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Abstract: Adult height is a highly heritable trait involving multipe genes. Recent genome-wide association studies have identified that SNP rs12338076 in the LHX3-QSOX2 locus, and rs1457595 and rs17032362 in the IGF1 locus are associated with human height in the Japanese population (Okada et al. Hum Mol Genet 2010; 19:2303-12). We performed a replication study to examine the associations between these 3 SNPs and adult height in the Japanese population based on autopsy cases. However, it was not possible to confirm that all these SNPs influenced adult height in the study population. We first conducted a wide-ranging survey of these 3 SNPs in the above genes using 9 different populations including Asians, Africans and Caucasians, and demonstrated that the genotypes of rs12338076 and rs17032362 were distributed in an ethnicity-dependent manner; even within Asian populations, the genotype distributions of the SNPs differed widely. Although there are differences in height distribution between different populations, possibly due to genetic factors and/or gene-environmental interactions, the contradictory results of the association study and ethnic differences in genotype distribution allow us to assume that these height-related SNPs in the genes may contribute to adult height to a slight extent, at least in the Japanese population. It is anticipated that the present information will be useful for developing a reliable tool for personal identification through elucidation of the genetic basis of human height.

27 October 2011

To: Dr. N. Ikeda
Editor-in-Chief
Legal Medicine

Dear Dr. N. Ikeda

Please find the manuscript entitled "**Replication study of the association of SNPs in the LHX3-QSOX2 and IGF1 loci with adult height in the Japanese population; wide-ranging comparison of each SNP genotype distribution**"

We would be most grateful if the manuscript could be reviewed and considered for publication in *Legal Medicine* as Brief Communication.

Each of us has made a significant contribution to the design, execution, analysis and writing up of this study. All the authors and authorities in the institute have approved submission of this manuscript. We swear that materials have not been previously reported, and that it is not consideration for publication elsewhere.

We look forward to your favorable response.

Sincerely yours,

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(Brief communication)

Replication study of the association of SNPs in the *LHX3-QSOX2* and *IGF1* loci with adult height in the Japanese population; wide-ranging comparison of each SNP genotype distribution

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(Abstract)

Adult height is a highly heritable trait involving multipe genes. Recent genome-wide association studies have identified that SNP rs12338076 in the *LHX3-QSOX2* locus, and rs1457595 and rs17032362 in the *IGF1* locus are associated with human height in the Japanese population (Okada et al. Hum Mol Genet 2010; 19:2303–12). We performed a replication study to examine the associations between these 3 SNPs and adult height in the Japanese population based on autopsy cases. However, it was not possible to confirm that all these SNPs influenced adult height in the study population. We first conducted a wide-ranging survey of these 3 SNPs in the above genes using 9 different populations including Asians, Africans and Caucasians, and demonstrated that the genotypes of rs12338076 and rs17032362 were distributed in an ethnicity-dependent manner; even within Asian populations, the genotype distributions of the SNPs differed widely. Although there are differences in height distribution between different populations, possibly due to genetic factors and/or gene-environmental interactions, the contradictory results of the association study and ethnic differences in genotype distribution allow us to assume that these height-related SNPs in the genes may contribute to adult height to a slight extent, at least in the Japanese population. It is anticipated that the present information will be useful for developing a reliable tool for personal identification through elucidation of the genetic basis of human height.

Key words: Ethnic difference/Height /IGF1/LHX3-QSOX2 / Personal identification/SNPs

1. Introduction

In crime cases with no known suspect and no DNA database match, information on externally visible traits such as gender, eye and hair color, and height provided by DNA-based investigations would be valuable for forensic personal identification [1]. Among them, height is under strong genetic influence, with an estimated heritability of up to 80-90% [2, 3]. Recent genome-wide association studies conducted using single nucleotide polymorphisms (SNPs) have revealed many genetic loci responsible for human height: approximately 50 genetic variants [4-6]. Among height-related genes, 3SNPs (rs1047275, rs7868682, and rs7968902) in the high mobility group-A2 (HMGA2) gene have been shown to be associated with height in Caucasians [7]. Furthermore, we have confirmed the association between rs1042725 in *HMGA2* and adult height in Japanese autopsy cases [8]. Recently, Okada et al. have demonstrated that SNP rs12338076 in the LIM homeobox 3 (*LHX3*)-quiescin Q6 sulfhydryl oxidase 2 (*QSOX2*) locus, and rs1457595 and rs17032362 in the insulin-like growth factor 1 (*IGF1*) locus significantly influence adult height in Japanese subjects [9]. However, replication studies of genetic associations in independent populations, even those belonging to the same ethnic group, are indispensable for evaluating the role of related genes in complex traits such as height [7].

In this context, the first aim of the present study was to examine whether 3 SNPs, rs12338076 in *LHX3-QSOX2*, and rs1457595 and rs17032362 in *IGF1*, could be associated with adult height in Japanese autopsy samples as a replication study. As genetic and environmental backgrounds for height vary between different ethnic groups, our second aim was to clarify whether the distributions of the SNPs vary among different populations, and therefore we performed a wide-ranging population study of these 3 SNPs in 9 different populations, including Asians, Africans and Caucasians.

2. Materials and methods

2.1. Biological samples

Genomic DNA was extracted from blood or bloodstain using a QIAamp DNA mini kit (QIAGEN Inc., Chatsworth, CA) according to the manufacture's instruction. Samples collected randomly from healthy and unrelated subjects derived from 8 different populations: 251 Koreans (Seoul, Korea), 36 Mongolians (Ulaanbaatar, Mongolia), 70 Tibetans (Katmandu, Nepal), 31Sinhalese (Kandy, Sri Lanka), 71 Germans (Munchen, Germany), 210 Turks (Adana area, Turk), 41 Ovambos (Bantus, Namibia), and 41 Xhosas (Cape Town of South Africa). The study including usage of genomic DNA derived from autopsy cases was reviewed and approved by the Human Ethics Committee of Shimane University School of Medicine. This study was explained in writing to participants and written consent was obtained; since a part of participants had been without informed consent, usage of them as anonymous samples was approved by Ethics Committee of the Kurume University.

The height of 102 Japanese subjects (65 male and 35 female; mean age 57.5 years; mean height 160.1 cm) autopsied in Shimane prefecture was measured. Subjects less than 18 year old were excluded. Genomic DNA was extracted from blood samples of these subjects collected at autopsy using a QIAamp DNA mini kit.

2.2. SNP typing

In this study, all 3 SNPs were analyzed by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis [10]. Among them, we used a mismatched PCR-amplification method for genotyping SNPs (rs1457595 and rs17032362) [11]. Incorporation of a deliberate mismatch close to the 3'-terminus of a PCR primer allowed the creation of each enzyme recognition site. Primers for the specific amplification of the DNA fragments encompassing a substitution site corresponding to the SNPs were newly designed on the basis of the nucleotide sequence of the LHX3-QSOX2 (NM_181701) and IGF1 (AY260957) genes; the following primer sets were used: 12338076-F, CTTCCCGTAGATCTTGGTACAAGGTGGC, and 12338076-R, CCTCCCAAAGTGCTAGGATTACAGGCGTGA, for rs12338076; 1457595-R,

GGAGGTTGATAGAGTAGG, and 1457595-R, GCTGTGTTGGTTGGCTGGCAAATGATCGT, for rs1457595; 17032362-F, CCAAATACAGCCAACAGCAACTTC, and 17032362-R, TACGTGGCATTGGCTTAGGAGCCTG, for rs17032362. The underlined residues indicate the mismatched nucleotide. Amplification was performed in a 25-μl reaction mixture using approximately 2 ng of DNA. The reaction mixture contained a buffer (15 mM Tris-HCl, pH 8.0, 50 mM KCl), 1.5 mM $MgCl_2$, 0.5 μM of each primer, 200 μM dNTPs, and 1.25 U of Taq polymerase (AmpliTaq Gold; Applied Biosystems, Foster City, CA). Two μl of the PCR product obtained using each pair of primers was digested with each enzyme (New England Biolabs, Ipswich, MA, USA): *Hha I* for rs12338076, *Hpy188III* for rs1457595 and rs17032362 according to the manufacture's instruction. The digests were separated in an 8% polyacrylamide gel, and the patterns on the gels were visualized by silver staining as described previously [8]. Nucleotide sequences of the representative subjects were confirmed by direct sequencing of the PCR products in which a substitution site corresponding to each SNP was included; the dideoxy chain-terminating method with the BigDye®Terminator Cycle Sequencing kit was employed using a Genetic Analyzer 310 (Applied Biosystems) according to the manufacture's instruction.

2.3. Statistical analysis

χ^2 -analysis was performed to evaluate the Hardy-Weinberg equilibrium. Single regression analysis was used to compare adult height among different genotypes using the program STATCEL2 (OMS Publishing, Inc.). Differences at $p<0.01$ were considered to be statistically significant.

3. Results and discussion

A DNA fragment containing a substitution site at each SNP position in *LHX3-QSOX2* and *IGF1* was separately amplified using a set of primers and subjected to digestion with each

enzyme. In rs12338076, the product amplified from the A-allele was completely digested with *Hha I* to yield fragments of 149 and 37 bp, whereas that from the G-allele yielded neither of these fragments. The same procedure was employed for the other 2 SNPs. The validity of the genotyping results obtained by these methods was confirmed by sequencing analyses of genomic DNA derived from several representative subjects.

First, in order to evaluate the association of the SNPs, rs12338076 in *LHX3-QSOX2*, and rs1457595 and rs17032362 in *IGF1*, with adult height variation, we examined both the genotype of each SNP and height in autopsied Japanese subjects (n = 102). As shown in Fig. 1, no significant association between the genotypes in each SNP and height was found. Furthermore, linear regression analysis assuming an additive inheritance model also demonstrated no significant association of any of the 3 SNPs with height. Therefore, these findings allow us to conclude that all of the SNPs, rs12338076 in *LHX3-QSOX2*, and rs1457595 and rs17032362 in *IGF1*, did not influence adult height in the Japanese population examined.

Next, worldwide distribution analysis of the 3 SNPs (rs12338076, rs1457595 and rs17032362) was performed in 5 Asian, 2 African and 2 Caucasian populations. The genotype distributions and the allele frequencies determined in this study are summarized in Table 1. These genotype distributions were in Hardy-Weinberg equilibrium in all the populations examined. In the SNP rs12338076 (*LHX3-QSOX2*), the C-allele was predominant in African populations, and showed the highest frequency. In contrast, the A-allele was predominant in Caucasian and Asian populations. The C-allele of the SNP rs1457595 (*IGF1*) was predominant in all of the populations; the minor A-allele was not found in Germans. In the SNP rs17032362 (*IGF1*), the G-allele was not observed in Caucasian and African populations, being mono-allelic. Among Asian populations, the G-allele was predominant. Therefore, among the 3 SNPs, rs12338076 and rs17032362 were confirmed to show an ethnicity-dependent pattern in its genotype distribution. Furthermore, these findings indicate that Asians exhibit wide genetic diversity with regard to the 3 SNPs

among different populations. In contrast, 3 SNPs (rs1042725, rs7968902 and rs7868682) in the HMGA2 gene related to adult height showed a similar genotype distribution among Asian populations, including the same ones examined in this study [8]. Also, the genotype distributions of each of the 3 SNPs in this study were found to be consistent with those of HapMap studies (data not shown).

Okada et al. have reported a novel association of *LHX3-QSOX2* loci with height in the Japanese population [9]. They have also demonstrated an association of the *IGF1* locus with height. The LHX3, together with LHX4, is a homeodomain transcription factor playing essential roles in pituitary gland and nerve system development. Mutations in the LHX3 and LHX4 genes have been identified in patients with complex and variable syndromes involving short stature, and with combined pituitary hormone deficiency diseases [12]. IGF1 belongs to a family of proteins involved in growth and development, and especially mediates several growth-promoting effects of growth hormones [13, 14]. With regard to association of the *IGF1* locus with height, similar results have been replicated in a Korean population [15]. In contrast, no significant association between IGF1 polymorphism and adult height was found in Caucasians [16-22]. In the present study, we were unable to confirm a significant association of all of the 3 SNPs, rs12338076 in *LHX3-QSOX2*, and rs2457595 and rs17032362 in *IGF1*, with adult height in our study population. Contradictory results derived from different populations, even those belonging to the same ethnic group, might be attributable to differences in the effect size of SNPs among populations, differing frequencies of the causative alleles, study population sample size, or gene-gene or gene-environment interactions. The present study is the first to have conducted a worldwide population survey of height-related SNPs in the *LHX3-QSOX2* and *IGF1* loci. For rs17032362 in *IGF1* loci, the G-allele was not observed in Caucasian or African populations. Even within Asian populations, the genotype distributions of the 3 SNPs (rs12338076, rs1457595 and rs17032362) were different. Although there are differences in the distribution of height between different populations, possibly due to genetic factors and/or gene-environmental

interactions, these findings allow us to assume that these height-related SNPs in the above genes may influence adult height to a slight extent, at least in the Japanese population.

From a forensic perspective, the effective use of short tandem repeats has made it possible to perform personal identification with extremely high accuracy. However, in order to perform this type of identification, control DNA samples from the individuals concerned are indispensable. In this context, DNA markers associated with physical traits such as eye, hair and skin color, or height, have a distinct advantage in that control DNA samples are not required, making it possible to narrow down and group individuals with connections to forensic scenarios. It is plausible that SNPs associated with height would be applicable as one such type of DNA marker. In order to apply height-related SNPs for forensic personal identification in a practical setting, cumulative investigations of the genetic background of human height will be required. Therefore, it is anticipated that the present findings will provide information useful for developing a reliable tool for personal identification through elucidation of the genetic basis of human height.

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(Figure legend)

Fig. 1. Comparison of height among Japanese autopsied subjects with different gentotypes of 3 SNPs, rs12338076 in *LHX3-QSOX2*, and rs2457595 and rs17032362 in *IGF1*. The height is expressed as mean ± standard deviation; the bar represents the standard deviation. P-values were calculated by single regression analysis.

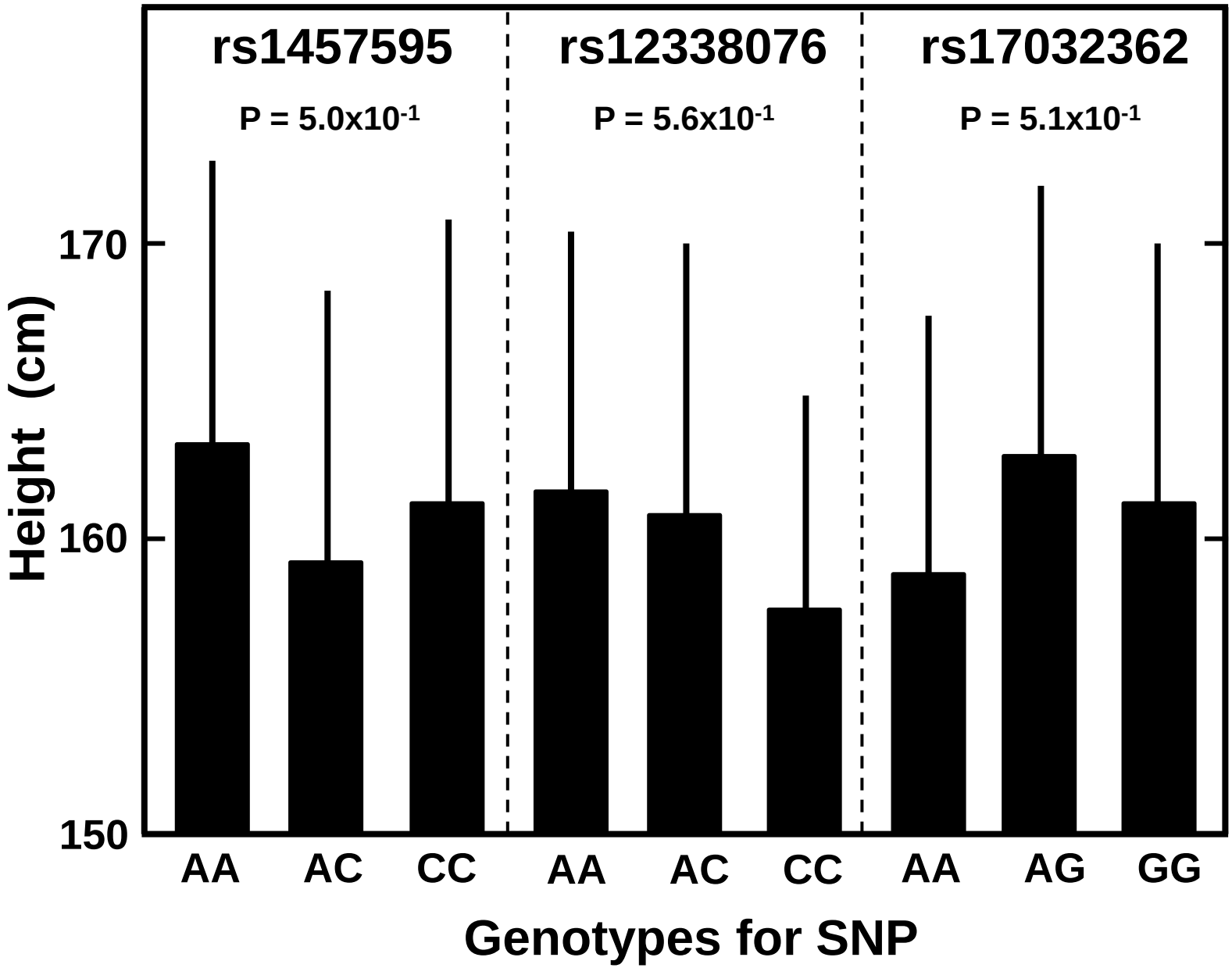
Table(s)

Table 1

Genotype distribution and allele frequencies (95% CI) of SNPs of *IGF1* and **L***HX3-QSOX2*

Population	rs12338076				rs1457595				rs17032362			
	Genotype, *n* (%)		Allele frequency		Genotype, *n* (%)		Allele frequency		Genotype, *n* (%)		Allele frequency	
Japanese	CC	7 (6.9)	C	0.275	CC	77 (75.5)	C	0.853	AA	18 (17.6)	A	0.324
(*n* = 102)	CA	42 (41.1)		(0.214 - 0.336)	CA	20 (19.6)		(0.804 - 0.902)	AG	30 (29.4)		(0.260 - 0.388)
	AA	53 (52.0)	A	0.725	AA	5 (4.9)	A	0.147	GG	54 (53.0)	G	0.676
				(0.664-0.786)				(0.098 - 0.196)				(0.612 - 0.740)
Korean	CC	34 (13.6)	C	0.365	CC	182 (72.5)	C	0.837	AA	41 (16.3)	A	0.311
(*n* = 251)	CA	115 (45.8)		(0.323 - 0.407)	CA	56 (22.3)		(0.805 - 0.869)	AG	74 (29.5)		(0.271 - 0.351)
	AA	102 (40.6)	A	0.635	AA	13 (5.2)	A	0.163	GG	136 (54.2)	G	0.689
				(0.593 - 0.677)				(0.131 - 0.195)				(0.649 - 0.729)
Mongolians	CC	5 (13.9)	C	0.375	CC	20(55.6)	C	0.708	AA	1 (2.8)	A	0.097
(*n* = 36)	CA	17 (47.2)		(0.263 - 0.487)	CA	11 (30.6)		(0.603 – 0.813	AG	5 (13.9)		(0.029 - 0.165)
	AA	14 (38.9)	A	0.625	AA	5 (13.9)	A	0.292	GG	30 (83.3)	G	0.903
				(0.513- 0.737)				(0.187 – 0.397)				(0.835 - 0.971)
Tibetans	CC	4 (5.7)	C	0.207	CC	47 (67.1)	C	0.779	AA	15 (21.4)	A	0.413
(*n* = 70)	CA	21 (30.0)		(0.113 - 0.301)	CA	15 (21.4)		(0.683 - 0.875)	AG	29 (37.2)		(0.299 - 0.527)
	AA	45 (54.3)	A	0.793	AA	8 (11.4)	A	0.221	GG	26 (41.4)	G	0.587
				(0.699 - 0.887)				(0.125 - 0.317)				(0.473 - 0.701)
SriLanka Shinhalese	CC	1 (3.2)	C	0.097	CC	21 (67.7)	C	0.742	AA	2 (6.5)	A	0.258
(*n* = 31)	CA	4 (12.9)		(0.023 - 0.171)	CA	4 (12.9)		(0.633 - 0.851)	AG	12 (38.7)		(0.149 - 0.367)
	AA	26 (83.9)	A	0.903	AA	6(19.4)	A	0.258	GG	17 (54.8)	G	0.742
				(0.829 - 0.977)				(0.149 - 0.367)				(0.633 - 0.851)
German	CC	5 (7.0)	C	0.239	CC	71(100)		1.000	AA	71(100)		1.000
(*n* = 71)	CA	24 (33.8)		(0.169-0.309)	CA	0 (0)			AG	0 (0)		
	AA	42 (59.2)	A	0.761	AA	0 (0)		0.000	GG	0 (0)		0.000
				(0.691-0.831)								
Turks	CC	26 (12.4)	C	0.350	CC	202 (96.2)	C	0.981	AA	210 (100)	A	1.000
(*n* = 210)	CA	95 (45.2)		(0.304 - 0.396)	CA	8 (3.8)		(0.968 - 0.994)	AG	0 (0)		
	AA	89 (42.4)	A	0.650	AA	0 (0.0)	A	0.019	GG	0 (0)	G	0.000
				(0.604 - 0.696)				(0.006 - 0.032)				
Ovambos	CC	29 (70.7)	C	0.817	CC	37 (90.2)	C	0.951	AA	41 (100)	A	1.000
(*n* = 41)	CA	9 (22.0)		(0.733-0.901)	CA	4 (9.8)		(0.905 - 0.997)	AG	0 (0)		
	AA	3 (7.3)	A	0.183	AA	0 (0.0)	A	0.048	GG	0 (0)	G	0.000
				(0.099-0.267)				(0.002 - 0.094)				
Xhosans	CC	32 (78.1)	C	0.878	CC	18 (43.9)	C	0.659	AA	41 (100)	A	1.000
(*n* = 41)	CA	8 (19.5)		(0.807-0.949)	CA	18 (43.9)		(0.556 - 0.762)	AG	0 (0)		
	AA	1 (2.4)	A	0.122	AA	5 (12.2)	A	0.341	GG	0 (0)	G	0.000
				(0.051 - 0.193)				(0.238 - 0.444)				

Figure(s)


rs1457595
P = 5.0x10-1
rs12338076
P = 5.6x10-1
rs17032362
P = 5.1x10-1
Height (cm)
170
160
150
AA
AC
CC
AA
AC
CC
AA
AG
GG
Genotypes for SNP