Abstract

Objective: Height variability is largely under genetic control, although identifying the genetic variants involved has been until recently challenging. Smallness for gestational age (SGA) is a risk factor for adult short stature. Genome-wide association studies have identified a single nucleotide polymorphism (SNP) (rs1042725) in the high mobility group A2 gene (HMGA2) that consistently associates with height variability but its interaction with SGA is unknown.

Design: We assess the contribution of rs1042725 SNP and height variability in a French population and the impact of rs1042725 on SGA status at birth and height at adulthood in SGA individuals.

Methods: We genotyped rs1042725 in 4710 healthy participants from the Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) cohort, 743 normal birth weight and 660 SGA individuals from the Haguenau study.

Results: rs1042725 is associated with increased height in the cohort participants (0.36 cm 95% CI (0.12–0.61) per C allele, P = 0.004) but not with the SGA status or birth length. Interestingly, rs1042725 had a stronger effect on height in SGA participants (0.94 cm 95% CI (0.24–1.64) per C allele, P = 0.009), especially in men (1.45 cm 95% CI (0.44–2.46) per C allele, P = 0.005) in whom rs1042725 may explain 3% of height variability. SGA men carrying at least one C allele copy experienced more frequent catch-up in height (Padd = 0.07; Pdom = 0.03).

Conclusions: Our study supports further the contribution of HMGA2 rs1042725 to height variability in European populations and shows an increased effect on height in SGA individuals where this variant favors height catch-up.

Introduction

Height is a complex genetic quantitative trait. Despite presenting the largest heritability ever estimated for a genetic complex trait (up to 98% between dizygotic twins) (1), identification of genetic variants that influence population variability of height has been a challenge for a long time. Genetic linkage studies of height in large numbers of population-based sibling pairs have pointed at several putative quantitative trait loci for height (1, 2). Some (3) but not all (4) association studies were successful in biological candidate genes, such as the ones belonging to the insulin-like growth factor-I signaling pathway. Genome-wide association (GWA) studies have recently allowed the analyses of hundreds of thousands of single nucleotide polymorphisms (SNPs) in large populations (5, 6). Hence, in a recent GWA study, a SNP located near the high-mobility group at hook 2 (HMGA2) gene showed highly significant and consistently replicated associations with height in an overall sample of 29 098 individuals (7). The rs4725 variant, a highly frequent transition from T to C (minor allele frequency = 0.46) located in the 3’ untranslated region of the HMGA2, may explain ~0.3% population variation in height, which corresponds to ~0.4 centimeter increase of height per copy of the C allele (7). The aim of this study is to assess the association of rs1042725 of HMGA2 in a French general population and test the effect of this genetic variant on adult height and birth anthropometric phenotypes in the context of smallness for gestational age (SGA), where we have previously shown strong adult height variability (8).
Subjects and methods

The Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) cohort

Details about the Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) cohort are provided elsewhere (9). Briefly, participants are middle aged volunteers (30–65 years) from the French national social security scheme, who were recruited at ten health examination centers in the western central region of France. Anthropometric measures, including height, were measured by trained personnel. We used baseline data collected between 1994 and 1996. Because the ethnic origin could not be legally documented at the beginning of the DESIR study, we estimated the proportion of subjects having non-European ancestry from a subgroup of 654 subjects selected in the DESIR cohort to be ~0.3% as previously described (6). In addition, to minimize ethnicity admixture, all individuals born overseas were also excluded before analyses. All subjects gave signed written consent. The DESIR cohort protocol was approved by the ethics committee of Bicêtre Hospital, Le Kremlin-Bicêtre, France.

The Haguenau study

The Haguenau study has been fully described previously (8). Briefly, subjects born between 1971 and 1985 were identified from a population-based registry in Haguenau, France. In this area, non-Caucasian subjects are estimated to be less than 0.1% of the general population (8). Only full-term singletons were included. Gestational age was determined from the date of the mother’s last menstrual period and by physical examination during pregnancy and was confirmed by ultrasound measurements when available (> 80%). Two groups were selected based on birth data compared with the French reference curves for gender and gestational age: SGA (birth weight ≤ 10th percentile) and appropriate for gestational age (AGA) (birth weight between 25th and 75th percentile). The mean birth length in SGA was –1.48 S.D. in comparison with the AGA group mean birth length. At age 22.1 ± 3.9 years, participants had a medical examination to assess anthropometric and clinical parameters; blood samples were taken for DNA extraction. Catch-up in height was defined as an adult height ≥ –2 S.D. of the mean adult height of the AGA, according to gender. The Haguenau study protocol was approved by the ethics committee of Paris-St Louis University, Paris, France.

Genotyping

We used Taqman technology (Applied Biosystems, Foster City, California, USA) to genotype rs1042725. Genotyping call rate was 99% in the Haguenau cohort and 98% in the DESIR cohort. One hundred and eighty-six DNAs were genotyped twice and rs1042725 showed 100% genotype consistency in this sample. Hardy-Weinberg equilibrium was verified in both cohorts (P > 0.12).

Statistical analyses

Height distribution did not deviate from normality in any of the populations or groups studied (Pearson χ² test for normality P values ≥ 0.06). Associations between rs1042725 and quantitative traits were tested using regression analyses under the additive model in the DESIR and SGA cohort participants. Analyses for association with height were adjusted for age and gender. Interactions between rs1042725 and gender were tested in both populations. Tests for deviation from Hardy Weinberg Equilibrium (HWE) and for association were performed by the De Finetti program (10). The effect on height catch-up was assessed using a χ² test and P values for the additive and the dominant models are shown. All analyses used the R statistical package (version 2.7.0).

Results

The association between rs1042725 and height, adjusted for gender and age is replicated in the French cohort DESIR (P = 0.004; Table 1). However, analysis stratified by gender showed that the rs1042725 allele is associated with a 0.53 cm (95% CI (0.17–0.88)) increase per C allele in height in men participants (P = 0.004), while no significant effect is observed in women (0.21 (–0.13; 0.54) (P = 0.2). However, the statistical interaction between gender and genotype is not significant (P = 0.51).

Case control analyses in 1403 unrelated individuals show no association between rs1042725 and SGA status (odds ratio = 0.90 95% CI (0.78–1.05), P = 0.19, data not shown), despite a lower prevalence of the C allele associated with increased height (frequency = 0.45 in SGA versus 0.48 in AGA). In the Haguenau cohort, rs1042725 do not associate with birth length or weight, stratified for SGA status, adjusted for gender and gestational age (data not shown). In the SGA adults, rs1042725 associate with 0.94 cm increase (95% CI (0.24–1.64)) in mean height per C allele copy (P = 0.009), with a stronger effect in men (β = 1.45 cm increase 95% CI (0.44–2.46) P = 0.005). SGA men carrying at least one C allele copy of rs1042725 show an increased height catch-up frequency at adulthood (Fdom = 0.03; Fadd = 0.07) (Fig. 1).

Discussion

Our study confirms the association between rs1042725 in HMG2 with height variability in a French general population and shows an important effect of this
women 352 0.46 161.08 (154.42; 167.45; 174.42) 0.36 (0.12; 0.61) 0.08 0.004
Men 308 0.45 173.12 (167.27; 183.25) 0.53 (0.17; 0.88) 0.3 0.004
Women 2354 0.46 169.82 (160.05; 170.34) 0.21 (−0.13; 0.54) 0.06 0.2
Haguenau SGA
Men 308 0.45 177.56 (175.94; 179.20) 0.94 (0.24; 1.64) 0.6 0.009
Women 352 0.46 159.83 (150.21; 159.94) 0.46 (−0.51; 1.44) 0.3 0.4

MAF, minor allele frequency; Coeff, regression coefficient \( \beta \) adjusted for age and gender that correspond to per C allele effect (cm) on height; Variability, proportion of height variability of height explained by rs1042725 genotypes.

We also observed a stronger effect on the height of rs1042725 in men, with no significant interactions with gender or age were found, although this needs further confirmation in larger cohorts. Similarly, no interaction was reported in the initial study of rs1042725 where a significant effect on height was also described in women (the ALSPAC mothers cohort) (7). As height variability is stronger in men than in women, and bearing in mind the sample size in our populations, our sample is probably underpowered to detect this effect in women.

Here, we did not show an association between rs1042725, neither with the SGA status nor with birth length, in agreement with the first report on HMGA2 SNP, where the effect of rs1042725 on birth length was assessed in the ALSPAC children cohort (7). In the Haguenau cohort, we have previously reported that the SGA group had a significantly smaller adult height in comparison with the AGA group, with a mean loss of 0.7 s.d. and with 89.7% of the SGA individuals having a catch-up in height at adulthood (8). Here, we report an effect of rs1042725 on the rate of catch-up in height at adulthood. It is well known that catch-up in height takes place during the first years of life and that the pubertal growth spurt has a marginal effect (11), which makes our measure a good estimate of the growth catch-up occurring in early life. In the ALSPAC cohort, there was a strong association of rs1042725 with height at age 7 years, with an increased height of 0.5 cm per C allele copy (7). In the same study, authors reported that combining all data from the children at ages 7–11 years, the overall effect was a 0.07 s.d. increase per allele (7). These observations point to an effect of rs1042725 on skeletal growth during childhood. HMGA2 codes for an architectural transcription factor that both positively and negatively regulates the transcription of a variety of genes and is up-regulated in tumors of mesenchymal origins such as lipomas. Data in mice show that hmga2-deficiency cause growth retardation (12). A chromosomal inversion that truncates HMGA2 product was described in an 8-year-old patient, with a severe overgrowth syndrome, which supports this hypothesis (13). As for HMGA2 SNP, it will also be of interest to assess the impact on height variability in the SGA condition of a series of new genetic variants that has recently become available (14–16).

Our study confirms the role of HGMA2 in the genetic determination of height, with a marked effect in the context of SGA. Our results need confirmatory replications in other SGA populations. Further physiological and molecular investigation is also required to

**Figure 1** Height catch-up at adulthood in SGA men. Height catch-up was defined as height at examination above −2 s.d. of mean height in AGA participants. \( P \) value is for \( \chi^2 \) test comparing height catch-up frequency in TT genotype carriers (\( n = 95 \)) versus CT or CC genotype carriers (\( n = 147 \) and \( n = 66 \) respectively). \( P \) values are indicated for the additive (\( P_{\text{add}} \)) and dominant (\( P_{\text{dom}} \)) models.
understand the role of HMGA2 in growth and the rs1042725 effect on HMGA2 regulation.

Declaration of interest
We declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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