ± 162 | 10.0 ± 0.6 | 7424 ± 188\*\*\* | 22.1 ± 0.9 | 12.1 | 2.22 | yes |
| G361A | c.1082 G>C | 2443 ± 73 | 7.2 ± 0.3 | 10112 ± 346\*\*\* | 30.0 ± 1.3 | 22.8 | 4.14 | yes |
| G361E | c.1082 G>A | 790 ± 21 | 2.6 ± 0.1 | 3894 ± 124\*\*\* | 13.4 ± 1 | 10.8 | 4.93 | yes |
| G361R | c.1081 G>A | 155 ± 15 | 0.5 ± 0.0 | 1004 ± 34\*\*\* | 3.0 ± 0.1 | 2.5 | 6.50 | no |
| P362L | c.1085 C>T | 947 ± 41 | 2.8 ± 0.1 | 6610 ± 196\*\*\* | 19.6 ± 0.8 | 16.8 | 6.98 | yes |
| P362T | c.1084 C>A | 9824 ± 630 | 32 ± 1.7 | 20927 ± 714\*\*\* | 70.5 ± 4.5 | 38.5 | 2.13 | yes |
| R363C | c.1087 C>T | 3994 ± 183 | 11.9 ± 0.6 | 12104 ± 379\*\*\* | 36.0 ± 1.6 | 24.1 | 3.03 | yes |
| R363H | c.1088 G>A | 7021 ± 382 | 20.0 ± 0.8 | 17613 ± 636\*\*\* | 50.5 ± 1.6 | 30.6 | 2.51 | yes |
| R363P | c.1088 G>C | BLD | N/A | 269 ± 17\*\*\* | 0.8 ± 0.0 | 0.8 | NC | no |
| A368T | c.1102 G>A | 17725 ± 667 | 54.6 ± 1.7 | 23438 ± 471\*\*\* | 72.6 ± 1.8 | 18.0 | 1.32 | yes |
| L372P | c.1115 T>C | 388 ± 23 | 1.2 ± 0.1 | 848 ± 34\*\*\* | 2.6 ± 0.1 | 1.4 | 2.18 | no |
| L372Q | c.1115 T>A | 260 ± 23 | 0.8 ± 0.1 | 522 ± 37\*\*\* | 1.6 ± 0.1 | 0.8 | 2.01 | no |
| L372R | c.1115 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G373D | c.1118 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G373R | c.1117 G>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G373S | c.1117 G>A | 1544 ± 69 | 4.8 ± 0.3 | 5128 ± 288\*\*\* | 15.7 ± 0.8 | 10.9 | 3.32 | yes |
| G375\_V376del | c.1124\_1129del GAGTGG | 807 ± 49 | 2.6 ± 0.2 | 1519 ± 69\*\*\* | 5 ± 0.3 | 2.4 | 1.88 | no |
| A377D | c.1130 C>A | BLD | N/A | 226 ± 20\*\*\* | 0.7 ± 0.1 | 0.7 | NC | no |
| c.1129\_1130 ins GCCTGTAATCCT, or ins377-4aa | c.1129 ins GCCTGTAATCCT; inserts after c.1128ntd | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C378R | c.1132 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C378Y | c.1133 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| 382del-1aa or 382del1 or 382del | c.1145 DelCTT | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C382W | c.1146 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| C382Y | c.1145 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I384N | c.1151 T>A | BLD | N/A | 283 ± 13\*\*\* | 0.8 ± 0.0 | 0.8 | NC | no |
| T385A | c.1153 A>G | 19434 ± 617 | 57.3 ± 2.1 | 24959 ± 770\*\*\* | 73.5 ± 2.4 | 16.1 | 1.28 | yes |
| T385P | c.1153 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q386P | c.1157 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| P389A | c.1165 C>G | 927 ± 33 | 2.7 ± 0.1 | 1348 ± 37\*\*\* | 4.0 ± 0.1 | 1.2 | 1.45 | no |
| P389L | c.1166 C>T | BLD | N/A | 188 ± 14\*\* | 0.6 ± 0 | 0.6 | NC | no |
| P389R | c.1166 C>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| V390frX8 | c.1168 Ins T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| K391T | c.1172 A>C | 9593 ± 351 | 30.1 ± 1.4 | 15199 ± 410\*\*\* | 47.4 ± 1.5 | 17.4 | 1.58 | yes |
| G395A | c.1184 G>C | 7664 ± 643 | 24.4 ± 1.3 | 9673 ± 668\*\* | 30.7 ± 1.0 | 6.3 | 1.26 | yes |
| G395E | c.1184 G>A | 3430 ± 248 | 11.9 ± 1.3 | 5489 ± 348\*\*\* | 19.7 ± 2.2 | 7.8 | 1.60 | yes |
| c.1184insTAG, or ins395aa | c.1184 ins TAG; inserts after c.1183 | 572 ± 29 | 1.9 ± 0.1 | 911 ± 30\*\*\* | 3.1 ± 0.2 | 1.2 | 1.59 | no |
| F396Y | c.1187 T>A | 35640 ± 1129 | 111.2 ± 4.0 | 37319 ± 960 | 116.4 ± 3.3 | 5.1 | 1.05 | no |
| E398K | c.1192 G>A | 20150 ± 818 | 63.2 ± 3.2 | 36488 ± 824\*\*\* | 113.6 ± 2.6 | 50.4 | 1.81 | yes |
| W399X | c.1196 G>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| 401ins(T-S) | c.1202 Ins GACTTC | 2075 ± 94 | 6.5 ± 0.4 | 4717 ± 230\*\*\* | 14.8 ± 0.8 | 8.3 | 2.27 | yes |
| 403del-1aa or 403del or 403del1 | c.1208 DelAAG | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L403S | c.1208 T>C | 4480 ± 136 | 14.0 ± 0.5 | 6076 ± 133\*\*\* | 19.0 ± 0.5 | 4.9 | 1.36 | yes |
| S405R | c.1213 A>C | 15547 ± 652 | 52.5 ± 3.7 | 17297 ± 744\* | 59.6 ± 5.1 | 7.1 | 1.11 | no |
| H406Rφ | c.1217 A>G | 23858 ± 567 | 74.2 ± 1.6 | 23512 ± 589 | 73.2 ± 1.7 | N/A | N/A | no |
| I407K | c.1220 T>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I407R | c.1220 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| I407Vφ | c.1219 A>G | 31074 ± 943 | 85.6 ± 2.8 | 35444 ± 671\*\*\* | 97.7 ± 2.3 | 12.1 | 1.14 | no |
| P409A | c.1225 C>G | 1111 ± 54 | 3.1 ± 0.2 | 10481 ± 445\*\*\* | 28.9 ± 1.3 | 25.9 | 9.43 | yes |
| P409S | c.1225 C>T | 883 ± 47 | 2.4 ± 0.1 | 8378 ± 315\*\*\* | 23.0 ± 0.8 | 20.6 | 9.49 | yes |
| P409T | c.1225 C>A | 986 ± 56 | 2.7 ± 0.2 | 8949 ± 558\*\*\* | 24.7 ± 1.6 | 22.0 | 9.07 | yes |
| T410A | c.1228 A>G | 380 ± 19 | 1.0 ± 0.1 | 4052 ± 135\*\*\* | 11.2 ± 0.4 | 10.1 | 10.65 | yes |
| T410I | c.1229 C>T | 146 ± 22 | 0.4 ± 0.1 | 4437 ± 274\*\*\* | 12.2 ± 0.8 | 11.8 | 30.37 | yes |
| T410K | c.1229 C>A | BLD | N/A | BLD | N/A | N/A | N/A | no |
| T410P | c.1228 A>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| G411D | c.1232 G>A | 409 ± 37 | 1.1 ± 0.1 | 3429 ± 148\*\*\* | 9.6 ± 0.4 | 8.5 | 8.38 | yes |
| T412N | c.1235 C>A | 360 ± 37 | 1.0 ± 0.1 | 5025 ± 255\*\*\* | 14.2 ± 0.8 | 13.2 | 13.95 | yes |
| L414S | c.1241 T>C | BLD | N/A | 403 ± 43\*\*\* | 1.2 ± 0.1 | 1.2 | NC | no |
| L415F | c.1243 C>T | 27736 ± 1380 | 91.8 ± 5.1 | 30643 ± 1340\* | 103.3 ± 7.2 | 11.6 | 1.10 | no |
| L415P | c.1244 T>C | BLD | N/A | BLD | N/A | N/A | N/A | no |
| Q416X | c.1246 C>T | BLD | N/A | BLD | N/A | N/A | N/A | no |
| L417R | c.1250 T>G | BLD | N/A | BLD | N/A | N/A | N/A | no |
| E418G | c.1253 A>G | 19226 ± 811 | 67.5 ± 1.7 | 25426 ± 910\*\*\* | 89.4 ± 1.5 | 21.9 | 1.32 | yes |
| M421V | c.1261 A>G | 25172 ± 1665 | 83.0 ± 3.4 | 32805 ± 2008\*\* | 108.6 ± 4.3 | 25.6 | 1.30 | yes |
| X430Q, X430Qins30aa, or, X430QextX30 | c.1288 T>C, c.1291 ins AATGTTTATTTTATTGCCAACTACTACTTCCTGTCCACCTTTTTCTCCATTCACTTTAAAAGCTCAAGGCTAGGTGGCTCATGCCTGTAA | 158 ± 13 | 0.5 ± 0.1 | 314 ± 28\*\*\* | 1.1 ± 0.1 | 0.5 | 1.99 | no conclusion |

|  |
| --- |
| Data are expressed as the mean ± SEM of twenty data points: mutant α‑Gal A activity expressed as a percent of the α‑Gal A activity measured in wild-type cell lysates incubated without migalastat (‑Migalastat) assayed in parallel.  “Absolute Increase at 10 µM (%WT)”: the percent wild-type α‑Gal A activity with 10 µM migalastat (+Migalastat) minus the baseline (‑Migalastat) percent wild-type α‑Gal A activity.  “ α-Gal A Activity at 10 µM –Fold Over Baseline ”: α‑Gal A activity in mutant-transfected cell lysate with 10 µM migalastat / α‑Gal A activity in mutant-transfected cell lysate without migalastat.  Statistically significant differences in α-Gal A activity without migalastat (n=20) versus with 10 μM migalastat (n=20) were determined using a one-tailed Mann-Whitney U non-parametric test: \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001. One or more asterisks indicate α‑Gal A mutant forms that show a statistically significant increase in α‑Gal A activity after incubation with 10 μM migalastat.  “BLD” indicates that the mean α‑Gal A activity (mean of n=20) was below the limit of detection (<142 nmol/mg/hr; value is equal to 3 \* standard deviation of the pcDNA activity in nmol/mg/hr after vector subtraction across 128 samples assayed in ten method validation experiments).  **“Meets Amenable Mutation Criteria? (Yes/No)”**:  **-“yes”**, if a mutant form shows a statistically significant increase in response to 10 µM migalastat and also meets the following criteria:  α‑Gal A activity in the presence of 10 µM migalastat that is ≥1.20-fold over baseline1 with an absolute increase of ≥3.0% of wild-type α‑Gal A activity2.  1The α-Gal A activity at 10 µM –fold over baseline is not calculated for mutant forms with a baseline α‑Gal A activity that is BLD; for these mutant forms the criteria are met solely on the basis of the absolute increase criterion.  2For mutant forms with a baseline α‑Gal A activity that is BLD, this criterion is met if the α‑Gal A activity at 10 µM migalastat is ≥3.0% of wild‑type.  **-“no”**, if a mutant form is not qualified for testing in the GLP HEK assay, does not show a statistically significant increase in response to 10 µM migalastat, and/or does not meet the above criteria  **-“no conclusion”**, if two independent lots of a specific plasmid failed the qPCR assay acceptance criteria after two consecutive transient transfection runs for each lot, but passed the GLP HEK assay acceptance criteria and the results for the α-Gal A mutant form did not meet the amenable mutation criteria.  N/A: Not Applicable. NC: not calculable. φMutation not yet reported as Fabry disease associated.  A listing of all Fabry disease mutations with literature phenotypes is provided in a separate Appendix. |

**Table 2S: Clinical Studies and Sources Used to Assess Clinical Validation of GLP HEK Assay by Parameter**

|  |  |  |
| --- | --- | --- |
| Parameter | Gender(s) Included | Clinical Source(s) |
| α-Gal A | M | Lymphoblast: 74 cell lines  PBMCs: Studies 201-203, 011, and 012 |
| GL-3 inclusions per kidney interstitial capillary | M | Study 011 |
| Lyso-Gb3 | M only  M and F | Studies 011 and 012 |
| Characteristics of amenable mutations from clinical studies compared to all amenable mutations identified in GLP HEK assay | M and F | Studies 201-204, 011, and 012 |

PBMCs: Peripheral blood mononuclear cells | M: males; F: females | α-Gal A: α-Galactosidase A | GL-3: Globotriaosylceramide | Lyso-Gb3: Plasma globotriaosylsphingosine **Table 3S: Comparison of the Mutant α-Gal A Responses to Migalastat in the GLP HEK Assay and in PBMCs of Male Fabry Patients after Oral Administration of Migalastat in Phase 2**

| **Meets Criteria** | **Patient** | **Protein change** | **Per Protocol**  **Dose and Regimen** | **Phase 2 PBMC Assay (% Normal)** | | | | | | | | **Phase 2 PBMC Response** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Baseline** | **+ Migalastat** | | | | | | |
| **Wk 2** | **Wk 4** | **Wk 6/8** | **Wk 12** | **Wk 24** | **Wk 36** | **Wk 48** |
| **Yes** | 201-101 | p.A143T | 25,100,250 mg BID, 50 mg QD | 23.6 | 66.4 | 60.5 | 64.1 | 79.1 | 70.5 | 87.3 | 90.0 | Good |
| 201-102 | p.T41I | 25,100,250 mg BID, 50 mg QD | 21.4 | 89.6 | 122.3 | 126.8 | 111.8 | NA | 110.5 | 112.3 | Good |
| 201-103 | p.T41I | 25,100,250 mg BID, 50 mg QD | 30.0 | 74.1 | 121.8 | 151.4 | 111.8 | NA | 136.8 | 118.2 | Good |
| 201-104 | p.A97V | 25,100,250 mg BID, 50 mg QD | 4.6 | 53.2 | 65.9 | 69.6 | 67.3 | NA | 62.7 | 42.7 | Good |
| 201-105 | p.A143T | 25,100,250 mg BID, 50 mg QD | 48.6 | NA | NA | NA | 72.3 | NA | NA | NA | Good |
| 201-106 | p.M51K | 25,100,250 mg BID, 50 mg QD | 4.1 | 23.6 | 30.0 | 20.5 | 17.7 | 15.9 | 17.7 | 28.2 | Good |
| 201-204 | p.G328A | 25,100,250 mg BID, 50 mg QD | 0.0 | 1.8 | 2.3 | 6.4 | 1.8 | 0.5 | 0.9 | NA | Good |
| 201-305 | p.L300P | 25,100,250 mg BID, 50 mg QD | 0.9 | 7.3 | 6.8 | 13.2 | 1.4 | 0.5 | 2.3 | 2.7 | Good |
| 201-109 | p.R301Q | 150 mg QD (*in vivo* screen) | 2.3 | 11.8 | NA | NA | NA | NA | NA | NA | Good |
| 202-202 | p.R301Q | 150 mg QOD | 1.4 | NA | 34.2 | 29.3 | 33.5 | 32.4 | 35.0 | 27.6 | Good |
| 202-103 | p.P259R | 150 mg QOD | 1.1 | NA | 10.1 | 8.0 | 10.5 | NA | NA | 1.6 | Good |
| 202-104 | p.P259R | 150 mg QOD | 1.0 | NA | 13.1 | 14.5 | 11.1 | 15.3 | 0.0 | 0.0 | Good |
| 203-301 | p.F295C | 150 mg QOD | 0.2 | NA | 0.5 | NA | 1.0 | 1.6 | 2.5 | 0.5 | Good |
| 203-RF01 | p.N215S | 150 mg QOD | 15.5 | NA | 38.5 | 55.0 | 48.2 | 49.6 | 50.9 | 33.6 | Good |
| 203-RF03 | p.P205T | 150 mg QOD | 0.8 | NA | 1.4 | 2.6 | 1.7 | 6.0 | 8.8 | 14.2 | Good |
| **No** | 201-107 | p.G171D | 150 mg QD (*in vivo* screen) | 1.8 | 1.8 | NA | NA | NA | NA | NA | NA | Non/Limited |
| 201-307 | p.G271C | 150 mg QD (*in vivo* screen) | 27.3 | 0.5 | NA | NA | NA | NA | NA | NA | Non/Limited |
| 201-401 | p.R227Q | 150 mg QD (*in vivo* screen) | 0.5 | 0.5 | NA | NA | NA | NA | NA | NA | Non/Limited |
| 201-501 | p.H225R | 150 mg QD (*in vivo* screen) | 1.8 | 1.4 | NA | NA | NA | NA | NA | NA | Non/Limited |
| 201-205 | p.S276G | 25,100,250 mg BID, 50 mg QD | 0.5 | 4.1 | 7.7 | 5.5 | 4.1 | 3.6 | 4.6 | NA | Good |
| 202-102 | p.L415P | 150 mg QOD | 0.6 | NA | 0.6 | 0.0 | 0.0 | 0.8 | NA | 0.6 | Non/Limited |
| 203-302 | p.C94S | 150 mg QOD | 0.3 | NA | 0.4 | 0.3 | NA | 0.6 | 0.3 | 0.5 | Non/Limited |
| 203-303 | p.R112C | 150 mg QOD | 0.6 | NA | NA | NA | NA | 1.4 | 1.0 | 1.5 | Non/Limited |

‘Meets Criteria’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK assay grouped according to the amenable mutation criteria. Then, these were compared to the PBMC α-Gal A responses of male Fabry patients with the corresponding *GLA* mutations who had been orally administered migalastat during Phase 2 clinical trials. Patients enrolled in FAB-CL-201 were orally administered migalastat at doses of 25 mg twice a day for the first two weeks, 100 mg twice a day during weeks 3 and 4, 250 mg twice a day during weeks 5 and 6, followed by 50 mg once per day during weeks 7 through 12. Separately, six other patients enrolled in FAB-CL-201, in the ‘Per Protocol Dose and Regimen’ section, were orally administered 150 mg migalastat every day for two weeks during a screening period and then tested for an *in vivo* PBMC α-Gal A response (this *in vivo* screen was conducted under a protocol amendment). Five of these six patients indicated by the phrase ‘(*in vivo* screen)’ are represented here; the sixth, had an insertion mutation which was not tested in the *in vitro* assay, and thus that patient is not represented in this table. None of these patients who met the other eligibility criteria (see ClinicalTrials.gov), responded with increased PBMC α-Gal A levels after migalastat administration, and thus did not participate in the remainder of the study. Patients enrolled in FAB-CL-202 and FAB‑CL‑203 were orally administered 150 mg migalastat every other day for the duration of the weeks indicated. In the PBMC assay, the baseline α-Gal A activity (-migalastat) presents the values from the last pre-dose sample. In the PBMC assay, the α-Gal A activity (+migalastat) presents the values after 150 mg (FAB-CL-202, FAB-CL-203, and FAB-CL-201 *in vivo* screen) or 25, 50, 100, or 250 mg (FAB-CL-201) migalastat administration at different regimens (‘QD’, ‘QOD’, and ‘BID’ refer to ‘every day’, ‘once every other day’ and ‘twice per day’) and time points (‘Wk’ refers to ‘week’) as specified in accordance with the different clinical protocols. In ‘Phase 2 PBMC Response’, patients were categorized according to their maximal net α-Gal A increase from baseline after treatment with migalastat. Patients with a 2% of normal or greater net increase were categorized as showing “good” responses, and patients with less than a 2% of normal net increase were categorized as showing “non/limited” responses. The mean normal α-Gal A activity in PBMCs from healthy volunteers was 22 nmol of free 4-MU released/mg protein/hr. ‘NA’ refers to ‘not available’ due to one or more of the following reasons: a) time point not part of the clinical study protocol, b) patient discontinued, c) sample not received, d) sample not analyzed due to poor sample quality.

**Table 4S: Comparison of the Mutant α-Gal A Responses in the GLP HEK Assay and in PBMCs of Male Patients After Oral Administration of Migalastat in Study 011**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **GLP HEK Amenable?** | **Patient** | **Protein change** | **Stage 1-Stage 2**  **Treatment Category** | **Study 011 PBMC α-Gal A (% of Normal)** | | | |
| **Baseline1** | **+ Migalastat** | | **Study 011**  **PBMC**  **Response** |
| **6 Months2** | **12 Months3** |
| **Yes** | 1101-005 | p.G183D | Placebo-Migalastat | 0 | 2.05 | 1.95 | Good |
| 1101-007 | p.L243F | Placebo-Migalastat | 1.14 | 2.64 | 3.45 | Good |
| 1601-003 | p.I253T | Migalastat-Migalastat | 2.86 | 17.68 | 33.55 | Good |
| 1601-009 | p.I253T | Migalastat-Migalastat | 2.64 | 41.18 | NA | Good |
| 1902-001 | p.C174R | Migalastat-Migalastat | 1.27 | 5.14 | NA | Good |
| 2001-001 | p.R356W | Placebo-Migalastat | 1.68 | 49.86 | 48.23 | Good |
| 2001-003 | p.D55V/Q57L | Placebo-Migalastat | 0.18 | 16.64 | 23.41 | Good |
| 2001-005 | p.G144V | Migalastat-Migalastat | 0.23 | 0.36 | 0.73 | Non/Limited |
| 2004-001 | p.R301Q | Placebo-Migalastat | 2.5 | 22.77 | 16.73 | Good |
| 2016-901 | p.G373S | Placebo-Migalastat | 0.82 | 5.36 | 4.5 | Good |
| 2026-906 | p.D322E | Migalastat-Migalastat | 0.91 | 7.09 | 5.91 | Good |
| 2701-014 | p.G325R | Migalastat-Migalastat | 0.32 | 0.59 | NA | Non/Limited |
| 3002-002 | p.Y216C | Migalastat-Migalastat | 0 | 6.77 | 2.45 | Good |
| 4001-015 | p.D33G | Placebo-Migalastat | 4.09 | 39.95 | 43.95 | Good |
| 5001-001 | p.P259R | Placebo-Migalastat | 3.27 | 13.27 | 10.55 | Good |
| 5001-003 | p.P259R | Placebo-Migalastat | 3.14 | 11.64 | 12.86 | Good |
| **No** | 2004-901 | p.R342Q | Placebo-Migalastat | 0 | 0 | 0.32 | Non/Limited |
| 2007-003 | p.R342Q | Migalastat-Migalastat | 0 | 0.23 | 0.27 | Non/Limited |
| 2008-006 | p.S276G | Migalastat-Migalastat | 0.32 | 0.36 | 0.5 | Non/Limited |
| 2015-001 | p.R342Q | Placebo-Migalastat | 0 | 0.18 | NA | Non/Limited |
| 4001-010 | p.S65I | Placebo-Migalastat | 0.14 | 0.77 | 0.36 | Non/Limited |
| 5003-008 | p.R342Q | Migalastat-Migalastat | 0.18 | 0.27 | 0 | Non/Limited |

‘GLP HEK Amenable’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK cell-based assay grouped according to the “amenable” mutation criteria. These groups are aligned with the PBMC α-Gal A results from male patients with the corresponding α-Gal A mutant forms who had been orally administered migalastat at 150 mg every other day (QOD) during the Study 011 Phase 3 clinical trial.

PBMC α-Gal A is expressed as a percentage of normal (% of normal). The median normal α-Gal A activity in PBMCs from 16 non-Fabry patients was 22 nmol of free 4-MU released/mg protein/hr.

In ‘Study 011 PBMC Response’, patients were categorized according to their maximal net α-Gal A (% of normal) increase from baseline after 6 or 12 months of treatment with migalastat. Subjects with a 2% of normal or greater net increase after either duration of treatment were categorized as showing “good” responses, and patients with less than a 2% of normal net increase were categorized as showing “non/limited” responses.

The PBMC α-Gal A value at baseline was missing for one male patient (1601-006, D244N) treated with migalastat in Stage 1 and Stage 2. Therefore, this patient was excluded from this analysis and is not represented in this table.

The PBMC α-Gal A value at baseline from one male patient (4001-004, A156T) was implausible because it was higher than any baseline value from all other male patients in the study (in fact, the baseline value is within the typical range of baseline values from female patients in AT1001-011), and it was higher than any one of this male’s other visits. Therefore, this patient was excluded from this analysis and is not represented in this table.

‘NA’ refers to ‘not available’ due to one or more of the following reasons: a) patient discontinued, b) sample not received, c) sample not analyzed due to poor sample quality.

1Baseline refers to the PBMC α-Gal A (% of normal) value at the Study 011 baseline visit (Visit 1) in patients treated with migalastat in Stage 1 and Stage 2; it refers to the PBMC α-Gal A (% of normal) value at month 6 in patients treated with placebo in Stage 1 and migalastat in Stage 2.

26 months of migalastat refers to the PBMC α-Gal A (% of normal) value at month 6 in patients treated with migalastat in both Stage 1 and Stage 2; it refers to the PBMC α-Gal A (% of normal) value at month 12 in patients treated with placebo in Stage 1 and migalastat in Stage 2.

312 months of migalastat refers to the PBMC α-Gal A (% of normal) value at month 12 in patients treated with migalastat in both Stage 1 and Stage 2; it refers to the PBMC α-Gal A (% of normal) value at month 18 (from the Open-Label Extension) in patients treated with placebo in Stage 1 and migalastat in Stage 2.

**Table 5S: Comparison of the Mutant α-Gal A Responses in the GLP HEK Assay to Those in PBMCs of Male Patients After Oral Administration of Migalastat in Study 012**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **GLP HEK Amenable?** | **Patient** | **Protein change** | **Baseline to Month 18**  **Treatment Category** | **Study 012 PBMC α-Gal A (% of Normal)** | | | |
| **Baseline1** | **+ Migalastat** | | **Study AT1001-012**  **PBMC**  **Response** |
| **6 Months2** | **12 Months3** |
| **Yes** | 1101-2401 | p.R363H | Migalastat | 15.23 | 79.55 | 56.0 | Good |
| 1701-2651 | p.A143T | Migalastat | 45.18 | 71.09 | 100.68 | Good |
| 2017-1451 | p.P205T | Migalastat | 4.09 | 8.09 | 7.59 | Good |
| 2023-1765 | p.N215S | Migalastat | 9.05 | 44.27 | 36.32 | Good |
| 2026-3101 | p.D322E | Migalastat | 2.64 | 5.55 | 6.0 | Good |
| 2026-3103 | p.D322E | Migalastat | 3.32 | 5.45 | 2.82 | Good |
| 2301-1154 | p.N215S | Migalastat | 10.14 | 44.36 | 43.64 | Good |
| 2301-1156 | p.N215S | Migalastat | 10.95 | 62.59 | 51.41 | Good |
| 2305-2301 | p.N215S | Migalastat | 9.55 | 49.23 | 45.77 | Good |
| 2601-1101 | p.A143T | Migalastat | 50.91 | 83.95 | 112.27 | Good |
| 4001-1053 | p.M284T | Migalastat | 0.73 | 2.77 | 2.23 | Good |
| 4101-2451 | p.Q312R | Migalastat | 7.68 | 56.09 | 41.05 | Good |
| 4102-2701 | p.L403S | Migalastat | 6.73 | 14.05 | 24.05 | Good |
| 4104-2802 | p.M96I | Migalastat | 5.59 | 20.68 | 25.14 | Good |
| **No** | 5003-1851 | p.R342Q | Migalastat | 0.27 | 0.27 | 0.36 | Non/Limited |

‘GLP HEK Amenable’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK cell-based assay grouped according to the “amenable” mutation criteria. These groups are aligned with the PBMC α-Gal A results from male patients with the corresponding α-Gal A mutant forms who had been orally administered migalastat HCl at 150 mg every other day (QOD) during the study AT1001-012 Phase 3 clinical trial.

PBMC α-Gal A is expressed as a percentage of normal (% of normal). The median normal α-Gal A activity in PBMCs from 16 non-Fabry patients was 22 nmol of free 4-MU released/mg protein/hr.

In ‘Study AT1001-012 PBMC Response’, patients were categorized according to their maximal net α-Gal A (% of normal) increase from baseline after 6 or 12 months of treatment with migalastat. Patients with a 2% of normal or greater net increase after either duration of treatment were categorized as showing “good” responses, and patients with less than a 2% of normal net increase were categorized as showing “non/limited” responses.

1Baseline refers to the PBMC α-Gal A (% of normal) value at the baseline visit in patients treated with migalastat.

26 months of migalastat refers to the PBMC α-Gal A (% of normal) value at month 6 in patients treated with migalastat.

312 months of migalastat refers to the PBMC α-Gal A (% of normal) value at month 12 in patients treated with migalastat.

The PBMC α-Gal A value at baseline was missing for one male subject (2301-1152, R342Q) treated with migalastat in Study AT1001-012. Therefore, this subject was excluded from this analysis and is not represented in this table.

| Table 6S: Comparison of the Mutant α-Gal A Responses in the GLP HEK Assay to Those in PBMCs of Male Patients After Oral Administration of Migalastat (150 mg QOD) in Phase 2 and 3 Clinical Studies | | | | |
| --- | --- | --- | --- | --- |
| Amenable | Subject | Protein change | Clinical Study | PBMC Response |
|
|
| 201-109 | p.R301Q | FAB-201 (*in vivo* screen) | Good |
| 202-202 | p.R301Q | FAB-202 | Good |
| 202-103 | p.P259R | FAB-202 | Good |
| 202-104 | p.P259R | FAB-202 | Good |
| 203-301 | p.F295C | FAB-203 | Good |
| 203-RF01 | p.N215S | FAB-203 | Good |
| 203-RF03 | p.P205T | FAB-203 | Good |
| 1101-005 | p.G183D | AT1001-011 | Good |
| 1101-007 | p.L243F | AT1001-011 | Good |
| 1601-003 | p.I253T | AT1001-011 | Good |
| 1601-009 | p.I253T | AT1001-011 | Good |
| 1902-001 | p.C174R | AT1001-011 | Good |
| 2001-001 | p.R356W | AT1001-011 | Good |
| 2001-003 | p.D55V/Q57L | AT1001-011 | Good |
| 2001-005 | p.G144V | AT1001-011 | Non/Limited |
| 2004-001 | p.R301Q | AT1001-011 | Good |
| 2009-001 | p.G373S | AT1001-011 | Good |
| 2026-906 | p.D322E | AT1001-011 | Good |
| 2701-014 | p.G325R | AT1001-011 | Non/Limited |
| 3002-002 | p.Y216C | AT1001-011 | Good |
| 4001-015 | p.D33G | AT1001-011 | Good |
| 5001-001 | p.P259R | AT1001-011 | Good |
| 5001-003 | p.P259R | AT1001-011 | Good |
| 1101-2401 | p.R363H | AT1001-012 | Good |
| 1701-2651 | p.A143T | AT1001-012 | Good |
| 2017-1451 | p.P205T | AT1001-012 | Good |
| 2023-1765 | p.N215S | AT1001-012 | Good |
| 2026-3101 | p.D322E | AT1001-012 | Good |
| 2026-3103 | p.D322E | AT1001-012 | Good |
| 2301-1154 | p.N215S | AT1001-012 | Good |
| 2301-1156 | p.N215S | AT1001-012 | Good |
| 2305-2301 | p.N215S | AT1001-012 | Good |
| 2601-1101 | p.A143T | AT1001-012 | Good |
| 4001-1053 | p.M284T | AT1001-012 | Good |
| 4101-2451 | p.Q312R | AT1001-012 | Good |
| 4102-2701 | p.L403S | AT1001-012 | Good |
| 4104-2802 | p.M96I | AT1001-012 | Good |
| **Non-Amenable** | **201-107** | **p.G171D** | **FAB-201 (*in vivo* screen)** | **Non/Limited** |
| **201-307** | **p.G271C** | **FAB-201 (*in vivo* screen)** | **Non/Limited** |
| **201-401** | **p.R227Q** | **FAB-201 (*in vivo* screen)** | **Non/Limited** |
| **201-501** | **p.H225R** | **FAB-201 (*in vivo* screen)** | **Non/Limited** |
| **202-102** | **p.L415P** | **FAB-202** | **Non/Limited** |
| **203-302** | **p.C94S** | **FAB-203** | **Non/Limited** |
| **203-303** | **p.R112C** | **FAB-203** | **Non/Limited** |
| **2016-001** | **p.R342Q** | **AT1001-011** | **Non/Limited** |
| **2007-003** | **p.R342Q** | **AT1001-011** | **Non/Limited** |
| **2008-006** | **p.S276G** | **AT1001-011** | **Non/Limited** |
| **2015-001** | **p.R342Q** | **AT1001-011** | **Non/Limited** |
| **4001-010** | **p.S65I** | **AT1001-011** | **Non/Limited** |
| **5003-008** | **p.R342Q** | **AT1001-011** | **Non/Limited** |
| **5003-1851** | **p.R342Q** | **AT1001-012** | **Non/Limited** |

‘GLP HEK Amenable’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK cell-based assay grouped according to the “amenable” mutation criteria. These groups are aligned with the PBMC α-Gal A results from male subjects with the corresponding α-Gal A mutant forms who had been orally administered migalastat at 150 mg every other day (QOD) during the Phase 2 and 3 clinical studies.

In ‘PBMC Response’, subjects were categorized according to their maximal net α-Gal A (% of normal) increase from baseline after treatment with migalastat. Subjects with a 2% of normal or greater net increase at any time after at least two weeks of treatment were categorized as showing “good” responses, and subjects with less than a 2% of normal net increase were categorized as showing “non/limited” responses.

**Table 7S: Comparison between Mutant α–Gal A Responses in GLP HEK and Male Fabry Patient Kidney Interstitial Capillary GL-3 Responses in Study 011**

| **GLP HEK Amenable?** | **Patient** | **Sex** | **Protein change** | **Stage 1-Stage 2**  **Treatment Category** | **Study 011 Male Patient Kidney IC GL-3** | |
| --- | --- | --- | --- | --- | --- | --- |
| **+ Migalastat** | **Study 011**  **Kidney IC GL-3**  **Response** |
| **Absolute Change after 6 Months**1 |
| **Yes** | 1101-005 | M | G183D | Placebo-Migalastat | -0.944 | Good |
| 1101-007 | M | L243F | Placebo-Migalastat | -1.134 | Good |
| 2001-003 | M | D55V/Q57L | Placebo-Migalastat | -0.093 | Good |
| 2004-001 | M | R301Q | Placebo-Migalastat | -0.053 | Good |
| 4001-015 | M | D33G | Placebo-Migalastat | -0.083 | Good |
| 5001-001 | M | P259R | Placebo-Migalastat | -2.281 | Good |
| 1601-003 | M | I253T | Migalastat-Migalastat | -0.083 | Good |
| 1601-006 | M | D244N | Migalastat-Migalastat | -1.125 | Good |
| 2001-005 | M | G144V | Migalastat-Migalastat | -1.775 | Good |
| 2026-906 | M | D322E | Migalastat-Migalastat | -1.102 | Good |
| 3002-002 | M | Y216C | Migalastat-Migalastat | -1.248 | Good |
| 4001-004 | M | A156T | Migalastat-Migalastat | -0.309 | Good |
| **No** | 2004-901 | M | R342Q | Placebo-Migalastat | 2.211 | Non/Limited |
| 2015-001 | M | R342Q | Placebo-Migalastat | 1.271 | Non/Limited |
| 4001-010 | M | S65I | Placebo-Migalastat | 0.982 | Non/Limited |
| 2007-003 | M | R342Q | Migalastat-Migalastat | 0.851 | Non/Limited |
| 2008-006 | M | S276G | Migalastat-Migalastat | 0.008 | Non/Limited |
| 5003-008 | M | R342Q | Migalastat-Migalastat | 0.013 | Non/Limited |

‘GLP HEK Amenable’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK cell-based assay grouped according to the “amenable” mutation criteria. These groups are aligned with the kidney IC GL-3 results from male (M) patients with the corresponding α-Gal A mutant forms who had been orally administered migalastat at 150 mg every other day (QOD) during Study 011.

1Each patient’s kidney IC GL-3 absolute change after 6 months of treatment (i.e., baseline to month 6 for migalastat-migalastat; from month 6 to month 12 for placebo-migalastat) is provided.

In ‘Study 011 Kidney IC GL-3 Response’, patients with a kidney IC GL-3 absolute change <0.0 after 6 months of treatment were categorized as showing “good” responses, and patients with ≥0.0 were categorized as showing “non/limited” responses.

This analysis includes only male patients with baseline values ≥0.1.

Table 8S: Comparison Between Mutant α–Gal A Responses in GLP HEK and Male and Female Fabry Patient Plasma Lyso-Gb3 Responses in Study 011

| **GLP HEK Amenable?** | **Patient** | **Sex** | **Protein change** | **Stage 1-Stage 2**  **Treatment Category** | **Study 011 Patient Plasma Lyso-Gb3** | |
| --- | --- | --- | --- | --- | --- | --- |
| **+ Migalastat** | **Study 011**  **Plasma Lyso-Gb3**  **Response** |
| **Absolute Change after 6 Months1** |
| **Yes** | 1101-007 | M | L243F | Placebo-Migalastat | -61.1 | Good |
| 2001-001 | M | R356W | Placebo-Migalastat | -2.72 | Good |
| 2001-003 | M | D55V/Q57L | Placebo-Migalastat | -43.2 | Good |
| 4001-015 | M | D33G | Placebo-Migalastat | -25.6 | Good |
| 5001-001 | M | P259R | Placebo-Migalastat | -51.8 | Good |
| 5001-003 | M | P259R | Placebo-Migalastat | -1.97 | Good |
| 1601-007 | F | I253T | Placebo-Migalastat | -8.49 | Good |
| 2701-012 | F | G325R | Placebo-Migalastat | -0.7 | Good |
| 3002-004 | F | D264Y | Placebo-Migalastat | -0.3 | Good |
| 4001-003 | F | R301Q | Placebo-Migalastat | -0.27 | Good |
| 4002-001 | F | P205T | Placebo-Migalastat | -1.02 | Good |
| 4002-005 | F | G260A | Placebo-Migalastat | -3.3 | Good |
| 9001-003 | F | G85D | Placebo-Migalastat | -0.93 | Good |
| 1601-006 | M | D244N | Migalastat-Migalastat | -23.7 | Good |
| 2001-005 | M | G144V | Migalastat-Migalastat | -15.0 | Good |
| 2026-906 | M | D322E | Migalastat-Migalastat | -54.1 | Good |
| 3002-002 | M | Y216C | Migalastat-Migalastat | -24.0 | Good |
| 4001-004 | M | A156T | Migalastat-Migalastat | -69.7 | Good |
| 1601-008 | F | I253T | Migalastat-Migalastat | -2.19 | Good |
| 2001-904 | F | Y216C | Migalastat-Migalastat | -3.53 | Good |
| 2006-001 | F | R112H | Migalastat-Migalastat | 0.17 | Non/Limited |
| 2026-904 | F | D322E | Migalastat-Migalastat | -2.37 | Good |
| 2102-004 | F | I270T | Migalastat-Migalastat | -1.01 | Good |
| 2302-003 | F | P259R | Migalastat-Migalastat | -2.37 | Good |
| 3002-003 | F | Y216C | Migalastat-Migalastat | -4.43 | Good |
| 4001-016 | F | P205T | Migalastat-Migalastat | -2.47 | Good |
| 4002-004 | F | M187I | Migalastat-Migalastat | 0.16 | Non/Limited |
| 6001-001 | F | P293T | Migalastat-Migalastat | 0.1 | Non/Limited |
| 6001-002 | F | P293T | Migalastat-Migalastat | 1.23 | Non/Limited |
| 9001-001 | F | G271S, D313Y | Migalastat-Migalastat | -0.67 | Good |
| 9001-004 | F | A156T | Migalastat-Migalastat | 1.8 | Non/Limited |
| **No** | 2004-901 | M | R342Q | Placebo-Migalastat | 9.33 | Non/Limited |
| 4001-010 | M | S65I | Placebo-Migalastat | 5.67 | Non/Limited |
| 2005-001 | F | G261D | Placebo-Migalastat | 15.2 | Non/Limited |
| 2015-002 | F | R342Q | Placebo-Migalastat | 2.33 | Non/Limited |
| 4001-014 | F | I117S | Placebo-Migalastat | -1.23 | Good |
| 5003-007 | F | R342Q | Placebo-Migalastat | 1.31 | Non/Limited |
| 6001-005 | F | L414S | Placebo-Migalastat | 1.97 | Non/Limited |
| 2007-003 | M | R342Q | Migalastat-Migalastat | 65.0 | Non/Limited |
| 2008-006 | M | S276G | Migalastat-Migalastat | 2 | Non/Limited |
| 5003-008 | M | R342Q | Migalastat-Migalastat | 29.7 | Non/Limited |
| 2008-005 | F | E48K | Migalastat-Migalastat | -8.57 | Good |
| 2017-001 | F | R49P | Migalastat-Migalastat | 2.83 | Non/Limited |
| 2101-001 | F | G183V | Migalastat-Migalastat | 1.93 | Non/Limited |

‘GLP HEK Amenable’ refers to the mutant α-Gal A responses to migalastat in the GLP HEK cell-based assay grouped according to the “amenable” mutation criteria. These groups are aligned with the plasma lyso-Gb3 results from male and female patients with the corresponding α-Gal A mutant forms who had been orally administered migalastat at 150 mg every other day (QOD) during Study 011.

1Each patients’ plasma lyso-Gb3 absolute change after 6 months of treatment (i.e., baseline to month 6 for migalastat-migalastat; from month 6 to month 12 for placebo-migalastat) is provided.

In ‘Study 011 Plasma Lyso-Gb3 Response’, patients with a plasma lyso-Gb3 absolute change <0.0 after 6 months of treatment were categorized as showing “good” responses, and patients with ≥0.0 were categorized as showing “non/limited” responses.

**Figure 3S: Relationship of the Magnitude of Increase in α-Gal A Activity in the GLP HEK Assay with the Magnitude of Kidney Interstitial Capillary GL-3 Reduction in Male Patients in Study 011**



**Left**: Correlation analysis of the absolute increase of GLP HEK amenable mutant forms compared with the absolute change in kidney GL-3 inclusions after six months of migalastat in male patients in study 011. The Pearson correlation coefficient [*r*] was 0.2172 [n=12] (*p*=0.4978) (two-tailed p-value). **Right**: Correlation analysis of the α-Gal A activity –fold over baseline of GLP HEK amenable mutant forms compared with the absolute change in kidney GL-3 inclusions after six months of migalastat in male patients in study 011. The Pearson correlation coefficient [*r*] was ‑0.0712 [n=11] (*p*=0.8353) (two-tailed p-value). The α-Gal A activity –fold over baseline was not calculated for 1 mutant form with baseline activity that was below the limit of detection in the GLP HEK assay.

**Figure 4S: Relationship of the Magnitude of Increase in α-Gal A Activity in the GLP HEK Assay with the Magnitude of Plasma Lyso-Gb3 Reduction in Male Patients in Study 011**



**Left**: Correlation analysis of the absolute increase of GLP HEK amenable mutant forms compared with the absolute change in plasma lyso-Gb3 after six months of migalastat in male patients in study 011. The Pearson correlation coefficient [*r*] was 0.1653 [n=11] (p=0.6272) (two-tailed p-value). **Right**: Correlation analysis of the α-Gal A activity –fold over baseline of GLP HEK amenable mutant forms compared with the absolute change in plasma lyso-Gb3 after six months of migalastat in male patients in study 011. The Pearson correlation coefficient [*r*] was ‑0.0248 [n=10] (*p*=0.9458) (two-tailed p-value). The α-Gal A activity –fold over baseline was not calculated for 1 mutant form with baseline activity that was below the limit of detection in the GLP HEK assay.

**Figure 5S: Relationship of the Magnitude of Increase in α-Gal A Activity in the GLP HEK Assay with the Magnitude of Plasma Lyso-Gb3 Reduction in Male and Female Patients in Study 011**



**Left**: Correlation analysis of the absolute increase of GLP HEK amenable mutant forms compared with the absolute change in plasma lyso-Gb3 after six months of migalastat in male (black dots) and female (red dots) patients in study 011. The Pearson correlation coefficient [*r*] was 0.0328 [n=31] (p=0.8608) (two-tailed p-value). **Right**: Correlation analysis of the α-Gal A activity –fold over baseline of GLP HEK amenable mutant forms compared with the absolute change in plasma lyso-Gb3 after six months of migalastat in male (black dots) and female (red dots) patients in study 011. The Pearson correlation coefficient [*r*] was 0.2130 [n=30] (p=0.2584) (two-tailed p-value). The α-Gal A activity ‑fold over baseline was not calculated for 1 mutant form with baseline activity that was below the limit of detection in the GLP HEK assay.

**Table 9S: Unique Amenable Mutations Represented in Phase 2 and 3 Studies**

| Unique Amenable Mutations | Clinical Study (# patients) |
| --- | --- |
| **L32P** | 204 (1), 012 (3) |
| **D33G** | 011 (1) |
| **G35R** | 012 (1) |
| **L36W** | 011 (2) |
| **T41I** | 201 (2) |
| **M51K** | 201 (1) |
| **D55V/Q57L** | 011 (1), 012 (1) |
| **G85D** | 011 (1), 012 (7) |
| **M96I** | 012 (1) |
| **A97V** | 201 (1), 012 (1) |
| **R112G** | 012 (1) |
| **R112H** | 204 (1), 011 (1), 012 (1) |
| **A143T** | 201 (2), 012 (3) |
| **G144V** | 011 (1) |
| **A156T** | 011 (3), 012 (6) |
| **C174R** | 011 (1) |
| **G183D** | 011 (2) |
| **M187I** | 011 (1) |
| **P205T** | 203 (1), 204 (1), 011 (2), 012 (1) |
| **N215S** | 203 (1), 012 (10) |
| **Y216C** | 011 (3), 012 (1) |
| **L243F** | 011 (1) |
| **D244N** | 011 (1) |
| **I253S** | 012 (1) |
| **I253T** | 011 (4) |
| **G258R** | 011 (2) |
| **P259R** | 202 (2), 204 (2), 011 (3) |
| **G260A** | 011 (1), 012 (1) |
| **D264Y** | 011 (1) |
| **I270T** | 011 (1) |
| **G271S** | 011 (0.5)\* |
| **Q279E** | 012 (1) |
| **M284T** | 011 (2), 012 (1) |
| **P293T** | 011 (2) |
| **F295C** | 203 (1), 011 (1) |
| **M296I** | 012 (1) |
| **L300P** | 201 (1), 011 (1) |
| **R301P** | 012 (3) |
| **R301Q** | 201 (1), 202 (1), 011 (3), 012 (1) |
| **Q312R** | 012 (1) |
| **D313Y** | 011 (0.5)\* |
| **I317T** | 011 (1) |
| **D322E** | 011 (2), 012 (4) |
| **G325R** | 011 (2) |
| **G328A** | 201 (1), 012 (1) |
| **R356Q** | 012 (1) |
| **R356W** | 011 (1) |
| **R363H** | 012 (1) |
| **G373S** | 011 (1) |
| **L403S** | 012 (1) |
| **P409T** | 012 (1) |
| \*indicates that G271S and D313Y were represented on two separate alleles in a female patient. | |

**Table 10S: Unique Non-amenable Mutations Represented in Phase 2 and 3 Studies**

| Unique Non-amenable Mutations | Clinical Study (# patients) |
| --- | --- |
| ***M1I*** | 204 (1) |
| ***E48K*** | 011 (1) |
| ***R49P*** | 011 (1) |
| ***C52G*** | 204 (1) |
| ***S65I#*** | 011 (2) |
| ***C94S*** | 203 (1) |
| ***R112C*** | 203 (1) |
| ***I117S*** | 011 (1) |
| ***G171D*** | 201 (1) |
| ***G183V*** | 011 (1) |
| ***H225R*** | 201 (1) |
| ***R227Q*** | 201 (1) |
| ***R227X#*** | 204 (1) |
| ***G261D*** | 011 (1) |
| ***G271C*** | 201 (1) |
| ***S276G*** | 201 (1), 011 (1) |
| ***E341D*** | 012 (1) |
| ***R342Q*** | 011 (8), 012 (3) |
| ***E358K*** | 204 (1) |
| ***L414S*** | 011 (1) |
| ***L415P*** | 202 (1) |
| ***82InsG#*** | 201 (1) |
| #S65I (putative splice site mutation based on change to the same nucleotide as reported in Lai et al, 2003), R227X (large truncation nonsense mutation), and 82InsG (frameshift mutation) did not qualify for testing in GLP HEK and are categorized as non-amenable. | |
|
|

**Figure 6S: Absolute Increase and α-Gal A Activity –Fold Over Baseline of Phase 2 and 3 Clinical Study Amenable Mutant Forms Compared to the Larger Subset That Met the Amenable Mutation Criteria**



Each horizontal line indicates the mean of the absolute increase or α-Gal A activity –fold over baseline in response to migalastat. The mean ±SEM absolute increases for the clinical study cohort and larger subset were 24.7±1.7 (95% confidence intervals, 21.2, 28.2; n=51) and 23.7±0.9 (95% confidence intervals, 21.8, 25.6; n=268), respectively. The mean ±SEM α-Gal A activity –fold over baseline for the clinical study cohort and larger subset were 6.1±0.8 (95% confidence intervals, 4.5, 7.7; n=48) and 4.9±0.3 (95% confidence intervals, 4.3, 5.6; n=252), respectively. The α-Gal A activity –fold over baseline was not calculated for 16 mutant forms with baseline activity that was below the limit of detection in the GLP HEK assay.

**Figure 7S: Amenable Mutations Grouped by Phenotype: Results for Phase 2 and 3 Clinical Studies Compared to the Larger Subset That Met the Amenable Mutation Criteria**

|  |  |  |
| --- | --- | --- |
|  |  | |
| Each bar represents the number of amenable mutations in each phenotype category; percentages (%) indicate the % of total amenable mutations with phenotype categories (n = 36 total for “Clinical Study Amenable Mutations”; n = 132 total for “All Amenable Mutations”); amenable mutations with unknown phenotype were excluded. “Both” = Amenable mutations associated with both classic and non-classic phenotypes. | |

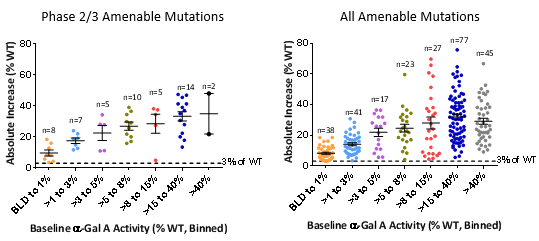
**Figure 8S: Proportions of Conservative and Non-conservative Amino Acid Substitutions**



The proportion of conservative and non-conservative amino acid substitutions of the amenable α-Gal A mutant forms in the clinical studies and the larger amenable subset are shown. The classification of “conservative” was made if the mutation resulted in the substitution of an amino acid with the same charge as the original residue, or with a similar hydrogen-bonding capacity. The classification of “non-conservative” was made if the mutation resulted in a substitution that changed the charge or the hydrogen-bonding capacity to a large degree. Six amenable complex missense mutations, small deletions, and small insertions were excluded from this analysis.

**Figure 9S:**

**Absolute Increase in α-Gal A Activity as a Function of Baseline**



The GLP HEK assay baseline α–Gal A activity of amenable mutant forms in clinical studies and of the larger subset was binned into categories of percentage of wild-type activity as indicated in the X-axis. The absolute increase in α-Gal A activity in response to 10 μM migalastat in the GLP HEK assay for the clinical study mutant forms and the larger subset are plotted on the Y-axis. Horizontal lines indicate the mean ± SEM. ‘n’ indicates the number of mutant forms in each category.

**Figure 10S:**

**α-Gal A Activity –Fold Over Baseline as a Function of Baseline**



The GLP HEK assay baseline α–Gal A activity of amenable mutant forms in clinical studies and of the larger subset was binned into categories of percentage of wild type activity as indicated in the X-axis. The α-Gal A activity –fold over baseline in response to 10 μM migalastat in the GLP HEK assay for the clinical study mutant forms and the larger subset are plotted on the Y-axis. Horizontal lines indicate the mean ± SEM. ‘n’ indicates the number of mutant forms in each category. Three and 16 amenable mutations in clinical studies and in the larger subset with baseline α-Gal A activity that was BLD, respectively, are excluded as the α-Gal A activity –fold over baseline was not calculable.

**Figure 11S:**

**Locations of Substituted Amino Acid Residues in the GLA Gene and α-Gal A Protein**



The *GLA* gene and α-Gal A protein structural distributions of the amenable mutations in the clinical studies and the larger amenable subset are shown. The left panel illustrates the structural distributions at the level of the *GLA* gene, and the right panel illustrates the structural distributions at the level of the protein. The junctions for each of the 7 exons translated to amino acid residues are as follows: amino acid residues 1-64, 65-123, 124-182, 183-213, 214‑267, 268-333, and 334-429 for exons 1, 2, 3, 4, 5, 6, and 7, respectively. The amino acid residue junctions for each of the 3 structural domains are as follows: 1-31, 32-330, and 331-429 for the signal sequence, the N-terminal (β/α)8-barrel structural domain, and the C-terminal anti-parallel β-sheet domain. One amenable complex missense mutation that affected more than one exon (N215S/D313Y) was excluded from the analysis in the left panel.

Figure 12S: Mean baseline α-Gal A activity



Each horizontal line indicates the mean baseline activity (expressed as a percentage of wild-type; % WT) of the amenable α-Gal A mutant forms in the GLP HEK assay. The mean ±SEM baseline activity for the clinical study cohort and larger subset of amenable mutant forms were 12.7±2.1 (n=51) and 20.0±1.4 (n=268), respectively. Values that were below the limit of detection were imputed to zero (0) for this analysis.

Table 11SA:

The Pharmacogenetic Reference Table Based on the GLP HEK Assay Results

| Amenable *GLA* Mutations *(assumes 150 mg dose of migalastat HCl)* | | |
| --- | --- | --- |
| Nucleotide Change | Nucleotide Change | Protein Sequence Change |
| c.8 T>C | c.T8C | L3P |
| c.37 G>A | c.G37A | A13T |
| c.37 G>C | c.G37C | A13P |
| c.43 G>A | c.G43A | A15T |
| c.44 C>G | c.C44G | A15G |
| c.58 G>C | c.G58C | A20P |
| c.59 C>A | c.C59A | A20D |
| c.70 T>C | c.T70C | W24R |
| c.70 T>G | c.T70G | W24G |
| c.72 G>C | c.G72C | W24C |
| c.95 T>C | c.T95C | L32P |
| c.97 G>T | c.G97T | D33Y |
| c.98 A>G | c.A98G | D33G |
| c.101 A>G | c.A101G | N34S |
| c.102 T>G | c.T102G | N34K |
| c.103 G>C | c.G103C | G35R |
| c.107 T>C | c.T107C | L36S |
| c.107 T>G | c.T107G | L36W |
| c.108 G>C | c.G108C | L36F |
| c.109 G>A | c.G109A | A37T |
| c.110 C>T | c.C110T | A37V |
| c.122 C>T | c.C122T | T41I |
| c.124 A>C | c.A124C | M42L |
| c.124 A>G | c.A124G | M42V |
| c.125 T>A | c.T125A | M42K |
| c.125 T>C | c.T125C | M42T |
| c.125 T>G | c.T125G | M42R |
| c.137 A>C | c.A137C | H46P |
| c.142 G>C | c.G142C | E48Q |
| c.152 T>A | c.T152A | M51K |
| c.153 G>A | c.G153A | M51I |
| c.157 A>G | c.A157G | N53D |
| c.[157 A>C; 158 A>T] | c. A157C/A158T | N53L |
| c.160 C>T | c.C160T | L54F |
| c.161 T>C | c.T161C | L54P |
| c.164 A>T | c.A164T | D55V |
| c.[164 A>T; 170 A>T] | c.A164T/A170T | D55V/Q57L |
| c.167 G>T | c.G167T | C56F |
| c.167 G>A | c.G167A | C56Y |
| c.170 A>T | c.A170T | Q57L |
| c.175 G>A | c.G175A | E59K |
| c.178 C>A | c.C178A | P60T |
| c.178 C>T | c.C178T | P60S |
| c.179 C>T | c.C179T | P60L |
| c.196 G>A | c.G196A | E66K |
| c.197 A>G | c.A197G | E66G |
| c.214 A>G | c.A214G | M72V |
| c.216 G>A | c.G216A | M72I |
| c.218 C>T | c.C218T | A73V |
| c.227 T>C | c.T227C | M76T |
| c.247 G>A | c.G247A | D83N |
| c.253 G>A | c.G253A | G85S |
| c.254 G>A | c.G254A | G85D |
| c.[253 G>A; 254 G>T; 255 T>G] | c. G253A/G254T/T255G | G85M |
| c.265 C>T | c.C265T | L89F |
| c.272 T>C | c.T272C | I91T |
| c.288 G>A | c.G288A | M96I |
| c.289 G>C | c.G289C | A97P |
| c.290 C>T | c.C290T | A97V |
| c.305 C>T | c.C305T | S102L |
| c.311G>T | c.G311T | G104V |
| c.322 G>A | c.G322A | A108T |
| c.326 A>G | c.A326G | D109G |
| c.334 C>G | c.C334G | R112G |
| c.335 G>A | c.G335A | R112H |
| c.337 T>C | c.T337C | F113L |
| c.352 C>T | c.C352T | R118C |
| c.361 G>A | c.G361A | A121T |
| c.368 A>G | c.A368G | Y123C |
| c. 374 A>T | c.A374T | H125L |
| c.376 A>G | c.A376G | S126G |
| c.383 G>A | c.G383A | G128E |
| c.404 C>T | c.C404T | A135V |
| c.408 T>A | c.T408A | D136E |
| c.416 A>G | c.A416G | N139S |
| c.419 A>C | c.A419C | K140T |
| c.427 G>A | c.G427A | A143T |
| c.431 G>A | c.G431A | G144D |
| c.431 G>T | c.G431T | G144V |
| c.436 C>T | c.C436T | P146S |
| c.455 A>G | c.A455G | Y152C |
| c.466 G>A | c.G466A | A156T |
| c.467 C>T | c.C467T | A156V |
| c.484 T>G | c.T484G | W162G |
| c.493 G>C | c.G493C | D165H |
| c.494 A>G | c.A494G | D165G |
| c.[496 C>G; 497 T>G] | c. C496G/T497G | L166G |
| c.496 C>G | c.C496G | L166V |
| c.506 T>C | c.T506C | F169S |
| c.520 T>C | c.T520C | C174R |
| c.520 T>G | c.T520G | C174G |
| c.525 C>G | c.C525G | D175E |
| c.548 G>C | c.G548C | G183A |
| c.548 G>A | c.G548A | G183D |
| c.550 T>A | c.T550A | Y184N |
| c.551A>G | c.A551G | Y184C |
| c.553 A>G | c.A553G | K185E |
| c.559 A>G | c.A559G | M187V |
| c.560 T>C | c.T560C | M187T |
| c.561 G>T | c.G561T | M187I |
| c.559\_564 dup | c.559\_564dup | p. M187\_S188 dup |
| c.572 T>A | c.T572A | L191Q |
| c.581 C>T | c.C581T | T194I |
| c.584 G>T | c.G584T | G195V |
| c.593 T>C | c.T593C | I198T |
| c.595 G>A | c.G595A | V199M |
| c.596 T>G | c.T596G | V199G |
| c.599 A>G | c.A599G | Y200C |
| c.602 C>T | c.C602T | S201F |
| c.602 C>A | c.C602A | S201Y |
| c.608 A>T | c.A608T | E203V |
| c.609 G>C | c.G609C | E203D |
| c.613 C>A | c.C613A | P205T |
| c.613 C>T | c.C613T | P205S |
| c.614 C>T | c.C614T | P205L |
| c.619 T>C | c.T619C | Y207H |
| c.620 A>C | c.A620C | Y207S |
| c.628 C>T | c.C628T | P210S |
| c.629 C>T | c.C629T | P210L |
| c.638 A>T | c.A638T | K213M |
| c.640 C>T | c.C640T | P214S |
| c.641 C>T | c.641T | P214L |
| c.643 A>G | c.A643G | N215D |
| c.644 A>G | c.A644G | N215S |
| c.[644 A>G; 937 G>T] | c. A644G/G937T | N215S/D313Y |
| c.646 T>G | c.T646G | Y216D |
| c.647 A>G | c.A647G | Y216C |
| c.656 T>A | c.T656A | I219N |
| c.656 T>C | c.T656C | I219T |
| c.659 G>A | c.G659A | R220Q |
| c.659 G>C | c.G659C | R220P |
| c.671 A>G | c.A671G | N224S |
| c.673 C>G | c.C673G | H225D |
| c.683 A>G | c.A683G | N228S |
| c.687 T>A | c.T687A | F229L |
| c.695 T>C | c.T695C | I232T |
| c.713 G>A | c.G713A | S238N |
| c.716 T>C | c.T716C | I239T |
| c.724 A>T | c.A724T | I242F |
| c.725 T>A | c.T725A | I242N |
| c.729 G>C | c.G729C | L243F |
| c.728 T>G | c.T728G | L243W |
| c.730 G>A | c.G730A | D244N |
| c.730 G>C | c.G730C | D244H |
| c.735 T>G | c.T735G | W245G |
| c.740 C>G | c.C740G | S247C |
| c.747 C>G | c.C747G | N249K |
| c.749 A>C | c.A749C | Q250P |
| c.758 T>C | c.T758C | I253T |
| c.758 T>G | c.T758G | I253S |
| c.760-762del GTT | c.760\_762delGTT | p.V254del |
| c.769 G>C | c.G769C | A257P |
| c.770 C>G | c.C770G | A257G |
| c.772 G>C | c.G772C | G258R |
| c.773 G>T | c.G773T | G258V |
| c.776 C>G | c.C776G | P259R |
| c.776 C>T | c.C776T | P259L |
| c.779 G>A | c.G779A | G260E |
| c.779 G>C | c.G779C | G260A |
| c.788 A>G | c.A788G | N263S |
| c.790 G>T | c.G790T | D264Y |
| c.794 C>T | c.C794T | P265L |
| c.800 T>C | c.T800C | M267T |
| c.805 G>A | c.G805A | V269M |
| c.806 T>C | c.T806C | V269A |
| c.809 T>C | c.T809C | I270T |
| c.811 G>A | c.G811A | G271S |
| c.[811 G>A; 937 G>T] | c. G811A/G937T | G271S/D313Y |
| c.812 G>A | c. G812A | G271D |
| c.827 G>A | c.G827A | S276N |
| c.829 T>G | c.T829G | W277G |
| c.831 G>T | c.G831T | W277C |
| c.835 C>G | c.C835G | Q279E |
| c.838 C>A | c.C838A | Q280K |
| c.840 A>T | c.A840T | Q280H |
| c.844 A>G | c.A844G | T282A |
| c.845 C>T | c.C845T | T282I |
| c.850 A>G | c.A850G | M284V |
| c.851 T>C | c.T851C | M284T |
| c.862 G>C | c.G862C | A288P |
| c.866 T>G | c.T866G | I289S |
| c.868 A>C | c.A868C | M290L |
| c.870 G>A | c.G870A | M290I |
| c.871 G>A | c.G871A | A291T |
| c.877 C>A | c.C877A | P293T |
| c.881 T>C | c.T881C | L294S |
| c.884 T>G | c.T884G | F295C |
| c.886 A>G | c.A886G | M296V |
| c.886 A>T | c.A886T | M296L |
| c.887 T>C | c.T887C | M296T |
| c.888 G>A | c.G888A | M296I |
| c.893 A>G | c.A893G | N298S |
| c.897 C>G | c.C897G | D299E |
| c.898 C>T | c.C898T | L300F |
| c.899 T>C | c.T899C | L300P |
| c.901 C>G | c.C901G | R301G |
| c.902 G>C | c.G902C | R301P |
| c.902 G>A | c.G902A | R301Q |
| c.902 G>T | c.G902T | R301L |
| c.908 T>A | c.T908A | I303N |
| c.911 G>A | c.G911A | S304N |
| c.911 G>C | c.G911C | S304T |
| c.919 G>A | c.G919A | A307T |
| c.924 A>T | c.A924T | K308N |
| c.925 G>C | c.G925C | A309P |
| c.928 C>T | c.C928T | L310F |
| c.931 C>G | c.C931G | L311V |
| c.935 A>G | c.A935G | Q312R |
| c.936 G>T | c.G936T | Q312H |
| c.937 G>T | c.G937T | D313Y |
| c.938 A>G | c.A938G | D313G |
| c.946 G>A | c.G946A | V316I |
| c.947 T>G | c.T947G | V316G |
| c.950 T>C | c.T950C | I317T |
| c.955 A>T | c.A955T | I319F |
| c.956 T>C | c.T956C | I319T |
| c.959 A>T | c.A959T | N320I |
| c.962 A>G | c.A962G | Q321R |
| c.962 A>T | c.A962T | Q321L |
| c.963 G>C | c.G963C | Q321H |
| c.964 G>A | c.G964C | D322N |
| c.966 C>A | c.C966A | D322E |
| c.973 G>A | c.G973A | G325S |
| c.973 G>C | c.G973C | G325R |
| c.979 C>G | c.C979G | Q327E |
| c.983 G>C | c.G983C | G328A |
| c.1001 G>A | c.G1001A | G334E |
| c.1012 G>A | c.G1012A | E338K |
| c.1016 T>A | c.T1016A | V339E |
| c.1028 C>T | c.C1028T | P343L |
| c.1033 T>C | c.T1033C | S345P |
| c.1046 G>C | c.G1046C | W349S |
| c.1055 C>T | c.C1055T | A352V |
| c.1061 T>A | c.T1061A | I354K |
| c.1066 C>G | c.C1066G | R356G |
| c.1066 C>T | c.C1066T | R356W |
| c.1067G>A | c.G1067A | R356Q |
| c.1073 A>C | c.A1073C | E358A |
| c.1073 A>G | c.A1073G | E358G |
| c.1074 G>T | c.G1074T | E358D |
| c.1076 T>C | c.T1076C | I359T |
| c.1078 G>A | c.G1078A | G360S |
| c.1078 G>T | c.G1078T | G360C |
| c.1079 G>A | c.G1079A | G360D |
| c.1082 G>A | c.G1082A | G361E |
| c.1082 G>C | c.G1082C | G361A |
| c.1084 C>A | c.C1084A | P362T |
| c.1085 C>T | c.C1085T | P362L |
| c.1087 C>T | c.C1087T | R363C |
| c.1088 G>A | c.G1088A | R363H |
| c.1102 G>A | c.G1102A | A368T |
| c.1117 G>A | c.G1117A | G373S |
| c.1153 A>G | c.A1153G | T385A |
| c.1172 A>C | c.A1172C | K391T |
| c.1184 G>A | c.G1184A | G395E |
| c.1184 G>C | c.G1184C | G395A |
| c.1192 G>A | c.G1192A | E398K |
| c.1202 Ins GACTTC | c.1202Ins GACTTC | p. T400\_S401dup |
| c.1208 T>C | c.T1208C | L403S |
| c.1225 C>G | c.C1225G | P409A |
| c.1225 C>T | c.C1225T | P409S |
| c.1225 C>A | c.C1225A | P409T |
| c.1228 A>G | c.A1228G | T410A |
| c.1229 C>T | c.C1229T | T410I |
| c.1232 G>A | c.G1232A | G411D |
| c.1235 C>A | c.C1235A | T412N |
| c.1253 A>G | c.A1253G | E418G |
| c.1261 A>G | c.A1261G | M421V |

The number of ‘GLA mutations that met the HEK-293 cell-based assay criteria’ is 268 of 841 in total.

**Table 11SB:**

**The Pharmacogenetic Reference Table Based on the GLP HEK assay Results**

| *Non-amenable GLA Mutations (assume 150 mg dose of migalastat HCl)* | | |
| --- | --- | --- |
| *Nucleotide Change* | | *Protein Sequence Change* |
| *c.1 A>C* | *c.A1C* | *M1L* |
| *c.1 A>G* | *c.A1G* | *M1V* |
| *c.2 T>G* | *c.T2G* | *M1R* |
| *c.2 T>C* | *c.T2C* | *M1T* |
| *c.2 T>A* | *c.T2A* | *M1K* |
| *c.3 G>A* | *c.G3A* | *M1I* |
| *c.19 G>T* | *c.G19T* | *E7X#* |
| *c.41 T>C* | *c.T41C* | *L14P* |
| *c.43 G>C* | *c.G43C* | *A15P* |
| *c.47 T>A* | *c.T47A* | *L16H* |
| *c.47 T>C* | *c.T47C* | *L16P* |
| *c.53 T>C* | *c.T53C* | *F18S* |
| *c.56 T>A* | *c.T56A* | *L19Q* |
| *c.56 T>C* | *c.T56C* | *L19P* |
| *c.59 C>T* | *c.C59T* | *A20V* |
| *c.61C>T* | *c.C61T* | *L21F* |
| *c.62 T>C* | *c.T62C* | *L21P* |
| *c.62 T>G* | *c.T62G* | *L21R* |
| *c.71 G>A* | *c.G71A* | *W24X#* |
| *c.92 C>T* | *c.C92T* | *A31V* |
| *c.118 C>G* | *c.C118G* | *P40A* |
| *c.118 C>T* | *c.C118T* | *P40S* |
| *c.119 C>A* | *c.C119A* | *P40H* |
| *c.119 C>G* | *c.C119G* | *P40R* |
| *c.119 C>T* | *c.C119T* | *P40L* |
| *c.127 G>C* | *c.G127C* | *G43R* |
| *c.127 G>A* | *c.G127A* | *G43S* |
| *c.128 G>A* | *c.G128A* | *G43D* |
| *c.128 G>T* | *c.G128T* | *G43V* |
| *c.131 G>A* | *c.G131A* | *W44X#* |
| *c.132 G>T* | *c.G132T* | *W44C* |
| *c.134 T>C* | *c.T134C* | *L45P* |
| *c.134 T>G* | *c.T134G* | *L45R* |
| c.134\_138delTGCACinsGCTCG | c.134\_138delTGCACinsGCTCG | *L45R/H46S* |
| *c.136 C>T* | *c.C136T* | *H46Y* |
| *c.137 A>T* | *c.A137T* | *H46L* |
| *c.137 A>G* | *c.A137G* | *H46R* |
| *c.139 T>G* | *c.T139G* | *W47G* |
| *c.140 G>A or 141 G>A* | *c.G140A or G141A* | *W47X#* |
| *c.140 G>T* | *c.G140T* | *W47L* |
| *c.141G>C* | *c.G141C* | *W47C* |
| *c.139T>C* | *c.T139C* | *W47R* |
| *c.142 G>A* | *c.G142A* | *E48K* |
| *c.144 G>T* | *c.G144T* | *E48D* |
| *c.145 C>T* | *c.C145T* | *R49C* |
| *c.145 C>A* | *c.C145A* | *R49S* |
| *c.146 G>T* | *c.G146T* | *R49G* |
| *c.146 G>C* | *c.G146C* | *R49P* |
| *c.146 G>T* | *c.G146T* | *R49L* |
| *c.149 T>G* | *c.T149G* | *F50C* |
| *c.154 T>G* | *c.T154G* | *C52G* |
| *c.154 T>C* | *c.T154C* | *C52R* |
| *c.155 G>C* | *c.G155C* | *C52S* |
| *c.155 G>A* | *c.G155A* | *C52Y* |
| *c.156 C>A* | *c.C156A* | *C52X#* |
| *c.156 C>G* | *c.C156G* | *C52W* |
| *c.166 T>G* | *c.T166G* | *C56G* |
| *c.167 G>C* | *c.G167C* | *C56S* |
| *c.168 C>A* | *c.C168A* | *C56X#* |
| *c.187 T>C* | *c.T187C* | *C63R* |
| *c.188 G>A* | *c.G188A* | *C63Y* |
| *c.188 G>C* | *c.G188C* | *C63S* |
| *c.194 G>C (putative splicing site\*)* | *c.G194C (putative splicing site\*)* | *UNKNOWN (S65T\*)#* |
| *c.194 G>T (putative splicing site\*)* | *c.G194T (putative splicing site\*)* | *UNKNOWN (S65I\*)#* |
| *c.196 G>C* | *c.G196C* | *E66Q* |
| *c.202 C>T* | *c.C202T* | *L68F* |
| *c.215 T>G* | *c.T215G* | *M72R* |
| *c.218 C>A* | *c.C218A* | *A73E* |
| *c.227 T>G* | *c.T227G* | *M76R* |
| *c.233 C>G* | *c.C233G* | *S78X#* |
| *c.235 G>T* | *c.G235T* | *E79X#* |
| *c.241 T>C* | *c.T241C* | *W81R* |
| *c.242 G>A* | *c.G242A* | *W81X#* |
| *c.242 G>C* | *c.G242C* | *W81S* |
| *c.243 G>T* | *c.G243T* | *W81C* |
| *c.244 A>T* | *c.A244T* | *K82X#* |
| *c.256 T>G* | *c.T256G* | *Y86D* |
| *c.256 T>C* | *c.T256C* | *Y86H* |
| *c.257 A>G* | *c.A257G* | *Y86C* |
| *c.258 T>G* | *c.T258G* | *Y86X#* |
| *c.262 T>G* | *c.T262G* | *Y88D* |
| *c.266 T>C* | *c.T266C* | *L89P* |
| *c.266 T>G* | *c.T266G* | *L89R* |
| *c.268 T>C* | *c.T268C* | *C90R* |
| *c.269 G>A* | *c.G269A* | *C90Y* |
| *c.270 C>A* | *c.C270A* | *C90X#* |
| *c.274 G>C* | *c.G274C* | *D92H* |
| *c.274 G>A* | *c.G274A* | *D92N* |
| *c.274 G>T* | *c.G274T* | *D92Y* |
| *c.275 A>G* | *c.A275G* | *D92G* |
| *c.275 A>T* | *c.A275T* | *D92V* |
| *c.277 G>A* | *c.G277A* | *D93N* |
| *c.277 G>T* | *c.G277T* | *D93Y* |
| *c.278 A>G* | *c.A278G* | *D93G* |
| *c.278 A>T* | *c.A278T* | *D93V* |
| *c.279 C>G* | *c.C279G* | *D93E* |
| *c.281 G>C* | *c.G281C* | *C94S* |
| *c.281 G>A* | *c.G281A* | *C94Y* |
| *c.284 G>A* | *c.G284A* | *W95X#* |
| *c.284 G>T* | *c.G284T* | *W95L* |
| *c.284 G>C* | *c.G284C* | *W95S* |
| *c.295 C>T* | *c.C295T* | *Q99X#* |
| *c.299 G>A* | *c.G299A* | *R100K* |
| *c.299 G>C* | *c.G299C* | *R100T* |
| *c.305 C>G* | *c.C305G* | *S102X#* |
| *c.307 G>C* | *c.G307C* | *E103Q* |
| *c.307 G>T* | *c.G307T* | *E103X#* |
| *c.317 T>G* | *c.T317G* | *L106R* |
| *c.319 C>T* | *c.C319T* | *Q107X#* |
| *c.320 A>T* | *c.A320T* | *Q107L* |
| *c.334 C>T* | *c.C334T* | *R112C* |
| *c.334 C>A* | *c.C334A* | *R112S* |
| *c.338 T>C* | *c.T338C* | *F113S* |
| *c.350 T>G* | *c.T350G* | *I117S* |
| *c.355 C>T* | *c.C355T* | *Q119X#* |
| *c.358 C>G* | *c.C358G* | *L120V* |
| *c.[358 C>T; 359 T>C]* | *c.C358T/T359C* | *L120S* |
| *c.359 T>C* | *c.T359C* | *L120P* |
| *c.361 G>C* | *c.G361C* | *A121P* |
| *c.371 T>A* | *c.T371A* | *V124D* |
| *c.374 A>C* | *c.A374C* | *H125P* |
| *c.379 A>T* | *c.A379T* | *K127X#* |
| *c.386 T>C* | *c.T386C* | *L129P* |
| *c.389 A>G* | *c.A389G* | *K130R* |
| *c.392 T>C* | *c.T392C* | *L131P* |
| *c.394 G>A* | *c.G394A* | *G132R* |
| *c.395 G>A* | *c.G395A* | *G132E* |
| *c.395 G>C* | *c.G395C* | *G132A* |
| *c.400 T>C* | *c.T400C* | *Y134H* |
| *c.400 T>G* | *c.T400G* | *Y134D* |
| *c.401 A>C* | *c.A401C* | *Y134S* |
| *c.402 T>G* | *c.T402G* | *Y134X#* |
| *c.406 G>C* | *c.G406C* | *D136H* |
| *c.406 G>T* | *c.G406T* | *D136Y* |
| *c.412 G>A* | *c.G412A* | *G138R* |
| *c.413 G>A* | *c.G413A* | *G138E* |
| *c.416 A>C* | *c.A416C* | *N139T* |
| *c.422 C>A* | *c.C422A* | *T141N* |
| *c.422 C>T* | *c.C422T* | *T141I* |
| *c.424 T>C* | *c.T424C* | *C142R* |
| *c.425 G>A* | *c.G425A* | *C142Y* |
| *c.426 C>A* | *c.C426A* | *C142X#* |
| *c.426 C>G* | *c.C426G* | *C142W* |
| *c.427 G>C* | *c.G427C* | *A143P* |
| *c.439 G>A* | *c.G439A* | *G147R* |
| *c.440 G>A* | *c.G440A* | *G147E* |
| *c.443 G>A* | *c.G443A* | *S148N* |
| *c.444 T>G* | *c.T444G* | *S148R* |
| *c.453 C>G* | *c.C453G* | *Y151X#* |
| *c.456 C>A* | *c.C456A* | *Y152X#* |
| *c.463 G>C* | *c.G463C* | *D155H* |
| *c.467 C>A* | *c.C467A* | *A156D* |
| *c.469 C>T* | *c.C469T* | *Q157X#* |
| *c.484 T>C* | *c.T484C* | *W162R* |
| *c.485 G>A* | *c.G485A* | *W162X#* |
| *c.485 G>T* | *c.G485T* | *W162L* |
| *c.486 G>C* | *c.G486C* | *W162C* |
| *c.488 G>T* | *c.G488T* | *G163V* |
| *c.491 T>G* | *c.T491G* | *V164G* |
| *c.493 G>T* | *c.G493T* | *D165Y* |
| *c.494 A>T* | *c.A494T* | *D165V* |
| *c.500 T>A* | *c.T500A* | *L167Q* |
| *c.500 T>C* | *c.T500C* | *L167P* |
| *c.503 A>G* | *c.A503G* | *K168R* |
| *c.504 A>C* | *c.A504C* | *K168N* |
| *c.508 G>A* | *c.G508A* | *D170N* |
| *c.508 G>C* | *c.G508C* | *D170H* |
| *c.509 A>G* | *c.A509G* | *D170G* |
| *c.509 A>T* | *c.A509T* | *D170V* |
| *c.511 G>C* | *c.G511C* | *G171R* |
| *c.511 G>T* | *c.G511T* | *G171C* |
| *c.512 G>A* | *c.G512A* | *G171D* |
| *c.514 T>G* | *c.T514G* | *C172G* |
| *c.514 T>C* | *c.T514C* | *C172R* |
| *c.515 G>C* | *c.G515C* | *C172S* |
| *c.515 G>T* | *c.G515T* | *C172F* |
| *c.515 G>A* | *c.G515A* | *C172Y* |
| *c.516 T>G* | *c.T516G* | *C172W* |
| *c.519 C>A* | *c.C519A* | *Y173X#* |
| *c.530 T>A* | *c.T530A* | *L177X#* |
| *c.547 G>A (putative splicing site\*)* | *c.G547A (putative splicing site\*)* | *UNKNOWN (G183S\*)* |
| *c.548 G>T* | *c.G548T* | *G183V* |
| *c.557 A>C* | *c.A557C* | *H186P* |
| *c.560 T>G* | *c.T560G* | *M187R* |
| *c.572 T>C* | *c.T572C* | *L191P* |
| *c.605 G>A* | *c.G605A* | *C202Y* |
| *c.604 T>C* | *c.T604C* | *C202R* |
| *c.606 T>G* | *c.T606G* | *C202W* |
| *c.607 G>A* | *c.G607A* | *E203K* |
| *c.611 G>A or 612G>A* | *c.G611A or G612A* | *W204X#* |
| *c.612 G>T* | *c.G612T* | *W204C* |
| *c.614 C>G* | *c.C614G* | *P205R* |
| *c.617 T>C* | *c.T617C* | *L206P* |
| *c.620 A>G* | *c.A620G* | *Y207C* |
| *c.634 C>T* | *c.C634T* | *Q212X#* |
| *c.658 C>T* | *c.C658T* | *R220X#* |
| *c.661 C>T* | *c.C661T* | *Q221X#* |
| *c.666 C>A* | *c.C666A* | *Y222X#* |
| *c.667 T>G* | *c.T667G* | *C223G* |
| *c.667 T>C* | *c.T667C* | *C223R* |
| *c.668 G>A* | *c.G668A* | *C223Y* |
| *c.670 A>G* | *c.A670G* | *N224D* |
| *c.674 A>G* | *c.A674G* | *H225R* |
| *c.676 T>C* | *c.T676C* | *W226R* |
| *c.677 G>A* | *c.G677A* | *W226X#* |
| *c.678 G>T* | *c.G678T* | *W226C* |
| *c.679 C>T* | *c.C679T* | *R227X#* |
| *c.680 G>A* | *c.G680A* | *R227Q* |
| *c.680 G>C* | *c.G680C* | *R227P* |
| *c.688 G>A* | *c.G688A* | *A230T* |
| *c.691 G>A* | *c.G691A* | *D231N* |
| *c.692 A>G* | *c.A692G* | *D231G* |
| *c.692 A>T* | *c.A692T* | *D231V* |
| *c.700 G>T* | *c.G700T* | *D234Y* |
| *c.702 T>G* | *c.T702G* | *D234E* |
| *c.704 C>A* | *c.C704A* | *S235Y* |
| *c.704 C>G* | *c.C704G* | *S235C* |
| *c.704 C>T* | *c.C704T* | *S235F* |
| *c.706 T>C* | *c.T706C* | *W236R* |
| *c.707 G>A* | *c.G707A* | *W236X#* |
| *c.707 G>T* | *c.G707T* | *W236L* |
| *c.708 G>C* | *c.G708C* | *W236C* |
| *c.712 A>C* | *c.A712C* | *S238R* |
| *c.718 A>T* | *c.A718T* | *K240X#* |
| *c.734 G>A or 735G>A* | *c.G734A or G735A* | *W245X#* |
| *c.739 T>C* | *c.T739C* | *S247P* |
| *c.748 C>T* | *c.C748T* | *Q250X#* |
| *c.751 G>T* | *c.G751T* | *E251X#* |
| *c.755 G>C* | *c.G755C* | *R252T* |
| *c.770 C>A* | *c.C770A* | *A257D* |
| *c.782 G>A* | *c.G782A* | *G261D* |
| *c.782 G>T* | *c.G782T* | *G261V* |
| *c.785 G>A* | *c.G785A* | *W262X#* |
| *c.785 G>T* | *c.G785T* | *W262L* |
| *c.786 G>C* | *c.G786C* | *W262C* |
| *c.791 A>C* | *c.A791C* | *D264A* |
| *c.791 A>T* | *c.A791T* | *D264V* |
| *c.793 C>T* | *c.C793T* | *P265S* |
| *c.794 C>G* | *c.C794G* | *P265R* |
| *c.796 G>C* | *c.G796C* | *D266H* |
| *c.796 G>T* | *c.G796T* | *D266Y* |
| *c.796 G>A* | *c.G796A* | *D266N* |
| *c.797 A>C* | *c.A797C* | *D266A* |
| *c.797 A>T* | *c.A797T* | *D266V* |
| *c.798 T>A* | *c.T798A* | *D266E* |
| *c.800 T>G* | *c.T800G* | *M267R* |
| *c.801 G>A (putative splicing site\*)* | *c. G801A (putative splicing site\*)* | *UNKNOWN (M267I\*)* |
| *c.803 T>C* | *c.T803C* | *L268S* |
| *c.806 T>A* | *c.T806A* | *V269E* |
| *c.811 G>T* | *c.G811T* | *G271C* |
| *c.812 G>T* | *c.G812T* | *G271V* |
| *c.815 A>G* | *c.A815G* | *N272S* |
| *c.816 C>A* | *c.C816A* | *N272K* |
| *c.819 T>G* | *c.T819G* | *F273L* |
| *c.820 G>A* | *c.G820A* | *G274S* |
| *c.821 G>T* | *c.G821T* | *G274V* |
| *c.823 C>T* | *c.C823T* | *L275F* |
| *c.826 A>G* | *c.A826G* | *S276G* |
| *c.830 G>A* | *c.G830A* | *W277X* |
| *c.835 C>A* | *c.C835A* | *Q279K* |
| *c.836 A>G* | *c.A836G* | *Q279R* |
| *c.837 G>C* | *c.G837C* | *Q279H* |
| *c.845 C>A* | *c.C845A* | *T282N* |
| *c.847 C>T* | *c.C847T* | *Q283X#* |
| *c.848 A>C* | *c.A848C* | *Q283P* |
| *c.848A>G* | *c.A848G* | *Q283R* |
| *c.853 G>C* | *c.G853C* | *A285P* |
| *c.854 C>A* | *c.C854A* | *A285D* |
| *c.859 T>G* | *c.T859G* | *W287G* |
| *c.860 G>A or 861G>A* | *c.G860A or G861A* | *W287X#* |
| *c.861 G>C* | *c.G861C* | *W287C* |
| *c.863 C>A* | *c.C863A* | *A288D* |
| *c.865 A>T* | *c.A865T* | *I289F* |
| *c.874 G>A* | *c.G874A* | *A292T* |
| *c.874 G>C* | *c.G874C* | *A292P* |
| *c.875 C>T* | *c.C875T* | *A292V* |
| *c.877 C>G* | *c.C877G* | *P293A* |
| *c.877 C>T* | *c.C877T* | *P293S* |
| *c.878 C>A* | *c. C878A* | *P293H* |
| *c.878 C>T* | *c. C878T* | *P293L* |
| *c.881 T>G* | *c.T881G* | *L294X#* |
| *c.890 C>G* | *c. C890G* | *S297C* |
| *c.890 C>T* | *c.C890T* | *S297F* |
| *c.892 A>C* | *c.A892C* | *N298H* |
| *c.894 T>G* | *c.T894G* | *N298K* |
| *c.896 A>G* | *c.A896G* | *D299G* |
| *c.899 T>A* | *c.T899A* | *L300H* |
| *c.901 C>T* | *c.C901T* | *R301X#* |
| *c.916 C>T* | *c.C916T* | *Q306X#* |
| *c.929 T>G* | *c.T929G* | *L310R* |
| *c.931 C>T* | *c.C931T* | *L311F* |
| *c.932 T>C* | *c.T932C* | *L311P* |
| *c.932 T>G* | *c.T932G* | *L311R* |
| *c.947 T>A* | *c.T947A* | *V316E* |
| *c.950 T>A* | *c.T950A* | *I317N* |
| *c.950 T>G* | *c.T950G* | *I317S* |
| *c.958 A>T* | *c.A958T* | *N320Y* |
| *c.960 T>G* | *c.T960G* | *N320K* |
| *c.961 C>G* | *c.C961G* | *Q321E* |
| *c.961 C>T* | *c.C961T* | *Q321X#* |
| *c.974 G>A* | *c.G974A* | *G325D* |
| *c.979 C>A* | *c.C979A* | *Q327K* |
| *c.982 G>A* | *c.G982A* | *G328R* |
| *c.982 G>T* | *c.G982T* | *G328W* |
| *c.983 G>A* | *c.G983A* | *G328E* |
| *c.983 G>T* | *c.G983T* | *G328V* |
| *c.988 C>T* | *c.C988T* | *Q330X#* |
| *c.997 C>T* | *c.C997T* | *Q333X#* |
| *c.998 A>G* | *c.A998G* | *Q333R* |
| *c.1012 G>T* | *c.G1012T* | *E338X#* |
| *c.1016 T>G* | *c.T1016G* | *V339G* |
| *c.1018 T>C* | *c.T1018C* | *W340R* |
| *c.1020 G>A* | *c.G1020A* | *W340X#* |
| *c.1021 G>A* | *c.G1021A* | *E341K* |
| *c.1023 A >C* | *c.A1023C* | *E341D* |
| *c.1024 C>T* | *c.C1024T* | *R342X#* |
| *c.1025 G>A* | *c.G1025A* | *R342Q* |
| *c.1025 G>C* | *c.G1025C* | *R342P* |
| *c.1025 G>T* | *c.G1025T* | *R342L* |
| *c.1031 T>C* | *c.T1031C* | *L344P* |
| *c.1034 C>G* | *c.C1034G* | *S345X#* |
| *c.1042 G>C* | *c.G1042C* | *A348P* |
| *c.1045 T>C* | *c.T1045C* | *W349R* |
| *c.1046 G>A* | *c.G1046A* | *W349X#* |
| *c.1048 G>C* | *c.G1048C* | *A350P* |
| *c.1054 G>C* | *c.G1054C* | *A352P* |
| *c.1055 C>A* | *c.C1055A* | *A352D* |
| *c.1065 C>A* | *c.C1065A* | *N355K* |
| *c.1069 C>T* | *c.C1069T* | *Q357X* |
| *c.1072 G>A* | *c.G1072A* | *E358K* |
| *c.1081 G>A* | *c.G1081A* | *G361R* |
| *c.1088 G>C* | *c.G1088C* | *R363P* |
| *c.1095 T>A* | *c.T1095A* | *Y365X#* |
| *c.1115 T>A* | *c.T1115A* | *L372Q* |
| *c.1115 T>C* | *c.T1115C* | *L372P* |
| *c.1115 T>G* | *c.T1115G* | *L372R* |
| *c.1117 G>C* | *c.G1117C* | *G373R* |
| *c.1118 G>A* | *c.G1118A* | *G373D* |
| *c.1124\_1129del* | *c.1124\_1129del* | *G375\_V376del* |
| *c.1129\_1140dup* | *c.1129\_1140dup* | *A377\_P380dup* |
| *c.1130 C>A* | *c.C1130A* | *A377D* |
| *c.1132 T>C* | *c.T1132C* | *C378R* |
| *c.1133 G>A* | *c.G1133A* | *C378Y* |
| *c.1145 G>A* | *c.G1145A* | *C382Y* |
| *c.1146 C>G* | *c.C1146G* | *C382W* |
| *c.1151 T>A* | *c.T1151A* | *I384N* |
| *c.1153 A>C* | *c.A1153C* | *T385P* |
| *c.1156 C>T* | *c.C1156T* | *Q386X#* |
| *c.1157 A>C* | *c.A1157C* | *Q386P* |
| *c.1165 C>G* | *c.C1165G* | *P389A* |
| *c.1166 C>G* | *c.C1166G* | *P389R* |
| *c.1166 C>T* | *c.C1166T* | *P389L* |
| *c.1181\_1183dup* | *c.1181\_1183dup* | *L394\_G395InsV* |
| *c.1187 T>A* | *c.T1187A* | *F396Y* |
| *c.1192 G>T* | *c.G1192T* | *E398X#* |
| *c.1196 G>A or1197 G>A* | *c.G1196A or G1197A* | *W399X* |
| *c.1202 C>G* | *c.C1202G* | *S401X#* |
| *c.1215 T>A* | *c.T1215A* | *S405R* |
| *c.1217 A>G* | *c.A1217G* | *H406R* |
| *c.1219 A>G* | *c.A1219G* | *I407V* |
| *c.1220 T>A* | *c.T1220A* | *I407K* |
| *c.1220 T>G* | *c.T1220G* | *I407R* |
| *c.1228 A>C* | *c.A1228C* | *T410P* |
| *c.1229 C>A* | *c.C1229A* | *T410K* |
| *c.1241 T>C* | *c.T1241C* | *L414S* |
| *c.1243 C>T* | *c.C1243T* | *L415F* |
| *c.1244 T>C* | *c.T1244C* | *L415P* |
| *c.1246 C>T* | *c.C1246T* | *Q416X* |
| *c.1250 T>G* | *c.T1250G* | *L417R* |
| *g.941\_5845del* | *c.1-179\_369+577del* | *p.?(Exon1\_2del)#* |
| *g.?\_?del* | *c.?\_?* | *UNKNOWN (del Exon1\_2?)#* |
| *c.18delA* | *c.18delA* | *p.P6fs\*114#* |
| *c.26delA* | *c.26delA* | *p.H9Lfs\*111#* |
| *c.32delG* | *c.32delG* | *p.G11Afs\*109#* |
| *c.33delC* | *c.33delC* | *p.G11fs\*109#* |
| *c.34\_42del* | *c.34\_42del* | *p.C12\_L14del* |
| *c.34\_57del* | *c.34\_57del* | *p.C12\_L19del* |
| *c.35\_47del* | *c.35\_47del* | *p.C12Ffs\*104#* |
| *c.147\_148 Ins CCC* | *c.147\_148 Ins CCC* | *p.49Ins P* |
| *c.58\_83del* | *c.58\_83del* | *p.A20\_G28delfs\*2#* |
| *c.58\_72del* | *c.58\_72del* | *p.A20\_W24del* |
| *c.85dupG* | *c.85dupG* | *p.A29Gfs\*1#* |
| *c.123delC* | *c.123delC* | *p.T41fs\*79#* |
| *c.123\_126dupCATG* | *c.123\_126dupCATG* | *p.G43Hfs\*13#* |
| *c.124\_125del* | *c.124\_125del* | *p.M42Gfs\*12#* |
| *c.125\_137del* | *c.125\_137del* | *p.M42Tfs\*74#* |
| *c.154delT* | *c.154delT* | *p.C52Afs\*68#* |
| *c.162delT* | *c.162delT* | *p.L54fs\*66#* |
| *c.181\_182dupA* | *c.181\_182dupA* | *p.D61Efs\*5#* |
| *c.184delT* | *c.184delT* | *p.S62Pfs\*58#* |
| *g.2594\_10904dup* | *c.195-2500\_999+197dup* | *UNKNOWN#* |
| *g.3422\_6041delinsCG* | *c.194+2049\_369+773del2620insCG* | *UNKNOWN#* |
| *g.?\_?del* | *c.195-?\_547+?del* | *UNKNOWN (del Exon2\_3?)#* |
| *g.?\_?dup* | *c.?\_?dup* | *UNKNOWN (Exon2\_4dup?)#* |
| *g.2934\_6378del* | *c.194+1561\_370-891del* | *UNKNOWN (E66\_Y123del; del Exon2?)#* |
| *g.3396\_6012del* | *c.194+2023\_370-1257del* | *UNKNOWN (E66\_Y123del; del Exon2?)#* |
| *g.3260\_6410del* | *c.194+1887\_370-859del* | *UNKNOWN (E66\_Y123del; del Exon2?)#* |
| *g.2979\_6442del* | *c.194+1606\_369+1174del* | *UNKNOWN (E66\_Y123del; del Exon2)#* |
| *c.256delT* | *c.256delT* | *p.Y88Mfs\*42#* |
| *g.5106\_5919delins231* | *c.207\_369+651del814ins231* | *UNKNOWN (del Exon2?)#* |
| *c.259\_276Del* | *c.259\_276 Del* | *p.87\_92del* |
| *c.267\_268dupCT* | *c.267\_268dupCT* | *p.C90Sfs\*31#* |
| *c.270delC* | *c.270delC* | *p.C90X#* |
| *c.281\_286delinsT* | *c.281\_286delinsT* | *p.C94Ffs\*26#* |
| *c.297\_298del* | *c.297\_298del* | *p.Q99fs\*22#* |
| *c.305delC* | *c.305delC* | *p.S102X#* |
| *c.317\_327del* | *c.317\_327del* | *p.S102fs\*16#* |
| *c.323\_324insCAGA* | *c.323\_324insCAGA* | *p.D109Rfs\*14#* |
| *c.336 Del18* | *c.336 Del18* | *p.113del6aa* |
| *c.358 Del6* | *c.358 Del6* | *p.120del2aa/L120H* |
| *c.363delT* | *c.363delT* | *p.A121fs\*8#* |
| *g.5271\_9366del4096insT* | *c.369+3\_639+954del3129insT* | *UNKNOWN (del Exon3 and 4?)#* |
| *g.7086\_7487del* | *c.370-183\_547+41del* | *UNKNOWN (del Exon3?)#* |
| *g.6736\_11545del* | *c.370-533\_c.1290+277del* | *UNKNOWN (del Exon3\_7?)#* |
| *g.6009\_9741del* | *c.369+741\_640-390del* | *UNKNOWN (del Exon3 and 4?)#* |
| *g.6547\_9783del* | *c.369+1279\_640-348del* | *UNKNOWN (del Exon3 and 4?)#* |
| *g.>5.5 kb del to 3UTR* | *c.?\_?del* | *UNKNOWN (del Exon3\_3’UTR?)#* |
| *c.[374 A>T;383 G>A]* | *c.A374T/G383A* | *H125L/G128E* |
| *c.402delT* | *c.402delT* | *p.Y134X#* |
| *c.409delG* | *c.409delG* | *p.V137Lfs\*27#* |
| *c.413dupG* | *c.413dupG* | *p.G138fs\*2#* |
| *c.421delA* | *c.421delA* | *p.T141Pfs\*23#* |
| *c.426dupC* | *c.426dupC* | *p.A143Rfs\*13#* |
| *c.452delA* | *c.452delA* | *p.Y151Sfs\*13#* |
| *c.457\_459del* | *c.457\_459del* | *p.153delD* |
| *c.477delT* | *c.477delT* | *p.F159Lfs\*5#* |
| *c.486\_498del* | *c.486\_498del* | *p.W162Cfs\*1#* |
| *c.516 InsGAC* | *c.516 InsGAC* | *p. 152 Ins D* |
| *c.520delT* | *c.520delT* | *p.C174Vfs\*17#* |
| *c.[604 T>C;644 A>G]* | *c.T604C/A644G* | *p. C202R/N215S* |
| *c.568delG* | *c.568delG* | *p.A190Pfs\*1#* |
| *c.590delG* | *c.590delG* | *p.S197Tfs\*42#* |
| *c.606delT* | *c.606delT* | *p.C202Wfs\*37#* |
| *c.613\_621del* | *c.613\_621del* | *p.205\_207del* |
| *c.614delC* | *c.614delC* | *p.P205Lfs\*34#* |
| *c.618\_619del* | *c.618\_619del* | *p.L206fs\*24#* |
| *c.621dupT* | *c.621dupT* | *p.M208Yfs\*24#* |
| *g.?\_?del* | *c.?\_?del* | *UNKNOWN (del Exon5\_7?)#* |
| *g.[10237\_11932del;*  *11933\_12083inv;*  *12084\_12097del]* | *g.[10237\_11932del;*  *11933\_12083inv;*  *12084\_12097del]* | *UNKNOWN#* |
| *c.646dupT* | *c.646dupT* | *p.Y216Lfs\*15#* |
| *c.646delT* | *c.646delT* | *p.Y216Ifs\*23#* |
| *c.650\_663dup14* | *c.650\_663dup14* | *p.Q221fs\*23#* |
| *c.672\_673ins37* | *c.672\_673ins37* | *p.H225Tfs\*18#* |
| *c.674\_732del* | *c.674\_732del* | *p.H225Lfs\*5#* |
| *c.678delG* | *c.678delG* | *p.A230Lfs\*9#* |
| *c.715\_717 del* | *c.715\_717 del* | *p.del I239* |
| *c.716dupT* | *c.716dupT* | *p.I239fs\*10#* |
| *c.718\_719del* | *c.718\_719del* | *p.K240Efs\*8#* |
| *c.719dupA* | *c.719dupA* | *p.K240fs\*9#* |
| *c.722delG* | *c.722delG* | *p.S241Ifs\*27#* |
| *c.723dupT* | *c.723dupT* | *p.S238fs\*8#* |
| *c.732delC* | *c.732delC* | *p.D244fs\*24#* |
| *c.741ins9* | *c.741ins9* | *p.247ins3* |
| *c.744delT* | *c.744delT* | *p.F248Lfs\*20#* |
| *c.744\_745del* | *c.744\_745del* | *p.F248Lfs\*6#* |
| *c.746\_747del* | *c.746\_747del* | *p.N249Tfs\*5#* |
| *c.759delT* | *c.759delT* | *p.I253Mfs\*15#* |
| *c.760dupG* | *c.760dupG* | *p.V254Gfs\*1#* |
| *c.761\_762del* | *c.761\_762del* | *p.V254Gfs\*9#* |
| *c.774\_775del* | *c.774\_775del* | *p.G258fx\*5#* |
| *c.777delA* | *c.777delA* | *p.P259fs\*9#* |
| *c.782dupG* | *c.782dupG* | *p.G261fs\*3#* |
| *c.807delG* | *c.807delG* | *p.V269fs\*12#* |
| *c.833dupA* | *c.833dupA* | *p.N278Kfs\*20#* |
| *c.833delA* | *c.833delA* | *p.N278Ifs\*3#* |
| *c.842\_844del* | *c.842\_844del* | *p.V281AdelT282* |
| *c.881delT* | *c.881delT* | *p.L294Yfs\*22#* |
| *c.892\_893insT* | *c.892\_893insT* | *p.N298I\*1#* |
| *c.893\_894insG* | *c.893\_894insG* | *p.N298Kfs\*1#* |
| *c.902dupG* | *c.902dupG* | *p.R301fs\*13#* |
| *c.909\_918del* | *c.909\_918del* | *p.I303Mfx\*10#* |
| *c.914delC* | *c.914delC* | *p.P305Lfs\*11#* |
| *c.931delC* | *c.931delC* | *p.L311Ffs\*5#* |
| *c.941\_961del* | *c.941\_961del* | *p.D315\_Q321del* |
| *c.946delG* | *c.946delG* | *p.V316X#* |
| *c.950\_954dupTTGCC* | *c.950\_954dupTTGCC* | *p.A318fs\*31#* |
| *c.974dupG* | *c.974dupG* | *p.G325fs\*7#* |
| *c.986delA* | *c.986delA* | *p.Y329Sfs\*18#* |
| *c.988delC* | *c.988delC* | *p.Q330Sfs\*17#* |
| *c.946\_966del* | *c.946\_966del* | *p.V316\_D322del* |
| *c.994delA* | *c.994delA* | *p.R332Dfs\*15#* |
| *c.996\_999del* | *c.996\_999del* | *p.R332fs\*14#* |
| *c.997dupC* | *c.997dupC* | *p.Q333Pfs\*5#* |
| *c.1011\_1029del* | *c.1011\_1029del* | *p.F337fs\*4#* |
| *c.1017\_1020delins24* | *c.1017\_1020delins24* | *p.V339fs\*7#* |
| *c.1017\_1027del* | *c.1017\_1027del* | *p.V339fs\*5#* |
| *c.1021delG* | *c.1021delG* | *p.E341Nfs\*6#* |
| *c.1025delG* | *c.1025delG* | *p.R342Hfs\*5#* |
| *c.1030\_1031insT* | *c.1030\_1031insT* | *p.L344fs\*30#* |
| *c.1033\_1034del* | *c.1033\_1034del* | *p.S345Rfs\*28#* |
| *c.1037delG* | *c.1037delG* | *p.G346Afs\*1#* |
| *c.1040dupT* | *c.1040dupT* | *p.L347Ffs\*27#* |
| *c.1041dupA* | *c.1041dupA* | *p.L347fs\*27#* |
| *c.1042dupG* | *c.1042dupG* | *p.A348Gfs\*26#* |
| *c.1043\_1044insG* | *c.1043\_1044insG* | *p.A348fs\*26#* |
| *c.1049delC* | *c.1049delC* | *p.A350Vfs\*1#* |
| *c.1151\_1152delinsAT* | *c.1151\_1152delinsAT* | *p.I384N* |
| *c.1055\_1057dup* | *c.1055\_1057dup* | *p.353InsT* |
| *c.1057\_1058del* | *c.1057\_1058del* | *p.M353Dfs\*20#* |
| *c.1072\_1074del* | *c.1072\_1074del* | *p.358delE* |
| *c.1074\_1075del* | *c.1074\_1075del* | *p.E358Dfs\*15#* |
| *c.1077delT* | *c.1077delT* | *p.I359Mfs\*31#* |
| *c.1081\_1100del* | *c.1081\_1100del* | *p.G360fs\*7#* |
| *c.1086\_1098del* | *c.1086\_1098del* | *p.P362fs\*24#* |
| *c.1088delG* | *c.1088delG* | *p.R363Pfs\*27#* |
| *c.1091\_1092del* | *c.1091\_1092del* | *p.S364Lfs\*9#* |
| *c.1093dupT* | *c.1093dupT* | *p.Y365Lfs\*9#* |
| *c.1095delT* | *c.1095delT* | *p.Y365X#* |
| *c.1096\_1100del* | *c.1096\_1100del* | *p.Y365fs\*7#* |
| *c.1102delGinsTTATAC* | *c.1102delGinsTTATAC* | *p.A368delinsFYfs\*23#* |
| *c.1122\_1125del* | *c.1122\_1125del* | *p.K374fs\*15#* |
| *c.1123\_1175del* | *c.1123\_1175del* | *p.G375\_R392del* |
| *c.1139delC* | *c.1139delC* | *p.380Lfs\*10#* |
| *c.1145\_1149del* | *c.1145\_1149del* | *p.C382Yfs\*14#* |
| *c.1146\_1148del* | *c.1146\_1148del* | *p.383delF* |
| *c.1156\_1157del* | *c.1156\_1157del* | *p.Q386Afs\*10#* |
| *c.1167dupT* | *c.1167dupT* | *p.P389fs\*9#* |
| *c.1168 Ins T* | *c.1168 Ins T* | *p. V390fs\*9* |
| *c.1176\_1179del* | *c.1176\_1179del* | *p.R392Sfs\*1#* |
| *c.1177\_1178del* | *c.1177\_1178del* | *p.K393Afs\*4#* |
| *c.1187dupT* | *c.1187dupT* | *p.F396fs\*2#* |
| *c.1187delT* | *c.1187delT* | *p.F396Sfs\*7#* |
| *c.1188delC* | *c.1188delC* | *p.F396fs\*7#* |
| *c.1201dupT* | *c.1201dupT* | *p.S401Ffs\*49#* |
| *c.1208delT* | *c.1208delT* | *p.L403X#* |
| *c.1208ins21* | *c.1208ins21* | *UNKNOWN#* |
| *c.1209\_1211del* | *c.1209\_1211del* | *p.404delR* |
| *c.1223delA* | *c.1223delA* | *p.N408Ifs\*9* |
| *c.1235\_1236del* | *c.1235\_1236del* | *p.T412Sfs\*37* |
| *c.1277\_1278del* | *c.1277\_1278del* | *p.K426Rfs\*23* |
| *c.1284\_1287del* | *c.1284\_1287del* | *p.L428Ffs\*23* |
| *c.359 T>C; c.361 G>A* | *c.T359C/G361A* | *L120P/A121T* |
| *c.644 A>G; c.811 G>A* | *c.A644G; c.G811A* | *N215S/G271S* |
| *c.[644 A>G; 811 G>A; 937 G>T]* | *c.A644G/G811A/G937T* | *N215S/G271S/D313Y* |
| *c.790 G>T; c.805 G>A* | *c.G790T/G805A* | *D264Y/V269M* |
| *c.963\_964 GG>CA* | *c.G963C/G964C* | *Q321H/D322N* |
| *c.1288 T>C* | *c. T1288C* | *X430Q* |
| *IVS1+2 T>C* | *c.194+2 T>C* | *UNKNOWN#* |
| *IVS1-1 G>A* | *c.195-1 G>A* | *UNKNOWN#* |
| *IVS1-1 G>T* | *c.195-1 G>T* | *UNKNOWN#* |
| *IVS1-2 A>G* | *c.195-2 A>G* | *UNKNOWN#* |
| *IVS1-2 A>G;IVS1-49 T>C* | *c.[195-2 A>G;195-49 T>C]* | *UNKNOWN#* |
| *IVS2+1 G>A* | *c.369+1 G>A* | *UNKNOWN#* |
| *IVS2+2 T>G* | *c.369+2 T>G* | *UNKNOWN#* |
| *IVS2-2 A>G* | *c.370-2A>G* | *UNKNOWN#* |
| *IVS3+1 G>A* | *c.547+1 G>A* | *UNKNOWN#* |
| *IVS3+1 G>C* | *c.547+1 G>C* | *UNKNOWN#* |
| *IVS3-2 A>G* | *c.548-2 A>G* | *UNKNOWN#* |
| *IVS3-1 G>A* | *c.548-1 G>A* | *UNKNOWN#* |
| *IVS3-1 G>C* | *c.548-1 G>C* | *UNKNOWN#* |
| *IVS3-1 G>T* | *c.548-1 G>T* | *UNKNOWN#* |
| *IVS4-1 G>T* | *c.639-1 G>T* | *UNKNOWN#* |
| *IVS4+1 G>A* | *c.639+1 G>A* | *UNKNOWN#* |
| *IVS4+1 G>C* | *c.639+1 G>C* | *UNKNOWN#* |
| *IVS4+4 A>T* | *c.639+4 A>T* | *UNKNOWN#* |
| *IVS4+861 C>T* | *c.639+861 C>T* | *UNKNOWN#* |
| *IVS4+919 G>A* | *c.639+919G>A* | *UNKNOWN#* |
| *IVS4-11 T>A* | *c.640-11 T>A* | *UNKNOWN#* |
| *IVS4-3 C>G* | *c.640-3 C>G* | *UNKNOWN#* |
| *IVS4-2 A>T* | *c.640-2 A>T* | *UNKNOWN#* |
| *IVS4-1 G>A* | *c.640-1 G>A* | *UNKNOWN#* |
| *IVS5+2 T>C* | *c.801+2 T>C* | *UNKNOWN#* |
| *IVS5+3 A>G* | *c.801+3 A>G* | *UNKNOWN#* |
| *IVS5+4 A>G* | *c.801+4 A>G* | *UNKNOWN#* |
| *IVS5-2 A>G* | *c.802-2 A>G* | *UNKNOWN#* |
| *IVS6+1 G>T* | *c.999+1 G>T* | *UNKNOWN#* |
| *IVS6+2 T>C* | *c.999+2 T>C* | *UNKNOWN#* |
| *IVS6-2 A>G* | *c.1000-2 A>G* | *UNKNOWN#* |
| *IVS6-2 A>T* | *c.1000-2 A>T* | *UNKNOWN#* |
| *IVS6-1 G>A* | *c.1000-1 G>A* | *UNKNOWN#* |
| *IVS6-1 G>C* | *c.1000-1 G>C* | *UNKNOWN#* |

#Mutation did not qualify for testing in the GLP HEK assay. Mutations that generally do not qualify for testing include large deletions, insertions, truncations, frameshift mutations, and splice site mutations. These types of mutations often lead to the loss of entire protein domains that grossly alter the structure and function of the enzyme, and may even result in the complete loss of expression. Splice site mutations, in particular, can lead to incorrect processing of mRNA precursors, including exon skipping or splicing at cryptic splice points, resulting in gross structural and functional alterations. Furthermore, splice site mutations are not testable in the GLP HEK assay because this assay uses recombinant *GLA* cDNA; thus, the mutant α-Gal A is expressed independent of pre-mRNA splicing. Mutations that do not qualify for testing in the GLP HEK assay are categorized as non-amenable without testing.

\*While these nucleotide changes cause apparent single amino acid residue substitutions (as indicated in the parenthesis in the column of ‘protein sequence change’), scientific evidence 3 indicate that these are putative splicing mutations that cause gross changes to α-Gal A protein sequences.

Question marks (?) in the columns of ‘Nucleotide Change’ indicate that the underlying mutations were not reported in the literature and therefore are not available.

UNKNOWN in the column of ‘protein sequence change’ indicate that the changes to the protein sequence caused by the mutations cannot be readily deduced from the nucleotide changes and need to be experimentally determined. In these cases, the question marks in the accompanying parentheses indicate that the changes provided therein have not been experimentally confirmed and may not be correct.

Two or more nucleotide changes that lead to the same stop codon indicate that more than one patient each with a different *GLA* mutation leading to the same nonsense mutant form of α-Gal A has been reported.

Notes to the pharmacogenetic reference table:

* Amenable mutations are defined as those in *GLA* that translate to mutant forms of the enzyme with α Gal A activity in the presence of 10 µM migalastat that is ≥1.20-fold over baseline and an absolute increase at 10 µM migalastat of ≥3.0% of wild-type α Gal A activity.
* The results listed in this table are based on GLP HEK-293 cell-based assay. Mutations may change in category if scientific evidence suggests that the mutations may lead to forms of the α-Gal A protein *in vivo* that are different from those expected based solely on the cDNA sequence.

**References**

1. Wu X, Katz E, Valle CD, et al. A pharmacogenetic approach to identify mutant forms of a-galactosidase A that respond to a pharmacological chaperone for Fabry disease. *Hum. Mutat.* 2011;32(8):965-977.

2. Johnson FK, Mudd PN, Bragat A, Adera M, Boudes P. Pharmacokinetics and Safety of Migalastat HCl and Effects on Agalsidase Activity in Healthy Volunteers. *Clin Pharmacol Drug Dev.* 2013;2(2):120-132.

3. Lai LW, Whitehair O, Wu MJ, O'Meara M, Lien YH. Analysis of splice-site mutations of the α-galactosidase A gene in Fabry disease. *Clin. Genet.* 2003;63(6):476-482.