Title

Genetic and environmental influences on growth from late childhood to adulthood: A longitudinal study of two Finnish twin cohorts

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ABSTRACT

Objectives: Human growth is a complex process that remains insufficiently understood. We aimed to analyze genetic and environmental influences on growth from late childhood to early adulthood.

Methods: Two cohorts of monozygotic and dizygotic (same-sex and opposite-sex) Finnish twin pairs were studied longitudinally using self-reported height at 11-12, 14, 17 years and adult age (FinnTwin12) and at 16, 17, 18 years and adult age (FinnTwin16). Univariate and multivariate variance component models for twin data were used.

Results: From childhood to adulthood, genetic differences explained 72-81% of the variation of height in boys and 65-86% in girls. Environmental factors common to co-twins explained 5-23% of the variation of height, with the residual variation explained by environmental factors unique to each twin individual. Common environmental factors affecting height were highly correlated between the analyzed ages (0.72-0.99 and 0.91-1.00 for boys and girls, respectively). Genetic (0.58-0.99 and 0.70-0.99, respectively) and unique environmental factors (0.32-0.78 and 0.54-0.82, respectively) affecting height at different ages were more weakly, but still substantially, correlated.

Conclusions: The genetic contribution to height is strong during adolescence. The high genetic correlations detected across the ages encourage further efforts to identify genes affecting growth. Common and unique environmental factors affecting height during

adolescence are also important, and further studies are necessary to identify their nature and test whether they interact with genetic factors.

KEYWORDS

Height, genetic, environment, adolescence, twins

Height is one of the most important traits defining human morphology during both the growth period and adulthood. Stature has been considered for more than 100 years as the model human polygenic trait for its ease of measurement in large population studies, normal distribution, high heritability, and relative stability in adulthood (Lettre, 2009). It is well known that childhood and adolescence are sensitive stages in the human life cycle and that life conditions during these periods are reflected in adult height. Previous studies have found that growth and adult stature are associated with cognitive ability (Silventoinen et al., 2006) and socioeconomic factors such as education (Magnusson et al., 2006). Conversely, a large body of literature has shown that adult stature is inversely associated with several metabolic outcomes in adulthood such as coronary heart disease (Paajanen et al., 2010), stroke (Song and Sung, 2008), type 2 diabetes (Asao et al., 2006), total mortality (Jousilahti et al., 2000) and directly associated with several cancers (Gunnell et al., 2001; Song and Sung, 2008).

Both genetic and environmental factors affect growth and adult stature. Growth during fetal life, childhood, and adolescence is a process under strong genetic control believed to be regulated through multiple endocrinological pathways (Malina et al., 2004). High heritability estimates of height were reported in previous twin studies, generally ranging from 0.70 to 0.90 in both childhood (Phillips and Matheny, 1990; Silventoinen et al., 2007; Silventoinen et al., 2008; Silventoinen et al., 2006) and adulthood (Silventoinen et al., 2000; Silventoinen et al., 2003b). In addition to the genetic component, height during the growth period is affected also by environmental factors, such as nutrition, psychosocial stress, chronic illness, and living circumstances (Batty et al., 2009). Some

of these environmental factors are shared by family members, while others are experiences unique to each individual. Previous studies have often (Dubois et al., 2007; Silventoinen et al., 2007) but not always (Silventoinen et al., 2008) shown that childhood family environment or other environmental factors shared by co-twins affect height in childhood and adolescence.

Although the genetics of attained height has been studied widely, little is known of the genetic regulation of growth. Few twin studies have explored changes in magnitude of genetic and environmental effects on height during childhood and adolescence; fewer still have analyzed the effect of genetic factors on growth utilizing longitudinal measures (Beunen et al., 2000; Dubois et al., 2007; Hauspie et al., 1994; Ooki and Asaka, 1993; Wilson, 1976). In an early Swedish study (Fischbein and Pedersen, 1987), genetic correlations between height at ages 10 and 15.5 were 0.92 in men and 0.75 in women, suggesting that more than 56% of the genes affecting height at these ages are common. Data from a large sample of Dutch twins showed that over 60% of the genes were common for height from age 3 to 12 years, and that common environmental correlations between these ages were also significant (Silventoinen et al., 2007). A recent study carried out in Swedish male twins found that 53% of the genes remained the same or closely linked between 2 and 18 years of age (Silventoinen et al., 2008).

A limitation of the previous studies is that none of them analyzed growth during adolescence in both boys and girls. Previous cross-sectional studies have shown no evidence of sex-specific genetic factors in height, and the taller stature in males is likely

to be due to endocrinological differences between men and women contributing to the general regulation of growth (Silventoinen, 2003; Silventoinen et al., 2001). However, in the absence of longitudinal studies providing information on opposite sex twins, the question whether sex-specific genetic effects could exist in growth patterns remains open. In this study, we aim (i) to analyze the genetic and environmental contributions to height, (ii) to determine whether these genetic and environmental factors affecting height at different ages are correlated with each other, and finally (iii) to explore the sex differences of these contributions in two independent population-based samples of Finnish twins.

MATERIALS AND METHODS

Data sources

The data were derived from two Finnish twin cohorts (FinnTwin12 and FinnTwin16) ascertained from the Population Register Centre and described in detail elsewhere (Kaprio et al., 2002). Both are longitudinal studies of behavioral development and health habits of Finnish twins enrolled at ages 11-12 or 16, respectively, and repeatedly assessed by self-report questionnaires. Data collection and analysis were approved by the ethics committee of the Department of Public Health of the University of Helsinki and the Institutional Review Board (IRB) of Indiana University. Written informed consent was obtained from all participating families. Zygosity was determined by well-validated items on physical similarity during school age. School photographs and additional information

from twins' mothers were obtained if classification was unclear. Subsets of twin pairs from the two FinnTwin studies were enrolled into laboratory protocols for which DNA was obtained and zygosity was confirmed; results for 395 same-sex pairs in FinnTwin12 confirmed questionnaire assignment of zygosity in 97% of these same-sex adolescent Finnish twins, a result validating questionnaire assignment of zygosity similar to that earlier found for adult Finnish twins (Sarna et al 1978). Persons with uncertain zygosity based on the questionnaire were removed from the analyses. Reliability of self-reported height, analyzed in sub-samples of both twin cohorts after completion of the last wave of questionnaires, was found highly correlated with measured height in FinnTwin12 (r=0.99, N=797) and FinnTwin16 (r=0.99, N=566) (Saarni et al., 2009) cohorts.

FinnTwin12 included five consecutive birth cohorts of Finnish twins born in 1983-1987, which have been assessed at 11-12, 14, 17 years and early adulthood (19-24 years). Questionnaires were mailed to twin individuals in the autumn of the year in which their birth cohort reached age 11, and 90% of the responses were received by the end of that year (mean age at response 11.4 years). Twins were sent a follow-up questionnaire in the month of their fourteenth birthday (mean age at response was 14.1 years) and the third wave follow-up was mailed at average age of 17.5 years. The last wave (mailed at average age of 22 years) was completed in 2009 for a subset of the cohort. Our final data comprised information from 2400 boys and 2314 girls, including 766 monozygotic (MZ), 780 same-sex dizygotic (SSDZ), and 749 opposite-sex dizygotic (OSDZ) complete twin pairs.

The other longitudinal cohort study (FinnTwin16) identified all twin births from 1975 to 1979 in Finland. The baseline survey questionnaire was sent during the years 1991-1995 to all Finnish twins born in 1975-1979 within two months after their 16th birthday with the response rate of 88%. Three follow-up questionnaires were sent to all persons who participated in the baseline survey. The first follow-up questionnaire was sent in the month after the 17th birthday, the second follow-up questionnaire, on average, six months after the 18th birthday and the third follow-up questionnaire at semi-annual intervals during the years 2000-2002 when the participants were, on average, 25-years-old (range 22-27 years). FinnTwin16 does not provide detailed information about pubertal growth, but inclusion of this older sample in our analysis permits us to replicate the results in another data set based on the same population. In the final data set, we had 2540 boys and 2859 girls, who formed 848 MZ, 867 SSDZ and 903 OSDZ complete twin pairs.

Statistical methods

The data were analyzed using quantitative genetic modeling for twin and family data (Neale and Cardon, 2003). The analysis is based on the fact that MZ twins share the same gene sequence, whereas DZ twins share, on average, 50% of their genes identical-by-descent. Therefore, higher resemblance within MZ twin pairs respect to DZ twin pairs would be indicative of genetic influences on the trait variability. Variance in height at each age was partitioned into additive genetic effects (A: correlated 1.0 for MZ and 0.5 for DZ pairs), common (shared) environmental effects (C: by definition, correlated 1.0

for all pairs), and unique (nonshared) environmental effects (E: uncorrelated in all pairs). In the classic twin design, estimates are based on the assumption that outcome-relevant environmental influences are shared to the same extent by MZ and DZ twin pairs. In the present study, this equal environment assumption (EEA) was tested by comparing twin models to saturated model. Measurement error is also included in the unique environmental effect.

On the basis of these assumptions, it is possible to estimate values for each of these variance components treating them as latent standardized variables in linear structural equation model. However, since our data included only twins reared together, we cannot simultaneously estimate common environmental and dominance genetic effects. Further, we need to make the assumptions of random mating and an absence of gene-environment interaction. As previously mentioned, the genetic correlation differs among MZ and DZ twins [1 and $\frac{1}{2}*(1 + \delta_{\mu}h^2)$, respectively], where δ_{μ} is selective association between the phenotypes of mates and h^2 the estimate of heritability. According to this equation, the genetic correlation between DZ twins is 0.5 if there is no selective association between the phenotypes of mates, i.e., $\delta_{\mu} = 0$. If $\delta_{\mu} > 0$, the correlation will exceed 0.5, as phenotypic assortment increases the genetic correlation among DZ twins (Reynolds et al., 1996). It is noteworthy, however, that spousal correlations can also be because of homogamic environment (S). This includes environmental factors that are common to both twins and their spouses and can be, for example, same region of residence. This does not necessarily increase genetic correlation between spouses and thus do not inflate DZ correlations. The possible effect of gene-environment interaction is estimated as part of

additive genetic component to the extent the environmental factors interacting with the genes are shared within the twin pairs. To the extent such environmental factors are not shared between co-twins, the unique environmental component will absorb the effect. When data from opposite-sex pairs are available, it is possible to test whether the same sets of genes influence variation in height in boys and girls. Furthermore the equality of components of variance in men and women can be tested. If EEA assumption is violated, it is seen as different variances in MZ and DZ twins.

The genetic models were carried out by the Mx statistical package (Neale, 2003). First, univariate models for height were fitted at each age. Equality of means and variances for MZ, SSDZ and OSDZ twins at each age were tested by comparing the fit of univariate variance components models respect to saturated models, which do not make these assumptions. This was done by comparing χ^2-goodness- of-fit statistics and degrees of freedom (d.f.) between nested models; large change in the χ^2-values compared to the change in d.f. ($\Delta\chi^2_{\text{d.f.}}$) between two nested models indicates that the simpler model does not describe the data as adequately as the more complex model and the eliminated parameters are thus important in the model. Additionally, the models were compared by computing Akaike´s information criterion (AIC) for each model. AIC allows the comparison of the goodness-of-fit between parallel, that is, non-nested, models; the model with the smallest AIC value is regarding as having the best fit.

We continued the analyses by studying the associations within all analyzed ages for both cohorts using multivariate correlation model based on reparametrization of Cholesky

decomposition. This procedure makes no assumptions on the underlying genetic architecture, but simply decomposes the variation and covariation in the data into a series of uncorrelated genetic and environmental factors. According to this model, the trait correlation between height at two different ages is due to additive genetic correlation (r_A) indicating the same or closely linked genes, common environmental correlation (r_C) indicating same or correlated environmental factors shared by co-twins and unique environmental correlation (r_E) indicating same or correlated environmental factors unique to each twin individual. Additionally we present standardized variance components, i.e. the proportions of height variation at each age explained by additive genetic, common environmental and unique environmental factors, based on the Cholesky decomposition instead of univariate models since it has more power to detect these effects (un-standardized variance components are presented in Appendix table 1). However we confirmed that the effects sizes were virtually identical to the estimates based on univariate models. Because of slight age differences within the age groups, all height values were adjusted for age at the time of the measurement by calculating regression residuals by linear regression model.

RESULTS

Table 1 presents basic descriptive statistics of height by sex and zygosity at each age for both twin cohorts. Mean values were expectedly higher for boys than for girls over the study period; only at 11-12 years girls were slightly taller. The standard deviation of height increased at 11-12 years of age among girls and at 14 years among boys,

coinciding with gender differences in pubertal timing. No systematic differences were seen in means or variances between MZ, SSDZ and OSDZ twins.

(Table 1)

Intraclass correlations for height are shown in Table 2. MZ correlations were clearly higher than SSDZ and OSDZ correlations consistent with the influence of genetic effects. Since DZ correlations were slightly greater than half of the size of MZ correlations, the ACE model (containing additive genetic, common environmental, and unique environmental effects) was taken as the starting point of genetic modeling. Slightly lower intraclass correlations were observed for OSDZ than for SSDZ twins warranting the testing of sex-specific genetic effects.

(Table 2)

Genetic analyses began by testing the assumptions of twin models and selecting the best fitting model at each age for both cohorts (Table 3). Regarding FinnTwin12, the fit of the models did not worsen when saturated models were compared with ACE models, which suggested that the assumption of equality of mean and variances between MZ and DZ twins was not violated. In FinnTwin16 data the ACE model was not accepted for 17 and 18 years, but the p-values were close to the limit (p=0.02 at age 17 and 0.05 at age 17) and AIC was lower for ACE at 18 years when compared to the saturated model. However, it is noteworthy that our data are large, so that even relatively minor deviances

easily lead to rejection of parsimonious models. Further multiple tests done increase the likelihood of false positive results. Common environmental effect was statistically significant at 12 years of age in FinnTwin12 cohort and at all ages in FinnTwin16 cohort. Parameters estimated could not be set equal between boys and girls, except at adult age in the FinnTwin12 cohort, but the sex-specific genetic effects were not statistically significant. For the sake of uniformity and because we had large sample size, we present parameter estimates for boys and girls separately at each age. Further because we found evidence for common environmental effects, albeit such effects were not statistically significant at all ages, we chose to use the ACE model in further multivariate analyses, because it has more power to detect these effects than univariate analyses.

(Table 3)

Figures 1, 2 and 3 present parameter estimates of the multivariate Cholesky decomposition for FinnTwin12 (a) and FinnTwin16 (b) cohorts. Although the estimates for additive genetic (Figure 1), common environmental (Figure 2) and unique environmental factors (Figure 3) belong to the same model, for a clearer understanding, each component was presented as separate figures. One head arrows from latent variance components to height measurements present the estimates of standardized variance components at each age. Most of the height variation was attributable to additive genetic factors, with heritability estimates ranging from 0.65 to 0.86 (Figure 1). These heritability estimates varied only slightly during the studied periods, and apart from the slightly higher values observed during puberty in girls, no clear age pattern was detected.

Differences in heritability estimates between sexes were greater in the older cohort, and whereas in FinnTwin16 the values obtained were in all cases higher for boys, the trend seems to be opposite in FinnTwin12. Although the proportion of variance explained by common environmental effects was lower (0.05-0.23), this component was significant for all ages considered in both cohorts, except for girls at 11-12 years (Figure 2). Unique environmental effects were all significant and varied only slightly between ages (0.07-0.12) (Figure 3).

(Figures 1, 2 and 3)

Finally, we analyzed genetic, common environmental and unique environmental correlations of height between different ages (two-head arrows between latent variance components). Correlations between additive genetic factors for FinnTwin12 (Figure 1a) were high as follows: 0.58-0.99 among boys and 0.70-0.99 among girls. Additive genetic correlations were greater between subsequent ages, but probably because of inter-individual variation in the onset and development of the pubertal growth spurt, the correlations temporally dropped at 11-12 years in girls and 14 years in boys. Since the adolescence period was not included, the correlations were substantially higher for both sexes (0.88-0.99 in boys and 0.98-0.99 in girls) in FinnTwin16 cohort (Figure 1b). Common environmental correlations (Figure 2) were also high and statistically significant (0.72-0.99 and 0.72-1.00, respectively), except at some ages during puberty, that is, at 11-12 years in girls (Figure 2a) and between 16 years and adult age in boys (Figure 2b). Unique environmental correlations were lower than genetic and common

environmental correlations and were greater for girls than for boys at all ages considered (Figure 3).

DISCUSSION

This study sheds light into the contribution of genetic and environmental factors on height, as well as on the respective correlations between stature at specific ages during adolescence and young adulthood. Our results confirm that variation in attained height after childhood is strongly influenced by genetic differences (65-86%), 49% of which remained the same or closely linked during this period. Common environmental factors are also important in the determination of height, and they were strongly correlated across the analyzed ages.

During adolescence and young adulthood, the influence of common environmental factors on height is not well established. Nutrition is universally the most important environmental factor affecting growth. For example, milk consumption has been found to be positively associated with height in children and adults (Wiley et al., 2005). However, other conditions including childhood diseases, chronic psychological stress and socioeconomic circumstances can also substantially contribute to the variation of height (Batty et al., 2009; Silventoinen, 2003). A common environmental effect influencing height variation from 3 to 12 years was found previously in a sample of 7755 Dutch twin pairs (Silventoinen et al., 2007). In the present study, the results from the univariate and multivariate analyses suggest that common environmental factors are also significant

from the adolescence to the adult age. The same result was also observed in four older cohorts of adult men and women born in Finland during the first half of the 20th century (Silventoinen et al., 2000) and in some twin cohorts from eight different countries (Silventoinen et al., 2003b). In contrast, common environmental effects were non-significant in other cohorts, for example in the Swedish children (375 pairs) from 2 to 18 years (Silventoinen et al., 2008) and in Dutch twin data (208 and 567 pairs in the adolescence and middle age cohorts, respectively) (Silventoinen et al., 2006). It should be noted, however, that the absence of common environmental effects may reflect the small sample size which constrained the analysis and limited statistical power. On the other hand, few studies have analyzed the mode in which common environmental factors correlate between height at different ages. The trend of lower correlations at the time of puberty observed in the present study for both boys and girls is in agreement with the lower correlation detected for girls between 3 and 12 years in comparison with that of boys (Silventoinen et al., 2007); this suggests that new common environmental factors could affect growth during this period, factors that include transition to middle school, with new dietary habits and onset of smoking as the adolescents become more independent.

The heritability estimates we obtained during adolescence matched closely those found for Dutch twins studied at age 12 (Silventoinen et al., 2007), but they are clearly lower than in other previous studies (Bodurtha et al., 1990; Phillips and Matheny, 1990; Silventoinen et al., 2008; Silventoinen et al., 2006) for which the AE model offered the best fit. In a similar way, the proportion of height variation explained by additive genetic

effects at the adult age was in the range of some studies (Schousboe et al., 2004; Silventoinen et al., 2003b) but lower than in others (Silventoinen et al., 2006). The higher heritability obtained in the studies which used an AE model is likely to be due to the fact that variance accounted for common environmental variation had been included in additive genetic variation. As is well established, heritability is a time specific estimate influenced by the environmental variation experienced by populations. Statistically significant change in the parameters over the birth cohorts has been previously observed in Finland since the beginning of the last century (Silventoinen et al., 2000). The results from this investigation agree with this study in determining that the relative effect of genetic factors was stronger in the younger cohort (FinnTwin12). As genetic variation is most important when environmental conditions are optimal (Silventoinen et al., 2003), these findings suggest that living conditions in Finland have improved from the 1970s to the 1980s.

The additive genetic correlations for height varied from 0.58 to 0.99 for boys and from 0.70 to 0.99 for girls in our data, showing that more than 33% and 49% of the genes responsible for variation in height in this population are common between specific ages from the early adolescence to the adult age. According to the results from two Swedish studies (Fischbein and Pedersen, 1987; Silventoinen et al., 2008), genetic correlations between subsequent ages were higher but decreased considerably when the period of puberty was considered. In our data sexual maturation was found to be closely correlated with growth from 12 to 14 in girls and from 14 to 16 in boys (Wehkalampi et al., 2008), which can well explain the decreasing genetic correlations at these ages in our data as

well. It is also possible that there are genes whose effects are temporarily inhibited during the growth process. Our findings agree with the older work (Fischbein and Pedersen, 1987) in determining a more linear pattern for girls, that is, genetic correlations are less stable for boys. The high genetic correlations obtained are encouraging for further linkage and association studies, since it may be easier to find specific genes affecting growth when multivariate modeling including measures at different ages can be used.

The variation of height explained by specific environmental factors in the present study (7% to 12%) is very similar than found in other populations (Silventoinen et al., 2007; Silventoinen et al., 2008; Silventoinen et al., 2006). Unique environmental factors between height measures at different ages showed correlations from 0.32 to 0.82. These results may partly be due to epigenetic inheritance (Wong et al., 2005), which is modeled as part of unique environmental factors. However, it is likely that these correlations also reflect real environmental factors, for example differences in nutrition within twin pairs. In general, great differences were detected in the magnitude of the correlations between sexes, with higher values for girls than for boys, and although these differences were not previously observed from 3 to 12 years (Silventoinen et al., 2007), in the present study they persist from the adolescence to the adult age.

Finally we found little evidence of sex-specific genetic effects on height. That finding is consistent with two recent Genome-Wide Association (GWA) meta-analysis studies for adult stature (Lango Allen et al., 2010; Soranzo et al., 2009), in which candidate genes were found to be located in the autosomal region of the genome. Gender differences in

stature are substantially affected by the extended period of prepubertal growth of males (compared to that of females); that is, boys tend to grow taller than girls because they enter puberty at a later stage. Indeed, growth before puberty is the main determinant of adult stature. Sexual skeletal dimorphism is influenced by the sex steroids effects on the initiation of the pubertal growth spurt and the closure of the epiphyses at the end of puberty, being estrogen the major hormone responsible for the acquisition and maintenance of bone mass in both male and females (Frank, 2003). Our findings confirm previous studies in cross-sectional samples (Silventoinen et al., 2001; Silventoinen et al., 2003b), but more longitudinal studies are needed in order to clarify the question of the effect of sex-specific genetic factors on the genetic regulation of growth.

Our study has several strengths including two large population-based twin samples drawn from the same small country and near in time of birth, high-participation rates, a large number of males and females of each zygosity, and follow-up ranging from early adolescence (11-12 years) to young adulthood (20-27 years), when human growth is completed. However the study also presents some potential limitations. Discrepancy between measured and self-reported data is generally due to increased measurement error in the self-reported case, with the subsequent increase in E component. In this study, however, the correlation between self-reported and measured height was very high ($r=0.99$) in both of the cohorts. Another limitation is that zygosity determination was based on self-reported information, but as previously noted, the methodology used has shown high validity and pairs of uncertain zygosity were exclued from analyses. Finally, assortative mating for height is well recognized, and a prior twin-spouse study indicates

that this was partly because of phenotypic assortment, which can increase the DZ correlation and may thus inflate the estimates of common environmental effect (Silventoinen et al., 2003a). It is possible that assortative mating affects height at specific ages during growth differently from final adult height. However, assortative mating should inflate common environmental effects in adulthood as well and previous studies have shown only small common environmental components in adult cohorts born after the Second World War (Silventoinen, 2003; Silventoinen et al., 2003b). Thus, even if assortative mating changes over time as the population changes, in the light of previous twin studies, it is not likely that assortative mating could explain a large part of the common environmental effect found in this study.

In conclusion, human growth from late childhood to adulthood is a complex process under strong genetic control, but environmental factors, which are partly shared by co-twins, are also substantial in the determination of variation in height. The magnitude of the genetic factors shared between the analyzed ages encourages further efforts to identify genes affecting growth. The influence of common environmental effects is relevant in public health and family based interventions hold a premise to influence the height by age and final height. A challenge in further studies is to identify these environmental factors and test whether they interact with genetic factors.

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