

## Ethambutol (EMB)

### Notes and Assumptions

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<sup>1</sup> N = 1,330.

<sup>2</sup> 5-Fold Cross-Validation is used to find the best Meta-Parameters for the Random Forest and the Neural Network Classifiers.

<sup>3</sup> Cross-Validation Criteria is ROC-AUC.

<sup>4</sup> 2 Hidden Layers are included in the Neural Network Classifier.

<sup>5</sup> Marginal Effects, ROC-AUC, Sensitivity and Specificity are computed 250 times (Boostraps).

<sup>6</sup> 2/3 of the Sample is Randomly Selected to Train the Classifiers in each Bootstrap.

Marginal Effects, ROC-AUC, Sensitivity and Specifity are Computed on the 1/3 of the Sample left

<sup>7</sup> The threshold used to predict the drug resistance maximizes Sensitivity + Specificity.

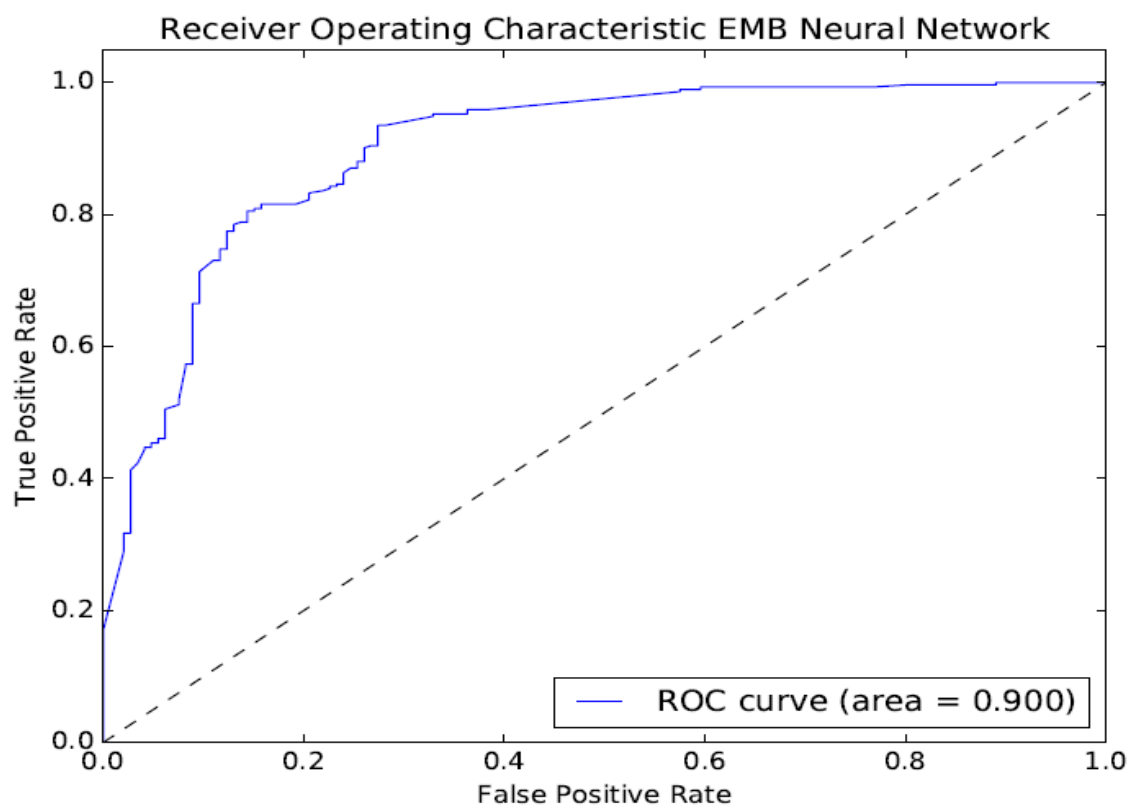
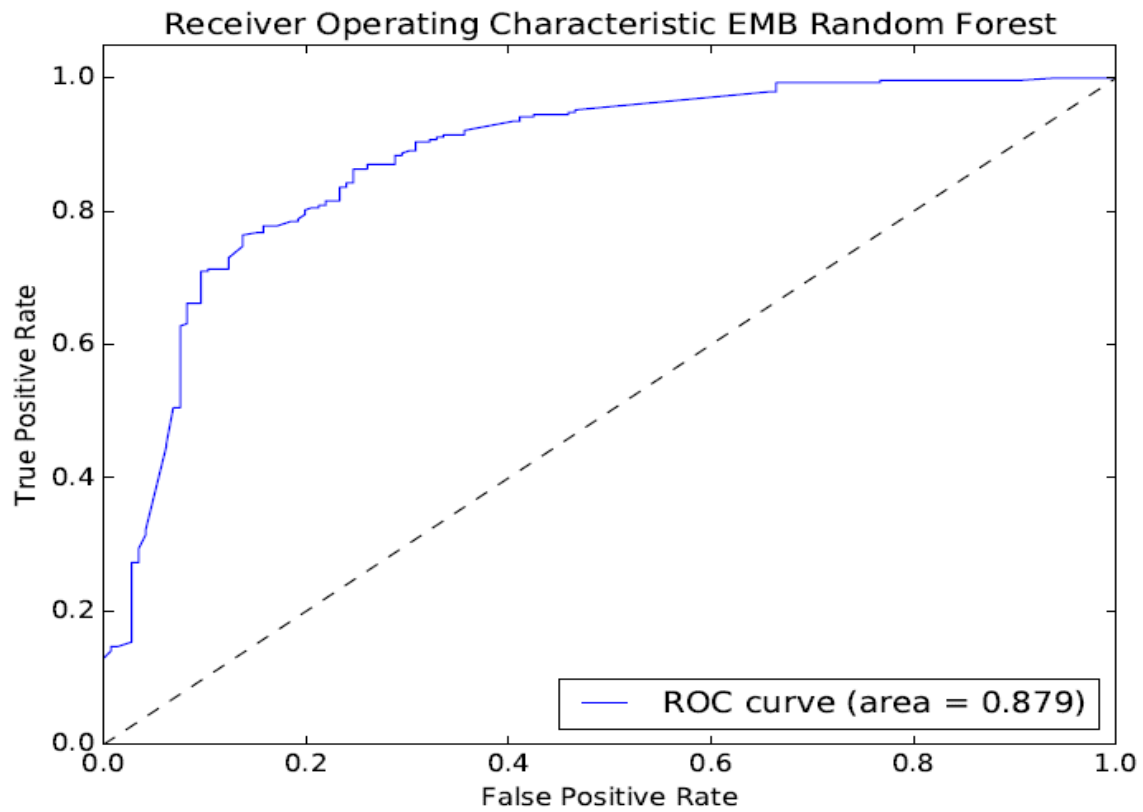
<sup>8</sup> Models (1) include 18 mutations selected in "*genetic determinants of drug resistance in Mycobacterium Tuberculosis and their diagnostic value*".

<sup>9</sup> Models (2) include all potential 141 mutations.

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**Ethambutol (EMB): Predictive Model Performance**

	<b>ROC-AUC</b>	<b>Sensitivity [1]</b>	<b>Specificity [2]</b>	<b>[1] + [2]</b>	<b>Optimal Threshold</b>
Original Random Forest		0.800 (0.020)	0.820 (0.030)	1.620	
Random Forest (1)	0.850 (0.017)	0.835 (0.018)	0.831 (0.028)	1.666	0.631 (0.091)
Neural Network (1)	0.865 (0.015)	0.833 (0.024)	0.841 (0.029)	1.674	0.643 (0.110)
Random Forest (2)	0.868 (0.017)	0.876 (0.033)	0.768 (0.039)	1.644	0.470 (0.101)
Neural Network (2)	0.895 (0.016)	0.872 (0.055)	0.801 (0.055)	1.672	0.566 (0.121)



## Ethambutol (EMB)

## Marginal Effects (Standard Errors in Parentheses)

Mutations	Random Forest	Marginal Effects (Standard Errors in Parentheses)			
	Variable Importance	Random Forest (1)	Neural Network (1)	Random Forest (2)	Neural Network (2)
SNP_CN_4247429_A916G_M306V_embB	0.163	0.398 (0.017)	0.404 (0.015)	0.400 (0.017)	0.402 (0.013)
SNP_CN_4247431_G918A_M306I_embB	0.106	0.303 (0.019)	0.326 (0.016)	0.310 (0.019)	0.318 (0.013)
SNP_CN_4247431_G918C_M306I_embB	0.059	0.283 (0.021)	0.303 (0.017)	0.270 (0.024)	0.289 (0.014)
SNP_CN_4247730_G1217C_G406A_embB	0.038	0.264 (0.021)	0.277 (0.018)	0.235 (0.027)	0.261 (0.014)
SNP_CN_4248003_A1490G_Q497R_embB	0.038	0.279 (0.019)	0.310 (0.014)	0.253 (0.023)	0.283 (0.012)
SNP_CN_4249518_A3005G_H1002R_embB	0.012	0.242 (0.028)	0.282 (0.020)	0.100 (0.074)	0.226 (0.020)
SNP_CN_409569_G208A_A70T_iniB	0.019	0.197 (0.034)	0.204 (0.026)	0.106 (0.056)	0.147 (0.022)
SNP_CN_4247729_G1216A_G406S_embB	0.021	0.218 (0.026)	0.258 (0.021)	0.181 (0.029)	0.231 (0.018)
SNP_CN_4247431_G918T_M306I_embB	0.015	0.277 (0.013)	0.317 (0.013)	0.229 (0.018)	0.239 (0.013)
SNP_CN_4247429_A916C_M306L_embB	0.013	0.275 (0.014)	0.316 (0.013)	0.218 (0.015)	0.235 (0.012)
SNP_P_4243222_C11A_promoter_embA_embB	0.008	0.270 (0.016)	0.314 (0.013)	0.184 (0.021)	0.234 (0.015)
SNP_CN_4247574_A1061C_D354A_embB	0.021	0.162 (0.026)	0.182 (0.024)	0.110 (0.038)	0.178 (0.019)
SNP_CN_4247495_G982T_D328Y_embB	0.007	0.268 (0.016)	0.314 (0.013)	0.177 (0.026)	0.206 (0.017)
SNP_CN_4249583_G3070A_D1024N_embB	0.014	0.143 (0.049)	0.097 (0.045)	0.108 (0.052)	0.129 (0.028)
SNP_CN_4243392_A160G_N54D_embA	0.009	0.032 (0.009)	0.248 (0.016)	0.121 (0.009)	0.109 (0.013)
SNP_P_4243225_C8T_promoter_embA_embB	0.010	0.117 (0.071)	0.053 (0.057)	0.103 (0.036)	0.092 (0.031)
SNP_CN_4242182_G2320T_A774S_embC	0.017	0.076 (0.024)	0.069 (0.023)	0.032 (0.022)	0.047 (0.021)
SNP_CN_4247729_G1216T_G406C_embB	0.004	0.176 (0.061)	0.306 (0.013)	0.121 (0.038)	0.141 (0.026)
SNP_CN_414042_C1286G_S429W_iniC	0.022			-0.120 (0.060)	-0.078 (0.028)
SNP_CN_4248725_T2212G_S738A_embB	0.020			-0.006 (0.040)	-0.049 (0.033)
SNP_CN_413903_T1147C_Y383H_iniC	0.019			-0.230 (0.038)	-0.286 (0.041)
SNP_CN_4242803_G2941C_V981L_embC	0.019			-0.011 (0.014)	-0.006 (0.014)
SNP_CN_4242425_C2563G_R855G_embC	0.019			-0.064 (0.017)	-0.028 (0.016)
SNP_CN_4247402_T889G_S297A_embB	0.018			0.105 (0.051)	0.160 (0.024)
SNP_CN_4247730_G1217A_G406D_embB	0.017			0.126 (0.028)	0.146 (0.020)
SNP_CN_4246423_T3191G_V1064G_embA	0.012			-0.089 (0.049)	-0.063 (0.036)
SNP_P_4243221_C12T_promoter_embA_embB	0.011			0.130 (0.033)	0.120 (0.023)
SNP_CN_414041_T1285G_S429A_iniC	0.010			-0.099 (0.039)	-0.059 (0.025)
SNP_CN_4245961_A2729G_Q910R_embA	0.010			-0.154 (0.039)	-0.081 (0.029)
SNP_CN_4249757_A3244G_T1082A_embB	0.010			-0.211 (0.047)	-0.107 (0.030)
SNP_P_4243217_C16T_promoter_embA_embB	0.008			0.121 (0.052)	0.115 (0.027)
SNP_CN_4248002_C1489A_Q497K_embB	0.008			0.079 (0.047)	0.127 (0.029)
SNP_P_4243217_C16G_promoter_embA_embB	0.008			0.033 (0.050)	0.145 (0.023)
SNP_CN_4242075_G2213A_R738Q_embC	0.008			-0.211 (0.041)	-0.160 (0.030)
SNP_CN_412017_C1180G_Q394E_iniA	0.007			-0.002 (0.061)	0.078 (0.024)
SNP_CN_4247469_A956G_Y319C_embB	0.007			0.126 (0.038)	0.141 (0.029)
SNP_CN_410962_A125G_H42R_iniA	0.007			0.123 (0.010)	0.144 (0.013)
SNP_CN_412339_C1502G_S501W_iniA	0.007			-0.056 (0.079)	-0.046 (0.043)
SNP_CN_4247861_A1348C_I450L_embB	0.006			0.062 (0.052)	0.120 (0.034)
SNP_CN_4247469_A956C_Y319S_embB	0.006			-0.038 (0.063)	0.084 (0.035)
SNP_P_409296_C66T_promoter_iniB_iniA_iniC	0.006			-0.255 (0.038)	-0.145 (0.024)
SNP_CN_4245055_C1823A_T608N_embA	0.006			0.031 (0.038)	0.050 (0.024)
SNP_CN_4242303_T2441A_L814Q_embC	0.006			-0.079 (0.050)	-0.094 (0.043)
SNP_CN_4242369_G2507C_R836P_embC	0.005			-0.148 (0.055)	-0.078 (0.023)
SNP_CN_412689_A1852G_S618G_iniA	0.005			-0.055 (0.049)	0.018 (0.029)
SNP_P_4243190_G43C_promoter_embA_embB	0.005			0.136 (0.039)	0.155 (0.028)
SNP_P_4243217_C16A_promoter_embA_embB	0.005			0.145 (0.041)	0.139 (0.028)
SNP_CN_4248441_C1928T_T643I_embB	0.004			0.088 (0.045)	0.112 (0.031)
SNP_CN_4247496_A983G_D328G_embB	0.004			0.107 (0.029)	0.155 (0.027)
SNP_I_414336_G45A_inter_iniC_lpqJ	0.004			-0.038 (0.043)	-0.093 (0.052)
SNP_CN_411582_G745A_A249T_iniA	0.003			-0.095 (0.045)	-0.096 (0.033)
SNP_CN_4245969_C2737T_P913S_embA	0.003			-0.038 (0.018)	-0.020 (0.009)
SNP_P_409360_A2C_promoter_iniB_iniA_iniC	0.003			0.075 (0.044)	0.092 (0.031)
SNP_CZ_413819_C1063T_Q355._iniC	0.003			-0.095 (0.040)	-0.063 (0.021)
SNP_CN_4246734_T221C_L74P_embB	0.003			-0.030 (0.053)	0.053 (0.028)
SNP_CN_4241042_A1180G_N394D_embC	0.003			-0.055 (0.021)	-0.067 (0.024)
SNP_P_409297_A65G_promoter_iniB_iniA_iniC	0.003			-0.064 (0.050)	-0.018 (0.024)
SNP_CN_413747_G991A_G331R_iniC	0.003			-0.133 (0.053)	-0.098 (0.025)
SNP_CN_409906_C545T_A182V_iniB	0.003			0.034 (0.026)	0.083 (0.039)
SNP_CN_4247553_G1040T_S347I_embB	0.003			0.095 (0.044)	0.134 (0.033)
SNP_CN_4247847_A1334G_Q445R_embB	0.003			0.119 (0.041)	0.138 (0.029)
SNP_CN_4242822_T2960G_V987G_embC	0.003			-0.120 (0.048)	-0.106 (0.031)

## Ethambutol (EMB)

## Marginal Effects (Standard Errors in Parentheses)

Mutations	Random Forest				
	Variable Importance	Random Forest (1)	Neural Network (1)	Random Forest (2)	Neural Network (2)
SNP_CN_4246085_G2853T_E951D_embA	0.003			0.091 (0.043)	0.099 (0.033)
SNP_CN_4247646_A1133C_E378A_embB	0.003			-0.034 (0.016)	-0.014 (0.010)
SNP_CN_4247728_G1215C_E405D_embB	0.003			0.104 (0.043)	0.128 (0.028)
SNP_CN_4241358_C1496A_A499D_embC	0.003			0.068 (0.045)	0.082 (0.036)
SNP_CN_4249071_A2558C_Q853P_embB	0.002			-0.072 (0.036)	-0.061 (0.028)
SNP_CN_4247429_A916T_M306L_embB	0.002			-0.058 (0.055)	-0.003 (0.033)
SNP_CN_4243848_G616A_V206M_embA	0.002			-0.027 (0.023)	0.001 (0.025)
SNP_CN_4249773_G3260A_G1087D_embB	0.002			0.029 (0.013)	0.067 (0.022)
SNP_CN_411958_C1121T_A374V_iniA	0.002			-0.065 (0.033)	-0.023 (0.012)
SNP_CN_4248437_A1924G_T642A_embB	0.002			0.055 (0.025)	0.085 (0.027)
SNP_CN_4246970_A457T_T153S_embB	0.002			0.091 (0.024)	0.096 (0.021)
SNP_CN_4239891_T29C_I10T_embC	0.002			-0.012 (0.027)	0.023 (0.034)
SNP_CN_4245025_A1793G_H598R_embA	0.002			0.005 (0.023)	-0.071 (0.039)
SNP_P_4243218_C15G_promoter_embA.embB	0.002			-0.014 (0.053)	0.024 (0.026)
SNP_CN_4248315_C1802G_A601G_embB	0.002			0.038 (0.016)	0.100 (0.024)
SNP_CN_4244958_G1726A_A576T_embA	0.002			-0.057 (0.053)	-0.017 (0.027)
SNP_CN_4243963_T731G_V244G_embA	0.002			-0.022 (0.056)	-0.013 (0.041)
SNP_CN_412280_T1443G_H481Q_iniA	0.002			-0.016 (0.012)	0.002 (0.008)
SNP_CN_4241562_G1700A_R567H_embC	0.002			-0.119 (0.023)	-0.048 (0.011)
SNP_CN_4244668_T1436G_V479G_embA	0.002			-0.005 (0.035)	-0.008 (0.035)
SNP_CN_4240671_C809T_T270I_embC	0.002			-0.003 (0.009)	0.043 (0.011)
SNP_CN_411928_T1091G_V364G_iniA	0.002			0.007 (0.023)	-0.021 (0.031)
SNP_CN_4240172_G310A_V104M_embC	0.002			-0.111 (0.021)	-0.048 (0.011)
INS_CF_409548_i186G_63_iniB	0.002			-0.020 (0.024)	-0.003 (0.033)
SNP_CN_411934_G1097A_G366D_iniA	0.002			0.026 (0.018)	0.054 (0.028)
SNP_CN_4245961_A2729C_Q910P_embA	0.001			-0.055 (0.052)	-0.031 (0.025)
SNP_CN_4247972_A1459G_T487A_embB	0.001			-0.044 (0.039)	-0.016 (0.025)
SNP_CN_409516_G155T_G52V_iniB	0.001			-0.048 (0.045)	-0.072 (0.042)
SNP_P_4243222_C11T_promoter_embA.embB	0.001			0.024 (0.014)	0.067 (0.027)
SNP_CN_413727_C971T_A324V_iniC	0.001			-0.041 (0.041)	-0.069 (0.056)
SNP_CN_4249512_T2999G_M1000R_embB	0.001			0.027 (0.014)	0.095 (0.032)
SNP_CN_4248003_A1490C_Q497P_embB	0.001			0.148 (0.041)	0.177 (0.024)
SNP_CN_4248004_G1491T_Q497H_embB	0.001			0.045 (0.013)	0.051 (0.014)
SNP_CN_4244403_G1171C_V391L_embA	0.001			0.023 (0.040)	0.061 (0.028)
DEL_CD_412976_d219GCCACCGAG_74_iniC	0.001			0.024 (0.038)	0.061 (0.028)
SNP_CN_414182_C1426T_R476C_iniC	0.001			0.001 (0.017)	0.026 (0.020)
SNP_CN_4247420_A907C_I303L_embB	0.001			0.023 (0.011)	0.027 (0.013)
SNP_CN_4245621_G2389C_A797P_embA	0.001			0.020 (0.010)	0.019 (0.010)
DEL_P_4243202_d31C_promoter_embA.embB	0.001			0.046 (0.018)	0.057 (0.020)
SNP_CN_413276_G520A_V174M_iniC	0.001			-0.020 (0.032)	-0.036 (0.047)
INS_CF_4243703_i470AGAT_157_embA	0.001			0.010 (0.008)	0.051 (0.030)
SNP_CN_4246551_A38G_N13S_embB	0.001			0.018 (0.008)	0.021 (0.008)
SNP_CN_413022_C266T_T89I_iniC	0.001			-0.028 (0.021)	-0.027 (0.019)
INS_CF_4247350_i836TTCCAGAATATTGG_279_emt	0.001			0.028 (0.014)	0.048 (0.024)
SNP_CN_4244148_T916C_W306R_embA	0.001			0.005 (0.003)	0.019 (0.013)
DEL_CD_4247356_d842CGTGGT_281_embB	0.001			0.028 (0.015)	0.048 (0.024)
SNP_CN_4243245_G13C_G5R_embA	0.001			0.005 (0.003)	0.019 (0.013)
SNP_CN_413772_G1016C_R339P_iniC	0.001			0.029 (0.013)	0.028 (0.012)
SNP_CN_411100_A263G_N88S_iniA	0.001			0.018 (0.008)	0.021 (0.008)
INS_CF_4242521_i2658TCCCCGCCATGCT_887_emb	0.000			0.023 (0.012)	0.034 (0.015)
DEL_P_4243192_d41A_promoter_embA.embB	0.000			0.015 (0.011)	0.014 (0.010)
INS_CF_4247020_i506CC_169_embB	0.000			0.014 (0.011)	0.038 (0.025)
SNP_CN_412114_C1277T_A426V_iniA	0.000			0.021 (0.009)	0.009 (0.005)
INS_CF_4247970_i1456GT_486_embB	0.000			0.008 (0.005)	0.027 (0.016)
SNP_CN_4243590_G358A_D120N_embA	0.000			0.026 (0.013)	0.024 (0.012)
SNP_CN_4241022_C1160T_A387V_embC	0.000			0.023 (0.011)	0.016 (0.008)
SNP_CN_4247619_T1106C_V369A_embB	0.000			0.018 (0.009)	0.021 (0.010)
SNP_P_4243225_C8A_promoter_embA.embB	0.000			0.014 (0.010)	0.017 (0.011)
SNP_CN_412645_G1808T_R603L_iniA	0.000			0.030 (0.013)	0.023 (0.010)
SNP_CN_4245945_A2713G_I905V_embA	0.000			0.020 (0.011)	0.017 (0.009)
SNP_CN_409384_T23C_I8T_iniB	0.000			0.019 (0.008)	0.020 (0.008)
SNP_CN_4245966_T2734C_F912L_embA	0.000			0.013 (0.009)	0.008 (0.006)

Ethambutol (EMB)		Marginal Effects (Standard Errors in Parentheses)			
Mutations	Random Forest	Random Forest (1)	Neural Network (1)	Random Forest (2)	Neural Network (2)
	Variable Importance				
SNP_CN_4241699_A1837G_M613V_embC	0.000			0.048 (0.021)	0.066 (0.024)
SNP_CN_4240592_G730A_A244T_embC	0.000			0.010 (0.007)	0.015 (0.010)
SNP_CN_4244841_C1609T_R537W_embA	0.000			0.012 (0.006)	0.015 (0.007)
SNP_CN_410560_A1199C_N400T_iniB	0.000			0.012 (0.006)	0.015 (0.007)
SNP_CN_411694_T857A_F286Y_iniA	0.000			-0.026 (0.018)	-0.025 (0.016)
SNP_CN_4243872_G640T_V214F_embA	0.000			0.000 (0.000)	0.000 (0.000)
SNP_CN_409770_G409C_G137R_iniB	0.000			0.018 (0.010)	0.015 (0.007)
SNP_CN_4241093_T1231C_C411R_embC	0.000			-0.135 (0.059)	-0.069 (0.026)
SNP_CN_4247451_C938T_A313V_embB	0.000			-0.078 (0.057)	-0.040 (0.024)
DEL_CF_410982_d144CTGAACG_49_iniA	0.000			-0.026 (0.018)	-0.025 (0.016)
SNP_CN_4245193_C1961T_S654L_embA	0.000			0.074 (0.026)	0.117 (0.025)
SNP_CN_411009_C172T_R58W_iniA	0.000			-0.042 (0.030)	-0.050 (0.029)
INS_CF_411691_i853C_285_iniA	0.000			-0.026 (0.018)	-0.025 (0.016)
DEL_CF_4241603_d1740TTCACCCCGAC_581_embC	0.000			-0.025 (0.018)	-0.025 (0.016)
SNP_CN_4248320_G1807C_G603R_embB	0.000			0.105 (0.043)	0.125 (0.031)
SNP_CZ_411090_C253T_Q85._iniA	0.000			0.014 (0.010)	0.018 (0.011)
SNP_I_410806_C32G_inter_iniB_iniA	0.000			0.026 (0.012)	0.031 (0.012)