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Clinical and Genetic Predictors of Priapism in Sickle Cell Disease: Results from the Recipient Epidemiology and Donor Evaluation Study III Brazil Cohort Study

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Abstract

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Introduction: Priapism is the persistent and painful erection of the penis and is a common sickle cell disease (SCD) complication.

Aim: The goal of this study was to characterize clinical and genetic factors associated with priapism within a large multi-center SCD cohort in Brazil.

Methods: Cases with priapism were compared to SCD type-matched controls within defined age strata to identify clinical outcomes associated with priapism. Whole blood single nucleotide polymorphism genotyping was performed using a customized array, and a genome-wide association study (GWAS) was conducted to identify single nucleotide polymorphisms associated with priapism.

Main Outcome Measure: Of the 1,314 male patients in the cohort, 188 experienced priapism (14.3%).

Results: Priapism was more common among older patients ($P = .006$) and more severe SCD genotypes such as homozygous SS ($P < .0001$). In the genotype- and age-matched analyses, associations with priapism were found for pulmonary hypertension ($P = .05$) and avascular necrosis ($P = .01$). The GWAS suggested replication of a previously reported candidate gene association of priapism for the *gene transforming growth factor beta receptor 3* (*TGFBR3*) ($P = 2 \times 10^{-4}$).

Clinical Implications: Older patients with more severe genotypes are at higher risk of priapism, and there is a lack of consensus on standard treatment strategies for priapism in SCD.

Strengths & Limitations: This study characterizes SCD patients with any history of priapism from a large multi-center cohort. Replication of the GWAS in an independent cohort is required to validate the results.

Conclusion: These findings extend the understanding of risk factors associated with priapism in SCD and identify genetic markers to be investigated in future studies to further elucidate priapism pathophysiology.

Keywords

Sickle Cell Disease; Priapism; Genome-Wide Association Study; Single Nucleotide Polymorphism

INTRODUCTION

Sickle cell disease (SCD) is a monogenic disease caused by a point mutation in the β-globin gene (*HBB*). This mutation leads to the generation of abnormal hemoglobin S (HbS), which polymerizes when deoxygenated and distorts red blood cells.[1] Homozygous patients (HbSS) generally have higher levels of HbS and a more severe phenotype than compound heterozygous, such as HbSC or other variants. However, the course of disease, severity, and organs affected vary greatly among patients, even within HbSS patients, and HbS mutation alone is not able to completely explain the heterogeneity.

Priapism is defined as an unwanted, prolonged, and painful penile erection that may cause complications such as erectile dysfunction and impotence. Priapism is a common SCD

complication, with a reported prevalence of 30–45% among homozygous HbSS male patients.[2–5] In SCD patients, priapism most frequently occurs as the ischemic type,[6] with decreased or absent cavernous blood flow, corporal rigidity, and pain.[7] Ischemic priapism can be major, lasting 6 hours or longer, or stuttering, with repeated episodes with intervening periods of detumescence.[7]

Priapism in SCD patients was first linked to vascular occlusion and ischemia, as a consequence of decreased efflux of blood from corporal tissue.[8,9] The decreased efflux was postulated to be a consequence of the interaction of sickled erythrocytes with endothelial cells, leukocytes, platelets, and other plasma components leading to vascular obstruction. However, later studies linked priapism in SCD patients with disruptions of the nitric oxide (NO) signal transduction pathway. NO is a key signaling molecule in pathways mediating erection.[10] Hemolysis would contribute to the reduction of NO bioavailability, as plasma free hemoglobin is released and can scavenge NO.[11,12] Recently, priapism has also been associated with an excess of adenosine, RhoA/Rho-kinase (ROCK), and opiorphin upregulation.[13–22]

Previous studies have investigated the association of single nucleotide polymorphisms (SNPs) in candidate genes with the risk of priapism in SCD patients. Associations were found for polymorphisms in the *Klotho* gene, involved in vascular functions and NO biology[23]; transforming growth factor-β receptor type III (TGFBR3), related to inflammatory pathways; aquaporin, associated with hydration; integrin α-V, which encodes a receptor related to red cell adhesion; and the A1 subunit of coagulation factor XIII, which has an important role in the coagulation system.[24] However, no study has confirmed these associations and no genome-wide association studies of priapism have been conducted.

The goal of this study was to characterize clinical and genetic factors associated with priapism within a large multi-center SCD cohort in Brazil. This evaluation will help us to better understand the impact of priapism in SCD patients and the associated risk factors.

METHODS

Patient Recruiting

The REDS-III Brazil SCD cohort is part of the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program of the National Institutes of Health's National Heart, Lung, and Blood Institute.[25] REDS-III is a collaboration among investigators in the United States, Brazil, China, and South Africa to study the safety and adequacy of the blood supply and impact of blood transfusion. The REDS-III Brazil SCD cohort study aims to characterize health and transfusion outcomes in patients with SCD.[26] The Brazilian National Ethical Committee for Research, local ethical committees at each participating center, and the Institutional Review Boards at the University of California, San Francisco, and the REDS-III data coordinating center, RTI International, all reviewed and approved the study. Written informed consent was obtained from participants 18 years or older or from guardians of younger patients. Age-appropriate assent was also obtained from minors.

The REDS-III Brazil SCD cohort enrolled almost 2,800 Brazilian patients with sickle cell disease at 6 sites in Brazil: Fundação Hemominas, in the cities of Belo Horizonte, Juiz de Fora, and Montes Claros in the state of Minas Gerais; Fundação Hemorio, in Rio de Janeiro in the state of Rio de Janeiro; Fundação Hemope, in Recife in the state of Pernambuco; and Instituto da Criança, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo in São Paulo in the state of São Paulo. The study methods and baseline results have been previously published.[26] Briefly, participants were randomly selected from participating centers and recruited at routine visits. Sociodemographic information was obtained through an interview with participants (or legal guardian for participants < 18 years of age). SCD outcomes were abstracted from medical records using standardized definitions of the phenotypic manifestations of SCD as defined by Ballas et al.[27] This included an abstraction of any history of priapism in a patient's lifetime and the year of the first episode from the medical records at the enrollment visit. Two follow-up visits were conducted during the cohort study. At these visits, more detailed information regarding all priapism episodes during the follow-up time were abstracted, including duration of episodes and treatments used.

For an analysis of demographic characteristics, all male patients with no history of priapism were compared to patients with a history of priapism. For an analysis of clinical outcomes associated with priapism in the cohort, frequency matching was used to identify controls without priapism matched on SCD genotype and age strata to priapism cases, considering an interval of ± 2 years for participants younger than 18 years of age and an interval of ± 6 years for participants older than 18 years of age in a 1:2 ratio. Two HbSβ0 patients did not have a match among controls and were not included in the clinical analysis. Participants with a history of priapism were compared to participants without priapism using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

The Kaplan-Meier method was used to estimate time to event of priapism and a genome-wide association study (GWAS) was performed to identify SNPs associated with priapism. Both the Kaplan-Meier analysis and GWAS were restricted to the genotypes HbSS, HbSβ0, and HbSβ+, as these genotypes had similar prevalences of priapism in this study. HbSC patients were excluded from these analyses, as the prevalence of priapism in our cohort was significantly lower in HbSC patients. For the GWAS, cases were defined as HbSS, HbSβ0, or Hbβ+ male patients with at least 1 episode of priapism. Control subjects were HbSS, HbSβ0, or Hbβ+ male patients 12 years old or older who had never experienced priapism, to control for patients who might have priapism but had not yet experienced it because of their young age.

Genotyping

Genotyping was performed using a customized Affymetrix (Santa Clara, CA) transfusion medicine array.[28] The array includes 749,000 SNPs and is enriched for blood- and transfusion-related polymorphisms. The array also includes 48 genes specifically related to SCD, including possible SCD bio-markers, such as for fetal hemoglobin (HbF) levels, hemolysis, hyperbilirubinemia, and proteinuria. Genotype calls were generated using Axiom Analysis Suite software (Affymetrix), human leukocyte antigen alleles were called with

Axiom HLA Analysis software (Affymetrix), and copy number polymorphisms were called with Axiom CNV Summary Tools, with further analysis being performed with PennCNV (http://penncnv.openbioinformatics.org/en/latest/).

Samples with dish quality control values less than 0.85 or call rates < 97% were excluded. Plates with plate quality control metrics < 95% or average call rates < 98.5% were also excluded. For SNP quality control, SNPolisher was used, and SNPs in the recommended categories (PolyHighRes, MonoHighRes, NoMinorHom, and Hemizygous) were retained. Samples with inconsistent gender definitions found by genotyping and the database were excluded. PLINK[29] was used to calculate identity-by-descent, and the sample with a lower call rate from pairs of samples with PI_HAT > 0, 4 or IBS > 0, 9 was excluded. SNPs with call rates < 97% or significant deviation from Hardy-Weinberg equilibrium ($P \leq 10^{-4}$) were excluded. Phasing was then conducted with SHAPEIT[30] and imputation with IMPUTE2,[31] with haplotypes derived from the 1000 Genomes Project Phase 3[32] as reference data. After quality control and imputation procedures, a final set of 831,797 SNPs was used in the GWAS.

Genome-Wide Association Study

Population substructure was determined by generating principal components using EIGENSTRAT[33] software on linkage disequilibrium (LD)-pruned autosomal SNPs with unrelated participants only. The top 10 principal components were included in the association analyses to adjust for population substructure. Genome-wide association analyses were conducted using GEMMA[34] software with a logistic mixed model, adjusted for age as covariate, as age was associated with priapism occurrence, as well as cryptic kinship relatedness. The online tool HaploReg v4.1[35] was used to explore the genes nearest to the index SNPs. LocusZoom[36] was used to generate LocusZoom plots, with 1000 Genomes Project Phase 3 LD estimation. A genome-wide P value threshold of 5×10^{-8} was used to define statistical significance in the GWA analysis. Only variants with minor frequency alleles > 0.05 were considered. Odds ratios for each SNP were transformed from the effect sizes from linear mixed modelwith LMOR[37] in order to obtain a comparative scale for the genetic effects.

RESULTS

Overall Characteristics of Patients

Among the REDS-III Brazil SCD cohort study participants, there were 1,314 male patients 0 to 77 years of age, of which 188 had priapism (14.3%) (Figure 1). This included 51 of 745 males younger than 18 years (6.9%) and 137 of 568 males 18 years old or older (24.1%) (Table 1). Older age was significantly associated with priapism ($P < .0001$). The mean age of the first priapism episode was 16 years (median, 15 years; range, 2–41 years), with 25% of the cases occurring before 10 years of age and 60% of the cases occurring before 20 years of age (Figure 2). The Kaplan-Meier analysis included 993 HbSS, HbSβ0, and HbSβ+ patients, 158 with a history of priapism and known age of first episode and 835 with no history of priapism. This demonstrated that 80% of the patients included in the analysis remained

priapism free by 20 years of age and that the number of new cases stabilizes near the age of 40 (Figure 3).

Clinical Variables Associated with the Occurrence of Priapism

Patients with a history of priapism were mainly HbSS patients (89.4% of the total number of cases and 18% of the total of HbSS males); a smaller number were HbSβ+ (3% of the total number of cases and 12% of the total HbSβ+ males) and HbSβ0 (3% of the total number of cases and 14% of the total HbSβ0 males). Patients with HbSC were proportionally rarer (5% of the total number of cases and 3% of the total of 295 HbSC males). There was no occurrence of priapism in the small number of patients with other SCD variants, such as SD, S/Hereditary Persistence of Fetal Hemoglobin, S/K-Woolwich, or HbS/Quebec-Chori genotypes. No association was found for biomarkers and priapism (Table 2). Pulmonary hypertension and avascular necrosis were significantly more frequent in the patients with priapism (15% and 19%, respectively) than in patients who never had priapism (9% and 11%, respectively) (Table 3).

Priapism Episodes Reported During the Follow-Up Time

During the follow-up period, 37 participants had priapism episodes; 13 of the 37 had priapism for the first time, and 24 of the 37 were patients with a history of priapism at enrollment had recurrent episodes in the follow-up period. Most of the patients had 1 episode (21 of 37, 57%) although 16 of the 37 participants had repeated episodes, with a range of 2 to 6 episodes. Episodes lasted from 1 to 6 hours, with the majority of the episodes lasting for 1 hour (16%) or 3 hours (17.5%), and a minority were of cases of stuttering priapism (13%). There were 18 episodes in which patients did not receive treatment (28.5%), although 81% of the episodes without treatment lasted only 1 or 2 hours and may have resolved prior to presentation for care. Among the treated episodes, the most common treatment was red blood cell transfusion (28.5%). The remainder were treated with various treatments and combinations of treatments (Table 4).

Genome-Wide Association Analysis

The GWAS included 169 HbSS, HbSβ0, or Hbβ+ male patients with a history of priapism as cases and 433 HbSS, HbSβ0, or Hbβ+ males older than 12 years without a history of priapism as controls (Figure 1). The analysis did not show any *P* value bias ($\lambda_{GC} = 1.003$), and the Q-Q plot (Figure 4) suggests that there was no genomic inflation or any additional confounding factors. Figure 5 shows the distribution of *P* values for the association of the SNPs and priapism, summarizing the results of the GWAS. SNP rs77635018 reached genome-wide significance ($P < 5 \times 10^{-8}$), and SNPs rs116116525, rs60503510, and rs190103771 reached *P* values approximately to the threshold of genome-wide significance (Table 5). The odds ratios show a protective effect of the minor alleles against priapism. SNP rs190103771 is located in an intronic region of chromosome 3q26.31, in the *N-acetylated alpha-linked acidic dipeptidase like 2* (*NAALADL2*) gene (Figure 6). The 3 other SNPs are located on chromosome 6p21.1 in a nonintronic region that contains *long intergenic non-protein coding RNA 2537* (*LINC02537*) (Table 5).

A targeted analysis of previously reported SNPs associated with priapism in candidate gene studies using a less stringent threshold found rs3103333 to be nominally significant ($P = 2 \times 10^{-4}$; odds ratio = 0.56), suggesting some evidence of an association of priapism with the *transforming growth factor beta receptor 3* (*TGFBR3*) gene. Other previously reported SNPs did not show P values $< 10^{-3}$ and were not considered significant.

DISCUSSION

Priapism is a painful SCD complication with complex pathophysiology. This study evaluated the clinical and genetic predictors of priapism in a large cohort of Brazilian SCD patients. Older age, pulmonary hypertension, and avascular necrosis were associated with priapism. A GWAS replicated the association of 1 SNP in the *TGFBR3* gene and identified 2 previously unreported genetic markers with unclear functional significance associated with priapism. In the present cohort, priapism occurred at a lower prevalence (24.2% in adults) than the 30–45% prevalence reported in other studies.[2–5] Considering only patients younger than 18 years, the prevalence was 6.9%, which is similar to the reported prevalence of priapism in pediatric SCD populations (12%,[26] 6.9%,[38] and 3.6%[39]).

HbSS patients represented 89% of the priapism cases, consistent with other reports that identified HbSS accounted for 81–87% of priapism cases.[38,40] Although HbSS patients were at the highest risk of suffering from priapism, cases were also seen in HbSβ0 (14% of HbSβ0), HbSβ+ (12% of all HbSβ+), and HbSC (3% of all HbSC) patients. Although HbSβ+ is typically considered to exhibit a milder phenotype, there is significant heterogeneity based on the type of β-thalassemia mutation and resulting amount of normal hemoglobin A produced. In this cohort, many HbSβ+ participants were known to have more severe β+mutations, which could explain the higher prevalence of priapism in our HbSβ+ participants. Cases were rarer in HbSC patients, consistent with some studies (0 out of 10 HbSC patients[5] and 3 out of 91 cases[40]), although a prevalence of 20% (16 out of 82 HbSC patients) was reported in one study of SC patients[41] and 19% (5 out of 27 HbSC patients in the study) in another.[42]

Bilirubin levels were not associated with the occurrence of priapism, although the association with biomarkers of hemolysis has been previously reported.[12,43] Priapism is assumed to be associated with hemolysis[12,43,44] as a result of the impaired bioavailability of NO, which has an important role in penile erection. During hemolysis episodes, free hemoglobin consumes NO that would be used to convert guanosine triphosphate to cyclic guanosine monophosphate to induce vasodilatation; therefore, the balance is skewed toward vasoconstriction, favoring the occurrence of priapism.[11]

Priapism is postulated to be associated with pulmonary hypertension, stroke, and leg ulcers, with hemolysis as a biomarker for these complications.[44] Although we replicated the finding of pulmonary hypertension, leg ulcers and stroke were not associated with priapism in our analysis. In addition, avascular necrosis, which has been postulated to be related to blood-viscosity and vaso-occlusion and therefore is more common in SCD patients with higher hemoglobin/lower hemolysis,[11,42,45] was associated with priapism in this cohort.

Twenty-eight percent of the priapism episodes during the follow-up period were not treated. Some of these may have resolved prior to presenting for medical care, as 81% of the untreated episodes lasted for only 1 or 2 hours. Among the patients that were treated, the majority received conservative treatments, and urologic procedures were rarely performed, consistent with other literature reporting on priapism treatment.[46] Even though intravenous hydration and oxygen supplementation are commonly applied to treat priapism, these treatments were not frequently described in the medical records and are not listed here. There was heterogeneity among treatments, reflecting the lack of consensus in standard treatment strategies for priapism in SCD.

Recent studies suggest that priapism is mainly associated with disruption of the endothelium-derived NO signaling and phosphodiesterase 5 (PDE_5) pathways and an excess of adenosine, as well as disruption of the RhoA/ROCK pathway and opiorphin upregulation.[13–22] Alterations in NO/PDE_5 pathways would result in priapism, as the pathways play important roles in the erection control mechanisms.[10,47,48] Adenosine is a potent vasodilator, and adenosine signaling is part of a regulatory control of signal transduction systems interacting with the PDE_5 pathway.[15,49–51] ROCK is a vasoconstrictor factor involved in endothelial NO synthase regulation, and the RhoA/ROCK pathway alters erectile function.[20,21,52–54] Ophiorphins are pentapeptides associated with erectile function,[55,56] and enhanced activation and expression of these peptides can cause smooth muscle relaxation.[57] However, the genomic regions identified by our GWAS as significantly associated with priapism in SCD patients were related to different pathways.

We identified four SNPs significantly associated with priapism in *LINC02537* and *NAALADL2*. *LINC02537* is a long intergenic non-protein coding RNA with unknown function, previously associated with vascular endothelial growth factor phenotypic variance,[58,59] a growth factor associated with prostate cancer.[60–64] *NAALADL2* is ubiquitously expressed in the prostate, and, although its function is unknown, it has been associated with Kawasaki disease, a pediatric, autoimmune vascular disease,[65] as well as venous thromboembolism[66] and prostate carcinoma.[67] The disposition of *NAALADL2* near genes involves vascular development and maintenance,[68] suggesting a possible relationship with vascular pathways. Further studies are needed to determine the functional significance of *LINC02537* and *NAALADL2* in the occurrence of priapism.

In accordance with previous literature, our data showed that *TGFBR3* was associated with priapism. *TGFBR3* encodes a membrane proteoglycan expressed in endothelial cells that acts as a co-factor in inflammatory pathways. It is important in endothelial cell migration and transformation.[69] *TGFBR3* is also a member of the TGF-β receptor superfamily. TGF-β pathways have been correlated with risks of stroke,[70] leg ulcers,[71] bacteremia,[72] and priapism.[24] However, TGF-β pathways are also hypothesized to be related to SCD severity and survival[73]; therefore, the *TGFBR3* polymorphism could be associated with disease severity in general rather than priapism pathophysiology specifically.

CONCLUSION

We described the burden of priapism and identified clinical factors associated with priapism development in a large cohort of Brazilian SCD patients. These findings extend our understanding of the risk factors associated with priapism in SCD and identify genetic markers to be investigated in future studies to further elucidate priapism pathophysiology and to be considered as drug targets for priapism treatment.

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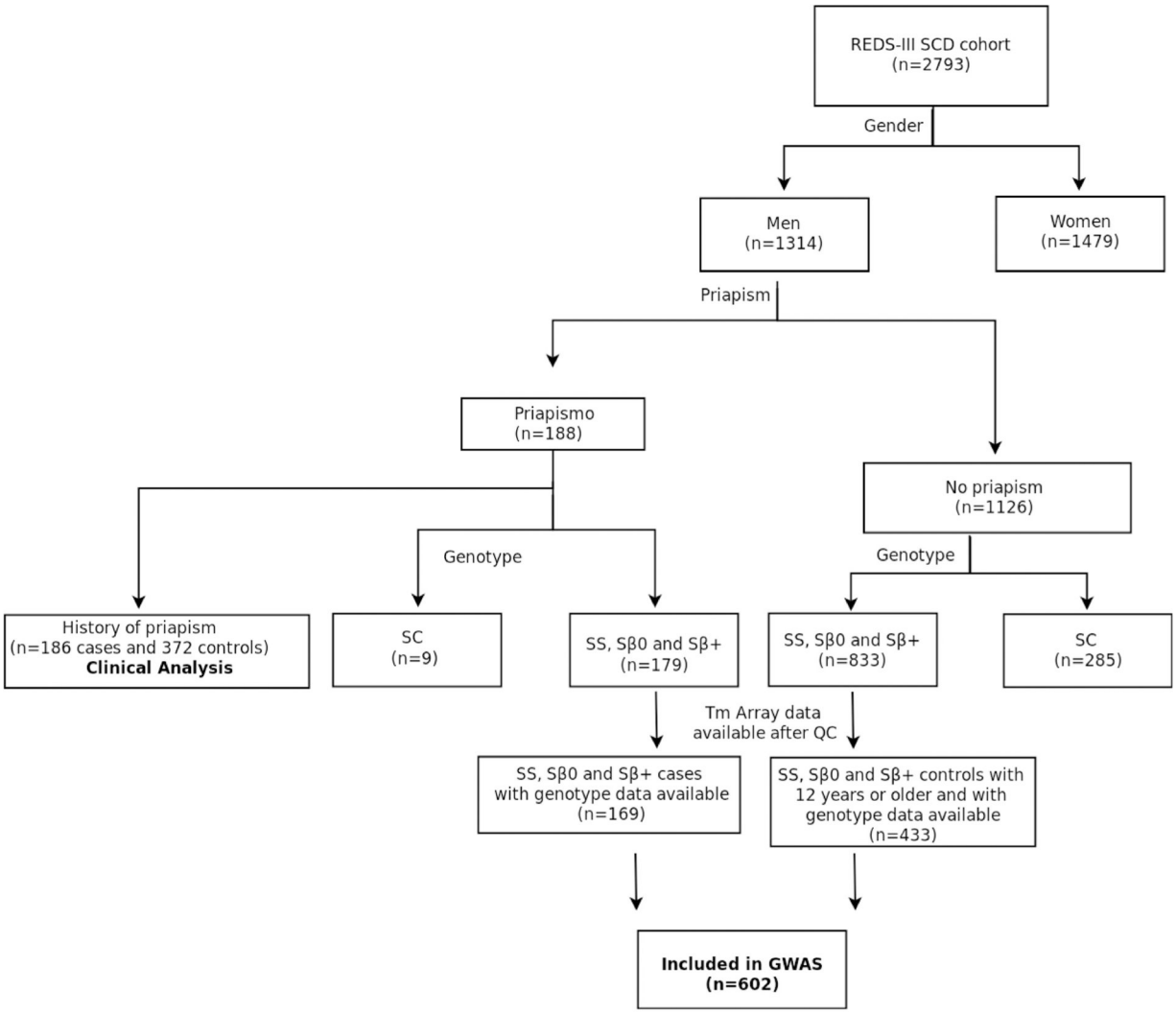

Figure 1.

Flow diagram showing the number of participants included in the REDS-III Brazil SCD Cohort and subset of participants included in the clinical and genetic priapism analyses.

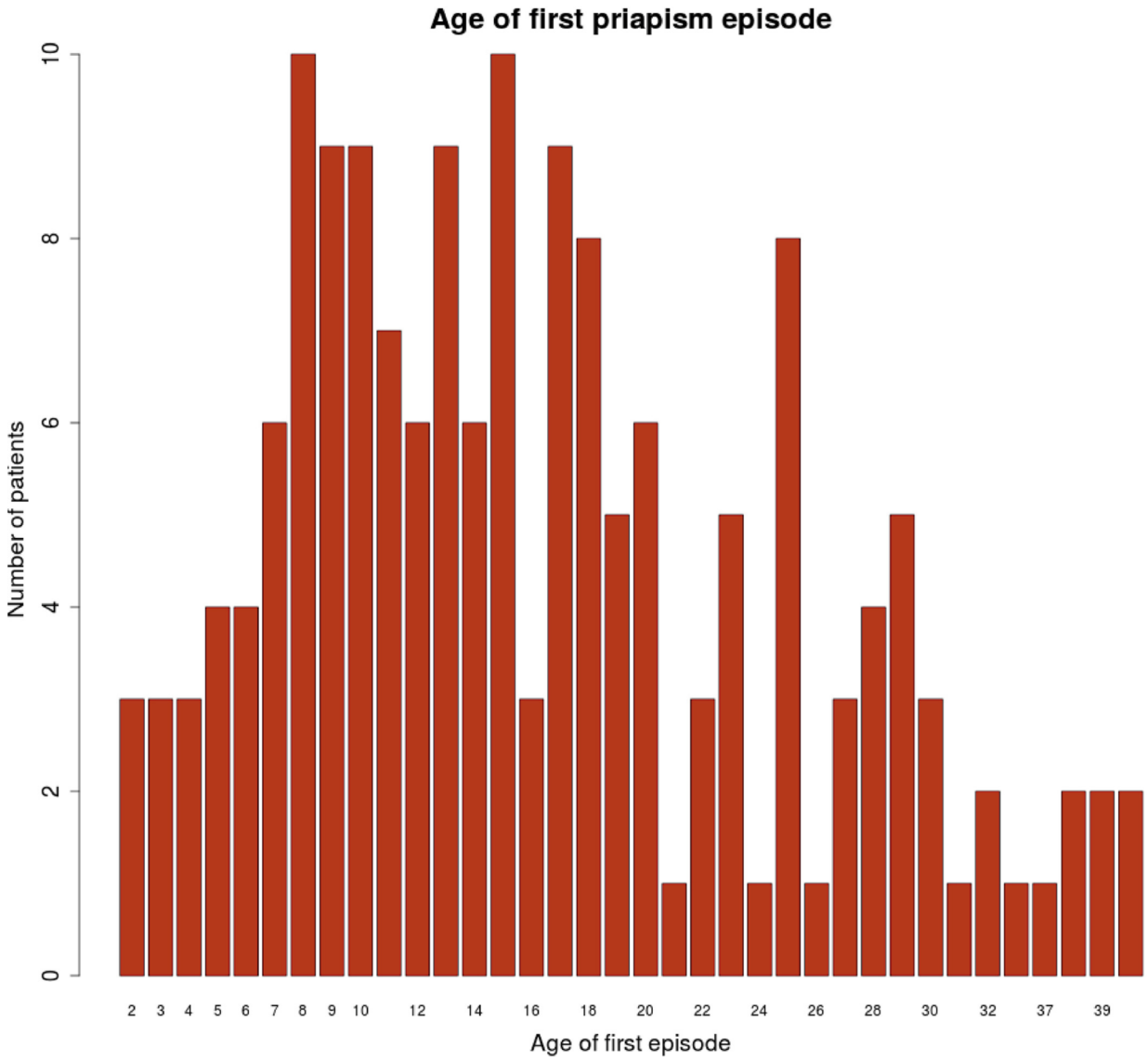

Figure 2.
Distribution of the age at first priapism occurrence among participants with priapism in the REDS III Brazil SCD cohort study.

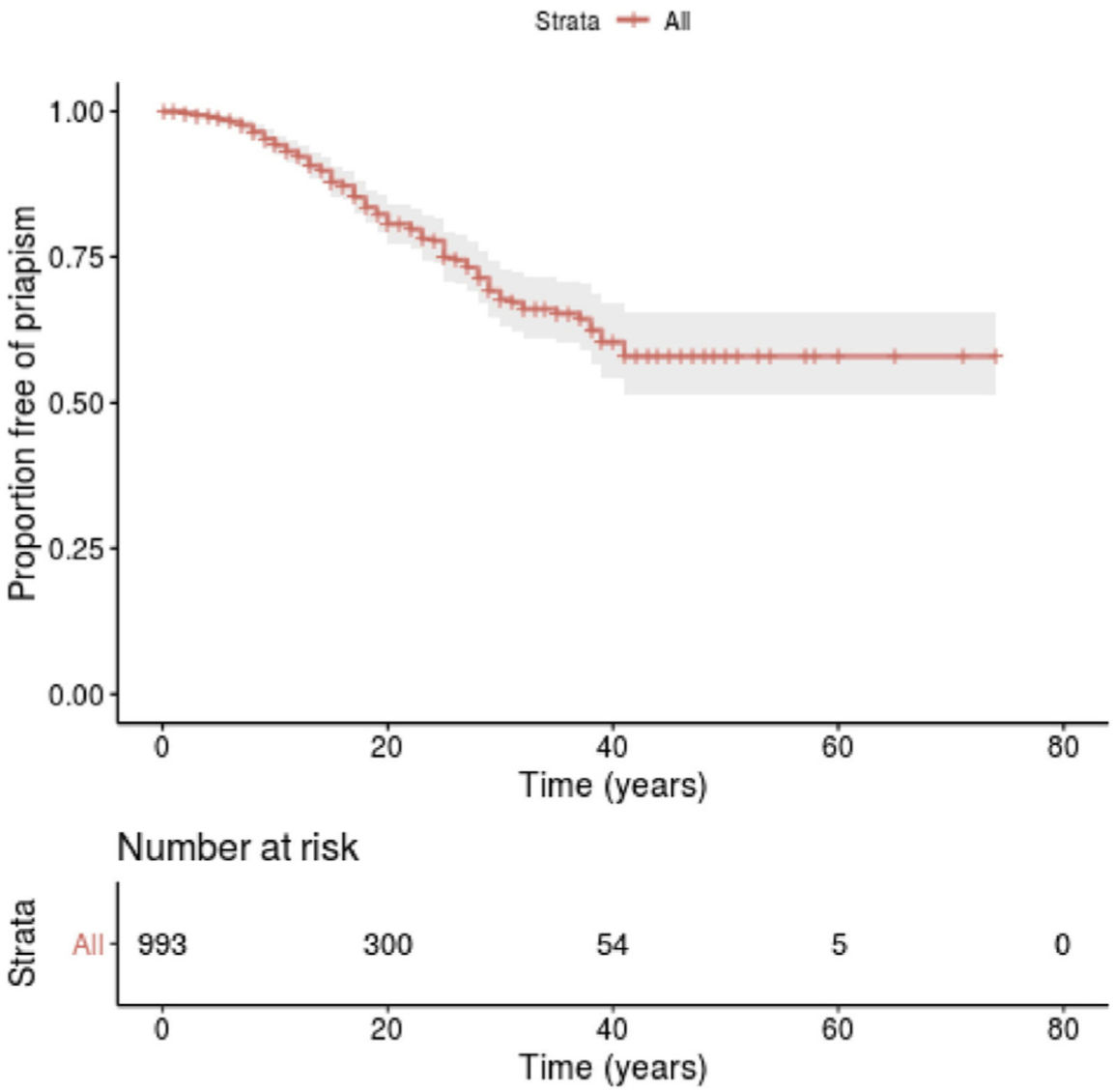

Figure 3.
Time estimates for first priapism episode with Kaplan-Meier analysis method.

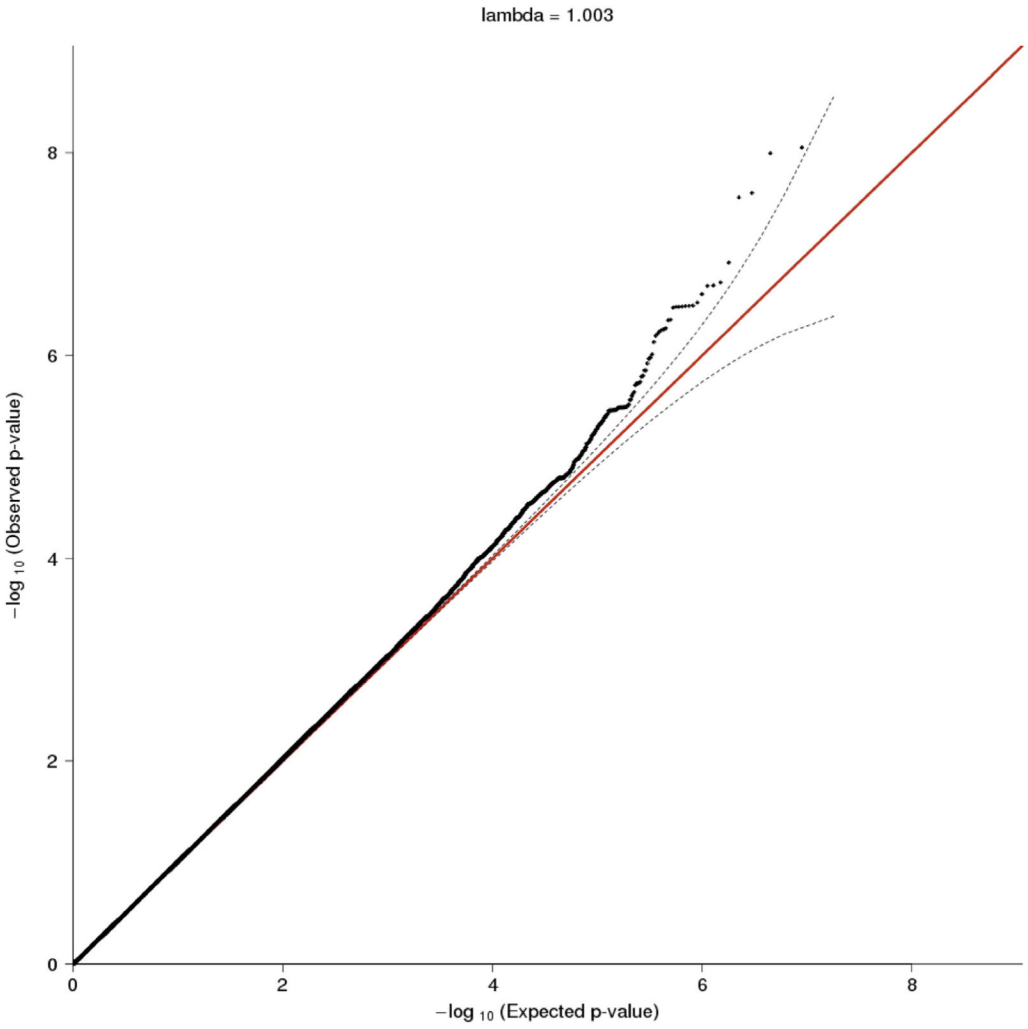

Figure 4.
Q-Q plot of the observed (y axis) versus expected (x axis) -log(P-values), REDS III SCD cohort study.

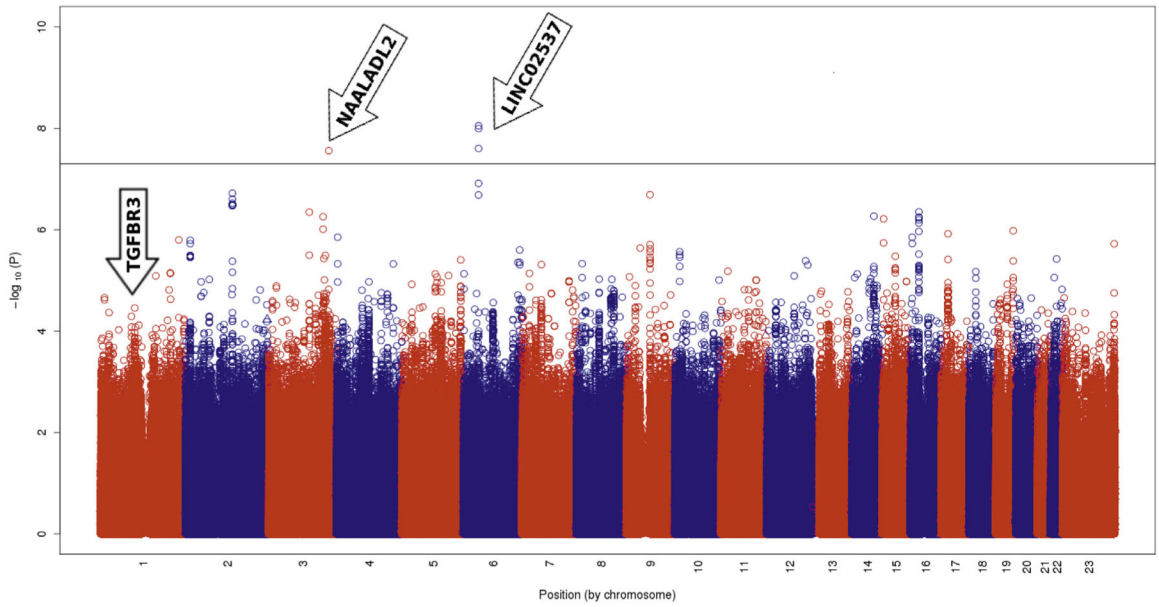

Figure 5.

Manhattan plot showing the genome wide −log 10 P-values plotted against the position on each chromosome showing the association of SNPs with priapism in the REDS-III Brazil SCD cohort study. The black horizontal line indicates genome wide significance at 5 × 10 −8.

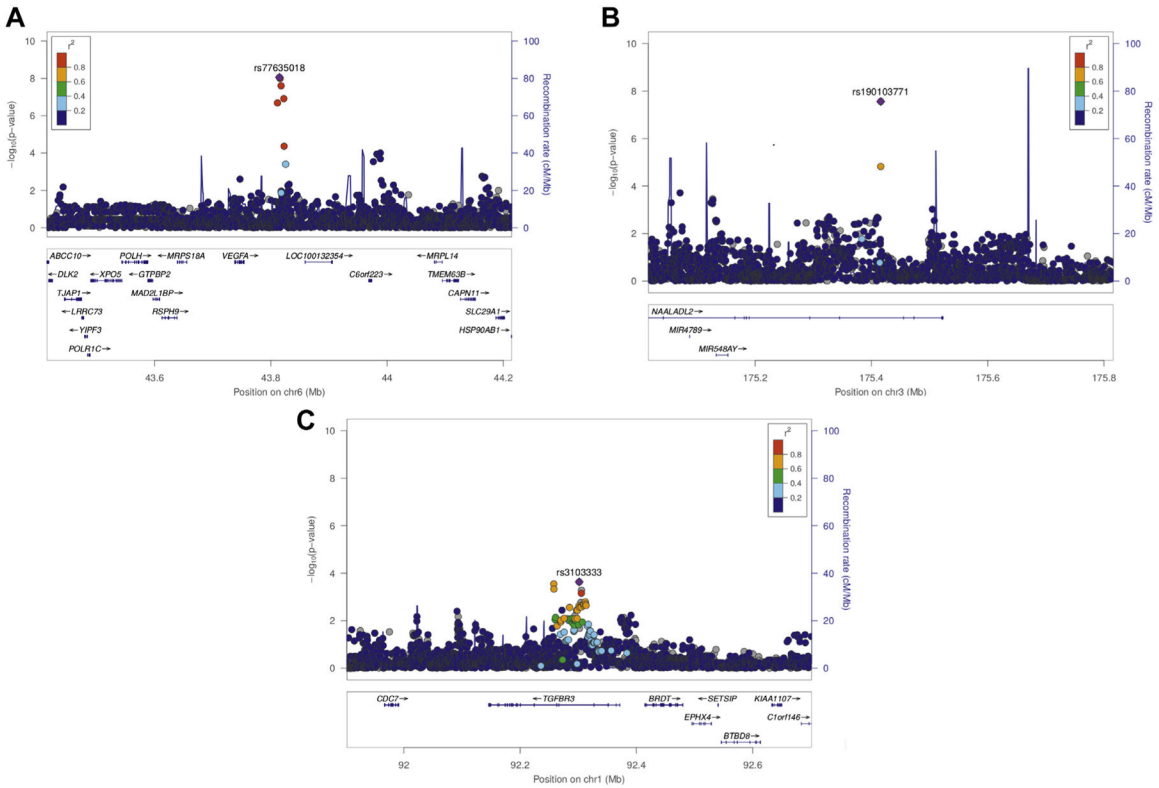

Figure 6.

Regional plot on chromosomes 6, 3 and 1. Axis y represents the negative of the logarithm of Pvalues for the association of the SNPs with priapism. SNPs are represented as dots. Axis x shows the relative positions of the SNPs in this region of the chromosome, representing the recombination rate in centimorgans (cM) per megabase (Mb). Colors coding the level of linkage disequilibrium (measured by r2) of SNPs with A) rs77635018, B) rs190103771 and C) rs3103333 represented by a purple diamond.

Table 1.

Sociodemographic characteristics of patients with and without history of priapism

Demographic	No priapism (N = 1,126) n (%)	Priapism (N = 188) n (%)	Total	*P* value
Clinical site, Brazilian city				
Hemominas, Belo Horizonte	276 (80)	67 (20)	343	.0001
Hemominas, Juiz de Fora	113 (90)	13 (10)	126	
Hemominas, Montes Claros	170 (95)	9 (5)	179	
Hemorio, Rio de Janeiro	289 (84)	54 (16)	343	
Hemope, Recife	220 (84)	41 (16)	261	
Institute of Childhood Cancer, Sao Paulo	56 (93)	4 (7)	60	
Ethnicity				
Caucasian	129 (87)	20 (13)	148	.18
Black	285 (82)	62 (18)	347	
Mixed	674 (87)	101 (13)	773	
Other	37 (88)	5 (12)	42	
Income (reais *), ≥18 y old				
<700	181 (90)	21 (10)	201	.19
701–1400	642 (86)	107 (14)	747	
1401–3000	220 (86)	37 (14)	257	
≥3000	49 (79)	13 (21)	62	
Age (y)				
0–9	360 (94)	22 (6)	382	<.0001
10–17	334 (92)	29 (8)	363	
18–29	252 (76)	79 (24)	331	
30–41	113 (73)	42 (27)	155	
42+	66 (80)	16 (20)	82	
Sickle cell disease genotype				
SS	763 (82)	168 (18)	931	<.0001
SC	286 (97)	9 (3)	295	
Sβ0	36 (86)	6 (14)	42	
Sβ+	37 (88)	5 (12)	42	

Demographic	No priapism (N = 1,126) n (%)	Priapism (N = 188) n (%)	Total	*P* value
Other[†]	3 (100%)	0 (0)	3	

[*] Exchange rate in 2014: 1 BRL = 0.43 USD.

[†] Includes 1 SD, 1 S/HPFH, and 1 S/K-Woolwich.

Table 2.

Clinical characteristics of patients with priapism and patients matched on age and *HBB* genotype without history of priapism

	No priapism (N = 372)		Priapism (N = 186)		
Variable	**Mean/median**	**Range**	**Mean/median**	**Range**	***P* value**
Reticulocyte (%)	10.15/9.5	1–25.8	10.36/9.77	0.8–26.2	.66
Total bilirubin (mg/dL)	1.76/1.35	0.12–15.21	1.75/1.37	0.13–12.37	.86
HbF (%)	10.9/6.95	0.1–45	11.3/8.9	0.1–42	.36
Indirect bilirubin (mg/dL)	1.2/0.87	0–12.11	1.26/0.87	0.02–11.29	.73
Leukocyte (/mm^3)	11,218/10,810	2,370–28,800	10,664.06/10,200	3,560–23,700	.11
Hemoglobin (g/dL)	8.82/8.6	3.52–15.9	9.04/8.98	4.86–15.7	.11
Platelet count (10^3/mm^3)	397/387	82–999	396/373	89.8–930	.94

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Table 3.

Clinical complications of patients with priapism and patients matched on age and *HBB* genotype without history of priapism

Complication	No priapism (N = 372) n (%)	Priapism (N = 186) n (%)	Total	*P* value
Pulmonary hypertension	33 (9)	28 (15)	61	.05
Leg ulcers	66 (18)	31 (17)	97	.83
Vaso-occlusive pain episodes	348 (94)	176 (95)	524	.84
Acute chest syndrome	262 (72)	146 (80)	408	.07
Avascular necrosis	42 (11)	36 (19)	78	.01
Ischemic stroke	39 (10)	17 (9)	56	.74

Table 4.

Priapism recurrences between visits

Priapism episodes	**n (%)**
Number of episodes during follow-up	
1	21 (57)
2	11 (30)
3	3 (8)
4	0 (0)
5	1 (2.5)
6	1 (2.5)
Duration (h)	
1	10 (16)
2	6 (9.5)
3	11 (17.5)
4	2 (3)
6	6 (9.5)
Unknown	28 (44.5)
Stuttering priapism	
Yes	8 (13)
No	31 (49)
Unknown	24 (38)
Treatment *	
Transfusion	18 (28.5)
No treatment	18 (28.5)
Cavernous aspiration	11 (17.5)
Finasteride	8 (13)
Analgesics	8 (13)
Hydroxyurea	1 (1.5)

* Most of the patients were treated with a combination of different treatments. Additionally, 3 patients were treated with undescribed medicine, 1 with hydration, and 1 with estrogen.

Table 5.

SNPs associated with priapism with genome-wide significance ($P < 10^{-8}$)

Chromosome	SNP	Locus	*P* value	Odds ratio
6	rs77635018	Long intergenic non-protein coding RNA 2537 (LINC02537)	8.9×10^{-9}	0.22
6	rs116116525	Long intergenic non-protein coding RNA 2537 (LINC02537)	1×10^{-8}	0.22
6	rs60503510	Long intergenic non-protein coding RNA 2537 (LINC02537)	2.5×10^{-8}	0.25
3	rs190103771	*N*-acetylated-alpha-linked acidic dipeptidase-like 2 (NAALADL2)	2.8×10^{-8}	0.3