ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
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Andes pediatr. 2024;95(1):
DOI: 10.32641/andespediatr.v95i1.4752

ORIGINAL ARTICLE

Population characterization of mutations for sickle cell anemia and its treatment: One step towards personalized medicine for the disease

Caracterización poblacional de mutaciones relevantes para la Anemia Falciforme y su tratamiento: Un paso hacia la personalización de la enfermedad

Supplementary Table 1. Selected SNPs; the present table summarizes the selected SNPs for the construction of the database

SNP	Descripción
'rs17599586'	'HbF change, %'
'rs2295644'	'HbF change, %'
'rs10483801'	'HbF and HbF response to hydroxyurea'
'rs2182008'	'HbF and HbF response to hydroxyurea'
'rs9319428'	'HbF and HbF response to hydroxyurea'
'rs3751395'	'HbF and HbF response to hydroxyurea'
'rs2387634'	'HbF and HbF response to hydroxyurea'
'rs10494225'	'HbF and HbF response to hydroxyurea,'
'rs7977109'	'HbF and HbF response to hydroxyurea'
'rs816361'	'HbF and HbF response to hydroxyurea'
'rs7309163'	'HbF and HbF response to hydroxyurea'
'rs5006884'	'Regulation of HbA2 level'
'rs8002446'	'HbF and HbF response to hydroxyurea'
'rs826729'	'HbF and HbF response to hydroxyurea'
'rs765587'	'HbF and HbF response to hydroxyurea'
'rs9693712'	'HbF and HbF response to hydroxyurea'
'rs172652'	'HbF and HbF response to hydroxyurea'
'rs380620'	'HbF and HbF response to hydroxyurea'
'rs2693430'	'HbF and HbF response to hydroxyurea'
'rs12155519'	'HbF and HbF response to hydroxyurea,'
'rs28384513'	'Basal Levels of HBF'
'rs9402686'	'Basal Levels of HBF'
'rs9399137'	'Basal Levels of HBF'
'rs4895441'	'Basal Levels of HBF'
'rs7581162'	'Basal Levels of HBF'
'rs10189857'	'Basal Levels of HBF'
'rs1427407'	'Basal Levels of HBF'

‘rs7599488’	'Basal Levels of HBF'
‘rs766432’	'Basal Levels of HBF'
‘rs11886868’	'Basal Levels of HBF'
‘rs4671393’	'Basal Levels of HBF'
‘rs7557939’	'Basal Levels of HBF'
‘rs10184550’	'Basal Levels of HBF'
‘rs10128556’	'Basal Levels of HBF'
‘rs2310991’	'HBF levels in response to Hydroxyurea treatment'
‘rs61743453’	'HBF levels in response to Hydroxyurea treatment'
‘rs334’	'sickle cell anemia

Supplementary Table 2. Selected SNPs related to the prognosis of the SCA

gene_id	gene	SNP	Alleles	description	ref
4602	HBS1L-MYB	rs28384513	T>C / T>G	Basal Levels of HBF	D. R. Higgs, W. G. Wood, Genetic complexity in sickle cell disease. *Proc Natl Acad Sci U S A* **105**, 11595-11596 (2008).
4602	HBS1L-MYB	rs9402686	G>A	Basal Levels of HBF	S. L. Thein *et al.* , Intergenic variants of HBS1L-MYB are responsible for a major quantitative trait locus on chromosome 6q23 influencing fetal hemoglobin levels in adults. *Proc Natl Acad Sci U S A* **104**, 11346-11351 (2007)
4602	HBS1L-MYB	rs9399137	T>C	Basal Levels of HBF	S. L. Thein *et al.* , Intergenic variants of HBS1L-MYB are responsible for a major quantitative trait locus on chromosome 6q23 influencing fetal hemoglobin levels in adults. *Proc Natl Acad Sci U S A* **104**, 11346-11351 (2007)
4602	HBS1L-MYB	rs4895441	A>G	Basal Levels of HBF	S. L. Thein *et al.* , Intergenic variants of HBS1L-MYB are responsible for a major quantitative trait locus on chromosome 6q23 influencing fetal hemoglobin levels in adults. *Proc Natl Acad Sci U S A* **104**, 11346-11351 (2007)
53335	BCL11A	rs7581162	T>A	Basal Levels of HBF	S. Le Hellard *et al.* , Identification of Gene Loci That Overlap Between Schizophrenia and Educational Attainment. *Schizophr Bull* **43**, 654-664 (2017)
53335	BCL11A	rs10189857	A>G	Basal Levels of HBF	G. Galarneau *et al.* , Fine-mapping at three loci known to affect fetal hemoglobin levels explains additional genetic variation. *Nat Genet* **42**, 1049-1051 (2010).
53335	BCL11A	rs1427407	T>C / T>G	Basal Levels of HBF	L. A. Hindorff *et al.* , Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci U S A* **106**, 9362-9367 (2009).
53335	BCL11A	rs7599488	C>T	Basal Levels of HBF	G. Galarneau *et al.* , Fine-mapping at three loci known to affect fetal hemoglobin levels explains additional genetic variation. *Nat Genet* **42**, 1049-1051 (2010).
53335	BCL11A	rs766432	C>A	Basal Levels of HBF	J. Borg *et al.* , Haploinsufficiency for the erythroid transcription factor KLF1 causes hereditary persistence of fetal hemoglobin. *Nat Genet* **42**, 801-805 (2010).
53335	BCL11A	rs11886868	C>T	Basal Levels of HBF	G. Lettre et al., DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proc Natl Acad Sci U S A 105, 11869-11874 (2008).
53335	BCL11A	rs4671393	A>C / A>G	Basal Levels of HBF	D. R. Higgs, W. G. Wood, Genetic complexity in sickle cell disease. *Proc Natl Acad Sci U S A* **105**, 11595-11596 (2008).
53335	BCL11A	rs7557939	G>A	Basal Levels of HBF	G. Lettre et al., DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proc Natl Acad Sci U S A 105, 11869-11874 (2008).
53335	BCL11A	rs10184550	G>A	Basal Levels of HBF	H. T. Bae *et al.* , Meta-analysis of 2040 sickle cell anemia patients: BCL11A and HBS1L-MYB are the major modifiers of HbF in African Americans. *Blood* **120**, 1961-1962 (2012).
3043	HBB	rs10128556	C>T	Basal Levels of HBF	G. Galarneau *et al.* , Fine-mapping at three loci known to affect fetal hemoglobin levels explains additional genetic variation. *Nat Genet* **42**, 1049-1051 (2010).
56681	SAR1A	rs2310991	C>A	HBF levels in response to Hydroxyurea treatment	C. Kumkhaek *et al.* , Fetal haemoglobin response to hydroxycarbamide treatment and sar1a promoter polymorphisms in sickle cell anaemia. *Br J Haematol* **141**, 254-259 (2008).
6297	SALL2	rs61743453	G>C	HBF levels in response to Hydroxyurea treatment	K. Mnika, G. D. Pule, C. Dandara, A. Wonkam, An Expert Review of Pharmacogenomics of Sickle Cell Disease Therapeutics: Not Yet Ready for Global Precision Medicine. *OMICS* **20**, 565-574 (2016).
3048	HBG2	rs7482144	G>A	HBF levels	B. A. Miller *et al.* , Molecular analysis of the high-hemoglobin-F phenotype in Saudi Arabian sickle cell anemia. *N Engl J Med* **316**, 244-250 (1987).

Supplementary Table 3. Selected SNPs related to the treatment of the SCA

gen_id	gen	SNP	Alleles	description	reference
383	ARG1	rs17599586	C>T	HbF change, %	R. E. Ware *et al.*, Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. *Blood* **118**, 4985-4991 (2011)
384	ARG2	rs2295644	A>T	HbF change, %	R. E. Ware *et al.*, Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. *Blood* **118**, 4985-4991 (2011)
384	ARG2	rs10483801	C>A	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
2321	FLT1	rs2182008	A>G	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
2321	FLT1	rs9319428	G>A	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
2321	FLT1	rs3751395	C>A	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
2321	FLT1	rs2387634	T>C	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
51179	HAO2	rs10494225	C>G	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
4842	NOS1	rs7977109	G>A / G>T	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
4842	NOS1	rs816361	C>G	HbF and HbF response to hydroxyurea	D. L. Demeo et al., IL10 polymorphisms are associated with airflow obstruction in severe alpha1-antitrypsin deficiency. Am J Respir Cell Mol Biol 38, 114-120 (2008).
4842	NOS1	rs7309163	C>T	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
390058	OR51B6	rs5006884	C>T	Regulation of HbA2 level	Cyrus, Cyril et al. "Haemoglobin switching modulator SNPs rs5006884 is associated with increased HbA2 in β-thalassaemia carriers." Archives of medical science : AMS vol. 17,4 1064-1074. 18 Jul. 2019, doi:10.5114/aoms.2019.86705
2321	FLT1	rs8002446	G>A	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs826729	G>A / G>C	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs765587	T>C	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs9693712	C>T	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs172652	A>G / A>T	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs380620	C>A / C>G	HbF and HbF response to hydroxyurea	P. Sebastiani et al., A hierarchical and modular approach to the discovery of robust associations in genome-wide association studies from pooled DNA samples. BMC Genet 9, 6 (2008).
9760	TOX	rs2693430	A>G	HbF and HbF response to hydroxyurea	A. Driss et al., Sickle Cell Disease in the Post Genomic Era: A Monogenic Disease with a Polygenic Phenotype. Genomics Insights 2009, 23-48 (2009).
9760	TOX	rs12155519	G>A / G>C	HbF and HbF response to hydroxyurea	P. Sebastiani et al., A hierarchical and modular approach to the discovery of robust associations in genome-wide association studies from pooled DNA samples. BMC Genet 9, 6 (2008).

Supplementary Table 4. Rows and Columns in the new generate database

Columm	Description
'snp':	ID of the SNP
'Population'	Population were the frequency of the SNP was evaluated. AFR; AMR; EAS; EUR; SAS
'pp'	Homozygous genotype of the ancestral base
'frecuencia_pp'	pp genotype frequency
'ndeind_pp'	Number of individuals presenting the genotype in the evaluated population
'qq'	Homozygous genotype of the mutant base
'frecuencia_qq'	Observed frequency of the qq genotype
'ndeind_qq'	Number of individuals presenting the genotype in the evaluated population
'2pq'	Heterozygous genotype
'frecuencia_2pq'	Observed frequency of heterozygous genotype
'ndeind_2pq'	Number of individuals presenting the genotype in the evaluated population
'p'	Ancestral Allele
'frecuencia_p'	Observed frequency of ancestral allele
'ndeind_p'	Number of individuals presenting the ancestral allele
'q'	Mutant allele
'frecuencia_q'	Observed frequency of the mutant allele
'ndeind_q'	Number of individuals presenting the mutant allele
'total_ind_ob'	Total number of individuals evaluated
'p_esperada'	Expected p frequency according to HWE
'q_esperada'	Frequency of q expected according to HWE
'pp_esperada'	Frequency of pp expected according to HWE
'pq_esperada'	Frequency of 2pq expected according to HWE
'qq_esperada'	Frequency of qq expected according to HWE
'total_ind_esp'	Total expected individuals (must be equal to the number of observed individuals)
'chi_value'	Chi square value corresponding to the HWE analysis
'p_value'	Statistical p value corresponding to the HWE analysis with significance of 5%
'significative'	Indicates whether the p value of the "p_value" column is significant, three alternatives, "yes", "no", and "nan". The value of nan is indicated when one of the alleles of the SNP has a frequency of 1 in a population.
'description'	Descript2ion associated with the function of the SNP. Two alternatives "Basal levels of HBF" or "HBF levels in response to Hydroxyurea treatment"

Supplementary Table 5. Description of values of columns of the second database generated and used at logistic regression analysis

Column	Description
'suma'	Take values 0, 1 or 2.
0 = homozygous of ancestral allele	Toma valores 0 o 1. Para individuo femenino es 1
1 = heterozygous	Toma valores 0 o 1. Para individuo masculino es 1
2 = homozygous of mutant allele	Toma valores 0 o 1. Para AFR es 1
'F'	Takes values 0 or 1. For female individual is 1
'M'	Takes values 0 or 1. For male individual is 1
' AFR'	Takes values 0 or 1. For AFR is 1
' AMR'	Takes values 0 or 1. For AMR is 1
' EAS'	Takes values 0 or 1. For EAS is 1
' EUR'	Takes values 0 or 1. For EUR is 1
' SAS'	Takes values 0 or 1. For SAS is 1.
'rs10128556'	Takes values 0 or 1. For rs10128556 is 1.
'rs10184550'	Takes values 0 or 1. For rs10184550 is 1.
'rs10189857'	Takes values 0 or 1. For rs10189857 is 1.
'rs10483801'	Takes values 0 or 1. For rs10483801 is 1.
'rs10494225'	Takes values 0 or 1. For rs10494225 is 1.
'rs11886868'	Takes values 0 or 1. For rs11886868 is 1.
'rs12155519'	Takes values 0 or 1. For rs12155519 is 1.
'rs1427407'	Takes values 0 or 1. For rs1427407 is 1.
'rs172652'	Takes values 0 or 1. For rs172652 is 1.
'rs17599586'	Takes values 0 or 1. For rs17599586 is 1.
'rs2295644'	Takes values 0 or 1. For rs2295644 is 1.
'rs2310991'	Takes values 0 or 1. For rs2310991 is 1.
'rs2387634'	Takes values 0 or 1. For rs2387634 is 1.
'rs2693430'	Takes values 0 or 1. For rs2693430 is 1.
'rs28384513'	Takes values 0 or 1. For rs28384513 is 1.
'rs3751395'	Takes values 0 or 1. For rs3751395 is 1.
'rs380620'	Takes values 0 or 1. For rs380620 is 1.
'rs4671393'	Takes values 0 or 1. For rs4671393 is 1.
'rs4895441'	Takes values 0 or 1. For rs4895441 is 1.
'rs5006884'	Takes values 0 or 1. For rs5006884 is 1.
'rs61743453'	Takes values 0 or 1. For rs61743453 is 1.
'rs7309163'	Takes values 0 or 1. For rs7309163 is 1.
'rs7557939'	Takes values 0 or 1. For rs7557939 is 1.
'rs7581162'	Takes values 0 or 1. For rs7581162 is 1.
'rs7599488'	Takes values 0 or 1. For rs7599488 is 1.
'rs765587'	Takes values 0 or 1. For rs765587 is 1.
'rs766432'	Takes values 0 or 1. For rs766432 is 1.
'rs7977109'	Takes values 0 or 1. For rs7977109 is 1.
'rs8002446'	Takes values 0 or 1. For rs8002446 is 1.
'rs816361'	Takes values 0 or 1. For rs816361 is 1.
'rs826729'	Takes values 0 or 1. For rs826729 is 1.
'rs9319428'	Takes values 0 or 1. For rs9319428 is 1.
'rs9399137'	Takes values 0 or 1. For rs9399137 is 1.
'rs9402686'	Takes values 0 or 1. For rs9402686 is 1.
'rs9693712'	Takes values 0 or 1. For rs9693712 is 1.
'Basal Levels of HBF'	Takes values 0 or 1. For 'Basal Levels of HBF' is 1.
'HBF levels in response to Hydroxyurea treatment'	Takes values 0 or 1. For 'HBF levels in response to Hydroxyurea treatment' is 1.
'HbF and HbF response to hydroxyurea'	Takes values 0 or 1. For 'HbF and HbF response to hydroxyurea' is 1.
'HbF change, %'	Takes values 0 or 1. For 'HbF change, %' is 1.
'Regulation of HbA2 level'	Takes values 0 or 1. For 'Regulation of HbA2 level' is 1.