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# DATABASES



# Update of the Pompe variant database for the prediction of clinical phenotypes: Novel disease-associated variants, common sequence variants, and results from newborn screening

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# Abstract

Pompe disease is an inherited disorder caused by disease-associated variants in the acid  $\alpha$ -glucosidase gene (GAA). The Pompe disease GAA variant database (http:// www.pompevariantdatabase.nl) is a curated, open-source, disease-specific database, and lists disease-associated GAA variants, in silico predictions, and clinical phenotypes reported until 2016. Here, we provide an update to include 226 diseaseassociated variants that were published until 2020. We also listed 148 common GAA sequence variants that do not cause Pompe disease. GAA variants with unknown severity that were identified only in newborn screening programs were listed as a new feature to indicate the reason why phenotypes were still unknown. Expression studies were performed for common missense variants to predict their severity. The updated Pompe disease GAA variant database now includes 648 disease-associated variants, 26 variants from newborn screening, and 237 variants with unknown severity. Regular updates of the Pompe disease GAA variant database will be required to improve genetic counseling and the study of genotype-phenotype relationships.

### KEYWORDS

database, disease-associated variants, GAA, NBS, Pompe disease, SNP

# 1 | INTRODUCTION

Pompe disease (glycogen storage disease type II; MIM #232300) is an autosomal recessive disorder caused by disease-associated variants in the acid  $\alpha$ -glucosidase (GAA) gene, resulting in a deficiency of the GAA enzyme, accumulation of lysosomal glycogen, and

progressive muscle weakness. The clinical spectrum of Pompe disease is broad (Güngör & Reuser, 2013). The most severe classic infantile phenotype presents shortly after birth with hypertrophic cardiomyopathy and generalized muscle weakness. These patients die in the first year of life due to cardiorespiratory insufficiency if left untreated. The slower progressing phenotype is characterized by

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muscle weakness that can appear at any age from <1 year into adulthood. These patients are generally spared from cardiac symptoms (Kohler et al., 2018; van der Ploeg & Reuser, 2008). Enzyme replacement therapy (ERT) with intravenously applied recombinant human GAA is available since 2006. ERT normalizes hypertrophic cardiomyopathy, improves motor function, and extends survival.

The differences between phenotypes in Pompe disease can, in part, be attributed to the severity of the disease-associated variants present in the GAA gene. Classic infantile patients carry two diseaseassociated variants that completely disrupt the function of GAA (i.e., null alleles). This group of patients can be subdivided based on their cross-reactive immunological material (CRIM) status, which is defined by the disease-associated variants involved. When two GAA variants are present that do not result in GAA protein expression, the patient is classified as CRIM-negative. When at least one GAA variant gives rise to GAA protein expression (in which the GAA protein can be enzymatically inactive), the patient is classified as CRIM-positive. The clinical importance of CRIM status is highlighted by the fact that CRIM-negative classic infantile patients have a poorer prognosis compared with CRIM-positive classic infantile patients, possibly due to the formation of high sustained anti-GAA antibody titers upon treatment with ERT (Bali et al., 2012; van Gelder et al., 2015). Patients who do not have the classic infantile phenotype carry at least one disease-associated variant that allows some residual enzymatic activity. These patients are, by definition, CRIM-positive (Kroos et al., 2012b; Kulessa et al., 2020).

The "Pompe disease GAA variant database" (http://www. pompevariantdatabase.nl) is an open-access database that lists and classifies all reported variants in the GAA gene. We recently revised this database to include clinical data from patients collected from the literature, adapted the classification system for variant severity, and added (predicted) CRIM status for disease-associated variants. The database included literature up to May 2016, resulting in a total of 561 variants (Niño et al., 2019). In recent years, many new patients and GAA variants have been reported. These include findings from large patient populations, such as the French nationwide study (246 patients with late-onset Pompe disease) and the Pompe registry (1079 patients from 26 countries; Reuser et al., 2019; Semplicini et al., 2018).

In addition, various countries, including Taiwan, the United States, Italy, Brazil, and Japan, have implemented newborn screening (NBS) programs for Pompe disease, resulting in an increase of variants of unknown significance (VUS; Bravo et al., 2017; Burlina et al., 2018; Chien et al., 2019; Elliott et al., 2016; Momosaki et al., 2019; Yang et al., 2014). For variants associated with late onset, the associated phenotypes from NBS cases are still unknown as symptom onset could, in principle, be delayed until (late) adulthood. It will be important to monitor the onset and progress of symptoms in patients identified via NBS programs closely to determine the severity of the newly identified genetic variants.

Public databases, such as dbSNP (https://www.ncbi.nlm.nih.gov/ snp) and gnomAD (https://gnomad.broadinstitute.org), provide a source of variants that have been detected in various genome-wide studies (Karczewski et al., 2020; Sherry et al., 2001). A large percentage of these variants represent common sequence variants that have a minor allele frequency (MAF)  $\geq$  1%. Several of these variants have already been reported for the GAA gene and have been ruled out to cause Pompe disease (Kroos et al., 2007; Labrousse et al., 2010; Turaça et al., 2015). However, most of the common sequence variants in these databases are listed as VUSs and may lead to misinterpretation during molecular diagnostics.

In this study, we provide an update of the Pompe disease GAA variant database with variants and patients described in the literature up to January 2020. We included information on novel GAA variants that were identified via NBS and for which no phenotype was yet known. Known common sequence variants in the GAA gene that do not cause Pompe disease have now also been added to prevent misdiagnosis. In addition, selected common missense variants were tested in expression studies and also this information was added to the updated database. The database provides a curated up-to-date reference source for the molecular diagnosis of Pompe disease.

# 2 | METHODS

The Pompe disease GAA variant database is publicly available at http://www.pompevariantdatabase.nl. The previous version of the database included literature until 2016; the update described here contains variants from publications up to January 2020. Additionally, NBS studies that screened for Pompe disease were now included if the authors provided the genotypes of the described cases. Novel variants were analyzed as described in Niño et al. (2019). Variants were annotated based on the reference sequences NM 000152.3 for GAA messenger RNA (mRNA), LRG 673 genomic sequence for describing variants in intronic sequences, and NP\_000143.2 for GAA protein. Exon annotations were based on the human genomic build (GRCH37/hg19) for exons 2-20; however, changes were made to the annotation of exon 1 to reflect the findings of (GRCH38/hg38). Within this region, a new 195-bp intron was identified at positions c.-112 and c.-113. Therefore, the region that was previously annotated as exon 1 has been split between exons 1A and 1B, which are separated by intron 1A. Intron 1 has been renamed to intron 1B. This numbering was made to maintain the same numbering of subsequent exons compared with existing literature.

Common sequence variants in the GAA gene (hg38 Chr17:80,101,556-80,119,881) were extracted from gnomAD and were categorized as "not disease-associated." Combined Annotation-Dependent Depletion (CADD) in silico predictions were performed using the CADD (https://cadd.gs.washington.edu) platform, which compiles different tools for analysis of intronic insertion and deletion variants (Rentzsch et al., 2019). The MAF and CADD scores were obtained in April 2020. Predictions of effect on pre-mRNA splicing were performed using Alamut Visual v.2.15 (Interactive Biosoftware).

Functional studies were performed using site-directed mutagenesis (SDM) to generate complementary DNA (cDNA) expression

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### TABLE 1 Novel disease-associated variants added to the Pompe variant database

DNA nomenclature	Phenotype combined with a null allele	DNA nomenclature	Phenotype combined with a null allele
Ch37/hg19 chr17:78,059,821_ 78,076,592del	Unknown (disease-associated)	c.1057C>T	Unknown (disease-associated)
c113+2T>A	Unknown (disease-associated)	c.1057del	Unknown (disease-associated)
c32-1732-10delins(30)	Classic infantile	c.1099T>G	Unknown (disease-associated)
c32-1G>C	Unknown (disease-associated)	c.1106T>A	Unknown (disease-associated)
c.40_47del	Classic infantile	c.1109G>A	Unknown (disease-associated)
c.104T>C	Classic infantile	c.1114C>G	Unknown (disease-associated)
c.169C>T	Classic infantile	c.1114C>T	Unknown (disease-associated)
c.205C>T	Unknown (disease-associated)	c.1121G>A	Unknown (disease-associated)
c.258C>A	Unknown (disease-associated)	c.1127_1130del	Unknown (disease-associated)
c.265C>T	Unknown (disease-associated)	c.1129G>A	Unknown (disease-associated)
c.295_314del	Unknown (disease-associated)	c.1153del	Unknown (disease-associated)
c.323G>C	Unknown (disease-associated)	c.1192del	Unknown (disease-associated)
c.365del	Unknown (disease-associated)	c.1193del	Unknown (disease-associated)
c.380G>A	Unknown (disease-associated)	c.1201C>A	Unknown (disease-associated)
c.397T>G	Unknown (disease-associated)	c.1209C>A	Unknown (disease-associated)
c.437del	Classic infantile	c.1211A>C	Unknown (disease-associated)
c.445A>C	Unknown (disease-associated)	c.1211A>T	Classic infantile
c.484A>C	Classic infantile	c.1212C>G	Unknown (disease-associated)
c.502C>T	Unknown (disease-associated)	c.1216G>A	Childhood
c.505C>A	Unknown (disease-associated)	c.1219T>C	Unknown (disease-associated)
c.517_519del	Childhood	c.1221C>A	Classic infantile
c.541_545del	Classic infantile	c.1221del	Unknown (disease-associated)
c.547-1G>C	Unknown (disease-associated)	c.1226_1227insG	Classic infantile
c.568C>T	Unknown (disease-associated)	c.1231del	Unknown (disease-associated)
c.665T>G	Classic infantile	c.1240T>C	Unknown (disease-associated)
c.686G>C	Unknown (disease-associated)	c.1241del	Classic infantile
c.691C>T	Unknown (disease-associated)	c.1242C>A	Unknown (disease-associated)
c.692T>C	Unknown (disease-associated)	c.1249A>C	Unknown (disease-associated)
c.692+1G>T	Unknown (disease-associated)	c.1281G>T	Classic infantile
c.693-2A>C	Classic infantile	c.1292_1295dup	Classic infantile
c.693-1G>C	Unknown (disease-associated)	c.1293_1326+57del	Unknown (disease-associated)
c.715_716del	Unknown (disease-associated)	c.1298A>C	Classic infantile
c.730C>T	Classic infantile	c.1311_1312ins(26)	Classic infantile
c.736del	Unknown (disease-associated)	c.1320_1322del	Classic infantile
c.756_757insT	Unknown (disease-associated)	c.1327-54_1437+178del	Classic infantile
c.759del	Unknown (disease-associated)	c.1358_1361del	Classic infantile
c.766_784del	Unknown (disease-associated)	c.1378G>T	Unknown (disease-associated)
c.781G>A	Classic infantile	c.1388_1406del	Unknown (disease-associated)
c.784G>C	Unknown (disease-associated)	c.1396dup	Unknown (disease-associated)

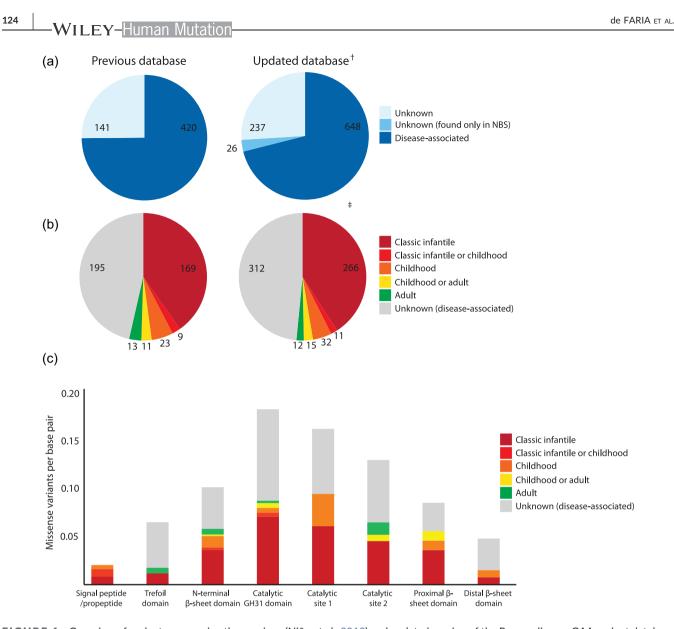
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DNA nomenclature	Phenotype combined with a null allele		Phenotype combined with a null allele
c.796C>A	Childhood	c.1402A>T	Unknown (disease-associated)
c.799_803delinsA	Unknown (disease-associated)	c.1409A>G	Unknown (disease-associated)
c.837G>C	Unknown (disease-associated)	c.1431del	Classic infantile
c.841C>T	Unknown (disease-associated)	c.1441del	Unknown (disease-associated)
c.876C>G	Classic infantile	c.1447G>T	Unknown (disease-associated)
c.878G>T	Unknown (disease-associated)	c.1456G>T	Unknown (disease-associated)
c.883C>A	Unknown (disease-associated)	c.1464dup	Classic infantile
c.930_932del	Classic infantile	c.1470C>A	Childhood
c.942C>A	Unknown (disease-associated)	c.1477C>T	Unknown (disease-associated)
c.947A>G	Classic infantile	c.1493G>A	Classic infantile
c.950C>T	Unknown (disease-associated)	c.1501_1515del	Unknown (disease-associated)
c.955+1G>A	Classic infantile	c.1507del	Classic infantile
c.971dup	Classic infantile	c.1526A>T	Unknown (disease-associated)
c.982_988del	Classic infantile	c.1531C>A	Unknown (disease-associated)
c.983T>C	Classic infantile	c.1537G>A	Unknown (disease-associated)
c.994_995insTT	Unknown (disease-associated)	c.1538A>G	Classic infantile
c.1000G>T	Classic infantile	c.1551+3A>T	Unknown (disease-associated)
c.1004_1005dup	Unknown (disease-associated)	c.1551+5G>A	Unknown (disease-associated)
c.1047del	Unknown (disease-associated)	c.1559A>G	Unknown (disease-associated)
c.1560C>G	Unknown (disease-associated)	c.2096T>C	Unknown (disease-associated)
c.1579_1580del	Classic infantile	c.2109del	Unknown (disease-associated)
c.1583G>C	Unknown (disease-associated)	c.2131A>C	Classic infantile
c.1594G>A	Adult	c.2146G>C	Unknown (disease-associated)
c.1597T>G	Classic infantile	c.2153_2156delinsACGCCG	Classic infantile
c.1602_1605delinsAGG	Classic infantile	c.2182_2183del	Unknown (disease-associated)
c.1610del	Unknown (disease-associated)	c.2190-345A>G	Unknown (disease-associated)
c.1627T>G	Unknown (disease-associated)	c.2205dup	Classic infantile
c.1629C>G	Unknown (disease-associated)	c.2213G>A	Classic infantile
c.1636G>C	Unknown (disease-associated)	c.2221G>A	Classic infantile
c.1636+5G>A	Classic infantile	c.2222A>T	Unknown (disease-associated)
c.1650del	Unknown (disease-associated)	c.2234T>C	Classic infantile
c.1657C>T	Classic infantile	c.2235dup	Classic infantile
c.1681_1699dup	Unknown (disease-associated)	c.2237G>T	Unknown (disease-associated)
c.1688A>T	Unknown (disease-associated)	c.2240G>A	Unknown (disease-associated)
c.1716C>A	Classic infantile	c.2261dup	Unknown (disease-associated)
c.1721T>C	Unknown (disease-associated)	c.2294G>A	Classic infantile
c.1753_2799del	Classic infantile	c.2296T>A	Classic infantile
- c.1754+1dup	Unknown (disease-associated)	c.2297A>C	Classic infantile
c.1754+2T>C	Unknown (disease-associated)	c.2304del	Unknown (disease-associated)
c.1780C>T	Unknown (disease-associated)	c.2320G>A	Unknown (disease-associated)
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DNA nomenclature	Phenotype combined with a null allele	DNA nomenclature	Phenotype combined with a null allele
c.1784C>T	Unknown (disease-associated)	c.2331+5G>C	Classic infantile
c.1799G>C	Unknown (disease-associated)	c.2331+102del	Unknown (disease-associated)
c.1822del	Unknown (disease-associated)	c.2334_2335dup	Unknown (disease-associated)
c.1825T>G	Unknown (disease-associated)	c.2377_2378insAC	Classic infantile
c.1835A>C	Unknown (disease-associated)	c.2380dup	Unknown (disease-associated)
c.1835A>G	Unknown (disease-associated)	c.2395C>T	Unknown (disease-associated)
c.1837T>G	Unknown (disease-associated)	c.2407C>T	Unknown (disease-associated)
c.1839G>C	Unknown (disease-associated)	c.2411G>A	Classic infantile
c.1844_1846del	Unknown (disease-associated)	c.2459_2461del	Unknown (disease-associated)
c.1844G>T	Classic infantile	c.2460dup	Unknown (disease-associated)
c.1844G>A	Classic infantile	c.2474C>G	Unknown (disease-associated)
c.1847dup	Unknown (disease-associated)	c.2480A>G	Unknown (disease-associated)
c.1859C>A	Unknown (disease-associated)	c.2515C>T	Unknown (disease-associated)
c.1879_1881del	Classic infantile	c.2537C>A	Unknown (disease-associated)
c.1888+2_1888+15del	Classic infantile	c.2544del	Unknown (disease-associated)
c.1895T>C	Unknown (disease-associated)	c.2563G>C	Classic infantile
c.1895T>G	Classic infantile	c.2578G>A	Unknown (disease-associated)
c.1903A>G	Unknown (disease-associated)	c.2584G>A	Childhood
c.1913G>A	Classic infantile	c.2585del	Classic infantile
c.1944_1950del	Unknown (disease-associated)	c.2596del	Unknown (disease-associated)
c.1952dup	Unknown (disease-associated)	c.2619C>G	Unknown (disease-associated)
c.1961C>G	Unknown (disease-associated)	c.2636T>C	Classic infantile
c.2004C>A	Unknown (disease-associated)	c.2655_2656del	Unknown (disease-associated)
c.2015G>T	Unknown (disease-associated)	c.2716G>A	Unknown (disease-associated)
c.2020C>G	Unknown (disease-associated)	c.2720T>C	Unknown (disease-associated)
c.2020C>T	Unknown (disease-associated)	c.2725G>A	Unknown (disease-associated)
c.2024A>G	Classic infantile	c.2740dup	Unknown (disease-associated)
c.2040+2dup	Unknown (disease-associated)	c.2742dup	Classic infantile
c.2040+29_2190-270del	Classic infantile	c.2757del	Unknown (disease-associated)
c.2041-2A>G	Classic infantile	c.2799+5G>A	Unknown (disease-associated)
c.2051C>A	Unknown (disease-associated)	c.2800-1G>C	Classic infantile
c.2051C>G	Unknown (disease-associated)	c.2843dup	Classic infantile
c.2051C>T	Classic infantile	c.2845_2847del	Unknown (disease-associated)
c.2056_2057delinsCC	Unknown (disease-associated)		
c.2084dup	Unknown (disease-associated)		

constructs containing the missense variant of interest as described (in 't Groen et al., 2020). The activity of the GAA protein produced by the constructs was measured using 4-methylumbelliferyl- $\alpha$ -D-glucopyranoside (4-MU) as a substrate in transfected COS-7 cells, as

described in Kroos et al. (2008). Statistical analysis was performed using one-way analysis of variance with Tukey honestly significant difference post hoc multiple testing corrections. p < .05 was considered significant.



**FIGURE 1** Overview of variants, comparing the previous (Niño et al., 2019) and updated version of the Pompe disease GAA variant database (http://www.pompevariantdatabase.nl). (a) Number of disease-associated and unknown variants in the previous database (left) and the updated version of the database (right). (b) Number of disease-associated variants classified based on the predicted clinical phenotype when combined with a null allele in the previous database (left) and in the updated version of the database (right). (c) Distribution of disease-associated missense variants listed in the updated database, based on the protein domains of GAA and the predicted clinical phenotype when combined with a null allele. Numbers are corrected for the length of each domain. †Two entries in the previous version of the database were removed as the variants were described twice using different nomenclatures. ‡For 36 variants listed in the previous version of the database, a reclassification of the phenotypic severity was performed due to the addition of novel patients included in this update

# 3 | RESULTS AND DISCUSSION

Table 1 provides an overview of the novel variants. We performed a literature search covering the past 4 years and identified 80 publications (listed in the updated database and Table S1) that described 350 novel variants, of which 226 were considered to be disease-associated (Table 1 and Figure 1a). Seventy-six novel variants (33%) were present in combination with a null allele, which allowed prediction of the clinical severity of these variants (Table 1 and Figure 1b). In addition, the inclusion of new patient information allowed us to classify the severity of 55 variants that were already present in the database. This resulted in a new total of 911 GAA variants, of which 648 were disease-associated (71%). In total, 336 out of 648 diseaseassociated variants (52%) could be associated with a clinical phenotype. The geographical or ethnical distribution of reported patients remained similar to what was described previously. The majority of patients had a Caucasian background or were of Caucasian descent (data not shown). This introduces a bias in the current version of the database and indicates the necessity of extending the database to patients of other descent. Mapping of missense variants to GAA protein domains revealed an even

# TABLE 2 List of common sequence variants located within the boundaries of the GAA gene

xborn 14, S'UTR         c-200G>C         rs2304849         16%         No effect on splicing         8.996           xborn 14, S'UTR         c-178G>A         rs77514632         2%         No effect on splicing         9.948           xborn 18, S'UTR         c-727G-G         rs80020206         0.%K (3% in African population)         No effect on splicing         9.999           ntron 18         c-33121XG>C         rs889761         75%         No effect on splicing         9.799           ntron 18         c-3313TC>T         rs8077056         20%         No effect on splicing         4.579           ntron 18         c-33147C>T         rs5751636         31%         No effect on splicing         4.564           ntron 18         c-331407L>C         rs24913147         5%         No effect on splicing         0.664           ntron 18         c-33141267A         rs142315         5%         No effect on splicing         0.644           ntron 18         c-33141007T         rs12002593         10%         No effect on splicing         2.604           ntron 18         c-321420471         rs4202650         33%         No effect on splicing         3.993           ntron 18         c-32.2716>C         rs153666739         2%         No effect on splicing         3.9	Location	Variant	Variant ID	Global allele frequency (GnomAD)	Predictions of pre-mRNA splicing	CADD score PHRED
Scon 1A, S UTR         c178G>A         rs77514632         2%         No effect on splicing         9,949           Scon 1A, S'UTR         c75C>G         rs80020204         0.9% (3% in African population)         No effect on splicing         9,999           Intron 1B         c334:316C>C         rs489791         75%         No effect on splicing         9,079           Intron 1B         c334:316C>C         rs8077055         20%         No effect on splicing         8,579           Intron 1B         c334:316C>C         rs55751634         31%         No effect on splicing         4,564           Intron 1B         c334:172C>         rs244:13147         5%         No effect on splicing         4,974           Intron 1B         c334:1172C>         rs12450199         34%         No effect on splicing         6,964           Intron 1B         c334:1172C>         rs1246219         33%         No effect on splicing         2,664           Intron 1B         c334:1190C>T         rs1240219         33%         No effect on splicing         2,684           Intron 1B         c32:1298G>C         rs1240210         33%         No effect on splicing         2,694           Intron 1B         c32:4298G>C         rs12402314         76%         No effect on s	Exon 1A, 5' UTR	c338C>G	rs144639114	2%	No effect on splicing	6.524
Storn 18, S <sup>1</sup> UTR         c7SC-G         rs8002026         0.9% (3% in African population)         No effect on splicing         9.989           ntron 18         c33+219C-C         rs4889961         75%         No effect on splicing         0.866           ntron 18         c33+317C-T         rs8077055         20%         No effect on splicing         9.799           ntron 18         c33+671A-C         rs5575153         20%         No effect on splicing         4.574           ntron 18         c33+776-A         rs24451347         5%         No effect on splicing         4.574           ntron 18         c33+104A-G         rs1142019         34%         No effect on splicing         6.76           ntron 18         c33+1172C-A         rs1442315         5%         No effect on splicing         1.784           ntron 18         c33+1190C>C         rs1442315         5%         No effect on splicing         1.784           ntron 18         c33+1905C>C         rs12602510         33%         No effect on splicing         2.592           ntron 18         c32+196C>C         rs1260250         2%         No effect on splicing         3.993           ntron 18         c32+404C>T         rs12602610         33%         No effect on splicing	Exon 1A, 5' UTR	c260G>C	rs2304849	16%	No effect on splicing	8.996
ntron 1B         c-33+219G>C         rs4889961         75%         No effect on splicing         0.866           ntron 1B         c-33+316C>A         rs8077055         20%         No effect on splicing         9.079           ntron 1B         c-33+316C>A         rs8077055         20%         No effect on splicing         8.579           ntron 1B         c-33+757C>A         rs2811317         5%         No effect on splicing         4.976           ntron 1B         c-33+104A>G         rs1150841         75%         No effect on splicing         6.976           ntron 1B         c-33+104A>G         rs11260253         10%         No effect on splicing         1.744           ntron 1B         c-33+107C>         rs12602593         10%         No effect on splicing         1.752           ntron 1B         c-33+107C>         rs142214         76%         No effect on splicing         1.752           ntron 1B         c-32+129G>C         rs16202610         33%         No effect on splicing         3.993           ntron 1B         c-32+129G>C         rs142214         76%         No effect on splicing         3.993           ntron 1B         c-32-129G>C         rs1520026         0.7% (3% in African population)         No effect on splicing         3.993	Exon 1A, 5' UTR	c178G>A	rs77514632	2%	No effect on splicing	9.948
ntron 18         c-33+316C>A         rs8077055         20%         No effect on splicing         9.079           ntron 18         c-33+317C>T         rs8077056         20%         No effect on splicing         8.579           ntron 18         c-33+671A>C         rs55751636         31%         No effect on splicing         4.74           ntron 18         c-33+757C>A         rs28113147         5%         No effect on splicing         4.74           ntron 18         c-33+104A>C         rs11450199         34%         No effect on splicing         6.76           ntron 18         c-33+1102A>C         rs1442315         5%         No effect on splicing         1.782           ntron 18         c-33+1190C>T         rs142016         33%         No effect on splicing         2.825           ntron 18         c-32+1120C>T         rs1420260         0.7% (3% in African population         No effect on splicing         3.993           ntron 18         c-32+1120C>T         rs14502606         0.7% (3% in African population         No effect on splicing         3.993           ntron 18         c-32-7120>C         rs147264695         0.3% (1% in Finnish population         No effect on splicing         0.34           ntron 18         c-32-460A>C         rs147264695         0.3% (1% in Fin	Exon 1B, 5' UTR	c75C>G	rs80020206	0.9% (3% in African population)	No effect on splicing	9.989
ntron 18         c-33+317C>T         n8077054         20%         No effect on splicing         8.579           ntron 18         c-33+671A>C         rs55751636         31%         No effect on splicing         4.974           ntron 18         c-33+7576>A         rs28413147         5%         No effect on splicing         4.974           ntron 18         c-33+104A>C         rs12450199         34%         No effect on splicing         6.976           ntron 18         c-33+1102A>C         rs1150841         75%         No effect on splicing         6.976           ntron 18         c-33+1102A>C         rs1442315         5%         No effect on splicing         1.784           ntron 18         c-33+1090A>C         rs142314         76%         No effect on splicing         2.604           ntron 18         c-32+1298C>C         rs142314         76%         No effect on splicing         2.604           ntron 18         c-32-1298C>C         rs14532064         0.9% (3% in African population)         No effect on splicing         4.941           ntron 18         c-32-7210>C         rs5754966         2%         No effect on splicing         4.349           ntron 18         c-32-240C>T         rs147264095         0.3% (15 in Finnish population)         No effect on splici	Intron 1B	c33+219G>C	rs4889961	75%	No effect on splicing	0.866
ntron 18c-33+671A>Crs5575163631%No effect on splicing1.456ntron 18c-33+7576>Ars284131475%No effect on splicing4.974ntron 18c-33+903A>Crs1245019934%No effect on splicing6.076ntron 18c-33+11706>Ars1115084175%No effect on splicing6.076ntron 18c-33+11702>Ars1423155%No effect on splicing1.764ntron 18c-33+11702>Ars14231476%No effect on splicing1.764ntron 18c-33+11905>Crs1260259310%No effect on splicing2.604ntron 18c-32+1296>Crs1260261033%No effect on splicing3.993ntron 18c-32-1298C>rs145262060.9% (3% in African population)No effect on splicing3.993ntron 18c-32-7216>Crs155667392%No effect on splicing4.041ntron 18c-32-7216>Crs175754662%No effect on splicing0.366ntron 18c-32-7216>Crs175754662%No effect on splicing0.364ntron 18c-32-240C>Trs12600855%No effect on splicing0.364ntron 18c-32-240C>Ars1002951%No effect on splicing0.226ntron 18c-32-447C>Grs1403255722%No effect on splicing0.226xon 2c2476>Ars14023665%No effect on splicing0.226xon 2c2476>Ars14023665%No effect on splicing <td>Intron 1B</td> <td>c33+316C&gt;A</td> <td>rs8077055</td> <td>20%</td> <td>No effect on splicing</td> <td>9.079</td>	Intron 1B	c33+316C>A	rs8077055	20%	No effect on splicing	9.079
ntron 1Bc-33+757G>Ars284131475%No effect on splicing4.974ntron 1Bc-33+903A>Crs1245019934%No effect on splicing6.976ntron 1Bc-33+1170A>Grs1115084175%No effect on splicing0.064ntron 1Bc-33+1190G>Trs1260259310%No effect on splicing1.784ntron 1Bc-33+1190G>Trs1260259310%No effect on splicing1.784ntron 1Bc-33+1190G>Trs1260259310%No effect on splicing1.784ntron 1Bc-32+1246>Trs1895960020%No effect on splicing3.993ntron 1Bc-32-884T>Crs1453620660.9% (3% in African population)No effect on splicing3.993ntron 1Bc-32-793C>Grs55667392%No effect on splicing1.008ntron 1Bc-32-640A>Grs1472640950.3% (1% in Finnish population)No effect on splicing1.036ntron 1Bc-32-640C>Trs1200084513%No effect on splicing0.364ntron 1Bc-32-494C>Grs140325722%No effect on splicing0.226ntron 1Bc-32-494C>Grs140325722%No effect on splicing0.226ntron 1Bc-32-494C>Grs140325722%No effect on splicing0.226ntron 1Bc-32-494C>Grs140325722%No effect on splicing0.226attron 1Bc-32-494C>Grs140325722%No effect on splicing0.226attron 1Bc-32-494C>G	Intron 1B	c33+317C>T	rs8077056	20%	No effect on splicing	8.579
thron 1Bc33+903A-Crs1245019934%No effect on splicing8.196ntron 1Bc33+1104A-Grs1115084175%No effect on splicing0.064ntron 1Bc33+1190C>Trs1240257310%No effect on splicing1.784ntron 1Bc33+1190C>Trs1240257310%No effect on splicing1.784ntron 1Bc33+1097>Crs144231476%No effect on splicing2.604ntron 1Bc32-1298C>Crs1260261033%No effect on splicing2.604ntron 1Bc32-1298C>Crs1453020660.5% (3% in African population)No effect on splicing3.993ntron 1Bc32-793C>Grs556667392%No effect on splicing4.041ntron 1Bc32-793C>Grs556667392%No effect on splicing4.041ntron 1Bc32-701C>Crs757549662%Selfect on splicing4.349ntron 1Bc32-640C>Trs120004551%No effect on splicing0.366ntron 1Bc32-494C>Grs14702404950.3% (1% in Finnish population)No effect on splicing0.256oton 2c.32-494C>Grs140325722%No effect on splicing0.256oton 2c.32-494C>Grs140325722%No effect on splicing0.256oton 2c.32-494C>Grs140325722%No effect on splicing0.256oton 2c.32-494C>Grs140325722%No effect on splicing1.252ntron 1Bc32-494C>G <t< td=""><td>Intron 1B</td><td>c33+671A&gt;C</td><td>rs55751636</td><td>31%</td><td>No effect on splicing</td><td>1.456</td></t<>	Intron 1B	c33+671A>C	rs55751636	31%	No effect on splicing	1.456
ntron 18         c33+1104A-G         rs11150841         75%         No effect on splicing         6.976           ntron 18         c33+1172G-A         rs142315         5%         No effect on splicing         0.064           ntron 18         c33+1190G>T         rs12602593         10%         No effect on splicing         1.784           ntron 18         c33+1309T>C         rs142314         76%         No effect on splicing         2.004           ntron 18         c32+124G>T         rs5895960         20%         No effect on splicing         3.973           ntron 18         c32-1724G>C         rs1450666         0.9% (3% in African population)         No effect on splicing         3.973           ntron 18         c32-721G>C         rs755666739         2%         No effect on splicing         4.041           ntron 18         c32-721G>C         rs75754966         2%         Generates a new cryptic         0.036           ntron 18         c32-40C>T         rs11506025         1%         No effect on splicing         0.39           ntron 18         c32-440C>G         rs140325572         2%         No effect on splicing         0.236           ntron 18         c32-440C>G         rs14032066         5%         No effect on splicing	Intron 1B	c33+757G>A	rs28413147	5%	No effect on splicing	4.974
ntron 18         c33+1172G>A         rs1442315         5%         No effect on splicing         0.064           ntron 18         c33+1190G>T         rs12602593         10%         No effect on splicing         1.782           ntron 18         c33+1309T>C         rs1442314         76%         No effect on splicing         2.604           ntron 18         c32-1298G>C         rs12602610         33%         No effect on splicing         2.604           ntron 18         c32-1124C>T         rs58959600         20%         No effect on splicing         3.993           ntron 18         c32-2884T>C         rs145362066         0.9% (3% in African population)         No effect on splicing         3.993           ntron 18         c32-793C>G         rs55666739         2%         No effect on splicing         4.041           ntron 18         c32-272G>C         rs5754966         2%         Cenesplace accepter splice         1.008           ntron 18         c32-494C>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         0.439           ntron 18         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           ntron 18         c32-494C>G         rs140325572         2%	Intron 1B	c33+903A>C	rs12450199	34%	No effect on splicing	8.196
ntron 1B         c-33+1190G>T         rs12602593         10%         No effect on splicing         1.784           ntron 1B         c-33+1309T>C         rs1442314         76%         No effect on splicing         1.752           ntron 1B         c-32-1298G>C         rs12602610         33%         No effect on splicing         5.825           ntron 1B         c-32-1124C>T         rs58959690         20%         No effect on splicing         3.993           ntron 1B         c-32-793C>G         rs145362066         0.9% (3% in African population)         No effect on splicing         3.993           ntron 1B         c-32-793C>G         rs5566739         2%         No effect on splicing         4.041           ntron 1B         c-32-721G>C         rs75754966         2%         No effect on splicing         0.108           ntron 1B         c-32-640C>T         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         0.136           ntron 1B         c-32-440C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c-32-440C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c-32-440C>G         rs140325572         2%         No effect o	Intron 1B	c33+1104A>G	rs11150841	75%	No effect on splicing	6.976
ntron 1B         c -33+13097-C         rs1442314         76%         No effect on splicing         1.752           ntron 1B         c -32-12986-C         rs12602210         33%         No effect on splicing         2.604           ntron 1B         c -32-1124C>T         rs58959690         20%         No effect on splicing         3.993           ntron 1B         c -32-384T>C         rs145362066         0.9% (3% in African population)         No effect on splicing         3.993           ntron 1B         c -32-721G>C         rs75754966         2%         Senerates a new cryptic         1.008           ntron 1B         c -32-686A>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           ntron 1B         c -32-640C>T         rs1200845         51%         No effect on splicing         0.036           ntron 1B         c -32-640C>T         rs1200845         51%         No effect on splicing         0.036           ntron 1B         c -32-494C>G         rs140325572         2%         No effect on splicing         0.226           xon 2         c 271G>A         rs1800299         2%         No effect on splicing         0.226           xon 2         c 2442S>A         rs74003606         5%         No effect on sp	Intron 1B	c33+1172G>A	rs1442315	5%	No effect on splicing	0.064
Arton 18         c32-1298G>C         rs12602610         33%         No effect on splicing         5.825           Intron 18         c32-1124C>T         rs58959690         20%         No effect on splicing         5.825           Intron 18         c32-884T>C         rs145362066         0.9% (3% in African populatio)         No effect on splicing         3.993           Intron 18         c32-793C>G         rs5566739         2%         No effect on splicing         4.041           Intron 18         c32-721G>C         rs75754966         2%         Generates a new cryptic         1.008           Intron 18         c32-686A>G         rs147264095         0.3% (1% in Finnish populatio)         No effect on splicing         4.349           Intron 18         c32-640C>T         rs12600845         51%         No effect on splicing         0.036           Intron 18         c32-440C>G         rs110500925         1%         No effect on splicing         0.226           intron 18         c32-440C>G         rs1002097         2%         No effect on splicing         0.226           ixon 2         c.2447G>A         rs1300300         72%         No effect on splicing         1.252           ixon 2         c.546+293G>A         rs8476710         20%         No e	Intron 1B	c33+1190G>T	rs12602593	10%	No effect on splicing	1.784
ntron 18         c32.1124C>T         rs58959690         20%         No effect on splicing         5.825           ntron 18         c32.884T>C         rs145362066         0.9% (3% in African population)         No effect on splicing         3.993           ntron 18         c32.793C>G         rs55666739         2%         No effect on splicing         4.041           ntron 18         c32.721G>C         rs75754966         2%         Generates a new cryptic splice accepter site         1.008           ntron 18         c32.640C>T         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           ntron 18         c32.640C>T         rs12600845         51%         No effect on splicing         0.036           ntron 18         c32.440C>G         rs140325572         2%         No effect on splicing         0.226           exon 2         c.271G>A         rs1000292         2%         No effect on splicing         0.226           exon 2         c.324T>C         rs100300         72%         No effect on splicing         0.226           exon 2         c.3447C>A         rs1800300         72%         No effect on splicing         1.252           exon 2         c.3447C>A         rs3289536         0.5% (3% in East Asian popu	Intron 1B	c33+1309T>C	rs1442314	76%	No effect on splicing	1.752
Arthon 1B         c32-884T>C         rs145362066         0.9% (3% in African population)         No effect on splicing         3.993           Intron 1B         c32-793C>G         rs55666739         2%         No effect on splicing         4.041           Intron 1B         c32-721G>C         rs75754966         2%         Generates a new cryptic splice accepter site         1.008           Intron 1B         c32-686A>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           Intron 1B         c32-640C>T         rs12600845         51%         No effect on splicing         0.036           Intron 1B         c32-2494C>G         rs140305572         2%         No effect on splicing         0.036           Intron 1B         c32-4492C>G         rs14030297         2%         No effect on splicing         0.226           Intron 1B         c32-4492C>G         rs1800300         72%         No effect on splicing         0.226           Intron 1B         c32-4492C>G         rs14764710         20%         No effect on splicing         1.891           Intron 1B         c.547-243C>G         rs805426         67%         No effect on splicing         1.252           Intron 2         c.547-243C>G         rs806491	Intron 1B	c32-1298G>C	rs12602610	33%	No effect on splicing	2.604
ntron 1B         c32-793C>G         rs55666739         2%         No effect on splicing         4.041           ntron 1B         c32-721G>C         rs75754960         2%         Generates a new cryptic splice accepter site         1.008           ntron 1B         c32-686A>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           ntron 1B         c32-640C>T         rs12600845         51%         No effect on splicing         0.136           ntron 1B         c32-521G>T         rs115060925         1%         Generates a new cryptic splice donor site         0.639           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           cxon 2         c.271G>A         rs1800299         2%         No effect on splicing         0.226           cxon 2         c.324+7C         rs1800300         72%         No effect on splicing         8.391           cxon 2         c.547-243C         rs34746710         20%         No effect on splicing         1.252           cxon 2         c.547-243C>G         rs34746710         20%         No effect on splicing         1.337           ntron 2         c.547-243C>G         rs3065426         67%         No effect o	Intron 1B	c32-1124C>T	rs58959690	20%	No effect on splicing	5.825
ntron 1B         c32-721G>C         rs75754966         2%         Generates a new cryptic splice accepter site         1.008           ntron 1B         c32-686A>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           ntron 1B         c32-640C>T         rs12600845         51%         No effect on splicing         0.036           ntron 1B         c32-521G>T         rs115060925         1%         Generates a new cryptic splice donor site         0.639           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c32-492C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c32-492C>G         rs1400320572         2%         No effect on splicing         0.226           ntron 2         c.271G>A         rs1800209         2%         No effect on splicing         1.252           ntron 2         c.547-23A         rs289536         0.5% (3% in East Asi	Intron 1B	c32-884T>C	rs145362066	0.9% (3% in African population)	No effect on splicing	3.993
ntron 1B         c32-686A>G         rs147264695         0.3% (1% in Finnish population)         No effect on splicing         4.349           ntron 1B         c32-640C>T         rs12600845         51%         No effect on splicing         0.639           ntron 1B         c32-521G>T         rs115060925         1%         Septed conor site         0.639           ntron 1B         c32-494C>G         rs11000925         2%         No effect on splicing         0.226           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.226           ntron 1B         c32-494C>G         rs1800299         2%         No effect on splicing         0.226           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         0.256           ixon 2         c.447G>A         rs1800300         2%         No effect on splicing         1.891           ntron 2         c.547-233C         rs289536         2%         No effect on splicing         1.891           ntron 2         c.547-233C         rs8065426         67%         No effect on splicing         1.337           ntron 2         c.547-67C>G         rs8065421         67%         No effect on splicing         1.337	Intron 1B	c32-793C>G	rs55666739	2%	No effect on splicing	4.041
ntron 1B         c32-640C>T         rs12600845         51%         No effect on splicing         0.136           ntron 1B         c32-521G>T         rs115060925         1%         Generates a new cryptic splice donor site         0.639           ntron 1B         c32-494C>G         rs140325572         2%         No effect on splicing         0.036           ntron 1B         c32-462G>A         rs74003606         5%         No effect on splicing         0.226           ixon 2         c.271G>A         rs1800299         2%         No effect on splicing         0.256           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         8.391           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         1.252           ixon 2         c.447G>A         rs2289536         0.5% (3% in East Asian population)         No effect on splicing         1.252           intron 2         c.547-2432C>G         rs8065426         67%         No effect on splicing         1.367           intron 2         c.547-238T>C         rs12452263         20%         No effect on splicing         1.337           intron 2         c.547-39T>G         rs12452721         67%         No effect on splicing <td< td=""><td>Intron 1B</td><td>c32-721G&gt;C</td><td>rs75754966</td><td>2%</td><td></td><td>1.008</td></td<>	Intron 1B	c32-721G>C	rs75754966	2%		1.008
Intron 1B       c32-521G>T       rs115060925       1%       Generates a new cryptic       0.639         Intron 1B       c32-494C>G       rs140325572       2%       No effect on splicing       0.036         Intron 1B       c32-462G>A       rs74003606       5%       No effect on splicing       0.226         ixon 2       c.271G>A       rs1800299       2%       No effect on splicing       0.256         ixon 2       c.324T>C       rs1800300       72%       No effect on splicing       8.391         ixon 2       c.447G>A       rs2289536       0.5% (3% in East Asian population)       No effect on splicing       1.252         ixon 2       c.546+293G>A       rs34746710       20%       No effect on splicing       1.899         ntron 2       c.547-243C>G       rs8065426       67%       No effect on splicing       1.337         ntron 2       c.547-39T>C       rs12452263       20%       No effect on splicing       1.337         ntron 2       c.547-39T>G       rs12452721       67%       No effect on splicing       2.56         ntron 2       c.547-39T>G       rs18423721       67%       No effect on splicing       4.721         xon 3       c.596A>G       rs1042393       67%       No effect	Intron 1B	c32-686A>G	rs147264695	0.3% (1% in Finnish population)	No effect on splicing	4.349
ntron 1B       c32-494C>G       rs140325572       2%       No effect on splicing       0.036         ntron 1B       c32-462G>A       rs74003606       5%       No effect on splicing       0.226         ixon 2       c.271G>A       rs1800299       2%       No effect on splicing       0.256         ixon 2       c.324T>C       rs1800300       72%       No effect on splicing       8.391         ixon 2       c.324T>C       rs1800300       72%       No effect on splicing       8.391         ixon 2       c.447G>A       rs1800300       72%       No effect on splicing       1.252         ixon 2       c.546+293G>A       rs3249536       0.5% (3% in East Asian population)       No effect on splicing       1.899         ntron 2       c.547-243C>G       rs8065426       67%       No effect on splicing       5.667         ntron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       1.337         ntron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         ntron 2       c.547-24SG       rs12452721       67%       No effect on splicing       4.721         ixon 3       c.59A>G       rs1042393       67%       No effect on splicing </td <td>Intron 1B</td> <td>c32-640C&gt;T</td> <td>rs12600845</td> <td>51%</td> <td>No effect on splicing</td> <td>0.136</td>	Intron 1B	c32-640C>T	rs12600845	51%	No effect on splicing	0.136
ntron 1B         c32-462G>A         rs74003606         5%         No effect on splicing         0.226           ixon 2         c.271G>A         rs1800299         2%         No effect on splicing         0.256           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         8.391           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         8.391           ixon 2         c.447G>A         rs2289536         0.5% (3% in East Asian population)         No effect on splicing         1.252           ntron 2         c.546+293G>A         rs34746710         20%         No effect on splicing         1.899           ntron 2         c.547-243C>G         rs8065426         67%         No effect on splicing         5.567           ntron 2         c.547-238T>C         rs12452263         20%         No effect on splicing         1.337           ntron 2         c.547-39T>G         rs12452263         20%         No effect on splicing         1.337           ntron 2         c.547-39T>G         rs12452721         67%         No effect on splicing         4.721           ntron 2         c.547-47C>G         rs180301         67%         No effect on splicing         5.486      x	Intron 1B	c.−32-521G>T	rs115060925	1%		0.639
ixon 2         c.271G>A         rs1800299         2%         No effect on splicing         0.256           ixon 2         c.324T>C         rs1800300         72%         No effect on splicing         8.391           ixon 2         c.447G>A         rs289536         0.5% (3% in East Asian population)         No effect on splicing         1.252           ixon 2         c.447G>A         rs289536         0.5% (3% in East Asian population)         No effect on splicing         1.252           intron 2         c.546+293G>A         rs34746710         20%         No effect on splicing         1.899           intron 2         c.547-243C>G         rs8065426         67%         No effect on splicing         5.667           intron 2         c.547-67C>G         rs8069491         67%         No effect on splicing         1.337           intron 2         c.547-39T>G         rs12452721         67%         No effect on splicing         4.721           intron 2         c.547-4C>G         rs3816256         67%         No effect on splicing         4.721           ixon 3         c.642C>T         rs1800301         18%         No effect on splicing         1.805           ixon 3         c.648G>A         rs1042395         67%         No effect on splicing         1.805 <td>Intron 1B</td> <td>c32-494C&gt;G</td> <td>rs140325572</td> <td>2%</td> <td>No effect on splicing</td> <td>0.036</td>	Intron 1B	c32-494C>G	rs140325572	2%	No effect on splicing	0.036
Exon 2         c.324T>C         rs1800300         72%         No effect on splicing         8.391           Exon 2         c.447G>A         rs2289536         0.5% (3% in East Asian population)         No effect on splicing         1.252           Intron 2         c.546+293G>A         rs34746710         20%         No effect on splicing         1.899           Intron 2         c.547-243C>G         rs8065426         67%         No effect on splicing         2.529           Intron 2         c.547-238T>C         rs12452263         20%         No effect on splicing         5.667           Intron 2         c.547-67C>G         rs8065426         67%         No effect on splicing         1.337           Intron 2         c.547-67C>G         rs8069491         67%         No effect on splicing         1.337           Intron 2         c.547-39T>G         rs12452721         67%         No effect on splicing         4.721           Intron 2         c.547-4C>G         rs3816256         67%         No effect on splicing         0.548           Intron 2         c.547-4C>G         rs1042393         67%         No effect on splicing         0.548           Intron 2         c.547-4C>G         rs1042393         67%         No effect on splicing         1.805 </td <td>Intron 1B</td> <td>c32-462G&gt;A</td> <td>rs74003606</td> <td>5%</td> <td>No effect on splicing</td> <td>0.226</td>	Intron 1B	c32-462G>A	rs74003606	5%	No effect on splicing	0.226
ixon 2       c.447G>A       rs2289536       0.5% (3% in East Asian population)       No effect on splicing       1.252         intron 2       c.546+293G>A       rs34746710       20%       No effect on splicing       1.899         intron 2       c.547-243C>G       rs8065426       67%       No effect on splicing       2.529         intron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       5.667         intron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         intron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         intron 2       c.547-39T>G       rs12452721       67%       No effect on splicing       2.78         intron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         ixon 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         ixon 3       c.648G>A       rs1042395       67%       No effect on splicing       1.805         ixon 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Exon 2	c.271G>A	rs1800299	2%	No effect on splicing	0.256
ntron 2       c.546+293G>A       rs34746710       20%       No effect on splicing       1.899         ntron 2       c.547-243C>G       rs8065426       67%       No effect on splicing       2.529         ntron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       5.667         ntron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       1.337         ntron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         ntron 2       c.547-39T>G       rs12452721       67%       Loss of cryptic splice donor site       2.78         ntron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         exon 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         exon 3       c.648C>A       rs1042395       67%       No effect on splicing       1.805         exon 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Exon 2	c.324T>C	rs1800300	72%	No effect on splicing	8.391
ntron 2       c.547-243C>G       rs8065426       67%       No effect on splicing       2.529         ntron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       5.667         ntron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         ntron 2       c.547-39T>G       rs12452721       67%       Loss of cryptic splice donor site       2.78         ntron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         fixon 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         fixon 3       c.642C>T       rs1800301       18%       No effect on splicing       1.805         fixon 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Exon 2	c.447G>A	rs2289536		No effect on splicing	1.252
ntron 2       c.547-238T>C       rs12452263       20%       No effect on splicing       5.667         ntron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         ntron 2       c.547-39T>G       rs12452721       67%       Loss of cryptic splice donor site       2.78         ntron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         atron 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         atron 3       c.642C>T       rs1800301       18%       No effect on splicing       1.805         atron 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Intron 2	c.546+293G>A	rs34746710	20%	No effect on splicing	1.899
Intron 2       c.547-67C>G       rs8069491       67%       No effect on splicing       1.337         Intron 2       c.547-39T>G       rs12452721       67%       Loss of cryptic splice donor site       2.78         Intron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         Exon 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         Exon 3       c.642C>T       rs1800301       18%       No effect on splicing       1.805         Exon 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Intron 2	c.547-243C>G	rs8065426	67%	No effect on splicing	2.529
Intron 2c.547-39T>Grs1245272167%Loss of cryptic splice donor site2.78Intron 2c.547-4C>Grs381625667%No effect on splicing4.721Exon 3c.596A>Grs104239367%No effect on splicing0.548Exon 3c.642C>Trs180030118%No effect on splicing1.805Exon 3c.668G>Ars104239567%No effect on splicing1.46	Intron 2	c.547-238T>C	rs12452263	20%	No effect on splicing	5.667
Intron 2       c.547-4C>G       rs3816256       67%       No effect on splicing       4.721         Exon 3       c.596A>G       rs1042393       67%       No effect on splicing       0.548         Exon 3       c.642C>T       rs1800301       18%       No effect on splicing       1.805         Exon 3       c.668G>A       rs1042395       67%       No effect on splicing       1.46	Intron 2	c.547-67C>G	rs8069491	67%	No effect on splicing	1.337
Exon 3         c.596A>G         rs1042393         67%         No effect on splicing         0.548           Exon 3         c.642C>T         rs1800301         18%         No effect on splicing         1.805           Exon 3         c.668G>A         rs1042395         67%         No effect on splicing         1.46	Intron 2	c.547-39T>G	rs12452721	67%		2.78
Exon 3         c.642C>T         rs1800301         18%         No effect on splicing         1.805           Exon 3         c.668G>A         rs1042395         67%         No effect on splicing         1.46	Intron 2	c.547-4C>G	rs3816256	67%	No effect on splicing	4.721
Exon 3c.668G>Ars104239567%No effect on splicing1.46	Exon 3	c.596A>G	rs1042393	67%	No effect on splicing	0.548
	Exon 3	c.642C>T	rs1800301	18%	No effect on splicing	1.805
ntron 3 c.692+38C>T rs2304848 3% 5.574	Exon 3	c.668G>A	rs1042395	67%	No effect on splicing	1.46
	Intron 3	c.692+38C>T	rs2304848	3%		5.574

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Location         Variant ID         Clobal allele frequency (GenomAD)         Predictions of pre-mNA splica donue state         CADD Splica donue state           Intron 3         c.692-144A-5C         rs204497         67%         No effect on splicing         3.633           Intron 3         c.692-144A-5C         rs806205         66%         No effect on splicing         3.633           Intron 3         c.692-167A-5C         rs806305         67%         No effect on splicing         2.363           Intron 3         c.692-15715-C         rs806635         67%         No effect on splicing         2.363           Intron 3         c.693-3657-C         rs1060515         67%         No effect on splicing         2.363           Intron 3         c.693-4915-A         rs12402422         67%         No effect on splicing         3.629           Intron 3         c.693-441C-G         rs1240249         66%         No effect on splicing         3.629           Intron 3         c.693-441C-G         rs1241269         66%         No effect on splicing         4.416           Intron 3         c.693-441C-G         rs1241269         66%         No effect on splicing         2.66           Intron 3         c.693-441C-G         rs1241269         66%         No effect on splicing						
Intron 3         C492 H44A-G         rs230447         67%         No effect on splicing         3.651           Intron 3         C492-5974C-G         rs0082005         67%         No effect on splicing         2.301           Intron 3         C492-5974C-G         rs0082051         67%         No effect on splicing         2.301           Intron 3         C492-5975C-         rs0082051         67%         No effect on splicing         2.311           Intron 3         C493-5807C-         rs1200422         67%         No effect on splicing         2.321           Intron 3         C493-5957C-         rs120422         67%         No effect on splicing         3.629           Intron 3         C493-4910-A         rs1294201         67%         No effect on splicing         3.629           Intron 3         C493-414C-G         rs129022         67%         No effect on splicing         2.301           Intron 3         C493-414C-G         rs1291249         66%         No effect on splicing         2.302           Intron 3         C493-414C-G         rs1291249         67%         No effect on splicing         2.302           Intron 3         C493-214T-A         rs119044         77%         No effect on splicing         2.302           I	Location	Variant	Variant ID		•	CADD score PHRED
Intron 3         c.692+5071-C         rs8082405         66%         No effect on splicing         3.271           Intron 3         c.692+674G×C         rs8078350         67%         No effect on splicing         2.363           Intron 3         c.692+674G×C         rs8078350         67%         No effect on splicing         2.364           Intron 3         c.693-5867-C         rs806850         67%         No effect on splicing         4.133           Intron 3         c.693-5867-C         rs1202422         67%         No effect on splicing         3.627           Intron 3         c.693-441C-G         rs12202420         67%         No effect on splicing         4.143           Intron 3         c.693-441C-G         rs12941289         66%         No effect on splicing         4.146           Intron 3         c.693-414C-G         rs1297590         67%         Loss of a cryptic splice splice acceptor site         0.077           Intron 3         c.693-2167-A         rs11150844         67%         No effect on splicing         4.134           Intron 3         c.693-2167-A         rs74003611         67%         No effect on splicing         2.374           Intron 4         c.893-376-C         rs7003611         67%         No effect on splicing         2.37					, · ·	
Intron 3         C.692.4674C-C         rs8078350         67%         No effect on splicing         4.501           Intron 3         C.692.751T-C         rs8068051         67%         No effect on splicing         2.363           Intron 3         C.693.586C-A         rs112308142         3%         No effect on splicing         2.71           Intron 3         C.693.585T-C         rs806855         67%         No effect on splicing         3.62           Intron 3         C.693.586T-C         rs1260242         67%         No effect on splicing         3.62           Intron 3         C.693.441C-C         rs1240240         67%         No effect on splicing         4.104           Intron 3         C.693.414C-C         rs12941289         66%         No effect on splicing         4.104           Intron 3         C.693.413A-C         rs1291289         66%         No effect on splicing         4.104           Intron 3         C.693.413A-C         rs12937590         67%         No effect on splicing         9.666           Intron 3         C.693.413A-C         rs1290251         C.597         No effect on splicing         1.54           Intron 3         C.693.413A-C         rs1290251         C.597         No effect on splicing         2.374 <t< td=""><td>Intron 3</td><td>c.692+144A&gt;G</td><td>rs2304847</td><td>67%</td><td>No effect on splicing</td><td>3.653</td></t<>	Intron 3	c.692+144A>G	rs2304847	67%	No effect on splicing	3.653
Intron 3         c.492+7511>C         rs8068051         67%         No effect on splicing         2.363           Intron 3         c.693-586G>A         rs112308142         3%         No effect on splicing         4.133           Intron 3         c.693-586T>C         rs8068555         67%         No effect on splicing         4.133           Intron 3         c.693-491G>A         rs12908421         67%         No effect on splicing         4.20           Intron 3         c.693-441C>G         rs129082420         67%         No effect on splicing         7.59           Intron 3         c.693-441C>G         rs12941269         66%         No effect on splicing         4.416           Intron 3         c.693-414C>G         rs12937590         67%         Loss of a cryptic splice         1.544           Intron 3         c.693-413A>G         rs11937590         67%         No effect on splicing         4.13           Intron 3         c.693-413A>G         rs1193042         67%         No effect on splicing         4.13           Intron 3         c.693-413A>G         rs11930507         7%         No effect on splicing         4.13           Intron 3         c.693-413A>G         rs11920321         67%         No effect on splicing         0.66	Intron 3	c.692+509T>C	rs8082405	66%	No effect on splicing	3.271
Intron 3         C.693-586S-A         ris12308142         3%         No effect on splicing         2.71           Intron 3         C.693-585T-C         rs8068555         67%         No effect on splicing         4.133           Intron 3         C.693-585T-C         rs12602422         67%         No effect on splicing         3.229           Intron 3         C.693-491G-A         rs12602420         67%         No effect on splicing         3.229           Intron 3         C.693-441C-G         rs12602440         67%         No effect on splicing         4.14           Intron 3         C.693-441C-G         rs12941269         66%         No effect on splicing         4.14           Intron 3         C.693-413A-G         rs1297590         67%         No effect on splicing         4.13           Intron 3         C.693-413A-G         rs1150844         67%         No effect on splicing         4.13           Intron 3         C.693-410C-T         rs79849256         0.2% (3% in East Asian population)         No effect on splicing         0.66           Intron 4         C.693-49C-T         rs79849256         0.2% (3% in East Asian population)         No effect on splicing         0.67           Intron 4         C.693-49C-T         rs74984950         7%         No effect	Intron 3	c.692+674G>C	rs8078350	67%	No effect on splicing	4.501
Intron 3         c.693-5857>C         rs8068555         67%         No effect on splicing         4.13           Intron 3         c.693-559C>T         rs12602422         67%         No effect on splicing         3.629           Intron 3         c.493-491C>A         rs12948631         67%         No effect on splicing         3.629           Intron 3         c.493-441C>G         rs12941269         66%         No effect on splicing         4.140           Intron 3         c.693-414C>G         rs12941269         66%         No effect on splicing         4.141           Intron 3         c.693-413A>G         rs12937590         67%         Sos of a cryptic splice         1.544           Intron 3         c.693-2167>A         rs1150844         67%         No effect on splicing         4.13           Intron 3         c.693-340C>T         rs7984256         0.2% (3% in East Asian population)         No effect on splicing         2.57           Intron 3         c.693-78C>T         rs7984256         0.2% (3% in East Asian population)         No effect on splicing         0.66           Intron 4         c.852G>A         rs142626724         0.6% (1% in East Asian population)         No effect on splicing         0.107           Intron 5         c.921A>T         rs1800303         8	Intron 3	c.692+751T>C	rs8068051	67%	No effect on splicing	2.363
Intron 3         c.693.559C>T         rs12602422         67%         No effect on splicing         1.879           Intron 3         c.693.491G>A         rs12948631         67%         No effect on splicing         3.629           Intron 3         c.693.441C>G         rs12941269         66%         No effect on splicing         4.416           Intron 3         c.693.434C>A         rs12941289         66%         No effect on splicing         4.416           Intron 3         c.693.413A>G         rs12937590         67%         No effect on splicing         4.13           Intron 3         c.693.413A>G         rs1150844         67%         No effect on splicing         4.13           Intron 3         c.693.413A>G         rs12937590         62% (3% in East Asian population)         No effect on splicing         9.666           Intron 3         c.693.49C>T         rs74003611         6%         No effect on splicing         0.67           Intron 4         c.8526>A         rs142626724         0.6% (1% in East Asian population)         No effect on splicing         0.67           Intron 5         c.921A>T         rs7400301         6%         No effect on splicing         9.61           Intron 5         c.921A>T         rs7400303         6%         No effect on splicin	Intron 3	c.693-586G>A	rs112308142	3%	No effect on splicing	2.71
Intron 3         c. 693.491G>A         rs12948631         67%         No effect on splicing         3.629           Intron 3         c. 693.441C>G         rs12602440         67%         Loss of a cryptic splice acceptor site         7.559           Intron 3         c. 693.441C>G         rs12941289         66%         No effect on splicing         4.416           Intron 3         c. 693.414C>G         rs12947289         66%         Loss of a cryptic splice acceptor site         0.007           Intron 3         c. 693.413A>G         rs1150844         67%         No effect on splicing         4.13           Intron 3         c. 693.413A>G         rs1150844         67%         No effect on splicing         4.13           Intron 3         c. 693.416C>T         rs70849256         0.2% (3% in East Asian population)         No effect on splicing         0.06           Intron 4         c. 693.49C>T         rs7085517         %         No effect on splicing         0.06           Intron 4         c. 852G>A         rs142626724         0.6% (1% in European population)         No effect on splicing         0.06           Intron 4         c. 852G>A         rs1290319         6%         No effect on splicing         0.101           Intron 5         c. 955+12G>A         rs2524188	Intron 3	c.693-585T>C	rs8068555	67%	No effect on splicing	4.133
Intron 3c.693.441C>Grs1260244067%Loss of a cryptic splice acceptor site7.559Intron 3c.693.434C>Ars1294126966%No effect on splicing4.416Intron 3c.693.414C>Grs1294128966%Loss of a cryptic splice acceptor site0.077Intron 3c.693.413A>Grs1293759067%Loss of a cryptic splice acceptor site1.544Intron 3c.693.216T>Ars1115084467%No effect on splicing4.13Intron 3c.693.44C>Trs798492560.2% (3% in East Asian population)No effect on splicing0.66Intron 3c.693.44C>Trs740036116%No effect on splicing0.66Intron 4c.852G>Ars1426267240.66(1% in European population)No effect on splicing0.067Exon 4c.852G>Ars1426267240.66(1% in European population)No effect on splicing0.067Exon 5c.921A>Trs18003038%No effect on splicing0.981Intron 5c.955+13C>Ars22524556%No effect on splicing0.716Intron 5c.955+13C>Ars222418873%No effect on splicing0.716Intron 5c.956-107G>Ars22418873%No effect on splicing0.431Intron 5c.956-107G>Ars224188767%No effect on splicing5.835Intron 6c.1075+13C>Trs71271640.7% (1% in East Asian population)No effect on splicing5.835Intron 5c.956-84C>T<	Intron 3	c.693-559C>T	rs12602422	67%	No effect on splicing	1.879
Intron 3         C.693.434C>A         rs12941269         66%         No effect on splicing         4.416           Intron 3         C.693.414C>G         rs12941289         66%         Coss of a cryptic splice acceptor site         0.077           Intron 3         C.693.414C>G         rs12937590         67%         Loss of a cryptic splice acceptor site         1.544           Intron 3         C.693.216T>A         rs11150844         67%         No effect on splicing         4.13           Intron 3         C.693.78C>T         rs70949256         0.2% (3% in East Asian population)         No effect on splicing         0.06           Intron 3         C.693.78C>T         rs7003611         6%         No effect on splicing         0.06           Intron 4         C.693.78C>T         rs7003611         6%         No effect on splicing         0.06           Intron 5         C.693.49C>T         rs7003611         6%         No effect on splicing         0.067           Intron 4         C.893.49C>T         rs7805075         7%         No effect on splicing         0.067           Intron 5         C.951.40C>T         rs203080         6%         No effect on splicing         0.067           Intron 5         C.955.15C>A         rs2901190         5%         No effect on spli	Intron 3	c.693-491G>A	rs12948631	67%	No effect on splicing	3.629
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intron 3         c.693-216T>A         rs1150844         67%         No effect on splicing         4.13           Intron 3         c.693-94C>T         rs79849256         0.2% (3% in East Asian) population)         No effect on splicing         9.666           Intron 3         c.693-78C>T         rs74003611         6%         No effect on splicing         0.06           Intron 3         c.693-78C>T         rs74003611         6%         No effect on splicing         0.374           Intron 4         c.893-78C>T         rs74855075         7%         No effect on splicing         0.374           Exon 4         c.8526>A         rs124262724         0.6%(1% in European population)         No effect on splicing         0.067           Intron 4         c.858+30T>C         rs204845         66%         No effect on splicing         0.067           Intron 5         c.921A>T         rs1800303         8%         No effect on splicing         9.014           Intron 5         c.955+15C>A         rs9901190         5%         No effect on splicing         9.081           Intron 5         c.955+167C>T         rs77717164         0.7% (6% in East Asian population)         No effect on splicing         6.348           Intron 5         c.956+107C>A         rs2241887         73%	Intron 3	c.693-414C>G	rs12941289	66%	<i></i>	0.077
Intron 3c.693-94C>Trs798492560.2% (3% in East Asian population)No effect on splicing9.666Intron 3c.693-78C>Trs740036116%No effect on splicing0.04Intron 3c.693-78C>Trs788550757%No effect on splicing2.374Exon 4c.852G>Ars1426267240.6% (1% in European population)No effect on splicing0.067Exon 5c.921A>Trs18003038%No effect on splicing0.067Exon 5c.955+12G>Ars25245569%No effect on splicing0.981Intron 5c.955+15C>Ars90011905%No effect on splicing7.196Intron 5c.955+167C>Trs777171640.7% (6% in East Asian population)No effect on splicing6.348Intron 5c.956-107G>Ars224188773%No effect on splicing0.661Intron 6c.1075+13C>Trs72171641%No effect on splicing5.835Intron 6c.1075+13C>Trs224188773%No effect on splicing0.641Intron 6c.1075+13C>Trs180030467%No effect on splicing5.972Exon 8c.1226A>Grs81033467%No effect on splicing1.999Intron 8c.1326+430C>Trs74073770.7% (6% in East Asian 	Intron 3	c.693-413A>G	rs12937590	67%	,, ,	1.544
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Intron 3         c.693.49C>T         rs78855075         7%         No effect on splicing         2.374           Exon 4         c.852G>A         rs142626724         0.6% (1% in European population)         No effect on splicing         0.095           Intron 4         c.858+30T>C         rs204845         66%         No effect on splicing         0.067           Exon 5         c.921A>T         rs1800303         8%         No effect on splicing         0.911           Intron 5         c.955+12G>A         rs252455         69%         No effect on splicing         0.981           Intron 5         c.955+15SC>A         rs901190         5%         No effect on splicing         0.348           Intron 5         c.955+167C>T         rs7717164         0.7% (6% in East Asian population)         No effect on splicing         0.348           Intron 5         c.956+40         rs2241887         73%         No effect on splicing         5.835           Intron 6         c.1075+13C>T         rs1292402         1%         No effect on splicing         5.835           Intron 6         c.1075+13C>T         rs1800304         67%         No effect on splicing         5.835           Intron 6         c.1075+13C>T         rs1800304         67%         No effect on splicing	Intron 3	c.693-94C>T	rs79849256		No effect on splicing	9.666
Exon 4         c.852G>A         rs142626724         0.6% (1% in European population)         No effect on splicing         1.095           Intron 4         c.858430T>C         rs2304845         66%         No effect on splicing         0.067           Exon 5         c.921A>T         rs1800303         8%         No effect on splicing         9.101           Intron 5         c.955+12G>A         rs2252455         69%         No effect on splicing         0.981           Intron 5         c.955+15SC>A         rs9901190         5%         No effect on splicing         0.436           Intron 5         c.955+167C>T         rs77717164         0.7% (6% in East Asian population)         No effect on splicing         0.438           Intron 5         c.956-107G>A         rs2241887         73%         No effect on splicing         0.641           Intron 6         c.1075+13C>T         rs120202         1%         No effect on splicing         5.722           Intron 6         c.1007S+13C>T         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1326+32G>T         rs900294882         0.07% (1% in East Asian population)	Intron 3	c.693-78C>T	rs74003611	6%	No effect on splicing	0.06
intron 4         c.858+30T>C         rs2304845         66%         No effect on splicing         0.067           Exon 5         c.921A>T         rs1800303         8%         No effect on splicing         9.101           Intron 5         c.955+12G>A         rs2252455         69%         No effect on splicing         0.981           Intron 5         c.955+15C>A         rs9901190         5%         No effect on splicing         0.981           Intron 5         c.955+167C>T         rs77717164         0.7% (6% in East Asian population)         No effect on splicing         5.835           Intron 5         c.956-107G>A         rs2241887         67%         No effect on splicing         0.061           Intron 5         c.956-84C>T         rs129202         1%         No effect on splicing         5.835           Intron 6         c.1075+13C>T         rs120294882         0.07% (1% in East Asian population)         No effect on splicing         5.972           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         0.068           Intron 5         c.1326+43C>T         rs1800304         67%         No effect on splicing         1.999           Exon 8         c.1326+43G>A         rs894306         67%         No effect on splicing <td>Intron 3</td> <td>c.693-49C&gt;T</td> <td>rs78855075</td> <td>7%</td> <td>No effect on splicing</td> <td>2.374</td>	Intron 3	c.693-49C>T	rs78855075	7%	No effect on splicing	2.374
Exon 5         c.921A>T         rs1800303         8%         No effect on splicing         9.101           Intron 5         c.955+12G>A         rs2252455         69%         No effect on splicing         0.981           Intron 5         c.955+15G>A         rs9901190         5%         No effect on splicing         7.196           Intron 5         c.955+167C>T         rs77717164         0.7% (6% in East Asian population)         No effect on splicing         6.348           Intron 5         c.956-107G>A         rs2241888         73%         No effect on splicing         5.835           Intron 5         c.956-84C>T         rs2241887         67%         No effect on splicing         0.061           Intron 6         c.1075+13C>T         rs41292402         1%         No effect on splicing         5.972           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1326+132G>A         rs894306         67%         No effect on splicing         1.999           Intron 8         c.1326+132G>A         rs894306         67%         No effect on splicing         1.999           Intron 8         c.1326+459C>T         rs74679377         0.7% (6% in East Asian population)         No effect on splicing<	Exon 4	c.852G>A	rs142626724		No effect on splicing	1.095
Intron 5         c.955+12G>A         rs2252455         69%         No effect on splicing         0.981           Intron 5         c.955+155C>A         rs9901190         5%         No effect on splicing         7.196           Intron 5         c.955+167C>T         rs77717164         0.7% (6% in East Asian population)         No effect on splicing         6.348           Intron 5         c.956-107G>A         rs2241887         73%         No effect on splicing         5.835           Intron 5         c.956-84C>T         rs2241887         67%         No effect on splicing         0.61           Intron 6         c.1075+13C>T         rs41292402         1%         No effect on splicing         7.496           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1286A>G         rs20294882         0.07% (1% in East Asian population)         No effect on splicing         0.968           Intron 8         c.1326+132G>A         rs894306         67%         No effect on splicing         1.999           Intron 8         c.1326+459C>T         rs74679377         0.7% (1% in East Asian population)         No effect on splicing         0.435           Intron 8         c.1326+460G>A         rs12150323         2% </td <td>Intron 4</td> <td>c.858+30T&gt;C</td> <td>rs2304845</td> <td>66%</td> <td>No effect on splicing</td> <td>0.067</td>	Intron 4	c.858+30T>C	rs2304845	66%	No effect on splicing	0.067
Intron 5         c.955+155C>A         rs9901190         5%         No effect on splicing         7.196           Intron 5         c.955+167C>T         rs7717164         0.7% (6% in East Asian population)         No effect on splicing         6.348           Intron 5         c.956-107G>A         rs2241887         73%         No effect on splicing         5.835           Intron 5         c.956-84C>T         rs2241887         67%         No effect on splicing         0.061           Intron 6         c.1075+13C>T         rs41292402         1%         No effect on splicing         7.496           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         5.972           Exon 8         c.1203G>A         rs1800304         67%         No effect on splicing         1.999           Intron 8         c.1326+ASG         rs20294882         0.07% (1% in East Asian population)         Loss of cryptic splice acceptor site arceptor site and generates a new cryptic splice donor site         1.999           Intron 8         c.1326+132G>A         rs894306         67%         No effect on splicing         0.435           Intron 8         c.1326+459C>T	Exon 5	c.921A>T	rs1800303	8%	No effect on splicing	9.101
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population)site and generates a new cryptic splice donor siteIntron 8c.1326+132G>Ars89430667%No effect on splicing1.999Intron 8c.1326+459C>Trs746793770.7% (6% in East Asian population)No effect on splicing0.435Intron 8c.1326+460G>Ars121503232%No effect on splicing0.322Intron 8c.1327-514G>Ars728508265%No effect on splicing1.914	Exon 8	c.1203G>A	rs1800304	67%	No effect on splicing	5.972
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Intron 8         c.1326+460G>A         rs12150323         2%         No effect on splicing         0.322           Intron 8         c.1327-514G>A         rs72850826         5%         No effect on splicing         1.914	Intron 8	c.1326+132G>A	rs894306	67%	No effect on splicing	1.999
Intron 8         c.1327-514G>A         rs72850826         5%         No effect on splicing         1.914	Intron 8	c.1326+459C>T	rs74679377		No effect on splicing	0.435
	Intron 8	c.1326+460G>A	rs12150323	2%	No effect on splicing	0.322
Intron 8 c.1327-356G>T rs6565640 73% No effect on splicing 0.258	Intron 8	c.1327-514G>A	rs72850826	5%	No effect on splicing	1.914
	Intron 8	c.1327-356G>T	rs6565640	73%	No effect on splicing	0.258

backbainVariant D(Jonamb)splicingsplicingPHEDIntron 8c1327-32144ri403851447%No effect on splicing0.88Intron 8c1327-297A-Xri5269A-X7%No effect on splicing0.121Intron 8c1327-297A-Xri5269A-X20%No effect on splicing0.434Intron 8c1327-178A-Xri52062A20%No effect on splicing0.124Intron 8c1327-18A-Xri52005A7%No effect on splicing0.204Intron 9c1327-178A-Xri52005A7%No effect on splicing0.204Intron 9c1438-106C-Xri52042A7%No effect on splicing0.204Intron 9c1438-106C-Xri52042A7%No effect on splicing1.521Intron 10c15142C-Xri114275180% (% in African population)No effect on splicing1.732Intron 10c15144C-Xri114275180%No effect on splicing1.732Intron 11c163641174Fri11972712%No effect on splicing1.731Intron 11c163641174Fri199782013%No effect on splicing1.731Intron 11c163641174Fri199782013%No effect on splicing1.731Intron 11c163641174Fri199782013%No effect on splicing1.731Intron 11c163641174Fri199782013%No effect on splicing1.732Intron 11c16364205CFri1162513%No effect on splicing1.7		aca,				
Intron 8         C.1327.269A-G         rs565641         67%         No effect on splicing         4.207           Intron 8         C.1327.209C>T         rs76604157         0.3% (6% in East Asian population)         No effect on splicing         0.441           Intron 8         C.1327.179C>A         rs2278620         20%         No effect on splicing         0.184           Intron 8         C.1327.18A-G         rs2278619         7%         No effect on splicing         0.214           Exem 9         C.1347C>T         rs1800305         7%         No effect on splicing         0.026           Intron 9         C.1438.20A-G         rs2278618         67%         No effect on splicing         0.013           Intron 9         C.1438.108C>A         rs115427918         0.9% (3% in African population)         No effect on splicing         7.121           Intron 10         C.1551142C>A         rs114227918         0.9% (3% in African population)         No effect on splicing         0.132           Intron 11         C.1636443C>T         rs204842         5%         Generates a new compute splice accepter site splice         6.897           Intron 11         C.16364176C+T         rs199788201         5%         No effect on splicing         0.131           Intron 11         C.16364176C+T	Location	Variant	Variant ID		•	CADD score
Intron 8         c.1327.209C>T         rs76604157         0.3% (6% in East Asian population)         No effect on splicing         0.471           Intron 8         c.1327.179CA         rs2278620         20%         No effect on splicing         0.184           Intron 8         c.1327.18A-G         rs2278619         7%         No effect on splicing         0.134           Intron 9         c.138.20A-G         rs2278619         7%         No effect on splicing         0.206           Intron 9         c.138.20A-G         rs2278619         7%         No effect on splicing         0.206           Intron 9         c.1438.20A-G         rs2278618         67%         No effect on splicing         0.201           Intron 9         c.1438.108C-A         rs12944802         67%         No effect on splicing         0.579           Intron 10         c.1551.442C-A         rs204843         67%         No effect on splicing         0.711           Exen 11         c.1636.413C-F         rs204842         5%         No effect on splicing         0.045           Intron 11         c.1636.413CeI         rs199788201         59%         No effect on splicing         0.131           Intron 11         c.1636.413CeI         rs19978308         13%         No effect on splicing	Intron 8	c.1327-321del	rs140385114	7%	No effect on splicing	0.888
population         population         population           Intron 8         c.1327.179CrA         rs.2278620         20%         No effect on splicing         0.143           Intron 8         c.1327.118A>G         rs.200305         7%         No effect on splicing         0.124           Exon 9         c.1372.18A>G         rs.2278618         67%         No effect on splicing         0.006           Intron 9         c.1438.108C>         rs.2278618         67%         No effect on splicing         6.607           Intron 9         c.1438.108C>         rs.2278618         67%         No effect on splicing         5.521           Intron 9         c.1438.108C>         rs.220484         67%         No effect on splicing         7.131           Intron 10         c.151442C>A         rs.1042396         23%         No effect on splicing         6.781           Exon 11         c.1636+172C>T         rs.204842         5%         No effect on splicing         0.045           Intron 11         c.1636+172C>T         rs.2904842         5%         No effect on splicing         0.811           Intron 11         c.1636+172C>T         rs.19294584         11%         No effect on splicing         0.811           Intron 11         c.1636+240C>T         rs.	Intron 8	c.1327-269A>G	rs6565641	67%	No effect on splicing	4.207
Intron 8         c.1327-118A×G         rs74003628         7%         No effect on splicing         0.144           Intron 8         c.1327-18A×G         rs2278619         72%         No effect on splicing         0.206           Exon 9         c.1338-20A×G         rs2278618         67%         No effect on splicing         0.206           Intron 9         c.1438-108G×A         rs12744802         67%         No effect on splicing         0.329           Intron 9         c.1438-108G×A         rs12744802         67%         No effect on splicing         5.792           Intron 10         c.1551+42G×A         rs115427918         0.9% (3% in African population)         No effect on splicing         7.131           Exon 11         c.1581+49C×A         rs1042396         23%         No effect on splicing         0.781           Exon 11         c.1636+137c+T         rs1294820         5%         Generates a new cryptic         3.829           Intron 11         c.1636+137c+T         rs12945868         11%         No effect on splicing         0.013           Intron 11         c.1636+137c+T         rs19793080         3%         No effect on splicing         0.181           Intron 11         c.1636+137c+T         rs11295868         13%         No effect on splicing	Intron 8	c.1327-209C>T	rs76604157	•	No effect on splicing	0.471
Intron 8         c.1327-18A-G         rs2278619         72%         No effect on splicing         0.124           Exon 9         c.1374C>T         rs1800305         7%         No effect on splicing         0.006           Intron 9         c.1438-20A-G         rs2278618         67%         No effect on splicing         0.013           Intron 9         c.1438-19G-C         rs2278618         67%         No effect on splicing         0.579           Intron 9         c.1438-19G-C         rs230484         67%         No effect on splicing         5.792           Intron 10         c.1551+42G-A         rs11427918         0.9% (3% in African population)         No effect on splicing         7.131           Exon 11         c.1581+42G-A         rs2304842         5%         Senfect on splicing         0.015           Intron 11         c.1636+117Ge1         rs19279788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117Ge1         rs1979788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117Ge1         rs1979788201         5%         No effect on splicing         0.181           Intron 11         c.1636+127C+T         rs7973008         3%         No effect on splicing	Intron 8	c.1327-179G>A	rs2278620	20%	No effect on splicing	0.643
Exon 9         c.1374C>T         rs1800305         7%         No effect on splicing         0.206           Intron 9         c.1438-220A>G         rs2278618         67%         No effect on splicing         0.013           Intron 9         c.1438-106C>A         rs12944802         67%         No effect on splicing         0.329           Intron 10         c.1551+42C>A         rs115427918         0.9% (3% in African population)         No effect on splicing         5.792           Intron 10         c.1551+42C>A         rs102394         67%         No effect on splicing         6.758           Intron 11         c.1636+413G>T         rs12304842         5%         No effect on splicing         0.013           Intron 11         c.1636+1176e1         rs1979788201         5%         No effect on splicing         0.014           Intron 11         c.1636+118C>T         rs4839817         5%         No effect on splicing         0.181           Intron 11         c.1636+20SC>T         rs7978208         3%         No effect on splicing         0.181           Intron 11         c.1636+20SC>T         rs11625854         2%         No effect on splicing         0.181           Intron 11         c.1636+30PCG         rs111625854         2%         No effect on splicing	Intron 8	c.1327-118A>G	rs74003628	7%	No effect on splicing	0.184
Intron 9         c.1438 220A-G         rs2278618         67%         No effect on splicing         6.607           Intron 9         c.1438-108G>A         rs12944802         67%         No effect on splicing         0.013           Intron 9         c.1438-108G>A         rs12944802         67%         No effect on splicing         3.529           Intron 10         c.1551+42G>A         rs115427918         0.9% (3% in African population)         No effect on splicing         5.772           Intron 10         c.1531+43G>A         rs1042396         23%         No effect on splicing         6.859           Intron 11         c.1636+13G>T         rs2304842         5%         Generates a new cryptic         6.859           Intron 11         c.1636+117C>T         rs19788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117C>T         rs19788201         5%         No effect on splicing         0.81           Intron 11         c.1636+20G>T         rs11162584         13%         No effect on splicing         0.82           Intron 11         c.1636+266         rs79787084         5%         No effect on splicing         1.82           Intron 11         c.1636+266         rs7211551014         2%         No effect on splicing	Intron 8	c.1327-18A>G	rs2278619	72%	No effect on splicing	0.124
Intron 9         c.1438-108G>A         rs12944802         67%         No effect on splicing         0.013           Intron 9         c.1438-19G>C         rs204844         67%         No effect on splicing         3.529           Intron 10         c.1551+42G>A         rs115427918         0.9% (3% in African population)         No effect on splicing         7.131           Exon 11         c.1551+42G>A         rs1042396         23%         No effect on splicing         6.758           Intron 11         c.1636+43G>T         rs204842         5%         Generates a new cryptic         6.859           Intron 11         c.1636+117C>T         rs199788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117C>T         rs199788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117C>T         rs1945868         11%         No effect on splicing         0.181           Intron 11         c.1636+217C>T         rs97987884         5%         No effect on splicing         1.829           Intron 11         c.1636+294C>C         rs111551014         2%         No effect on splicing         1.829           Intron 11         c.1636+390A>G         rs720921         63%         No effect on splicing	Exon 9	c.1374C>T	rs1800305	7%	No effect on splicing	0.206
Intron 9         c.1438-19C>C         rs2304844         67%         No effect on splicing         5.29           Intron 10         c.1551+42C>A         rs115427918         0.9% (3% in African population)         No effect on splicing         5.792           Intron 10         c.1551+49C>A         rs204843         67%         No effect on splicing         6.758           Intron 11         c.1636+43G>T         rs204842         5%         Cenerates a new cryptic splice accepter splice         6.859           Intron 11         c.1636+117del         rs19788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117CFT         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+117CFT         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.181           Intron 11         c.1636+205C>T         rs71487884         5%         No effect on splicing         0.181           Intron 11         c.1636+389C>G         rs721675         63%         No effect on splicing         0.573           Intron 11         c.1636+404A>G         rs2004936         7%209921	Intron 9	c.1438-220A>G	rs2278618	67%	No effect on splicing	6.607
Intron 10         c.1551+42G>A         rs115427918         0.9% (3% in African population)         No effect on splicing         5.792           Intron 10         c.1551+49C>A         rs2304843         67%         No effect on splicing         7.131           Exon 11         c.1581G>A         rs1042396         23%         No effect on splicing         6.859           Intron 11         c.1636+137del         rs199788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117del         rs199788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117G>T         rs12945868         11%         No effect on splicing         0.013           Intron 11         c.1636+117G>T         rs12945868         13%         No effect on splicing         0.181           Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.131           Intron 11         c.1636+205C>T         rs79487884         5%         No effect on splicing         0.328           Intron 11         c.1636+389C>G         rs721675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs7209721         63%         No effect on splicin	Intron 9	c.1438-108G>A	rs12944802	67%	No effect on splicing	0.013
Intron 10         c.1551+49C>A         rs204843         67%         No effect on splicing         7.131           Exon 11         c.1581-SA         rs1042396         23%         No effect on splicing         6.859           Intron 11         c.1636+43G>T         rs204842         5%         Generates a new cryptic splice accepter site         6.859           Intron 11         c.1636+117cel         rs199788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117c>T         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+118C>T         rs4889817         59%         No effect on splicing         0.163           Intron 11         c.1636+205C>T         rs79478840         5%         No effect on splicing         1.81           Intron 11         c.1636+205C>T         rs11162584         2%         No effect on splicing         0.573           Intron 11         c.1636+204C>C         rs11151014         2%         No effect on splicing         0.573           Intron 11         c.1636+204C>C         rs112555         55%         No effect on splicing         0.576           Intron 11         c.1637+185A>G         rs2304840         6%         No effect on splicing	Intron 9	c.1438-19G>C	rs2304844	67%	No effect on splicing	3.529
Exon 11         c.1581G>A         rs1042396         23%         No effect on splicing         6.758           Intron 11         c.1636+43G>T         rs2304842         5%         Generates a new cryptic splice accepter site         6.859           Intron 11         c.1636+117Cel         rs199788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117C>T         rs199788201         59%         No effect on splicing         0.181           Intron 11         c.1636+117C>T         rs199788201         59%         No effect on splicing         0.181           Intron 11         c.1636+118C>T         rs4889817         59%         No effect on splicing         0.013           Intron 11         c.1636+205C>T         rs7948784         5%         No effect on splicing         0.828           Intron 11         c.1636+269C>T         rs11152584         2%         No effect on splicing         0.573           Intron 11         c.1636+284C>C         rs111551014         2%         No effect on splicing         0.573           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         0.576           Intron 11         c.1637+185A>G         rs12951255         55%         No effect on splicing <td>Intron 10</td> <td>c.1551+42G&gt;A</td> <td>rs115427918</td> <td>0.9% (3% in African population)</td> <td>No effect on splicing</td> <td>5.792</td>	Intron 10	c.1551+42G>A	rs115427918	0.9% (3% in African population)	No effect on splicing	5.792
Intron 11         c.1636+43G>T         rs2304842         5%         Generates a new cryptic splice accepter site         6.859           Intron 11         c.1636+117del         rs199788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117C>T         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+118G>T         rs4889817         59%         No effect on splicing         0.103           Intron 11         c.1636+210G>A         rs79673008         3%         No effect on splicing         0.131           Intron 11         c.1636+228G>T         rs711625854         2%         No effect on splicing         3.828           Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         0.573           Intron 11         c.1636+3980         rs721675         63%         No effect on splicing         0.573           Intron 11         c.1636+3980         rs720921         63%         No effect on splicing         0.576           Intron 11         c.1637+185A>G         rs12951255         55%         No effect on splicing         0.576           Intron 11         c.1637+185A>G         rs12904826         0.9% (3% in African population)         <	Intron 10	c.1551+49C>A	rs2304843	67%	No effect on splicing	7.131
Intron 11         c.1636+117del         rs199788201         59%         No effect on splicing         0.045           Intron 11         c.1636+117C>T         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+118C>T         rs489817         59%         No effect on splicing         0.103           Intron 11         c.1636+210C>T         rs79673008         3%         No effect on splicing         0.013           Intron 11         c.1636+220C>T         rs7947884         5%         No effect on splicing         0.828           Intron 11         c.1636+240C>T         rs11162584         2%         No effect on splicing         0.573           Intron 11         c.1636+284C>C         rs11151014         2%         No effect on splicing         0.573           Intron 11         c.1636+284C>C         rs11551014         2%         No effect on splicing         0.573           Intron 11         c.1636+3430C>C         rs21255         55%         No effect on splicing         0.576           Intron 11         c.1637+185A         rs190307         2%         No effect on splicing         0.268           Intron 12         c.1756A         rs230480         6%         No effect on splicing         0.763	Exon 11	c.1581G>A	rs1042396	23%	No effect on splicing	6.758
Intron 11         c.1636+117C>T         rs12945868         11%         No effect on splicing         0.181           Intron 11         c.1636+118G>T         rs4889817         59%         No effect on splicing         0.013           Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.013           Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.013           Intron 11         c.1636+205C>T         rs71478784         5%         No effect on splicing         1.463           Intron 11         c.1636+269C>T         rs111525854         2%         No effect on splicing         3828           Intron 11         c.1636+389C>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs720921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         0.573           Intron 11         c.1637+185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1754+104A>G         rs201480         6%         No effect on splicing         1.422	Intron 11	c.1636+43G>T	rs2304842	5%		6.859
Intron 11         c.1636+118G>T         rs4889817         59%         No effect on splicing         3.161           Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.013           Intron 11         c.1636+205C>T         rs79487884         5%         No effect on splicing         1.463           Intron 11         c.1636+206C>T         rs111625854         2%         No effect on splicing         3.828           Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs7209921         63%         No effect on splicing         0.576           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         0.576           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1754+126>A         rs204840         6%         No effect on splicing         4.325           Intron 12         c.1754+100 <t< td="">         rs13686855         0.9% (3% in African population)         No effect on splicing</t<>	Intron 11	c.1636+117del	rs199788201	59%	No effect on splicing	0.045
Intron 11         c.1636+205C>T         rs79673008         3%         No effect on splicing         0.013           Intron 11         c.1636+210G>A         rs79487884         5%         No effect on splicing         1.463           Intron 11         c.1636+269C>T         rs111625854         2%         No effect on splicing         3.828           Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         0.573           Intron 11         c.1636+389C>G         rs720921         63%         No effect on splicing         0.573           Intron 11         c.1636+404A>G         rs489818         74%         No effect on splicing         1.902           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.573           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726C>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+12G>A         rs204840         6%         No effect on splicing         0.432           Intron 12         c.1754+140C>G         rs204836         0.9% (3% in African population)         No effect	Intron 11	c.1636+117C>T	rs12945868	11%	No effect on splicing	0.181
Intron 11         c.1636+210G>A         rs79487884         5%         No effect on splicing         1.463           Intron 11         c.1636+269C>T         rs111625854         2%         No effect on splicing         3.828           Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         1.81           Intron 11         c.1636+284G>C         rs721675         63%         No effect on splicing         0.573           Intron 11         c.1636+389C>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+4390A>G         rs720921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         0.576           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1754+10C>T         rs1800307         2%         Generates a new cryptic         0.268           Intron 12         c.1754+10C>T         rs13068685         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+140C>T         rs2304837         5%         No effect on splicing	Intron 11	c.1636+118G>T	rs4889817	59%	No effect on splicing	3.161
Intron 11         c.1636+269C>T         rs111625854         2%         No effect on splicing         3.828           Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         1.81           Intron 11         c.1636+389C>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs720921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         0.576           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.576           Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs113688685         0.9% (3% in African population)         No effect on splicing         0.763           Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         2.327           Intron 12         c.1754+144C>T         rs2304837         6%         No effect	Intron 11	c.1636+205C>T	rs79673008	3%	No effect on splicing	0.013
Intron 11         c.1636+284G>C         rs111551014         2%         No effect on splicing         1.81           Intron 11         c.1636+389C>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs7209921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs489818         74%         No effect on splicing         1.902           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs113686855         0.9% (3% in African population)         No effect on splicing         0.763           Intron 12         c.1754+104C>G         rs204830         5%         No effect on splicing         1.787           Intron 12         c.1754+144C>T         rs204836         61%         No effect on splicing         3.378           Intron 12         c.1755-186A>G         rs204836         72%         No effect on	Intron 11	c.1636+210G>A	rs79487884	5%	No effect on splicing	1.463
Intron 11         c.1636+389C>G         rs7221675         63%         No effect on splicing         0.573           Intron 11         c.1636+390A>G         rs7209921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         1.902           Intron 11         c.1637+185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs11368685         0.9% (3% in African population)         No effect on splicing         6.142           Intron 12         c.1754+144C>T         rs2304839         5%         No effect on splicing         2.032           Intron 12         c.1754+144C>T         rs2304839         61%         No effect on splicing         3.378           Intron 13         c.188+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+66C>T         rs2304836         72%         No effect on	Intron 11	c.1636+269C>T	rs111625854	2%	No effect on splicing	3.828
Intron 11         c.1636+390A>G         rs7209921         63%         No effect on splicing         1.829           Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         1.902           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+10C>T         rs1368685         0.9% (3% in African population)         No effect on splicing         4.325           Intron 12         c.1754+10C>T         rs2304840         6%         No effect on splicing         6.142           Intron 12         c.1754+10C>T         rs11368685         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+140C>G         rs2304837         5%         No effect on splicing         0.763           Intron 12         c.1755+186A>G         rs62075593         2%         No effect on splicing         3.378           Intron 13         c.1888+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+66C>T         rs2304836         72% <td>Intron 11</td> <td>c.1636+284G&gt;C</td> <td>rs111551014</td> <td>2%</td> <td>No effect on splicing</td> <td>1.81</td>	Intron 11	c.1636+284G>C	rs111551014	2%	No effect on splicing	1.81
Intron 11         c.1636+404A>G         rs4889818         74%         No effect on splicing         1.902           Intron 11         c.1637-185A>G         rs12951255         55%         No effect on splicing         0.576           Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs113688685         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         0.763           Intron 12         c.1754+104C>G         rs2304837         61%         No effect on splicing         1.787           Intron 12         c.1755+186A>G         rs62075593         2%         No effect on splicing         3.378           Intron 13         c.1888+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+60A>T         rs2304837         7%         No effect on splicing         3.54           Intron 14         c.2040+66A>T         rs2304834         6%         No effect on sp	Intron 11	c.1636+389C>G	rs7221675	63%	No effect on splicing	0.573
Intron 11c.1637-185A>Grs1295125555%No effect on splicing0.576Exon 12c.1726G>Ars18003072%Generates a new cryptic splice acceptor0.268Intron 12c.1754+12G>Ars23048406%No effect on splicing4.325Intron 12c.1754+100C>Trs1136886850.9% (3% in African population)No effect on splicing8.142Intron 12c.1754+100C>Trs23048395%No effect on splicing0.763Intron 12c.1754+144C>Trs230483861%No effect on splicing1.787Intron 12c.1755+186A>Grs620755932%No effect on splicing2.032Intron 13c.1888+21G>Ars230483672%No effect on splicing3.378Intron 14c.2040+20A>Grs23048367%No effect on splicing3.54Intron 14c.2040+66A>Trs23048346%No effect on splicing0.027Intron 14c.2040+66AArs23048346%No effect on splicing0.027	Intron 11	c.1636+390A>G	rs7209921	63%	No effect on splicing	1.829
Exon 12         c.1726G>A         rs1800307         2%         Generates a new cryptic splice acceptor         0.268           Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs113688685         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         0.763           Intron 12         c.1754+144C>T         rs2304838         61%         No effect on splicing         1.787           Intron 12         c.1755+186A>G         rs62075593         2%         No effect on splicing         2.032           Intron 13         c.1888+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+20A>G         rs2304836         72%         No effect on splicing         3.54           Intron 14         c.2040+66C>T         rs2304836         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304836         7%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304836         6%         No effect on splici	Intron 11	c.1636+404A>G	rs4889818	74%	No effect on splicing	1.902
Intron 12         c.1754+12G>A         rs2304840         6%         No effect on splicing         4.325           Intron 12         c.1754+100C>T         rs113686855         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         0.763           Intron 12         c.1754+144C>T         rs2304839         61%         No effect on splicing         1.787           Intron 12         c.1755-186A>G         rs62075593         2%         No effect on splicing         2.032           Intron 13         c.1888+21G>A         rs2304836         7%         No effect on splicing         3.378           Intron 14         c.2040+20A>G         rs2304836         7%         No effect on splicing         2.163           Intron 14         c.2040+66C>T         rs2304836         7%         No effect on splicing         3.54           Intron 14         c.2040+66A>G         rs2304836         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304836         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304831         6%         No effect on splicing	Intron 11	c.1637-185A>G	rs12951255	55%	No effect on splicing	0.576
Intron 12         c.1754+100C>T         rs113688685         0.9% (3% in African population)         No effect on splicing         8.142           Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         0.763           Intron 12         c.1754+104C>T         rs2304838         61%         No effect on splicing         1.787           Intron 12         c.1755+186A>G         rs62075593         2%         No effect on splicing         2.032           Intron 13         c.1888+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+20A>G         rs2304835         72%         No effect on splicing         3.54           Intron 14         c.2040+66C>T         rs2304835         7%         No effect on splicing         3.54           Intron 14         c.2040+66C>T         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304834         27%         No effect on splicing	Exon 12	c.1726G>A	rs1800307	2%		0.268
Intron 12         c.1754+104C>G         rs2304839         5%         No effect on splicing         0.763           Intron 12         c.1754+144C>T         rs2304838         61%         No effect on splicing         1.787           Intron 12         c.1755+186A>G         rs62075593         2%         No effect on splicing         2.032           Intron 13         c.1888+21G>A         rs2304837         6%         No effect on splicing         3.378           Intron 14         c.2040+20A>G         rs2304836         72%         No effect on splicing         2.163           Intron 14         c.2040+66C>T         rs2304835         7%         No effect on splicing         3.54           Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2040+66C>T         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2040+69A>G         rs2304833         27%         No effect on splicing         0.027           Intron 14         c.2041-64G>A         rs2304833         27%         No effect on splicing         0.371	Intron 12	c.1754+12G>A	rs2304840	6%	No effect on splicing	4.325
Intron 12       c.1754+144C>T       rs2304838       61%       No effect on splicing       1.787         Intron 12       c.1755-186A>G       rs62075593       2%       No effect on splicing       2.032         Intron 13       c.1888+21G>A       rs2304837       6%       No effect on splicing       3.378         Intron 14       c.2040+20A>G       rs2304836       72%       No effect on splicing       2.163         Intron 14       c.2040+66C>T       rs2304835       7%       No effect on splicing       3.54         Intron 14       c.2040+69A>G       rs2304834       6%       No effect on splicing       0.027         Intron 14       c.2040+69A>G       rs2304833       27%       No effect on splicing       0.027         Intron 14       c.2040+69A>G       rs2304833       27%       No effect on splicing       0.027         Intron 14       c.2041-64G>A       rs2304833       27%       No effect on splicing       0.371	Intron 12	c.1754+100C>T	rs113688685	0.9% (3% in African population)	No effect on splicing	8.142
Intron 12       c.1755-186A>G       rs62075593       2%       No effect on splicing       2.032         Intron 13       c.1888+21G>A       rs2304837       6%       No effect on splicing       3.378         Intron 14       c.2040+20A>G       rs2304836       72%       No effect on splicing       2.163         Intron 14       c.2040+66C>T       rs2304835       7%       No effect on splicing       3.54         Intron 14       c.2040+69A>G       rs2304834       6%       No effect on splicing       0.027         Intron 14       c.2040+69A>G       rs2304833       27%       No effect on splicing       0.027         Intron 14       c.2040+69A>G       rs2304833       27%       No effect on splicing       0.371	Intron 12	c.1754+104C>G	rs2304839	5%	No effect on splicing	0.763
Intron 13       c.1888+21G>A       rs2304837       6%       No effect on splicing       3.378         Intron 14       c.2040+20A>G       rs2304836       72%       No effect on splicing       2.163         Intron 14       c.2040+66C>T       rs2304835       7%       No effect on splicing       3.54         Intron 14       c.2040+69A>G       rs2304834       6%       No effect on splicing       0.027         Intron 14       c.2041-64G>A       rs2304833       27%       No effect on splicing       0.371	Intron 12	c.1754+144C>T	rs2304838	61%	No effect on splicing	1.787
Intron 14         c.2040+20A>G         rs2304836         72%         No effect on splicing         2.163           Intron 14         c.2040+66C>T         rs2304835         7%         No effect on splicing         3.54           Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2041-64G>A         rs2304833         27%         No effect on splicing         0.371	Intron 12	c.1755-186A>G	rs62075593	2%	No effect on splicing	2.032
Intron 14         c.2040+66C>T         rs2304835         7%         No effect on splicing         3.54           Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2041-64G>A         rs2304833         27%         No effect on splicing         0.371	Intron 13	c.1888+21G>A	rs2304837	6%	No effect on splicing	3.378
Intron 14         c.2040+69A>G         rs2304834         6%         No effect on splicing         0.027           Intron 14         c.2041-64G>A         rs2304833         27%         No effect on splicing         0.371	Intron 14	c.2040+20A>G	rs2304836	72%	No effect on splicing	2.163
Intron 14 c.2041-64G>A rs2304833 27% No effect on splicing 0.371	Intron 14	c.2040+66C>T	rs2304835	7%	No effect on splicing	3.54
	Intron 14	c.2040+69A>G	rs2304834	6%	No effect on splicing	0.027
Exon 15 c.2065G>A rs1800309 6% No effect on splicing 1.783	Intron 14	c.2041-64G>A	rs2304833	27%	No effect on splicing	0.371
	Exon 15	c.2065G>A	rs1800309	6%	No effect on splicing	1.783

			Global allele frequency	Predictions of pre-mRNA	CADD score
Location	Variant	Variant ID	(GnomAD)	splicing	PHRED
Exon 15	c.2133A>G	rs1800310	27%	No effect on splicing	1.134
Intron 15	c.2189+95C>T	rs72850840	5%	No effect on splicing	3,771
Intron 15	c.2189+263G>A	rs7221604	66%	Generates a new cryptic splice donor site	0.563
Intron 15	c.2189+510T>G	rs4889963	5%	No effect on splicing	1.444
Intron 15	c.2189+607G>A	rs112710614	7%	No effect on splicing	0.189
Intron 15	c.2189+616T>C	rs139307163	5%	No effect on splicing	1.94
Intron 15	c.2189+723G>A	rs4889819	20%	No effect on splicing	0.367
Intron 15	c.2189+729A>G	rs74737410	5%	No effect on splicing	0.498
Intron 15	c.2189+859A>G	rs4889964	5%	No effect on splicing	1.503
Intron 15	c.2189+884G>A	rs4889965	5%	No effect on splicing	0.355
Intron 15	c.2189+1153A>G	rs72850844	5%	No effect on splicing	3.687
Intron 15	c.2189+1201C>A	rs72850846	5%	No effect on splicing	2.352
Intron 15	c.2189+1208A>G	rs72850847	5%	No effect on splicing	0.367
Intron 15	c.2189+1263A>G	rs74700450	5%	No effect on splicing	2.97
Intron 15	c.2189+1290A>G	rs74003630	5%	No effect on splicing	6.015
Intron 15	c.2189+1600C>T	rs60668271	5%	No effect on splicing	0.481
Intron 15	c.2190-1531G>A	rs74702528	0.9% (3% in African population)	No effect on splicing	0.489
Intron 15	c.2190-1463G>A	rs116416508	0.9% (3% in African population)	No effect on splicing	0.328
Intron 15	c.2190-1139A>G	rs184803352	0.7% (2% in African population	No effect on splicing	0.095
Intron 15	c.2190-1005A>G	rs4889820	5%	No effect on splicing	2.452
Intron 15	c.2190-686G>A	rs12452616	19%	No effect on splicing	2.725
Intron 15	c.2190-647G>A	rs59362713	10%	No effect on splicing	0.227
Intron 15	c.2190-536G>A	rs60429724	10%	No effect on splicing	0.454
Intron 15	c.2190-490G>A	rs111477580	1%	No effect on splicing	3.101
Intron 15	c.2190-444A>G	rs4889967	73%	No effect on splicing	1.059
Intron 15	c.2190-336C>T	rs76178719	3%	No effect on splicing	1.566
Intron 16	c.2331+20G>A	rs2304832	75%	No effect on splicing	5.346
Intron 16	c.2331+24T>C	rs2304831	15%	No effect on splicing	0.204
Intron 16	c.2331+151C>T	rs111537160	2%	No effect on splicing	0.608
Intron 16	c.2332-198A>T	rs2304830	73%	No effect on splicing	3.363
Exon 17	c.2338G>A	rs1126690	72%	No effect on splicing	2.675
Exon 17	c.2446G>A	rs1800314	5%	No effect on splicing	5.793
Intron 17	c.2482-132C>T	rs113824706	0.9% (3% in African population)	No effect on splicing	0.066
Exon 18	c.2553G>A	rs1042397	57%	Weakens a cryptic splice donor site	1.241
Intron 18	c.2647-71G>C	rs4889821	5%	No effect on splicing	3.473
Exon 19	c.2780C>T	rs1800315	2%	No effect on splicing	0.222
Intron 19	c.2800-227C>G	rs9890469	66%	No effect on splicing	0.661
Intron 19	c.2800-60G>A	rs55662462	0.7% (11% in Latino population)	No effect on splicing	2.209
Exon 20, 3' UTR	c.*3G>A	rs1800317	5%	No effect on splicing	0.03

Location	Variant	Variant ID	Global allele frequency (GnomAD)	Predictions of pre-mRNA splicing	CADD score PHRED
Exon 20, 3' UTR	c.*91G>A	rs2229221	12%	No effect on splicing	6.887
Exon 20, 3' UTR	c.*223C>T	rs8132	22%	No effect on splicing	3.025
Exon 20, 3' UTR	c.*419G>T	rs7567	19%	No effect on splicing	4.17

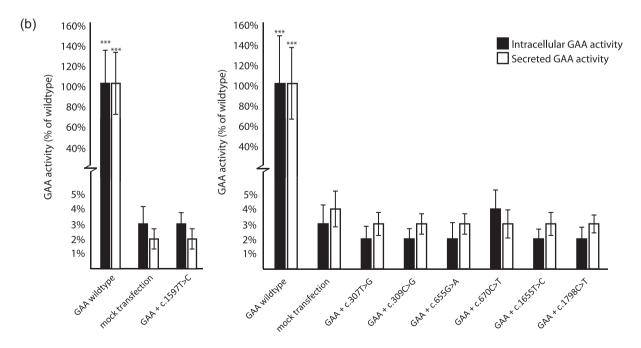
Abbreviations: CADD, Combined Annotation-Dependent Depletion; mRNA, messenger RNA; UTR, untranslated region.

stronger enrichment in the catalytic core compared with the mapping we performed previously (Niño et al., 2019; Figure 1c).

We included in the current version of the database common sequence variants that have a MAF  $\geq$  1% and do not cause Pompe disease. This resulted in a relative increase in the number of nondiseaseassociated variants (Table 2). We decided to include common sequence variants in response to the misreporting of these variants as the principal cause of disease in several patients. Examples of this are the c.547-67C>G (rs8069491) and 547-39T>G (rs12452721) variants, which were reported as the cause of disease while having an allele frequency of 67% in the global population (Bekircan-Kurt et al., 2017; Guevara-Campos et al., 2019). In total, the database now includes 148 variants with a MAF  $\geq$  1%. All variants had a low CADD score (<10; Table 2) and were classified as "unknown." We note that while these common sequence

(a)

Variant	Protein change	phenotype combined with a null allele	reported patients	Predictions on pre-mRNA splicing	CADD score PHRED
GAA + c.1597T>C	p.(Cys533Arg)	Classic infantile	1	no effect on splicing	25.5
GAA + c.307T>G	p.(Cys103Gly)	Classic infantile	11	loss of a cryptic splice donor site	25.1
GAA + c.309C>G	p.(Cys103Trp)	Unknown	1	no effect on splicing	5.6
GAA + c.655G>A	p.(Gly219Arg)	Classic infantile	14	no effect on splicing	28.2
GAA + c.670C>T	p.(Arg224Trp)	Classic infantile or Childhood	7	no effect on splicing	22.8
GAA + c.1655T>C	p.(Leu552Pro)	Classic infantile	41	no effect on splicing	29.9
GAA + c.1798C>T	p.(Arg600Cys)	Classic infantile	18	no effect on splicing	27.0



**FIGURE 2** Expression study of seven disease-associated missense variants in the GAA gene. (a) Overview of basic information regarding the pathogenicity of selected variants. (b) Measured GAA activity in both cells and medium of COS-7 cultures after transfection with the generated constructs. Findings for the c.1597T>C variants are plotted separately as this was performed in a separate experiment. Data represent means, error bars represent *SD* (*n* = 3 biological replicates), \*\*\**p* < .001. CADD, Combined Annotation-Dependent Depletion; mRNA, messenger RNA

		JIB111100110					
Variant	Protein change	Location	Type of variant (protein)	MAF	Predictions on splicing-Align GVGD-SIFT-Mutation taster-[CADD score]	Experimental data	Country and reference
c.317G>A*	p.(Arg106His)	Exon 2	Missense	MAF <1%	No effect on splicing-Class CO-Deleterious-Disease causing-[25.9]		Japan; Momosaki et al. (2019)
c.365T>A	p.(Met122Lys)	Exon 2	Missense	MAF not reported	No effect on splicing-Class CO-Tolerated-Polymorphism-[14.17]		USA; Scott et al. (2013)
c.424_440del	p.(Ser142Leufs*29)	Exon 2	Frameshift	MAF not reported	No effect on splicing-Results in an out of frame product-[32]		Taiwan; Chien et al. (2011)
c.533G>A*	p.(Arg178His)	Exon 2	Missense	MAF <1%	No effect on splicing-Class CO-Tolerated-Disease causing-[31]	No effect on splicing of exon 2 in minigene construct (Goina, et al., 2019)	Taiwan; Chien et al. (2011)
c.546+5G>T*	p.?	Intron 2	No category (splicing)	MAF <1%	Weakens exon 2 splice donor and generates a cryptic splice donor-[23.7]	Affects splicing of exon 2 in minigene construct (Goina, et al., 2019)	Taiwan; Labrousse et al. (2010)
c.705G>A	p.(=)	Exon 4	Silent	MAF <1%	No effect on splicing-[0.534]		Japan; Momosaki et al. (2019)
c.811A>G*	p.(Thr 271Ala)	Exon 4	Missense	MAF not reported	No effect on splicing-Class CO-Tolerated-Polymorphism-[16.93]	71% residual activity of GAA in expression study (Kroos, et al., 2012a)	Taiwan; Labrousse et al. (2010)
c.1054C>T	p.(Gln352*)	Exon 6	Nonsense	MAF not reported	No effect on splicing-Introduces an early stop codon-[43]		Taiwan; Liao et al. (2014)
c.1080C>G	p.(Tyr360*)	Exon 7	Nonsense	MAF not reported	No effect on splicing-Introduces an early stop codon-[39]		Taiwan; Chien et al. (2011)
c.1082C>A	p.(Pro361Arg)	Exon 7	Missense	MAF <1%	No effect on splicing-Class C65-Deleterious-Disease causing-[25.5]		Japan; Momosaki et al. (2019)
c.1220A>G	p.(Tyr407Cys)	Exon 8	Missense	MAF <1%	No effect on splicing-Class C65-Deleterious-Disease causing-[25.9]		Mexico; Navarrete- Martínez et al. (2017)
c.1244C>T	p.(Thr415Met)	Exon 8	Missense	MAF <1%	No effect on splicing-Class C15-Deleterious-Disease causing-[24.6]		Japan; Momosaki et al. (2019)
c.1324G>A*	p.(Val442Met)	Exon 8	Missense	MAF <1%	No effect on splicing-Class CO-Deleterious-Disease causing-[23.8]		Taiwan; Chien et al. (2011)
c.1409A>C	p.(Asn470Thr)	Exon 9	Missense	MAF <1%	No effect on splicing-Class C25-Deleterious-Disease causing-[23.2]		Hungary; Witmann et al. (2012)

TABLE 3 Variants of unknown significance that were found only through newborn screening programs

Variant	Protein change	Location	Type of variant (protein)	MAF	Predictions on splicing-Align GVGD-SIFT-Mutation taster-[CADD score]	Experimental data	Country and reference
c.1574T>A	p.(Phe525Tyr)	Exon 11	Missense	MAF not reported	No effect on splicing-Class C15-Deleterious-Disease causing-[28.8]	10% residual activity of GAA in expression study (Kroos, et al., 2012a)	Taiwan; Chien et al. (2011)
c.1805C>T	p.(Thr 602lle)	Exon 13	Missense	MAF not reported	No effect on splicing-Class C0-Tolerated-Disease causing-[24.1]		USA; Elliott et al. (2016)
c.1840A>G	p.(Thr 614Ala)	Exon 13	Missense	MAF not reported	No effect on splicing-Class C55-Deleterious-Disease causing-[24.3]		Taiwan; Liao et al. (2014)
c.1925T>A	p.(Val642Asp)	Exon 14	Missense	MAF not reported	No effect on splicing-Class C45-Deleterious-Disease causing-[29.2]		USA; Scott et al. (2013)
c.1958C>A	p.(Thr 653Asn)	Exon 14	Missense	MAF <1%	No effect on splicing-Class C15-Tolerated-Disease causing-[25.4]		Taiwan; Chien et al. (2011)
c.2003A>G*	p.(Tyr668Cys)	Exon 14	Missense	MAF not reported	No effect on splicing-Class C65-Deleterious-Disease causing-[31]		Japan; Momosaki et al. (2019)
c.2055C>G	p.(Tyr685*)	Exon 15	Nonsense	MAF not reported	No effect on splicing-Introduces an early stop codon-[36]		Japan; Momosaki et al. (2019)
c.2174G>A	p.(Arg725Gln)	Exon 15	Missense	MAF <1%	No effect on splicing-Class C0-Tolerated-Disease causing-[32]		Hungary; Witmann et al. (2012)
c.2482-5T>C*	p.?	Intron 17	No category (splicing)	MAF not reported	No effect on splicing-[8.409]		Taiwan; Liao et al. (2014)
c.2482-2A>G	p.?	Intron 17	No category (splicing)	MAF <1%	Loss of exon 18 splice acceptor site-[35]		Hungary; Witmann et al. (2012)
c.2647-23del	p.?	Intron 18	No category (intron variant)	MAF <1%	No effect on splicing-[0.451]		Taiwan; Liao et al. (2014)
c.2843dup	p.(Val949Argfs*69) Exon 20	Exon 20	Frameshift	MAF not reported	No effect on splicing-Results in an out of frame product-[23.1]		Taiwan; Liao et al. (2014)
Abbraviations.	Abhraviations: CADD Combined Annotation Denendent Denletion: MAE minor allele frequency	notation De	mendent Denletion.	MAE minor alle			

Abbreviations: CADD, Combined Annotation-Dependent Depletion; MAF, minor allele frequency.

\*Variants found in cis with the Asian pseudodeficiency allele c[1726G>A; 2065G>A].

TABLE 3 (Continued)

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variants do not result in clinical manifestation of Pompe disease, it remains possible that they might modify disease progression when present in cis with a disease-associated variant. In Pompe disease, this is the case for the Asian pseudodeficiency allele (c.[1726G>A (p.Gly576-Ser);2065G>A (p.Glu689Lys)]) and GAA2 (c.271G>A, (p.Asp91Asn)), which have a MAF of 14% for c.1726G>A, 23.5% for c.2065G>A (both East Asian), and 3.2% for GAA2 (European), and can be present in cis with known disease-associated variants (Kroos et al., 2006; Labrousse et al., 2010). Also, a variant with a low MAF in the general population, c.510C>T (p.=) (rs564758226), is known to be linked to the late-onset variant c.-32-13T>G (p.[=,0]) (IVS1). c.510C>T has a global MAF of 0.005%, but a MAF of 27.3% in compound heterozygous IVS1 patients with symptom onset at childhood. It worsens aberrant splicing caused by IVS1 and causes lower levels of leaky wild-type splicing and lower GAA enzyme activity, resulting in accelerated disease onset (Bergsma et al., 2019).

Figure 2a,b shows the results on the GAA variants we subjected to a more in-depth investigation. We selected the common missense variants c.307T>G (p.Cys103Gly), c.655G>A (p.Gly219Arg), c.670C>T (p.Arg224Trp), c.1655T>C (p.Leu552Pro), and c.1798C>T (p.Arg600-Cys) and performed in vitro analysis of their severity using SDM of GAA cDNA expression constructs. In addition, c.1597T>C (p.Cys533Arg) and c.309C>G (p.Cys103Trp) were tested due to a request for diagnostic purposes. All of these variants fully abrogated GAA enzymatic activity following transfection in COS-7 cells (Figure 2, compare mutant GAA with mock transfections). The c.309C>G variant was included because the patient that harbored this variant in combination with c.525del p.(Glu176Argfs\*45) showed an atypical Pompe disease phenotype (Mori et al., 2017). This case report described an adult patient with cardiomyopathy. Molecular analysis of primary skin fibroblasts identified a reduction in GAA activity, although not at pathogenic levels, and GAA activity was in the normal range for skeletal muscle tissue (Mori et al., 2017). We note that the c.309C>G variant was not detected in DNA from either parent and was described as a de novo variant (Mori et al., 2017). This variant might have been introduced during embryonic development, resulting in mosaicism similar to, as described previously in Labrijn-Marks et al. (2019) and in 't Groen et al. (2020). This might explain the "uneven pattern" of glycogen accumulation in histological sections derived from cardiac tissue (Mori et al., 2017). The in vitro analysis indicated that the c.309C>G variant is fully deleterious and has a predicted classic infantile phenotype in combination with a null allele. A comprehensive genetic analysis would be necessary to confirm this hypothesis.

Novel variants that have been reported only through NBS studies, but for which no clinical phenotype has been provided, were classified as "Unknown (found only in NBS)". In the current version of the database, 26 variants have been classified as such (Table 3). Seven out of 26 variants were also present in *cis* with the Asian pseudodeficiency allele, indicating that additional testing is required because the Asian pseudodeficiency is known to result in false-positive outcomes in dried blood spot-based assays (Liao et al., 2014; Momosaki et al., 2019). It is currently unknown at what age symptoms will develop in neonates diagnosed with disease-associated variants that are potentially associated with a late-onset phenotype. Symptoms might be delayed until late adulthood or, for some genetic variants, might not even lead to disease. In these cases, further research on the effect of the genetic variants is essential to better inform patients, families, and doctors. As reported, in these cases, the uncertainty of the diagnosis, the possibility of an emerging disease, and the doubt on when to start treatment with ERT could lead to emotional stress (Bodamer et al., 2017). This underscores the importance of phenotype prediction for disease-associated variants, especially in the case of asymptomatic patients identified through NBS programs.

The sharp increase in reports on patients with Pompe disease and GAA disease-associated variants highlights the need for regular updates of the Pompe disease GAA variant database. Increased awareness and improved diagnostic technology with exome and genome sequencing and NBS programs are expected to further increase the number of entries in the database in the coming years. It will be important to link variants to clinical information and to test their deleterious effect in vitro using expression and splicing assays. Curated disease-specific databases such as the Pompe disease GAA variant database will be important to provide guidance to clinicians and clinical geneticists to establish an accurate molecular diagnosis.

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### CONFLICT OF INTERESTS

Ans T. van der Ploeg has provided consulting services for various industries in the field of Pompe disease under an agreement between these industries and Erasmus MC, Rotterdam, the Netherlands. The remaining authors declare that there are no conflict of interests.

### WEB RESOURCES

Pompe disease GAA variant database: http://www.pompevariant database.nl/

LOVD: http://gaa.lovd.nl/ GnomAD: https://gnomad.broadinstitute.org/ dbSNP: https://www.ncbi.nlm.nih.gov/snp/ CADD score: https://cadd.gs.washington.edu/

### DATA AVAILABILITY STATEMENT

The data described in this study is available upon request from the corresponding authors, and new variants have been added to the Pompe disease GAA variant database (http://www.pompevariant database.nl/) and LOVD (http://gaa.lovd.nl/).

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### SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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