CHAPTER 8

The Genetic Epidemiology of Growth and Development

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8.1 INTRODUCTION

In spite of the predominant role of genetic variation in causing the observed variability among children in their growth and development, studies of genetic influences on growth and development are few in comparison to the plethora of descriptive studies, population comparisons and studies of the impact of specific environmental factors. There are two main reasons for this. First, the courses of study under which many investigators of growth and development are trained (e.g. physical anthropology or human biology) usually provide little formal training in human genetics and statistical genetic analysis. Second, in order to best study genetic influences on growth and development, data from related children are needed. Preferably those data from related children are longitudinal, and ideally they are longitudinal data from large numbers of related children reared under different household environments. Unfortunately, such data are very rare.

The purpose of this chapter is to provide an overview of the genetic epidemiology of normal human growth and development. Although a treatise on quantitative genetic approaches to the study of growth and development is beyond the scope of this chapter, as is a complete review of the existing literature on the genetics of growth and development, the references, suggested readings and internet resources will provide a good starting point for the interested student to pursue further study. This chapter is meant to serve as an introduction to how auxologists can most profitably study the genetics of growth and development with the methods and approaches available today.

Almost half a century ago, Neel and Schull[1] proposed that the epidemiological approach can be extended to the study of non-diseased states, and argued that, "… genetic concepts must be an integral part of the armamentarium of the modern epidemiologist" (p. 302). The "epidemiological genetics" that Neel and Schull[1] envisioned has become known as "genetic epidemiology". Upon the establishment of the International Genetic Epidemiology Society (IGES) in 1992, its founding president, James V. Neel, succinctly defined genetic epidemiology as, "The study of genetic components in complex biological phenomena".[2] From this perspective, the genetic epidemiology of growth and development may be considered as the study of the genetic underpinnings of the size, conformation and maturity status of individuals over the course of childhood. This includes characterizing the magnitude of genetic influences on growth and development phenotypes, examining how those genetic influences operate over time, identifying and localizing genes and specific genetic polymorphisms in those genes that contribute to variation in growth and development, and elucidating how genetic and environmental factors interact during growth and development. The advances made over the past few decades in both molecular and statistical genetics have led to current highly sophisticated analyses used to increasingly better elucidate the roles of genes and environment in the complex biological phenomena that comprise growth and development.

This chapter is divided into four sections that follow below. Section 8.2 provides an introduction to basic statistical genetic terminology. Section 8.3 discusses different study designs used to examine genetic influences on primarily quantitative traits. Section 8.4 summarizes published findings from various studies of the genetics of growth and development. Section 8.5 presents some example findings from current genetic epidemiological studies of the growth and development of US children in the well-established Fels Longitudinal Study. Throughout the chapter, important terms or concepts are italicized the first time they are mentioned. Those that are not defined in the text of the chapter are briefly defined in the Glossary.

8.2 STATISTICAL GENETIC TERMS AND CONCEPTS

Statistical genetics refers to a variety of methods for analyzing *phenotypic* variation among related individuals. These methods include those tailored for the study of both discrete and continuous traits. Most growth and development phenotypes exhibit a continuous distribution over a delimited range, and because the growth and development status of a child can usually be measured in some way, most growth and development phenotypes are quantitative traits. Growth and development phenotypes also are referred to as being complex traits, meaning that genes at a few and perhaps several loci contribute to the variation observed in the trait, as do environmental factors, possibly through interaction with those genes. The field of quantitative genetics deals with the analysis of complex traits. As with any specialized field of study, it contains a number of specific terms and concepts. This section provides a brief discussion of those quantitative genetic terms and concepts most important for an understanding of the genetic epidemiology of normal growth and development. Thorough discussion of quantitative genetic methods can be found in books listed in the Further Reading section at the end of this chapter.

8.2.1 Relatedness of Individuals

To start with, because related individuals are not independent, but share some of their genes by virtue of sharing common ancestry, it is necessary to consider their degree of relatedness in assessing the extent of their resemblance for a trait. The *coefficient of kinship* between two individuals is the probability that an *allele* taken at random from the two alleles at a locus in one individual is identical to an allele taken at random from the two alleles at the same *locus* in another individual. The coefficient of kinship between first degree relatives is 0.25, meaning that, for example, between a pair of full siblings there is a 25% chance that they each have at a locus the very same allele that they each inherited from a common ancestor. Most of what we know about the genetic control of growth and development comes from family-based studies in which the correlations between

relatives and between unrelated individuals for a trait such as stature or weight are calculated. The basic premise underlying these investigations is straightforward: if the variation in a trait is largely under genetic control, then related individuals will be more similar for the trait than will unrelated individuals (i.e. the intrafamily variance of the trait is low compared to the interfamily variance). Conversely, if the variation in a trait is only partly determined by genes, then related individuals may only resemble each other a little bit more so than do unrelated individuals (i.e. the intrafamily variance of the trait is a little smaller than the interfamily variance).

8.2.2 Heritability

Through examination of correlations between different pairs of relatives, heritabilities can be calculated. The concept of *heritability* (h^2) is central to understanding the nature of genetic control for any trait. The h^2 of a trait is a measure of the degree of genetic control of a phenotype, ranging from 0 (no genetic control) to 100% (complete genetic control). Heritabilities are population-level estimates, specific to a particular population in a given environment, and this can sometimes be an important consideration when comparing h^2 estimates across populations.

According to classical quantitative genetics theory (e.g. see texts by Falconer and Mackay, 1996, Lynch and Walsh, 1998)[3,4] the observed phenotypic variation (σ^2_P) in a trait can be expressed as the sum of both genetic (σ^2_G) and random environmental effects (σ^2_E). This is written as:

$$\sigma^2_P = \sigma^2_G + \sigma^2_E \qquad [8.1]$$

In its simplest form, this model provides a starting point for understanding the quantitative genetics of complex traits. For example, σ^2_P can be decomposed further into components representing the variance due to *additive effects* of genes at several loci (σ^2_A), *dominance effects* (σ^2_D) and *epistasis* (σ^2_I), while σ^2_E can be decomposed into the variance due to specific measured environmental factors ($\sigma^2_{E\ factor\ \#1}$) and that due to random, unmeasured environmental factors ($\sigma^2_{E\ random}$). *Broad-sense heritability* refers to the proportion of the phenotypic variance attributable to all sources of genetic variance, and is written as:

$$h^2 = \sigma^2_G/\sigma^2_P \qquad [8.1]$$

Narrow-sense heritability refers to the proportion of the phenotypic variance attributable only to the additive genetic variance, and is written as:

$$h^2 = \sigma^2_A/\sigma^2_P \qquad [8.3]$$

Generally speaking, at least initially, the narrow-sense heritability is the most useful in characterizing the genetic effects of continuously distributed traits such as stature or weight. Inheritance of such quantitative traits is likely to be influenced by a number of genes exerting mostly small to moderate effects. For that reason, quantitative traits are

often referred to as being *polygenic traits*. However, not all genes influencing a trait are likely to make the same contribution to the phenotypic variance of the trait. Also, since it is typically very difficult (e.g. because of sample size constraints) to identify genes explaining only a small proportion of the phenotypic variance of a trait (e.g. 5% or less), it is perhaps more practical to refer to most quantitative traits as being *oligogenic traits*, meaning that it is likely that a few genes with pronounced and identifiable effects of varying degrees are together responsible for most of the genetic contribution to the phenotypic variance of a trait. In most instances, h^2 estimates refer to narrow-sense heritabilities. The variance components approach to decomposing the phenotypic variation exhibited in a quantitative trait, briefly described here, has its roots in the seminal work by Fisher,[5] and is an elegant and powerful method for evaluating the different sources of variation contributing to the overall variance of a complex trait.

8.2.3 Genetic and Environmental Correlations

Quantitative genetics is much more than simply calculating h^2 estimates. Since it is well established that measures of growth and development have substantial and significant heritable components, intellectual focus turns to the nature of the genetic regulation of growth and development. For example, significant phenotypic correlations often exist between different measures of growth and development. These phenotypic correlations may be due to *pleiotropy*, the joint effects of a gene or genes on different traits, or to shared environmental factors. In most cases, significant phenotypic correlations between two traits are due to both pleiotropy and shared environmental effects.

Just as the phenotypic variance of one trait can be decomposed into genetic and environmental variance components, so too can the phenotypic correlation between two traits be decomposed into genetic and environmental covariance components. Thus, the phenotypic correlation between two traits is a function of the h^2 of each trait and the genetic and environmental correlations between them. This is written as:

$$\rho_P = \sqrt{h_1^2}\sqrt{h_2^2}\,\rho_G + \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}\,\rho_E \qquad [8.4]$$

where ρ_p is the phenotypic correlation, ρ_G is the genetic correlation, ρ_E is the environmental correlation, h_1^2 is the heritability of trait 1 and h_2^2 is the heritability of trait 2. If both traits have low heritabilities, the phenotypic correlation between them is due largely to the environmental correlation, whereas if both traits have high heritabilities, the phenotypic correlation between them is due largely to the genetic correlation.

As with phenotypic correlations, additive genetic and random environmental correlations range from -1.0 to 1.0. A genetic correlation of 1.0, for example, indicates complete positive pleiotropy between two traits. That is, there are genes that affect in the same manner both of the traits being examined. A genetic correlation significantly less than one indicates incomplete pleiotropy, meaning that the two traits are influenced to

some extent by the same set of genes, but that other genes also are influencing the value of one or the other of the two traits. A genetic correlation of zero between two traits indicates that the two traits have different genes controlling them. Finally, a negative genetic correlation indicates that the same set of genes operates in an opposite manner on the two traits. Similarly, the random environmental correlation is a measure of the direction and strength of the correlated response of two traits to non-genetic factors. If specific non-genetic factors have been identified and measured that influence the covariance of the two traits, however, then the environmental correlation can be decomposed into non-random and random components.

Multivariate quantitative genetic analyses, in which the heritabilities of two (or more) traits are estimated along with the genetic and environmental covariances between them, are powerful tools for investigating the nature of relationships between different aspects or measures of growth and development.

8.2.4 Applications of Genetic and Environmental Correlations to Longitudinal Data

Another topic of particular interest in the field of growth and development is the nature of the genetic control of a trait over time. For these types of analysis it is necessary to have serial measurements of the trait or traits of interest. Serial measurements of traits separated by time are normally correlated to some degree, with higher phenotypic correlations often found over short intervals and lower phenotypic correlations found over longer intervals. *Canalization* is a familiar term to auxologists, referring to the tendency of a trait to follow a certain course or trajectory over time. The more highly canalized a trait, the higher the phenotypic correlations between repeated measurements. From a genetic perspective, traits that are highly canalized, and that are relatively insensitive to changes in environmental conditions, are likely to have relatively high heritabilities. The same genes, however, may or may not be influencing the trait to the same extent over the entire course of growth and development.

To test hypotheses concerning the genetic control of growth at different ages, the same approach discussed above for the examination of two traits at one point in time is taken. In its simplest form, however, the "two traits" are now the same trait measured at two points in time. The genetic and environmental correlations between repeated measures of the trait at different ages are then calculated. This approach allows for disentangling shared genetic effects from shared environmental effects on a trait measured over the course of childhood.

The strength of a genetic correlation for a single trait with repeated measures is indicative of the degree of consistency or uniformity in the genetic control of the trait over time. For example, if a genetic correlation of 1.0 is found between stature measured at age 8 years and measured again at age 18, then it can be inferred that the genes influencing stature during the middle of childhood are the same as those that influence

height in early adulthood. If a genetic correlation is obtained that is significantly lower than 1.0, however, then there is evidence that a different suite of genes controls stature at ages 8 and 18 years. Similarly, the environmental correlation is a measure of the consistency or uniformity of the response of the trait to non-genetic factors over time. The discussion will return to genotype by age interaction after first discussing genotype by environment and genotype by sex interactions.

8.2.5 Genotype by Environment Interaction

Understanding how genes interact with aspects of the physical and internal biological environments is essential for better understanding the genetic architecture of complex traits. In studies where relatives live in different environments, genotype by environment ($G \times E$) interactions can be examined using extensions of variance components methods for studying quantitative trait variation.

$G \times E$ interaction is likely to be an important influence on the variation observed among children in their growth and development, particularly in populations with high prevalences of environmental factors known to negatively impact growth and development. The key to $G \times E$ interaction, however, is that not all children may respond the same to such environmental factors, and a portion of that differential response or susceptibility at the phenotypic level may be due to genetic variation among individuals.

The simplest approach to modeling $G \times E$ interaction is to make the genetic variance in a trait a function of a dichotomous environmental variable. Examples of this could be the presence or absence of a particular disease in a child, high or low protein intake, etc. Figure 8.1 shows a simple hypothetical depiction of the response of three genotypes at a locus to two different environments. In the presence of $G \times E$ interaction, the relationship between trait levels and specific genotypes will vary as a function of the environment. In this case, trait levels in Environment 1 are substantially less variable than trait levels in Environment 2. For genotypes AA and AB, trait levels remain stable or decrease from Environment 1 to Environment 2. For genotype BB, trait levels increase from Environment 1 to 2. This example demonstrates how gene expression may vary under different environmental conditions.

In $G \times E$ analyses of the response of a quantitative trait, the variance components method is expanded to include environment-specific additive genetic variances that are then estimated. For example, a large number of related children might be measured for a trait (e.g. stature) at a specific age, and also tested for the presence of a particular infection at that age. If the additive genetic variances of the measured trait are not significantly different between infected and non-infected children, then that would be an indication that there is no $G \times E$ interaction between that trait and that infection at that age. If, on the other hand, the additive genetic variances of the measured trait are significantly different between infected and non-infected children, then that would indicate a genetic basis to the differential response of the growth status of children to infection at that age. $G \times E$

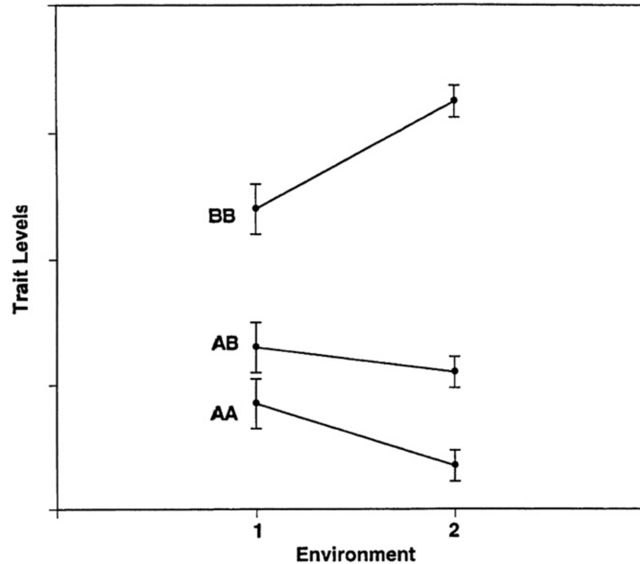

Figure 8.1 Hypothetical depiction of gene by environment interaction with the response of three genotypes at a locus to two different environments.

interaction is also tested by examining the genetic correlation between the trait measured in different environments. A genetic correlation significantly different from 1.0 is another indication of G × E interaction. In the example here, a genetic correlation significantly less than 1.0 would indicate that the G × E interaction is due to an incompletely correlated genetic response of the trait in infected and non-infected children.

8.2.6 Genotype by Sex Interaction

Sexual dimorphism in the growth and development of children is well known, but the genetic basis of this sexual dimorphism is poorly understood. The approach for studying G × E interaction using related individuals living in different environments described above can be used to study genotype by sex (G × S) interactions. The rationale here is that the hormonal environments of males and females differ considerably, and the expression of autosomal genes controlling a quantitative trait may be influenced by the sex—environment encountered.

In analyses of G × S interaction, the variance components method is again expanded. Additional parameters are estimated, the most important being sex-specific variance components and the genetic correlation between the sexes for the trait. G × S interaction is indicated by significantly different additive genetic variances for males and females and/or a genetic correlation between the sexes significantly less than 1.0.

G × S interaction analyses can be used to examine the genetic basis to the sexual dimorphism in measures of growth and development. The aim of G × S interaction

analyses is to determine whether the sexual dimorphism evidenced in a trait during childhood is itself a heritable trait. In some families, for example, male and female children might not be very different in a measure of growth or development at a particular age, while in other families there might be significant differences between male and female relatives in that measure of growth or development at that age.

8.2.7 Genotype by Age Interaction

The nature of genetic influences on measures of growth and development may change over the course of childhood. As initially discussed earlier, the genetic correlation between a trait measured at two points in time can provide insight into the genetic control of a trait over time. If extensive longitudinal data from related children are available, genotype by age (G × A) interactions can be more rigorously examined. Like G × S interactions, G × A interactions are a type of G × E interaction. In this case, the "environment" is the age of the child at the time of the measurement of a trait. In these analyses, the additive genetic variance of a trait is modeled as a function of age. From these age-specific additive genetic variances, age-specific heritabilities of the trait can be determined. Also estimated are the additive genetic and environmental correlations between the trait measured across time.

G × A interaction is indicated by an additive genetic variance of a trait changing over a span of ages. This suggests that the genetic expression of a trait is dependent upon the age of the child. G × A interaction also is indicated by a change in the genetic correlation between a trait measured over time. For example, a genetic correlation between time-points of a serially measured trait that decreases significantly from 1.0 over a span of ages indicates G × A interaction. And, if sufficient serial data are available, the function or shape of a genetic correlation curve can provide further insights into dynamic genetically mediated biological processes underlying such G × A interactions.

8.2.8 Identifying Genes Influencing Growth and Development

Once it has been determined that a trait has a significant heritability, interest quickly turns to locating and identifying the actual genes that influence variation in the trait. Advances in molecular and statistical genetic methods make it possible to search for genes and specific genetic polymorphisms influencing complex traits. Unlike monogenic traits that are influenced by a single gene with large effects, most complex traits are largely (but not exclusively) influenced by genes at a number of loci whose individual effects can be of small to moderate size. While understanding of monogenic growth disorders has significantly increased over the last several decades, understanding the genetics of normal variation in quantitative measures of growth and development has continued to be a daunting task. Technological advances in molecular biology, however, including relatively inexpensive high-throughput genotyping of upwards of millions of *single-nucleotide polymorphisms*

(*SNPs*) and increasingly lower cost exome and whole-genome sequencing, along with attendant methodological advances in statistical genetics, have made it possible to identify genes exerting small or moderate effects and even to identify rare polymorphisms influencing a trait in only some populations or pedigrees. There are two basic strategies to follow in the search for genes involved in the regulation of growth and development: population-based association studies or family-based quantitative trait linkage studies.

8.2.9 Population-Based Association Studies

The first approach is the candidate gene association approach. Here, genes suspected to be physiologically involved in the trait are examined. For example, a sample of unrelated individuals is selected and genotyped for a specific polymorphism in or near the candidate gene. Simple statistical tests are then used to evaluate associations between marker genotype status and the value of a trait. Carriers of a particular allele, for example, may have a mean value for the trait that is significantly different from the mean value of the trait in those who do not have a copy of that allele. Population-based association studies have obvious appeal, in that they are computationally straightforward compared to the analysis of marker genotype and quantitative trait data from family members.

There is a significant problem with population-based association studies, however, that has become evident as greater knowledge has been gained regarding *linkage disequilibrium*. Two loci are in *equilibrium* when alleles at the two loci are randomly associated with each other. If the relationship between the loci is not random, then linkage disequilibrium is present. Unfortunately, linkage disequilibrium can occur for a number of reasons including new mutations and genetic drift, and in the presence of selection. The main problem with association studies, however, is that disequilibrium is difficult to predict. Two loci may be very close to each other and yet be in equilibrium. Conversely, two loci may be relatively far apart from each other and yet be in disequilibrium. There is no sure way to know that the marker that has been typed is in disequilibrium with the true functional variant. Given that within a given locus, numerous genetic variants may be in high disequilibrium with one another, when a significant association of a variant and trait is found, this only points to a general region, and does not mean that the variant with the strongest association is the functional variant. If it is known a priori, however, that the typed marker is in fact a functional polymorphism (that is, there is a measurable difference among marker genotypes in gene expression; e.g. one genotype results in much lower levels of a particular protein compared to the other genotypes), then association studies become a more viable strategy to pursue.

8.2.10 Genome-Wide Association Studies

In recent years, *genome-wide association* (*GWA*) studies of complex traits have proliferated. GWA analysis is an extension of the candidate gene association approach, and is made possible by relatively low-cost genotyping of now typically from 500,000 to 1,000,000

SNPs in each subject in a study sample. SNPs are biallelic genetic markers that are coded either "0" or "1", and are most often separated by only fairly small intervals across the entire genome. Associations between genotypes and phenotypes are evaluated over every marker. Given the large number of markers, these analyses are computationally intensive and stringent strategies to control for multiple testing must be followed.

GWA study designs typically take one of two forms. One is the case–control approach where individuals with a certain disease or condition are compared to unaffected individuals with regard to genotype status at every genotyped SNP across the genome. SNPs significantly more prevalent in either cases or controls are identified for follow-up to assess possible causative or protective roles of nearby functional polymorphisms. A second GWA study design focuses on quantitative traits where different genotypes at a single locus are examined for differences in trait levels. Associations are denoted when individuals with certain SNP genotypes have consistently and significantly higher or lower trait values than individuals with the other SNP genotypes.

There are several strengths to the GWA approach. First, the high density of SNP markers helps to better localize association signals. GWA signals can be typically reduced to approximately a 500 kb interval, compared to a much broader interval obtained from quantitative trait linkage discussed below. Another strength, alluded to above, is that data can be obtained from unrelated individuals, potentially making data collection more efficient. Indeed, numerous GWA studies have been based on already existing epidemiological study samples. Potential problems with population stratification can be ameliorated by using principal component-based (or ancestral marker-based) adjustments obtained from the SNP marker set. Replication of findings is critically important for GWA studies, however, given the large number of comparisons made across the genome in a single study. Such replication of significant findings provides confirmation of the role that at least common polymorphisms play in contributing to phenotypic variation. All GWA studies should include plans for some form of replication in independent samples.

Despite the popularity of GWA studies over the past decade, important criticisms of the approach have emerged in recent years. To date, GWA studies have collectively had somewhat limited success, despite numerous published studies and several large meta-analyses of various complex traits that have sometimes included samples sizes of over 100,000 subjects. In most cases, reported associations have accounted only for a very small proportion of the overall heritability of the traits examined. Some researchers speculate that the reason for this is that GWA studies are only useful for identifying common disease variants. Unfortunately, it now appears that many common disease or quantitative risk factor variants explain only a relatively small proportion of the total phenotypic variance in the disease or trait examined. The population-based association approach is therefore not likely to be able to identify rare disease variants that are most likely to have larger effect sizes.

In addition, significant associations can be due to heterogeneity in the population sampled. This occurs when population subgroups differ systematically in both allele frequencies and levels of the quantitative trait of interest. Even among seemingly fairly homogeneous families (e.g. similar ethnic background) there can be significant differences in specific allele frequencies; and all families carry unique "private" polymorphisms, some of which may affect a trait in some families but not in others.

8.2.11 Quantitative Trait Linkage Analysis

The second predominant approach for discovering genes influencing the types of measurable traits of most interest to auxologists is quantitative trait linkage mapping. Linkage studies require a good deal of planning before their initiation in order to obtain maximal statistical power to detect genes of modest to moderate effect. The premise behind linkage analysis is that if two loci are physically located close to each other, then alleles at these loci will be more likely to be inherited together. In this case, the loci are said to be linked. As the distance between loci increases, the probability that alleles at these loci will *cross over* or *recombine* during meiosis increases. Through investigation of the frequency of recombination events among genetic markers one can identify chromosomal regions harboring genes that influence variation observed in a trait. Once a region has been identified, molecular mapping techniques such as high-density SNP typing or sequencing can be used to better delineate chromosomal regions of interest and to identify functional polymorphisms.

Over the past two decades there have been many advances in quantitative trait linkage analysis as applied to complex traits. Over that time, allele-sharing methods have gained prominence for the analysis of quantitative traits. The key premise behind allele-sharing methods is the concept of *identity by descent* (*IBD*). In comparisons between relatives, two alleles that are structurally identical are said to be *identical by state* (*IBS*); alleles that are structurally identical and inherited from a common ancestor (e.g. two siblings getting the same allele from their mother) are further classified as IBD. A pair of relatives can share zero, one or two alleles IBD at any given marker locus. The likelihood of their sharing zero, one or two alleles IBD is contingent upon their coefficient of kinship. Linkage between a quantitative trait locus (QTL) and a marker exists in chromosomal regions when pairs of relatives who are more phenotypically similar share more alleles at a marker locus than pairs of relatives who are less phenotypically similar.

The power to detect and localize QTLs is a function of several factors, the most important being the strength of the genetic effect. Traits that are highly heritable will tend to have a higher probability of being mapped compared to those with low to modest heritability, but this is not always the case. Also, as in any statistical analysis, sample size is of importance, but in linkage studies other aspects of the study sample are also important,

most especially the family structure of the study sample. Having many families is good, but having fewer more complex extended pedigrees, preferably with several generations represented, will yield increased statistical power because of the greater number and variety of relationships between relatives.

Linkage analysis has several strengths and some weaknesses. One strength of linkage analysis is the ability to identify rare genetic variants in family-based samples. Because genes segregate in families, the ability to identify rare genes of moderate effect is possible. Identification of rare variants may help to explain what has been termed the "missing heritability" observed from population-based GWA studies of common traits (i.e. the portion of the heritability not explained by the common variants).[6] Rare variants are likely to have larger effect sizes and could contribute to the unexplained heritability. Further, some researchers suggest that these rare variants are likely to have obvious functional consequences.[6,7] A benefit of pedigree-based studies for the identification of rare variation is that rarer variants, if present, will be present at a much higher frequency than in the general population. Thus, pedigree-based studies inherently have greater power to detect the effects of such rare variants. However, traditional linkage-based studies have limited resolution (owing to typically having fewer genetic markers typed, although this is somewhat ameliorated with SNP-based linkage analysis compared to earlier STR-based linkage analysis; see also below) and are only able to localize QTL to approximately 10–15 Mb of sequence, a much broader region than GWA studies.

8.2.12 Quantitative Trait Linkage and Association

In recent years there has been an effort to combine linkage and association approaches. This approach effectively utilizes the strength of both genetic paradigms. Combined linkage and association analysis can only be accomplished with family-based data, however. As a first step, a family-based approach to association analysis (e.g. measured genotype) can be implemented to test for associations assuming additive genetic effects on each available SNP in the panel.[8,9] Since data from family members cannot be treated as independent observations, family-based methods such as variance-component analysis are able to use a polygenic component to absorb any non-independence among individuals by incorporating a residual heritability parameter. In this context, quantitative trait linkage provides an additional, independent source of information that when used in conjunction with GWA can augment power to detect loci influencing growth-related traits. SNPs used for linkage can be selected from among the typed SNP panel to maximize *heterozygosity* and minimize linkage disequilibrium among the selected markers. Approximately 10,000 SNPs are required for adequate genomic coverage in SNP-based linkage analysis. A joint test of linkage and association can performed by comparing the likelihood of a model in which both the SNP-specific association

parameter and the linkage variance component are estimated to the likelihood of a model in which both are constrained to be zero. The power of this test depends on the underlying trait model and on how many functional variants there are within a gene or region; however, under certain circumstances combined linkage and association can be more powerful than association alone. In the coming years, the field of genetics will continue to move towards the use of more advanced technology and the new wave of studies will focus on the sequencing of entire exomic regions and ultimately whole-genome sequencing.

8.3 STUDY DESIGNS

Various family-based study designs can be used to examine the genetics of complex traits. Each study design has certain advantages and disadvantages. This section describes some of the major types of study design used by genetic epidemiologists to study complex quantitative traits.

8.3.1 Twin Studies

Over the years, studies of twins have been useful in establishing the familial aggregation of many complex traits. In its basic form, the twin model compares phenotypic differences between two classes of twins, monozygotic (MZ) and dizygotic (DZ). MZ twins share 100% of their genetic make-up, while DZ twins share on average only half of their genetic make-up (i.e. on the genetic level they are the same as any other pair of full sibs). Because of this, phenotypic differences observed between MZ twins are assumed to be the result of environmental factors only, while phenotypic differences between DZ twins are considered to be due to differences in both genes and environmental exposure. Thus, by calculating phenotypic correlations in groups of MZ and DZ twins and comparing them, assumptions can be made about the degree of genetic control of different traits.

One important assumption in the classical twin study design is that both MZ and DZ twin pairs are equally likely to share a common environment. This assumption may not necessarily be valid, however, because MZ twins are often more likely to share common activities, foods and other aspects of the environment to a greater extent than DZ twins. Because there is no fully satisfactory way to separate shared genetic and environmental effects, studies of twins often yield inflated h^2 estimates.

The twin study design is especially problematic if the focus of the study is a growth-related outcome. Twin births are physiologically different from singleton births owing to competition over maternal resources during pregnancy. Fetal growth rates among twins may therefore be considerably discordant, and the postnatal growth of twins is often different from that of siblings from singleton births (e.g. early catch-up growth in twins).

8.3.2 Nuclear Families

Another commonly used study design is that of nuclear families. In this study design, correlations between the various classes of first degree relatives in a nuclear family are estimated. These include parent—offspring, sibling—sibling and spouse—spouse correlations. Heritabilities can be estimated from these different familial correlations. Heritability estimates calculated from nuclear family data, however, are subject to inflation owing to the effects of shared environmental factors such as diet and lifestyle among family members living in a single residence. Given this, heritabilities are often adjusted by taking into account the degree of spousal correlation in the family. It is assumed that any correlation found between spouses is the result of shared environmental factors. Such spousal correlations may depend upon the length of time that the couple has been married. However, such spousal correlations may also be the result of assortative mating.

There are practical considerations to be taken into account in studies of nuclear family members apart from those just mentioned. For example, it is sometimes difficult to obtain information about certain life events because they are often separated in time by a generation: it may take 20 to 30 years of waiting to collect growth measures of the children of parents who were measured when they were children. Also, generational differences in growth may be due to secular trends. This may effectively reduce the heritability of certain traits by diminishing the degree of phenotypic correlation observed. These two problems can be eliminated by examining only sibling correlations, but the problem of shared environment remains.

8.3.3 Extended Pedigrees

The study design that offers considerable promise for elucidating the genetic architecture of complex traits is the extended family approach. This approach involves collecting information from all available family members and estimating phenotypic correlations between all relatives of varying degrees of relationship. By sampling members outside the immediate nuclear family, many of the problems encountered with immediate shared environmental effects in other study designs are minimized because family members come from a number of different households. This results in more accurate and reliable h^2 estimates. In addition, sampling family members in different households (who thereby live in potentially different environmental circumstances) provides the opportunity to investigate $G \times E$ interactions. With regard to the study of growth and development, within large extended pedigrees there will be several related children of approximately the same age. This will enable analyses to proceed very quickly after the initiation of data collection.

There are a few practical drawbacks to this approach, however. The single most important consideration is that the methods involved in calculating statistical genetic parameters can be computationally intensive. This, however, is much less of an obstacle as computer technologies continue to progress. Indeed, advances in computer

technology over the past three decades have made the statistical genetic analyses of data from large pedigrees tractable. In addition, collecting data from large numbers of related individuals of varying ages who may live some distance from each other requires a great deal of planning, effort and research funding.

8.4 STUDIES OF THE GENETICS OF GROWTH AND DEVELOPMENT

The preceding sections introduced several basic terms and concepts necessary for discussing genetic epidemiological approaches to growth and development. This section provides a brief overview of numerous studies of genetic influences on growth and development that have been conducted over the past century. These studies fall into two general categories: those that infer genetic determination of growth and development through comparison of different human populations, and those that examine growth and development traits in families. The review presented here provides a sampling of a considerable part of this literature, focusing on studies of height, birth weight, menarche and skeletal development.

8.4.1 Population Differences in Growth and Development

There is considerable variation across populations in growth in height, weight, and other body dimensions, as well as in the tempo and timing of maturation.[10] For example, mean adult height varies from approximately 150 cm for males in the shortest populations on earth (e.g. Mbuti pygmies of central Africa) to 180 cm for males in northern European populations. These long-standing observations of racial or ethnic differences in growth and development rendered support for the notion that genetic factors are likely involved. The degree to which genetic factors influence growth and development cannot be addressed, however, by the simple comparison of measures of growth and development traits across populations. The populations compared often are exposed to vastly different environments, and the shortest and smallest populations also tend to have the poorest economic status, while the tallest populations tend to be from industrialized nations. Between-population differences may be due to differences in both genetic and environmental factors, whose relative importance of is often confounded. For example, evidence of secular trends in stature and pubertal maturation,[10] and the degree of similarity for stature in high socioeconomic status groups from various parts of the world (e.g. Martorell, 1988)[11] argue that a significant part of interpopulation variation in growth and development is due to environmental factors.

8.4.2 Family Studies of Growth and Development

Population comparisons provide only indirect evidence of a connection between genetic factors and phenotypic variation in growth and development. Only family studies within

populations can clearly define the relationships between genes and growth, because it is with these designs that environmental and genetic sources of variation can be explicitly modeled.

As an initial overview of genetic influences on growth and development, Table 8.1 summarizes published familial correlations and/or the heritability estimates for birth weight, height, weight and other anthropometrics, as well as age at menarche in females, from a large selection of family studies from diverse populations. Table 8.1 does not contain an exhaustive listing of all published findings, but provides a starting point; the studies listed in Table 8.1 were published in widely circulated journals and represent the range of findings typically reported in the literature.

Several general comments can be made regarding these investigations. First, most studies have been based on first degree familial correlations. That is, they are based on either nuclear family or twin pair designs. As discussed above, there are important concerns when studying only first degree relatives, particularly when studying growth and development. These concerns include secular trends that may reduce correlations between parents and offspring, and the shared environments of siblings, especially twins, that may inflate correlations between them. Second, specific environmental sources of variation such as diet and disease usually have not been incorporated into the analyses. Not accounting for the variance in a trait attributable to such environmental factors can lead to underestimation of the h^2 of the trait. Third, the majority of studies have focused solely on height at a given point in time (mostly adult height). A smaller number of studies have examined other anthropometrics. Fourth, the majority of studies are based on cross-sectional data. Only a few studies have longitudinal growth and development data from related individuals that permit examination of genetic influences on patterns of change in height, weight and other measures over time. And fifth, almost all of the studies have focused solely on heritability estimation. There are very few multivariate quantitative genetic analyses of measures of growth and development, or analyses of genotype by environment, sex or age interactions.

Table 8.2 summarizes recently published results from GWA or linkage analyses of birth weight, height, body mass and age at menarche. Although relatively few studies of measures of growth and development have been conducted, this is an expanding area of auxological genetics research as primary interest has shifted to identifying specific genes and genetic polymorphisms that influence such measures. Again, Table 8.2 does not contain an exhaustive listing of all published findings, but provides a starting point for entry into the literature.

Birth Weight

The genetics of prenatal growth has largely been approached by examining the heritability of birth weight. Initially, genetic influences on birth weight were deduced from the known effects of quantitative changes in chromosomes. For example, supernumerary autosomes (trisomy 21, 18 and 13) and abnormal numbers of X chromosomes

Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
Birth weight							
	Penrose, 1954[12]	UK	Cross-sectional, nuclear			Fetal genetic factors: 18% Maternal genetic factors: 20% Environmental factors: 62%	Birth
	Morton, 1955[13]	Japan	Cross-sectional, nuclear/twins		$r_{twins} = 0.56$ $r_{sibs} = 0.52$ $r_{halfsibs-mo} = 0.58$ $r_{halfsibs-fa} = 0.10$		Birth
	Nance et al., 1983[14]	USA	Cross-sectional, nuclear/twins	Offspring of 385 twin pairs	$r_{sibs} = 0.48$ $r_{halfsibs-mo} = 0.31$ $r_{halfsibs-fa} = -0.03$		Birth
	Clausson et al., 2000[15]	Sweden	Cross-sectional, twins	868 MZ, 1141 DZ		$h^2 = 0.25-0.40$	Birth
	Magnus et al., 2001[16]	Norway	Cross-sectional, trios (Fa, Mo, first born)	67,795 trios	$r_{fa-mo} = 0.02$ $r_{fa-off} = 0.129$ $r_{fa-son} = 0.126$ $r_{fa-da} = 0.133$ $r_{mo-off} = 0.226$ $r_{mo-son} = 0.222$ $r_{mo-da} = 0.231$	$h^2 = 0.25$	Birth
	van Dommelen et al., 2004[17]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.14$ $h^2 = 0.24$	Birth, females Birth, males
	Arya et al., 2006[18]	USA (Mexican Americans)	Cross-sectional, nuclear/ extended	840 subjects		$h^2 = 0.72$	Birth

Grunnet et al., 2007[19]	Denmark	Cross-sectional, twins	138 MZ, 214 DZ	$r_{Mz} = 0.75$ $r_{Dz} = 0.56$	$h^2 = 0.38$	Birth
Choh et al., 2011[20]	USA	Longitudinal, nuclear/ extended	917 subjects		$h^2 = 0.67$	Birth
Height/recumbent length						
Vandenberg & Falkner, 1965[21]	USA	Longitudinal, twins (stature curve parameters)	29 MZ, 31 DZ	Concordance between MZ and DZ twins: MZ = DZ initial value (birth) MZ < DZ (velocity) MZ < DZ (acceleration)		Birth–6 y
Welon & Bielicki, 1971[22]	Warsaw, Poland	Longitudinal, nuclear	496 parent–child pairs	$r_{parent-son} = 0.36$ $r_{parent-son} = 0.43$ $r_{parent-da} = 0.54$ $r_{parent-da} = 0.59$		8 y, male 18 y, male 8 y, female 18 y, female
Garn et al., 1976[23]	USA	Cross-sectional, (adopted/ biological siblings)	6726 biological, 504 adoptive parent–offspring, pairs	$r_{adopted\ sibs} = 0.29$ $r_{adoptive-biological\ sibs} = 0.35$		Birth–18 y
Malina et al., 1976[24]	USA, white and black	Cross-sectional, nuclear	422 black families, 384 white families		$h^2 = 0.49$ (white) $h^2 = 0.37$ (black)	6–12 y
Mueller, 1976[25]	Colombia, Africa, Peru, New Guinea, Japan	Cross-sectional, nuclear		$r_{pc} = 0.29$ (average)		
Mueller, 1976[25]	USA, UK, West Europe, East Europe	Cross-sectional, nuclear		$r_{pc} = 0.37$ (average)		

(*Continued*)

Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Wilson, 1976[26]	USA	Longitudinal, twins	159 MZ, 195 DZ	$r_{MZ} = 0.58$ $r_{MZ} = 0.94$ $r_{DZ} = 0.69$ $r_{DZ} = 0.61$		Birth 4 y Birth 8 y
	Fischbein, 1977[27]	Sweden	Longitudinal, twins	94 MZ, 233 DZ	$r_{MZ} = 0.90$ $r_{DZ} = 0.60_0.70$		10—16 y
	Mueller & Titcomb, 1977[28]	Colombia	Cross-sectional, nuclear	403 families	$r_{mo-child} = 0.28$ $r_{fa-child} = 0.27$	$h^2 = 0.49$ (males) $h^2 = 0.47$ (females)	7—12 y
	Susanne, 1977[29]	Belgium	Cross-sectional, nuclear	125 families	$r_{pc} = 0.51$	$h^2 = 0.82$	17—35 y
	Roberts et al., 1978[30]	West Africa	Cross-sectional, nuclear, full and half siblings	276 sibships		Fa—child: $h^2 = 0.61$ Mo—child: $h^2 = 0.85$ Mid-parent—child: $h^2 = 0.65$ Full siblings: $h^2 = 0.81$ Paternal half-siblings: $h^2 = 0.56$	
	Fischbein & Nordqvist, 1978[31]	Sweden	Longitudinal, twins	94 MZ, 133 DZ	Average growth profile similarity within twin pair: $r_{MZ} = 0.85$ $r_{DZ} = 0.54$		10—16 y (growth curve concordance)
	Kaur & Singh, 1981[32]	India	Cross-sectional, nuclear	82 families	$r_{pc} = 0.48$	$h^2 = 0.92$	18—59 y

Solomon et al., 1983[33]	Finland	Cross-sectional, nuclear	2869 subjects		$h^2 = 0.58$	<55 y
Devi & Reddi, 1983[34]	India	Cross-sectional, nuclear	436 families	$r_{pc} = 0.34$ $r_{sibs} = 0.33$	$h^2 = 0.65$	6–13 y
Sharma et al., 1984[35]	India	Cross-sectional, nuclear/twins	610 subjects	$r_{sibs} = 0.30$ $r_{DZ} = 0.59$ $r_{MZ} = 0.98$		3–26 y
Byard et al., 1993[36]	USA	Longitudinal, nuclear (height growth curve parameters)	228 families	Age at TO: $r_{pc} = 0.17$, $r_{sibs} = 0.32$ TOV: $r_{pc} = 0.26$, $r_{sibs} = 0.35$ Age at PHV: $r_{pc} = 0.22$, $r_{sibs} = 0.35$ PHV: $r_{pc} =$ ns, $r_{sibs} = 0.32$		2–18 y
Towne et al., 1993[37]	USA	Longitudinal, nuclear/ extended (height curve parameters)	569 subjects		Recumbent length at birth: $h^2 = 0.83$ velocity 0–2 y: $h^2 = 0.67$ acceleration change 0–2 y: $h^2 = 0.78$	0–2 y
Hauspie et al., 1994[38]	Poland	Longitudinal, twins (stature curve parameters)	44 MZ, 42 DZ		Age at TO: $h^2 = 0.49$ age at PHV: $h^2 = 0.74$ PHV: $h^2 = 0.76$	8.5 y–adulthood
Beunen et al., 1998[39]	Belgium	Longitudinal, twins	99 twin pairs		age at TO: $h^2 = 0.93$ TOV: $h^2 = 0.90$ age at PHV: $h^2 = 0.92$	10–18 y

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Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Price et al., 2000[40]	USA (African-Americans)	Cross-sectional, extended families	1185 families	$r_{po} = 0.26$ $r_{sib} = 0.27$		18–92 y
	Price et al., 2000[40]	USA (Caucasians)	Cross-sectional, extended families	1185 families	$r_{po} = 0.37$ $r_{sib} = 0.37$		18–92 y
	Silventoinen et al., 2000[41]	Finland	Longitudinal, twins	3466 MZ, 7450 DZ		$h^2 = 0.66–0.82$	Birth cohorts 1928–earlier through birth cohort 1947–1957
	Luke et al., 2001[42]	Jamaicans	Cross-sectional, nuclear, extended	623 subjects		$h^2 = 0.74$ $h^2 = 0.44$ $h^2 = 0.84$	Mean 39.5 y Mean 38.8 y Mean 37.5 y
	Silventoinen et al., 2001[43]	Finland	Longitudinal, twins	4873 twin pairs		$h^2 = 0.78–0.87$	Birth cohort 1938–49
	Silventoinen et al., 2001[43]	Finland	Longitudinal, twins	2374 twin pairs		$h^2 = 0.67–0.82$	Birth cohort 1975–79
	Arya et al., 2002[44]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.36$	6–72 y
	Brown et al., 2003[45]	USA	Longitudinal, nuclear	2885 subjects		$h^2 = 0.88$ $h^2 = 0.88$ $h^2 = 0.88$	> 40 y > 55 y > 70 y
	Silventoinen et al., 2003[46]	Multiple European nationalities	Longitudinal, twins	30,111 twin pairs		$h^2 = 0.84–0.93$	20–40 y
	Li et al., 2004[47]	China	Nuclear	1169 subjects (385 families)		$h^2 = 0.65$	Mean Fa = 62.3 y, Mo = 59 y, Da = 31 y

Schousboe et al., 2004[48]	Denmark	Longitudinal, twins	299 male twin pairs, 325 female twin pairs		$h^2 = 0.69$ $h^2 = 0.81$	18–67 y 18–67 y
van Dommelen et al., 2004[17]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.10$ $h^2 = 0.44$ $h^2 = 0.52$ $h^2 = 0.15$ $h^2 = 0.74$ $h^2 = 0.58$	Birth females 1 y females 2 y females Birth males 1 y males 2 y males
Malkin et al., 2006[49]	Chuvashes (Russia)	Cross-sectional, nuclear	743 subjects		$h^2 = 0.87$	18–89 y males 17–90 y females
Macgregor et al., 2006[50]	Australia	Longitudinal, twins	618 MZ females 239 MZ males, 338 DZ females 143 DZ males, 334 DZ OS	$r_{MZ} = 0.92$ $r_{MZ} = 0.92$ $r_{DZ} = 0.44$ $r_{DZ} = 0.39$ $r_{DZ} = 0.42$	$h^2 = 0.911$	32–44 y
Saunders & Gulliford, 2006[51]	UK	Longitudinal, extended families	22,297 subjects		$h^2 = 0.49$	Standardized for age
Bayoumi et al., 2007[52]	Arab	Cross-sectional, consanguin-eous	1277 subjects		$h^2 = 0.68$	16–80 y
Czerwinski et al., 2007[53]	USA	Longitudinal, nuclear/ extended	403 subjects		$h^2 = 0.98$	Mean 38.5 y
Dubois et al., 2007[54]	Canada (Quebec)	Longitudinal, twins	85 MZ, 92 DZ		$h^2 = 0.445$ $h^2 = 0.223$ $h^2 = 0.241$ $h^2 = 0.54$	Birth 5 mo males 5 mo females 60 mo
Pan et al., 2007[55]	Hutterites	Longitudinal, extended, multiple lines of descent	806 subjects		$h^2 = 0.90$	6–89 y
Reis et al., 2007[56]	Brazil	Cross-sectional, twins	5 MZ, 9 DZ		$h^2 = 0.95$	Mean 13 y

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Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Silventoinen et al., 2007[57]	Netherlands	Longitudinal, twins	7753 pairs (at age 3)		$h^2 = 0.71-0.79$ $h^2 = 0.58-0.71$	3–12 y males 3–12 y females
	Silventoinen et al., 2008[58]	Sweden	Longitudinal, twins	99 MZ, 76 DZ, male twin pairs		0.97	17.5–20 y
	Silventoinen et al., 2008[59]	Sweden	Multiple, twins/siblings	1582 MZ, 1864 DZ, 154,970 full brother pairs		0.81	16–25 y
	Axenovich et al., 2009[60]	Netherlands	Cross-sectional, extended pedigrees	2940 subjects		0.86	Mean 48.26 y
	Jowett et al., 2009[61]	Mauritius	Cross-sectional, extended pedigrees	400 subjects		$h^2 = 0.84$	Mean 50 y
	Mathias et al., 2009[62]	Chennai (South India)	Cross-sectional, extended families	498 subjects from 26 pedigrees		$h^2 = 0.72$	Mean 42.65 y
	Poveda et al., 2010[63]	Belgium	Cross-sectional, nuclear	460 subjects		0.84	17–72 y
	Choh et al., 2011[20]	USA	Longitudinal, nuclear/extended	917 subjects		$h^2 = 0.95-0.96$ $h^2 = 0.74-0.95$	30–36 mo 0–24 mo
Weight							
	Garn et al., 1976[23]	USA	Cross-sectional, (adopted/biological siblings)	6726 biological, 504 adoptive parent–offspring pairs	$r_{\text{adopted sibs}} = 0.18$ $r_{\text{biological sibs}} = 0.27$		Birth–18 y

Wilson, 1976[26]	USA	Longitudinal, twins	159 MZ, 195 DZ	$r_{MZ} = 0.61$ $r_{MZ} = 0.86$ $r_{DZ} = 0.68$ $r_{DZ} = 0.55$		Birth 4 y Birth 8 y
Fischbein, 1977[27]	Sweden	Longitudinal, twins	94 MZ, 233 DZ	$r_{MZ} = 0.80-0.90$ $r_{DZ-males} = 0.60-0.70$ $r_{DZ-females} = 0.70-0.20$		10–16 y
Mueller & Titcomb, 1977[28]	Colombia	Cross-sectional, nuclear	403 families	$r_{mo-child} = 0.36$ $r_{fa-child} = 0.31$	$h^2 = 0.16$ (males) $h^2 = 0.21$ (females)	7–12 y
Susanne, 1977[29]	Belgium	Cross-sectional nuclear	125 families	$r_{pc} = 0.34$	$h^2 = 0.64$	17–35 y
Fischbein & Nordqvist, 1978[31]	Sweden	Longitudinal, twins	94 MZ, 133 DZ	Average growth profile similarity within twin pair: $r_{MZ} = 0.79$ $r_{DZ} = 0.22$ (females) $r_{DZ} = 0.53$ (males)		10–16 y Growth curve concordance
Kaur & Singh, 1981[32]	India	Cross-sectional nuclear	82 families	$r_{pc} = 0.34$	$h^2 = 0.39$	18–59 y
Arya et al., 2002[44]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.314$	6–72 y
van Dommelen et al., 2004[17]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.64$ $h^2 = 0.58$ $h^2 = 0.55$ $h^2 = 0.59$	1 y females 2 y females 1 y males 2 y males
Estourgie-van Burk et al., 2006[64]	Netherlands	Cross-sectional, nuclear/twins	478 MZ males, 517 DZ males, 561 MZ females, 478 DZ females, 962 DZ opposite sex		$h^2 = 0.59$ $h^2 = 0.78$	5 y males 5 y females
Dubois et al., 2007[54]	Canada (Quebec)	Longitudinal, twins	85 MZ, 92 DZ		$h^2 = 0.399$ $h^2 = 0.871$ $h^2 = 0.9$ $h^2 = 0.877$	Birth 5 mo males 5 mo females 60 mo

(*Continued*)

Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Silventoinen et al., 2008[59]	Sweden	Multiple, twins, siblings	1582 MZ pairs, 1864 DZ pairs, 154,970 full brother pairs		$h^2 = 0.64$	16–25 y
	Choh et al., 2011[20]	USA	Longitudinal, nuclear/ extended	917 subjects		$h^2 = 0.74–0.85$	1–36 mo
Biacromial breadth							
	Mueller & Titcomb, 1977[28]	Colombia	Cross-sectional, nuclear	403 families	$r_{mo-child} = 0.33$ $r_{fa-child} = 0.32$	$h^2 = 0.63$ (males) $h^2 = 0.40$ (females)	7–12 y
	Susanne, 1977[29]	Belgium	Cross-sectional, nuclear	125 families	$r_{pc} = 0.33$	$h^2 = 0.58$	17–35 y
	Kaur & Singh, 1981[32]	India	Cross-sectional, nuclear	82 families	$r_{pc} = 0.38$	$h^2 = 0.75$	18–59 y
	Devi & Reddi, 1983[34]	India	Cross-sectional, nuclear	436 families	$r_{pc} = 0.30$ $r_{sibs} = 0.37$	$h^2 = 0.49$	6–13 y
	Sharma et al., 1984[35]	India	Cross-sectional, nuclear/twins	610 subjects	$r_{sibs} = 0.32$ $r_{DZ} = 0.56$ $r_{MZ} = 0.95$		3–26 y
	Arya et al., 2002[44]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.44$	6–72 y

Salces et al., 2007[65]	India	Mixed-longitudinal, nuclear	238 brothers, 214 sisters (134 families)		$h^2 = 0.30-1.0$	4−19 y
Biiliac breadth						
Susanne, 1977[29]	Belgium	Cross-sectional, nuclear	125 families	$r_{pc} = 0.49$	$h^2 = 0.73$	17−35 y
Devi & Reddi, 1983[34]	India	Cross-sectional, nuclear	436 families	$r_{pc} = 0.18$ $r_{sibs} = 0.18$	$h^2 = 0.34$	6−13 y
Ikoma et al., 1988[66]	Japan	Cross-sectional, nuclear	3632 subjects	$r_{sibs} = 0.30$ $r_{pc} = 0.27$	$h^2 = 0.54-0.55$	>14 y
Salces et al., 2007[65]	India	Mixed-longitudinal, nuclear	238 brothers, 214 sisters (134 families)		$h^2 = 0.47-1.0$	4−19 y
Upper arm circumference						
Mueller & Titcomb, 1977[28]	Colombia	Cross-sectional, nuclear	403 families	$r_{mo-child} = 0.37$ $r_{fa-child} = 0.32$	$h^2 = 0.20$ (males) $h^2 = 0.34$ (females)	7−12 y
Susanne, 1977[29]	Belgium	Cross-sectional, nuclear	125 families	$r_{pc} = 0.30$	$h^2 = 0.50$	17−35 y
Kaur & Singh, 1981[32]	India	Cross-sectional, nuclear	82 families	$r_{pc} = 0.23$	$h^2 = 0.24$	18−59 y
Devi & Reddi, 1983[34]	India	Cross-sectional, nuclear	44 MZ, 436 families	$r_{pc} = 0.26$ $r_{sibs} = 0.24$	$h^2 = 0.46$	6−13 y
Sharma et al., 1984[35]	India	Cross-sectional, nuclear/twins	610 subjects	$r_{sib} = 0.26$ $r_{DZ} = 0.52$ $r_{MZ} = 0.95$		3−26 y
Arya et al., 2002[44]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.301$	6−72 y
Poveda et al., 2010[63]	Belgium	Cross-sectional, nuclear	460 subjects		$h^2 = 0.57$	17−72 y
Age at menarche						
Damon et al., 1969[67]	USA	Retrospective, nuclear	78 Mo−Da pairs	$r_{mo-da} = 0.24$		

(*Continued*)

Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Orley, 1977[68]	Hungary	Retrospective, nuclear	550 Mo—Da pairs	$r_{mo-da} = 0.25$		
	Kaur & Singh, 1981[32]	India	Retrospective, nuclear	72 Mo—Da pairs	$r_{mo-da} = 0.39$		
	Brooks-Gunn & Warren, 1988[69]	USA	Retrospective, nuclear (daughters)	307 Mo—Da pairs	$r_{mo-da} = 0.26$ (non-dancers) $r_{mo-da} = 0.32$ (ballet dancers)		14—17 y
	Meyer et al., 1991[70]	Australia	Retrospective, twins	1178 MZ	$r_{MZ} = 0.71$ $r_{DZ} = 0.22$	$h^2 = 0.17$ (additive effects) $d^2 = 0.54$ (dominance effects)	
	Malina et al., 1994[71]	USA	Retrospective, nuclear (university athletes)	109 mo—da pairs, 77 sib pairs	$r_{mo-da} = 0.25$ $r_{sib} = 0.44$		
	Loesch et al., 1995[72]	Poland	Longitudinal, twins (examined genetic correlations among maturity traits)	95 MZ female, 97 DZ female		h^2 (raw) $= 0.95$ $h^2 = 0.44$ (unique genetic effects) $h^2 = 0.53$ (shared genetic effects with skeletal maturity)	0—18 y
	Kirk et al., 2001[73]	Australia	Longitudinal, twins	1001 pairs, 708 subjects	$r_{MZ} = 0.51$ $r_{DZ} = 0.17$	$h^2 = 0.5$	Mean 13 y

Sharma, 2002[74]	India	Cross-sectional, twins	60 female twin pairs (30 MZ, 30 DZ)	$r_{MZ} = 0.93$ $r_{DZ} = 0.55$	$h^2 = 0.78$	Mean 17.5 y
Towne et al., 2005[75]	USA	Longitudinal, nuclear/ extended	371 subjects		$h^2 = 0.46$	9–16 y
Pan et al., 2007[55]	Hutterites	Longitudinal, extended, multiple lines of descent	806 subjects		$h^2 = 0.46$	
BMI						
Magnusson & Rasmussen, 2002[76]	Sweden	Cross-sectional, extended/ nuclear	196,743 sons, 19,972 fathers	Full bro = 0.36 mat half bro = 0.21 pat half bro = 0.11 father–son = 0.28		18–19 y
Silventoinen, et al., 2007[57]	Netherlands	Longitudinal, twins	7753 pairs (at age 3)		$h^2 = 0.60–0.78$ $h^2 = 0.57–0.82$	3–12 y males 3–12 y females
Haworth et al., 2008[77]	UK	Longitudinal, twins/nuclear	3582 twin pairs (at age 3)		$h^2 = 0.48$ $h^2 = 0.65$ $h^2 = 0.82$ $h^2 = 0.78$	4 y 7 y 10 y 11 y
Silventoinen et al., 2008[59]	Sweden	Multiple, twins/ siblings	1582 MZ pairs, 1864 DZ pairs, 154,970 full brother pairs		$h^2 = 0.59$	16–25 y
Wardle et al., 2008[78]	UK	Longitudinal, twins	5092 twin pairs		$h^2 = 0.77$	8–11 y
Lajunen et al., 2009[79]	Finland	Longitudinal, twins	2413 twin pairs		$h^2 = 0.69$ $h^2 = 0.58$ $h^2 = 0.66$ $h^2 = 0.58$ $h^2 = 0.83$ $h^2 = 0.74$	11–12 y males 11–12 y females 14 y males 14 y females 17 y males 17 y females

(*Continued*)

Table 8.1 Heritability estimates of anthropometrics during childhood and adolescence—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Martin et al., 2010[80]	USA	Longitudinal, nuclear	821 subjects		$h^2 = 0.70$	Mean 12.6 y
	Salsberry & Reagan, 2010[81]	USA	Longitudinal, mother–offspring	5453 subjects, 4994 subjects,		$h^2 = 0.29$ $h^2 = 0.20$ $h^2 = 0.61$ $h^2 = 0.56$	6–8 y males 6–8 y females 12–14 y males 12–14 y females
	Choh et al., 2011[20]	USA	Longitudinal, nuclear/extended	917 subjects		$h^2 = 0.43–0.78$	0–36 mo
Growth pattern parameters							
	Beunen et al., 2000[82]	Belgium	Longitudinal, twins	99 twin pairs		Adolescent stature growth curve parameters: $h^2 = 0.89–0.96$	10–18 y
	van Dommelen et al., 2004[17]	Netherlands	Longitudinal, twins	4649 twin pairs		Stature at different ages: $h^2 = 0.12–0.44$ $h^2 = 0.33–0.74$	Birth–2.5 y females Birth–2.5 y males
	Czerwinski et al., 2007[53]	USA	Longitudinal, nuclear/extended	403 subjects		Adolescent stature growth curve parameters: age at PHV: $h^2 = 0.72$ PHV: $h^2 = 0.65$ height at PHV: $h^2 = 0.98$	2–18 y
	Silventoinen et al., 2008[58]	Sweden	Longitudinal, twins	99 MZ males, 76 DZ males	$r_{MZ} = 0.92$ $r_{DZ} = 0.41$	$h^2 = 0.93$	17.5–20 y

Table 8.2 Recent genome-wide association and large-scale genetic association studies of growth and development traits

Trait	Reference	Population(s)	Study design	*N* (discovery and replication)	Trait age range (years)	No. of significant loci identified	% of variance explained by identified loci	Findings (loci/pathways identified)
Age at menarche								
	Liu et al., 2009[84]	EU, Chinese	GWA	3,480	~9–17	1	–	SPOCK-7 (proteoglycan; inhibits MMP-2 which mediates endometrial menstrual breakdown)
	Perry et al., 2009[85]	EU	GWA	17,510	9–17	2	–	The two loci identified were LIN28B (expressed in placental, fetal liver, testis; previously associated with normal variation in adult ht) and intergenic locus (9q31.2)
	Elks, et al., 2010[86]	EU	GWA	102,533	9–17	42	3.6–6.1%	Data indicate enrichment for gene pathways involved in (1) cellular growth, proliferation, function and maintenance; and (2) lipid metabolism, small molecule biochemistry and molecular transport, including fatty acid biosynthesis; specific loci include TAC3R, ESR1 (estrogen receptor) and four obesity-susceptibility loci (FTO, TMEM18, SEC16B, TRA2B)

(*Continued*)

Sulem et al., 2010[87]	EU, Icelandic	GWA	20,954	7–19	1	–	The locus identified was LIN28B
Birth weight							
Freathy et al., 2010[88]	EU		38,214	Birth	2	0.3–0.1%	Loci identified were (1) ADCY5 (encodes enzymes responsible for synthesis of cAMP, may influence on insulin secretion); and (2) CCNL1 (encodes protein associated with cyclin-dependent kinases)
Kilpeläinen et al., 2011[89]	EU	Association study of 12 obesity-susceptibility loci	28,219	Birth	2	–	Loci identified were (1) MTCH2 (encodes mitochondrial membrane protein critical for apoptosis); and (2) FTO (an obesity-susceptibility locus linked to food intake, energy expenditure and adiposity)
BMI							
den Hoed et al., 2010[90]	EU	Association study of 16 obesity-susceptibility loci	13,071	9–16	9	1%	Nine of 16 loci examined replicated in children, and were primarily those that are expressed in the hypothalamus, suggesting importance of neuronal control of energy balance
Kang et al., 2010[91]	African	GWA	1,931	18–74	0	–	No SNPs reached genome-wide significance

Fat mass							
Loos et al., 2008[92]	EU	GWA	5,988 Children	0–11	1	0.24%	In children aged 7–11 years, each additional copy of rs17782313 was associated with BMI changes. rs17782313 mapped 188 kb downstream of MC4R, a known obesity gene
Height							
Soranzo, et al 2009[93]	EU	GWA	19,798	16–99	17	< 0.20%	Numerous, including CATSPER4 (associated with male fertility), TMED10 (TMP21), NPR3 (encodes natriuretic peptide (NCP) involved in blood pressure regulation, JAZF1 (implicated in type 2 diabetes and prostate cancer susceptibility)
Kang et al., 2010[91]	African	GWA	1,931	18–74	14	0.20%	No SNPs reached genome-wide significance
Lango et al., 2010[94]	EU	GWA	183,727	Adults	180	10%	Numerous, including hedgehog signaling, TGF-β signaling, many skeletal growth and skeletal dysplasia genes and pathways identified

(*Continued*)

Lanktree et al., 2011[95]	6 Ethnicities	Association study of 2000 cardiovascular disease susceptibility loci	114,223	21–80	64	–	Numerous; results indicate enrichment of the following pathways: energy metabolism, insulin and growth hormone signaling, heart morphogenesis, cellular growth and apoptosis, circadian rhythm, and collagen formation, bone formation and remodeling
PHV, age at PHV							
Sovio et al., 2009[96]	EU	Association study of 43 height-related loci	3,538	0–31	24	–	Seven SNPs [SF3B4/SV2A, LCORL (×2), UQCC, DLEU7, HHIP, HIST1H1D] were associated with PHV (infancy); five SNPS (SF3B4/SV2A, SOCS2, C17orf67, CABLES1, DOT1L) were associated with PHV (puberty); no significant associations with age at PHV (puberty). HHIP is a component of the hedgehog signal transduction pathway which is involved with embryogenesis and development. SOCS2 is a negative regulator of cytokine/cytokine hormone pathway JAK/STAT which influences growth and development

BMI: body mass index; PHV: peak height velocity; GWA: genome-wide association; SNP: single-nucleotide polymorphism; TGF: transforming growth factor.

(as in Turner's syndrome) all result in growth retardation. Formal quantitative genetic analyses of birth weight find somewhat lower heritability estimates than for body weight and length in postnatal life, which are both highly heritable (see below). Assessment of genetic influences on birth weight is complicated, however, by the fact that prenatal growth (at least as measured by birth weight) is influenced by both the genetic make-up of the fetus and the maternal intrauterine environment. There is no fully satisfactory way to partition these two sources of variation. Therefore, not surprisingly, estimates of the influences of fetal genes, maternal genes, non-genetic maternal factors and random environmental effects on fetal growth vary considerably across studies. The role of fetal genes varies from 0 to 50%, maternal factors from 27 to 50%, and random environmental factors from 8 to 43% in the variation in birth weight.[97]

For example, a classic study by Penrose[12] attempted to partition the variance in birth weight among fetal genes, maternal genes, non-genetic maternal factors and random environmental effects. He concluded that fetal genes accounted for approximately 18% of the phenotypic variance, while "maternal factors" (a combination of both genetic and uterine environment) explained approximately 40% of the phenotypic variance. The importance of uterine environment in the control of prenatal growth is also demonstrated by the changes in twin correlations from birth onwards (e.g. Wilson, 1976).[26] Intrapair differences in the birth weight of MZ twins are often significant at birth (tending to be larger than differences between DZ twins) because MZ twins compete for placental resources. Differences in weight between MZ twins decrease over time. By 3 years of age, the MZ twin correlation is about 0.80–0.90 and the DZ twin correlation is about 0.40–0.50.

A problem with the use of birth weight as a measure of prenatal growth is that it represents growth status at a variety of maturational ages depending on gestational age. Most studies of the genetics of birth weight have not controlled for gestational age. This flaw has probably led to underestimates of genetic influences. Indeed, using a variance components method for pedigree data, and modeling a gestational age covariate effect, the present authors found a high heritability of birth weight in the Fels Longitudinal Study population ($h^2 = 0.67$;[20]). Continued work along these lines will help to identify specific factors influencing fetal growth and development. However, progress depends on measurement strategies that better capture the process of fetal development (e.g. serial ultrasound biometry).

Height

Data from nearly 4000 individuals in 1100 nuclear families in England analyzed by Pearson and Lee[98] provide perhaps the earliest evidence for the inheritance of height. In this landmark study, Pearson and Lee found a significant correlation between spouses (0.28), showing positive assortative mating for height, but higher correlations between

siblings (0.54) and between parents and offspring (0.50). Since the expected correlation between full siblings and between parents and offspring would be 0.50 if the h^2 of the trait was 1.0, they concluded that the population variation in height was highly determined by genetic factors. These early results have been corroborated by hundreds of subsequent family studies. In populations around the world, the estimates of the h^2 of height range from 0.60 to above 0.90, clearly showing that height is a highly heritable trait.

In a review of 24 studies of parent–child correlations of height and weight, however, Mueller[25] indicated that population estimates of heritability tend to be systematically lower in developing countries than in affluent countries. There are several reasons why this might be so. As mentioned earlier, according to classic quantitative genetic theory, the heritability of height or any trait is a function of the population in which the estimate is made, as well as of the trait itself. Heritability estimates will tend to be higher if there is positive assortative mating (i.e. a significant phenotypic correlation between parents). And indeed, assortative mating for height has been found in European or European-derived populations more frequently than in non-European populations. Also, non-European populations in the developing world tend to live under more nutritional and disease stress than European populations. In these populations such environmental factors have the potential to affect a given trait more than in affluent populations. Since heritability is the proportion of variance due to genetic influences, a larger proportion of environmentally induced variation will reduce the heritability. In addition, many non-European populations are experiencing rapid economic change, resulting in the growth environment of children differing quite markedly from that of their parents, thus decreasing parent–offspring correlations and the estimate of total variation attributable to genes.

Weight, Circumferences and Skinfolds

Whereas the heritability of skeletal lengths (e.g. height, sitting height) tends to be high, the h^2 of skeletal breadths (e.g. biiliac and biacromial diameters) tends to be somewhat lower, averaging between 0.40 and 0.80. In turn, skeletal breadths tend to have higher heritabilities than circumferences and skinfolds. It has been assumed that soft-tissue traits are more easily altered by the changing nutritional environment of individuals than are skeletal tissues, which respond less quickly to changes in nutritional status, and as a result have a greater proportion of their variance explained by environmental, rather than genetic, factors.

Longitudinal Studies

As mentioned earlier, the vast majority of family studies of growth and development are cross-sectional. Only a few studies have longitudinal growth and development data from related children that permit genetic analyses of the processes of growth and development.

Some of these longitudinal studies of the genetics of growth, for example, examined changes in parent—child or sibling correlations from age to age. Reports from the Fels Longitudinal Study,[99] Poland[22] and elsewhere[100,101] found that parent—child correlations for height increased during the first 4 years of life, decreased during adolescence (when heterogeneity of the maturational tempo disrupted familial similarity) and subsequently rose above the prepubertal level.

Modern longitudinal genetic epidemiological studies of growth and development use growth curve-fitting methods to pinpoint growth and maturational events, particularly of changes in the tempo of growth in a measure, and then examine growth curve parameters in genetic analyses. For example, Beunen et al.[82] report high h^2 estimates for the ages at take-off and at peak height velocities, and the heights at those ages. Van Dommelen et al.[17] fitted curves to serial infant height (length) and weight data from a large sample of Dutch twin infants and found significant heritabilities of various growth curve parameters. Similar analyses of Fels Longitudinal Study data are discussed in more detail in Section 8.5.

Maturation

Not only is physical size heritable, but the timing and tempo of maturation are also significantly controlled by genes. A number of early studies of dental development found that radiographic measures of the timing of tooth formation (calcification) and dental emergence were more highly correlated within MZ twin pairs than DZ twin pairs, suggesting a heritability of 0.85—0.90.[102] The number and pattern of dental cusps were also found to be under genetic control. The rate of skeletal maturation has been compared in siblings over time in several reports, with the general finding being that there is a great deal of similarity between siblings in the age of ossification onset of bones in the hand and foot. The general pattern of skeletal maturation (i.e. the tendency to be an "early" or "late" maturing individual) also suggests that the tempo of development is highly heritable, with sib—sib correlations of 0.45.[103]

The process of maturation is commonly believed to be controlled, at least partially, by genes independent from those controlling final size. This conjecture stems from the observation that siblings may reach identical height even though they differed in the timing of maturational events.[104] Further and more widespread use of the multivariate quantitative approaches discussed in Section 8.2, in which genetic and environmental correlations between different traits may be calculated, will allow for greater understanding of the extent of shared genetic and non-genetic factors underlying growth and development traits.

Age at menarche is one of the most studied developmental traits. A number of early studies suggested that age at menarche has a genetic basis (e.g. Boas, 1932).[105] The mother—daughter and sister—sister correlations in the age at menarche were close to 0.50, indicating a high degree of genetic determination of age at menarche. These and

later studies, however, have relied primarily on recalled ages at menarche, and thus recall bias (greater in mothers than in daughters) is introduced into these estimates. Later studies have confirmed a strong genetic influence on age at menarche,[67,106] although the familial correlations were lower than in the early studies (~0.25−0.45). In a sample of 371 female Fels Longitudinal Study subjects of varying degrees of relationship to each other, and from whom age at menarche data had been collected during their participation in the growth and development aspect of the study, Towne et al.[75] found a substantial and significant heritability of 0.49 for age at menarche.

8.5 EXAMPLES FROM THE FELS LONGITUDINAL STUDY

This final section highlights some of the topics discussed in the preceding sections through examples of published and ongoing genetic analyses conducted over the years in the Fels Longitudinal Study.

The Fels Longitudinal Study began in 1929 in Yellow Springs, Ohio. It was one of several longitudinal studies of child growth and development initiated in the USA between the end of World War I and the start of the Great Depression, and it is the only one that has survived to today. Although the Fels Longitudinal Study did not begin with an interest in genetics, familial data began to be collected soon after the study began. Most of the mothers who enrolled their children in the early years of the study had more children later, and many of those children were subsequently enrolled. A set of MZ, dichorionic triplets was recruited early in the study specifically to examine their similarities in growth and development. Another set of triplets and a few twin pairs were also recruited in later years. Over time, other relatives were incorporated into the study, the first of these being siblings of original subjects as mentioned above, and then offspring of original study subjects. The Fels Longitudinal Study today has more than 1000 active research subjects with various serial data from infancy, and mixed cross-sectional and longitudinal data from more than 1000 of their relatives. These individuals represent about 200 kindreds consisting of both nuclear and extended families.

The description of the "Genetics Program" of the Fels Longitudinal Study written by its first director, Lester W. Sontag,[107] is remarkable for its modern-sounding tone. Sontag noted that many aspects of growth and development were likely to have significant genetic determination, but are influenced by environmental factors as well. He noted that the study included many families with two or more children, and that these "... constitute the material for the study of inheritance of growth patterns as well as of metabolic characteristics".

For example, the set of MZ, dichorionic triplets mentioned above were the subject of three early reports that described their similarities in physical and mental traits as young children, striae in their bones and the onset of ossification from infancy through

pubescence.[108–110] Soon after the triplets' eighteenth birthday, Reynolds and Schoen[111] published a description of their growth patterns. A paper by Reynolds[112] is especially noteworthy because it used familial data from different types of relatives to examine the effects of degree of kinship on patterns of ossification. Included in this analysis were the set of identical triplets, as well as three pairs of identical twins, 22 pairs of siblings, eight pairs of first cousins and 18 unrelated children. Reynolds found that close relatives were very similar in pattern of ossification, distant relatives less so, and unrelated participants even less similar.

A series of studies from the late 1950s to the late 1960s by Garn and colleagues used data from siblings, parents and offspring to examine patterns of familial correlations in traits pertaining especially to dental and skeletal maturation. An example of the analyses and sample sizes from this period is provided by Garn et al.,[113] who examined ossification data from radiographs of the hand–wrist and chest for 72 parent–child pairs, 318 sibling pairs, four pairs of DZ twins and four pairs of MZ twins. Since these were serial data taken at half-yearly intervals from the ages of 1 to 7 years, there were 1211 pairings of parent–child data, 6690 pairings of sibling data, 102 pairings of data from DZ twins and 176 pairings of data from MZ twins. Garn et al.[113] concluded that, "In these well-nourished ... Ohio-born white children, genes appear to account for a major proportion of ossification variance during growth". These investigators also examined the genetics of various dental traits, including the timing of stages of dental development,[102] tooth morphology[114] and the appearance of discrete dental traits.[115] The influence of familial factors on growth in body size was also examined.[99,102]

Genetic analyses of growth and development data from the Fels Longitudinal Study have had a resurgence in the last 20 years. This is largely due to advances in statistical genetic methods that maximize the amount of information available in longitudinal data from large numbers of relatives of varying degrees of relationship to one another, as well as advances in molecular genetic methodology that allow for relatively low-cost genotyping. For example, Towne et al.[37] fitted a three-parameter function to serial recumbent lengths from 569 infants in order to characterize each individual's unique pattern of growth during infancy. Figure 8.2 shows the growth curves of two infant boys who differ in their patterns of growth. Boy #1 started out in life shorter than boy #2, but had a rate of increase in recumbent length that was much greater than that of boy #2. Both boys, however, experienced about the same amount of growth (~42 cm) from birth to the age of 2 years. In this study, substantial h^2 estimates of 0.83 for recumbent length at birth, 0.67 for rate of increase in length and 0.78 for a parameter describing the curvilinear shape of growth in recumbent length from birth to 2 years were found.

Fels Longitudinal Study investigators have used the triple logistic model of Bock et al.[116] as implemented in the AUXAL program[117] to fit growth curves to extensive serial stature data from some 600 study subjects in order to examine individual

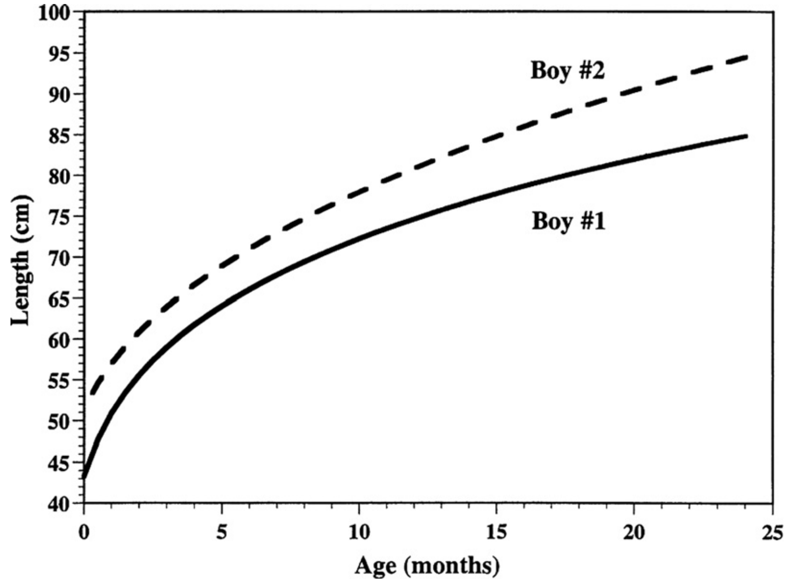

Figure 8.2 Height distance curves for two boys with differing growth patterns between birth and 24 months old.

differences in patterns of growth and to conduct multivariate quantitative genetic analysis of different parameters of the pubertal growth spurt. For example, Figure 8.3 shows the growth and velocity curves of two girls with visibly different growth patterns. Girl #1 was only 9.37 years old when she was at the peak of her pubertal growth spurt, whereas the age at peak height velocity of girl #2 was 13.09 years. At the time of peak height velocity, girl #1 was shorter than girl #2 (141.1 vs 156.5 cm), which is expected given her younger age at peak height velocity, but at the age at peak height velocity, girl #1 had a higher rate of growth than girl #2 (8.8 vs 6.4 cm/year). By the end of their growth, girl #1 was a petite woman (158.5 cm) while girl #2 was somewhat taller than average (170.6 cm). Highly significant h^2 estimates in the order of 0.85 for age at peak height velocity, 0.61 for growth rate at peak height velocity and 0.96 for stature at the age of peak height velocity were found. Especially interesting was the finding of additive genetic correlations between these pubertal growth spurt parameters that were significantly lower than 1.0, suggesting incomplete pleiotropic effects of genes on different aspects of growth. That is, these three different growth curve parameters may have, to some extent, unique genetic underpinnings.

In an association study, Towne et al.[118] found evidence of the effects of a functional polymorphism in the β-subunit of the luteinizing hormone gene (LH-β) on stature during childhood. A total of 736 individuals, from 137 nuclear and extended families, measured a total of 13,300 times between the ages of 2 and 18 years, were genotyped for the LH-β polymorphism. Individuals with the less common LH-β allele were shorter

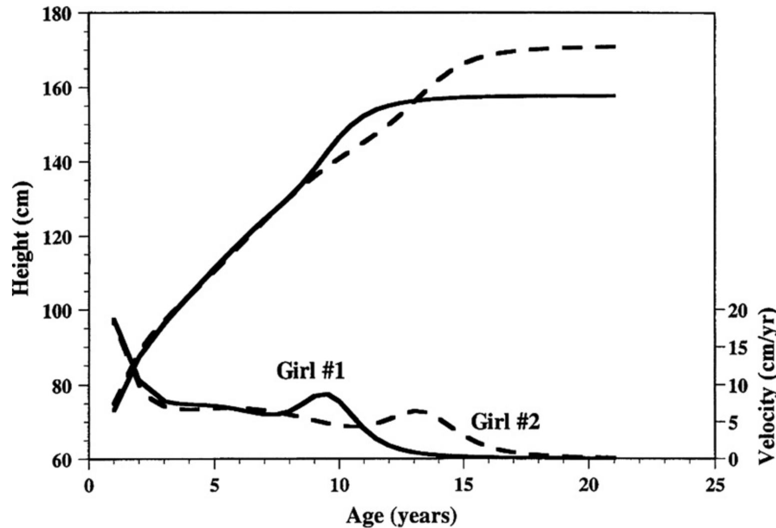

Figure 8.3 Height distance and velocity curves for two girls with different growth patterns between 12 months and 20 years old.

than those homozygous for the common LH-β allele at all ages, with this difference steadily increasing with age (e.g. on average, heterozygotes were 0.5 cm shorter than homozygotes at age 2, and they were 2.0 cm shorter at age 18). These results suggest that the LH-β polymorphism is associated with at least modest differences in the stature of children at all childhood ages.

Towne et al.[83] recently examined the mid-childhood growth spurt in Fels Longitudinal Study subjects. Presence of a mid-childhood growth spurt was found to have a significant heritability of 0.37 ± 0.14 ($p = 0.003$). From linkage analysis, two QTL with suggestive LOD scores were found: one at 12 cM on chromosome 17p13.2 (LOD = 2.13) and one at 85 cM on chromosome 12q14 (LOD = 2.06). While the chromosome 17 finding was novel, other investigators have found evidence of linkage or association of growth measures to markers in the same region of chromosome 12.

Fels Longitudinal Study investigators have used multivariate variance components methods incorporating parametric correlation functions to model the heritability and genetic and correlational structures of skeletal maturity throughout childhood. For example, a total of 6893 annual hand–wrist radiograph skeletal age assessments from a sample of 807 children aged 3–15 years representing 192 nuclear and extended families were simultaneously analyzed. The best fitting model had 65 parameters and allowed for an exponential decay in genetic and environmental correlations as a function of chronological age differences. From this model, the h^2 estimates of skeletal age at each chronological age were: 3 = 0.71, 4 = 0.73, 5 = 0.77, 6 = 0.93, 7 = 0.78, 8 = 0.77, 9 = 0.73, 10 = 0.63, 11 = 0.45, 12 = 0.39, 13 = 0.34, 14 = 0.23 and

15 = 0.11. The genetic correlation matrix showed a pattern of decreasing correlations between skeletal age at different chronological ages as age differences increased (e.g. ρ_G between skeletal age at age 3 and skeletal age at age 4 was 0.96, but between skeletal age at age 3 and skeletal age at age 15 ρ_G was 0.56). The random environmental correlation matrix showed an even more pronounced pattern of decreasing correlations between skeletal age at different chronological ages as age differences increased (e.g. ρ_E between skeletal age at age 3 and skeletal age at age 4 was 0.77, but ρ_E between skeletal age at age 3 and skeletal age at age 15 was only 0.12). These results show a high heritability of skeletal age through early puberty, and suggest that skeletal maturation at different stages of development is influenced by different sets of genes and environmental factors.

8.6 SUMMARY

For over a century there has been scientific interest in the genetic underpinnings of growth and development. But, as with any area of scientific inquiry, to one degree or another all of these studies were limited by the methods and technologies available to them at the time. For that reason, most of the literature on the genetics of growth and development until relatively recently is limited to h^2 estimates of measures of growth and development gathered once from first degree relatives. The opportunities exist today, however, for far more sophisticated genetic epidemiological studies of growth and development.

One major problem, though, is that modern genetic epidemiological studies of growth and development can be expensive undertakings. Such studies are readily justified, however, on very practical and applied grounds. Foremost among these is that the growth and development of children can have health consequences later in life. Thus, to a large extent, genetic epidemiological studies of growth and development are inherently of biomedical interest. Indeed, much of the current research emphasis in the Fels Longitudinal Study pertains to studies of the relationships between age-related changes in body composition (including those that occur during childhood) and the development and progression of cardiovascular disease (CVD) and type 2 diabetes mellitus risks in later life, an area of active research today.

For example, work by Barker and colleagues in the UK,[119] as well as others, suggests that early growth variation in size and body composition (during prenatal as well as postnatal periods) influences the risk of a number of disorders including hypertension, obesity, heart disease and diabetes. Longitudinal family studies of growth and development are needed to fully evaluate these hypotheses. A current Fels Longitudinal Study project is aimed at evaluating the role of birth weight and infant growth in predisposing to adult-onset disease risk factors, taking into account the significant heritable components of both early growth and various adult disease risk factors.

Demerath et al.,[120] for example, found that birth weight was negatively associated with fasting insulin concentration in adulthood after adjusting for body mass index and age, but after taking into account the significant heritability of insulin concentration, birth weight accounted for only 1–2% of the phenotypic variance of fasting insulin concentration.

Demerath et al.[121] found significant heritabilities of measures of infant weight and weight change, and Demerath et al.[122] found significant associations between measures of postnatal weight gain (which had earlier been found to be significantly heritable) and direct measures of adiposity in adulthood (which also are significantly heritable). In a similar vein, another ongoing Fels Longitudinal Study project is examining changes in traditional CVD risk factors during growth and development, and associations between growth-related events and CVD and type 2 diabetes risk in adulthood. For example, although serum lipid and lipoprotein levels track from childhood to adulthood, Czerwinski et al.[123] found differences in the heritabilities of lipid and lipoprotein measures in children sampled before and after puberty. In general, heritability estimates were higher after puberty, suggesting that the genetic control of lipid and lipoprotein levels may be influenced by maturational factors. Czerwinski et al.[53] found highly heritable measures of patterns of growth (e.g. timing of the pubertal growth spurt) to be associated, at least on the phenotypic level, with heritable measures of adult disease risk such as blood pressure and body mass index. Future studies based on these findings will explicitly explore pleiotropic effects of genes on measures of growth and measures of disease risk in adulthood.

Placing studies of growth and development more squarely in the context of biomedical research will allow auxological investigations to move beyond being descriptive studies, and will help to open the door to resources needed to conduct modern genetic epidemiological studies of growth and development.

GLOSSARY

Allele: A variant of the DNA sequence at a particular locus. Typically, individuals possess two allelic variants at each locus, one each derived from the maternal and paternal chromosomes. The two alleles may be identical or different, making the individual homozygous or heterozygous, respectively, at that locus.

Canalization: The tendency of a growth-related trait to follow a certain course or trajectory over time.

Complex trait/phenotype: Any phenotype whose expression is influenced by multiple genes, or by one or more genes and one or more environmental factors. Complex traits can be quantitative or discrete.

Epistasis: Interactions between alleles at different loci. Also known as gene × gene interaction.

Gene: A segment of DNA that codes for a specific protein or enzyme.

Genotype: The group of genes making up an organism. The genotype at a particular locus consists of the two alleles present at that locus.

Genome-wide association (GWA) study: Use of high-density SNPs to test for associations between genomic variation and trait variation across the genome.

Heritability: A measure that expresses the extent to which phenotypes are determined by genes transmitted from parents to their offspring. Heritability (in the narrow sense) is defined as the proportion of the total phenotypic variance that is attributable to the additive effects of genes.

Identity by descent (IBD): Identical alleles at the same locus found in two related individuals that are identical because they originated from a common ancestor.

Identity by state (IBS): Identical alleles found within two individuals. If the two individuals are related, the two alleles may also be identical by descent if they are replicates of the same ancestral allele from a previous generation.

Kinship coefficient: The probability that two genes from two individuals for a given locus are identical by descent. A general measure of relatedness.

Linkage analysis: A test of co-segregation of traits and genomic variants used to localize a trait to a chromosomal region.

Linkage disequilibrium: Non-random association within a population of alleles at two or more linked loci. Linkage disequilibrium decays with increasing genetic (recombination) distance between loci.

Locus: The particular position on a chromosome where a gene resides.

Monogenic: A trait is monogenic if that trait is influenced primarily or entirely by alleles at only one genetic locus.

Mutation: Specific sequence variants in the nucleotide sequence of a gene. These variants may or not be inherited.

Oligogenic: A trait is oligogenic if it is influenced by a few loci of significant, individually detectable effects.

Phenotype: The observable characteristics of an organism, or a specific trait produced by the genotype in conjunction with the environment.

Polygenic: A phenotype is polygenic if it is influenced by many genes of relatively small individual effects, such that the influence of any single locus is very difficult to detect on its own.

Polymorphism: The joint occurrence in a population of two or more genetically determined alternative phenotypes, each occurring at an appreciable frequency (arbitrarily, 1% or higher). A polymorphism may be defined at either the protein level (e.g. Rh+ and Rh− red blood cell groups) or at the DNA level (alternative alleles at a locus).

Quantitative trait locus (QTL): Any locus harboring genetic variants that influence variation in a complex phenotype.

Recombination (crossover): The exchange of segments of homologous chromosomes following chromosomal duplication and synapse formation during meiosis. Recombination is responsible for the production of offspring with combinations of alleles at linked loci that differ from those possessed by the two parents.

Single-nucleotide polymorphism (SNP): A type of DNA sequence variant where a single nucleotide (A, T, C or G) at a particular location in the genome differs between individuals.

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INTERNET RESOURCES

Analytical resources

Columbia University: Terwilliger laboratory (various analytical software): http://linkage.cpmc.columbia.edu/index_files/Page434.htm
Department of Genetics, Texas Biomedical Research Institute (various analysis programs including SOLAR): http://txbiomed.org/departments/genetics.aspx
Division of Statistical Genetics, University of Pittsburgh (various analytical resources): http://watson.hgen.pitt.edu/

Eigenstrat (software for population stratification adjustment): http://genepath.med.harvard.edu/~reich/Software.htm
Laboratory of Statistical Genetics: Rockefeller Univ. (a comprehensive analytical resource): http://linkage.rockefeller.edu/
Merlin (linkage analysis software): http://www.sph.umich.edu/csg/abecasis/Merlin
The Human Genetic Analysis Resource: http://darwin.cwru.edu/
UCLA Human Genetics (various analytical resources): http://www.biomath.medsch.ucla.edu/faculty/klange/software.html
University of Michigan, Center for Statistical Genetics: Abecesis Lab (various analytical software programs): http://www.sph.umich.edu/csg/abecasis/

General resources

GENATLAS (Database): http://www.dsi.univ-paris5.fr/genatlas/
National Center for Biotechnology Information: http://www.ncbi.nlm.nih.gov/
National Human Genome Research Institute (NHGRI): Genome - wide Association Database: http://www.genome.gov/gwastudies/
National Human Genome Research Institute (NHGRI): http://www.genome.gov/
Office of Genomics and Disease Prevention of the Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/genomics/default.htm
Online Mendelian Inheritance (Database): http://www.ncbi.nlm.nih.gov/omim
SNAP (database): http://www.broadinstitute.org/mpg/snap/
The Center for Human Genetics (Marshfield Clinic Research Foundation): http://www.marshfieldclinic.org/chg/pages/default.aspx
The Genome Database: http://www.ncbi.nlm.nih.gov/sites/genome
U.S. Department of Energy Genomics Site: http://genomics.energy.gov/
Wikipedia (general concepts in genetics): http://en.wikipedia.org/wiki/Statistical_genetics