Environmental Rather than Genetic Factors Determine the Variation in the Age of the Infancy to Childhood Transition: A Twins Study

Alina German, MD[1], Gregory Livshits, PhD[2], Inga Peter, PhD[3], Ida Malkin, PhD[2], Jonathan Dubnov, MD[4], Hannah Akons, MD[5], Michael Shmoish, PhD[6], and Ze'ev Hochberg, MD, PhD[7]

Objective Using a twins study, we sought to assess the contribution of genetic against environmental factor as they affect the age at transition from infancy to childhood (ICT).

Study design The subjects were 56 pairs of monozygotic twins, 106 pairs of dizygotic twins, and 106 pairs of regular siblings (SBs), for a total of 536 children. Their ICT was determined, and a variance component analysis was implemented to estimate components of the familial variance, with simultaneous adjustment for potential covariates.

Results We found substantial contribution of the common environment shared by all types of SBs that explained 27.7% of the total variance in ICT, whereas the common twin environment explained 9.2% of the variance, gestational age 3.5%, and birth weight 1.8%. In addition, 8.7% was attributable to sex difference, but we found no detectable contribution of genetic factors to inter-individual variation in ICT age.

Conclusions Developmental plasticity impacts much of human growth. Here we show that of the ~50% of the variance provided to adult height by the ICT, 42.2% is attributable to adaptive cues represented by shared twin and SB environment, with no detectable genetic involvement. *(J Pediatr 2015;166:731-5)*.

The understanding of natural and nurturing effects on child growth trajectories and adult height has evolved with alternating ascendance of one or the other as primary explanations for individual differences. With advent of the concept of "phenotypic plasticity,"[1,2] we now realize the preponderance to different phenotypes in response to different environments in the course of human development.[2,3] The time of maximal plasticity in physical growth appears to be during prenatal and early postnatal growth and development. This ability of the organism to facilitate change is termed "adaptability,"[4] and the expressions of suites of genes, particularly during development or life-history transitions, probably underlie the fundamental plasticity of an organism.[5]

Previous work has defined infancy and childhood, and the transition from infancy to childhood (ICT) was demonstrated to occur at age 7-12 months in affluent Western countries (**Figure 1**)[6-8]; it is marked by a growth spurt when the growth hormone (GH) axis sets in as a major regulator of childhood growth.[9] The ICT correlates negatively and predicts almost 50% of the final adult height variation.[10] A delay in ICT (DICT; **Figure 1**) has a lifelong impact on stature and is responsible for as many as 44% of children with a normal birth weight and no endocrine disease, who are referred to pediatric endocrine clinics as suffering from "idiopathic" short stature.[10] We have previously suggested that a DICT is a predictive adaptational strategy to withstand environmental cues and low energy stores, resulting in short stature.[2,3]

The genetic component of growth has been addressed by recent genome-wide association studies, which have led to the discovery of >200 loci associated with variation in adult height that, however, explain only a small fraction of the variation, as reviewed.[11] Studies of twins have the power to assess the contribution of genetic factors and common intrauterine environmental factors as they affect child growth by comparison of monozygotic twins (MZ) with dizygotic twins (DZ) and nontwin siblings (SBs). Dubois et al[12] reported that contribution of genetics appears to play an increasingly important role in explaining the inter-individual variation in weight, height, and body mass index from early childhood to late adolescence, particularly in boys, whereas common environmental factors exert their strongest and most independent influence specifically in pre-adolescent years and more significantly in girls. Jelenkovic et al[13] showed that the genetic contribution to height is strong during adolescence, whereas Silventoinen et al[14] suggested environmental factors shared by co-twins are important for growth during childhood. Using a twin study and variance

DICT	Delay in ICT
DZ	Dizygotic twins
GH	Growth hormone
ICT	Transition from infancy to childhood
MZ	Monozygotic twins
SB	Sibling

From the [1]Department of Pediatrics, Bnai Zion Medical Center, Haifa, Israel; [2]Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Haifa District Health Office, Ministry of Health, School of Public Health, Haifa University; [5]Haifa District Health Office, Ministry of Health; and [6]The Lorry I. Lokey Interdisciplinary Center for Life Sciences and Engineering and [7]Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

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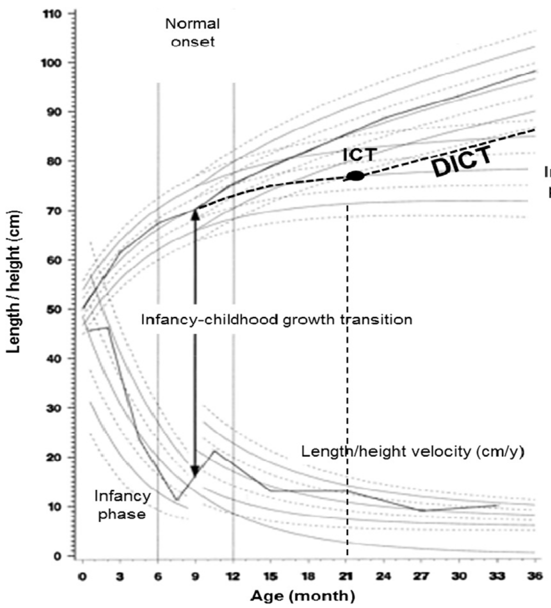

Figure 1. The infancy phase of the infancy-childhood-puberty growth model begins at mid-gestation and tails off at 2-3 years of age. The childhood growth phase sets on in affluent Western countries between 6 and 12 months of age (9 months in this **Figure**), and delayed infancy childhood transition (DICT) is defined beyond age 12 months (21 months for this hypothetical child); it has a permanent effect on final adult height. Adapted with permission from Hochberg et al.[5]

decomposition analysis, we have reported that the effect of intrauterine environment played a substantial role in early stages of child physical development, explaining 18%-71% of the total variance of growth curve parameters.[15]

The present study was framed with a hypothesis that, being the mechanism for a major influence on adult height, individual differences in ICT age are partly adaptive and partly genetically influenced. To this end, ICT age was determined from longitudinal growth data obtained from MZ and DZ twins and SB pairs of children and a variance decomposition analysis utilized to assess the relative roles of genes and family environment.

Methods

The data for this longitudinal study were gathered retrospectively from computerized database of Childcare Centers of the Tel Aviv and Haifa districts in Israel. Children with genetic anomalies, organic conditions, and bone disease were not included, and the incidence of malnutrition is unknown among this population. Twin concordance was determined by placental examination, hematologic test, or serologic tests. The infants were measured for body weight and length after birth and then during the first 24 months of their life in 12 well baby clinics at their routine follow-up visits by 24 trained nurses, via nationwide, standardized equipment for length and weight measurements. The twin population cohort was 784; 50 were excluded for being born small for gestational age, and 198 children did not have enough measurements. We analyzed growth of 56 pairs of MZ, 106 pairs of DZ, and 106 pairs of SBs, for a total of 536 children, and only those children who had at least 6 measurements between birth and 18 months—≥3 measurement before and ≥3 after the ICT, as previously described.[16,17] The summary of birth data of studied subjects are presented in the **Table**.

Determination of ICT

The data collected in the first 2 years of life of each subject were fitted via the use of a mathematical model that incorporated the functions and concepts of the Infancy and Childhood components of Karlberg's infancy-childhood-puberty growth model,[18] as previously described.[6] The infancy component is modeled with a negative exponential function: $Y = aI + bI\,(1 - \exp[-cIt])$, where the birth length is aI, the postnatal contribution of the infancy component is bI, and the growth rate of the infancy component is cI. The childhood component is represented by a second-degree polynomial function, in which t is age in years from birth: $Y = aC + bCt + cCt^2$. All measurements were automatically plotted on the infancy-childhood-puberty growth model growth model charts.[16] The age of ICT was determined to the nearest month by 2 observers (interobserver coefficient of variation <1 month, n = 100) by visual inspection of the plots, as previously described (**Figure 1**).[8,19,20] The ICT age of the studied children is presented in the **Table**.

Statistical Analyses

Basic descriptive statistics were used to describe general patterns of variation of all study variables. Intrapair correlations for the ICT-age were computed for each type of relatives: SB, DZ, and MZ pairs via the Spearman correlation analysis. Correlation coefficients were compared by a χ^2 test for

Table. Basic descriptive statistics of the study sample in relation to gestational age and sex

Characteristics	Group	Boys, n	Girls, n	*P* value for sex
Sample size	Preterm	82	117	
	Term*	164	173	
MZ	Preterm	30	38	
	Term	20	24	
DZ	Preterm	63	91	
	Term	33	25	
SB pairs	Preterm	16	8	
	Term	84	104	
Gestational age, wk	Preterm	34.3 ± 1.9†	34.1 ± 2†	.58
	Term	39.3 ± 1.2‡	39.4 ± 1.1‡	.46
Birth weight, g	Preterm	2275 ± 520†	2097 ± 435†	.002
	Term	3022 ± 511‡	2922 ± 509‡	.06
Birth length, cm	Preterm	46.5 ± 2.9†	46.2 ± 2.4†	.48
	Term	48.9 ± 2.2‡	48.7 ± 2.4‡	.45
ICT, mo	Preterm	10.1 ± 1.9†	9.3 ± 2†	.003
	Term	10.9 ± 1.7‡	10.1 ± 2.0‡	.001

*Term-born infants – gestational age ≥37 wk.
†Mean ± SD.
‡*P* < .05 in comparison of preterm and term-born children.