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GROWTH AND GENETICS

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Abstract: *From the many studies of growth from different view points, a series of principles can be derived summarising the genetic control of growth. These principles are illustrated in relation to fetal and postnatal growth. Genetic control is seen to be complex, operating throughout the whole growth period; genetic effects are tissue specifie and time specific; there are many genes involved, and many are pleiotropic.*

Key words: *Genetic defects; Growth factors; Switch mechanisms; Birth weight; Pleiotropism.*

Introduction: Growth and Genetics

What do we know of the genetic control of growth now that we did not know at mid-century? Almost all of our knowledge of growth, apart from the earlier descriptive studies, derives from this period, – recognition of the importance of longitudinal studies, the translation of measurements at given ages into velocities, the analysis of individual growth curves into the component segments, the explanation of differences in the growth curves between populations in terms of differences in these velocities, and the identification of the factors that affect them. So too almost all of our knowledge of the genetics of growth, slight though it is, derives from this period and the last few years especially.

Investigation of the genetic control of human growth and development is not straightforward. Growth in the fetal and postnatal phases is essentially a continuum, yet each phase presents characteristic difficulties. In the prenatal period classic methods of genetic analysis, examining patterns of variation within families and comparing relatives of different degrees, cannot be applied. There are virtually no data relating to more than one member of a sibship, except for the culmination of fetal growth, the weight of the infant at birth. Of noninterventive techniques, radiography did little more than trace growth in size (Russell 1969); more recently, ultrasonic scanning holds great promise, as it allows serial examinations from which can be collected data on growth of the body and its parts, and on the onset of specific functions, which can be used for analysis of familial correlations. With amniocentesis there is opportunity to accumulate data on biochemical variants. Yet so far most genetic knowledge of the prenatal phase of growth has only been obtained indirectly. As regards portnatal growth, it is easier to obtain information on sibs and other pairs of relatives of like age, yet from the duration of the human growth process there will be very few investigators who can trace development over a period in family members of more than one generation, though there are a few very farsighted studies where this is being done.

Single genes affecting normal growth

The Mendelian Template

One approach to identify specific genes acting both pre- and postnatally is that of the *Mendelian template* (Roberts 1981). A considerable amount about normal growth can be inferred from the genetic defects that occur. At the locus for every gene that produces an established pathological entity, there must also be a normal allele controlling normal growth. The well-established dominant condition, classical achondroplasia, is characterised by shortening of the long bones, particularly their proximal segments, wide shallow pelvic inlet, poorly developed iliac wings, narrowed sacrum and sciatic notch, short ribs, and other skeletal abnormalities. These many skeletal malformations all derive from a single functional defect, a quantitative defect in the endochondral ossification. The histology is normal, with regular columns of cells with normal matrix; it is the rate that is at fault. Therefore there must be at the achondroplasia locus a normal allele which is involved in the control of the rate of endochondral ossification.

In severe rhizomelic chondrodysplasia punctata, an autosomal recessive condition, the limbs are also strikingly short at birth, there is metaphyseal cupping, splaying and abnormal ossification especially of the femur and humerus, and there occur associated defects of the heart, skin, palatal and mental development. Here the mechanism of the bone defect is different, for it is the endochondral bone formation that is grossly abnormal as shown histologically in the deficient columnar arrangement, with slight calcification of the matrix. Therefore there must be at the same locus a normal allele controlling, or involved in, the endochondral ossification, but this time not quantitatively but qualitatively. The same allele may also have pleiotropic effects, being involved in normal heart and skin development. In chondro-ectodermal dysplasia (the Ellis van Creveld syndrome) another autosomal recessive, the distal limb long bones are shortened and indeed the distal phalanges are very hypoplastic, the radius is broadened distally and often dislocated proximally, and the proximal tibial shaft is flared. Here the error occurs in the control of differentiation as well as organisation, for often the capitate and hamate bones, and sometimes the other carpal bones, are fused, and there may be ulnar polydactyly. Histologically the cell columns, though generally parallel in arrangement, are disordered, shortened, and fewer than normal. There must therefore be a normal allele directing the differentiation of the normal centres. But it must also control formation of hair and tooth buds, for hypotrichosis and hypodontia are characteristic of the condition.

In Crouzon's craniofacial dysostosis, a dominant condition, with its characteristic frontal bossing, flat face, hypertelorism, small maxilla but normal lower jaw, the defects are due to a shortening of the anterior part of the base of the skull and early closure of the coronal, sagittal and lambdoid sutures. There must therefore be a normal allele controlling growth in this restricted part of the skeleton. Such a template approach shows the complexity of genetic factors in fetal growth, the interaction of quantitative and qualitative control, the large number of genes involved, and particularly the

pleiotropic effects of many of them. But this approach is gross, and more detailed information comes from other sources.

Physiological

Another approach is the *physiological cum genetic*. There is no doubt that systemic effects are extremely important in coordinating overall body growth during fetal and postnatal periods and though these operate at the gross level these too are under genetic control. Several genes are known.

a) *Growth hormone* (GH), produced by the anterior pituitary is critical, for overproduction produces gigantism and underproduction dwarfism. Growth hormone is controlled by a gene whose existence and effects can be demonstrated by the use of transgenic experimental animals (Palmiter et al. 1983). The hormone can be produced artificially and applied to ameliorate disorders of growth in children The genes for growth hormone are located at chromosome 17q22–24, and that for its receptor (GHR) at 5p13–12. But growth hormone production and release are stimulated by the growth hormone releasing hormone (GHRH), and the gene for this is located at 20p11.23.

b) There are the insulin like growth factors, the *somatomedins,* peptides that are growth hormone-dependent that promote cellular proliferation (Hintz 1980). In man there are at least two distinct somatomedin peptides. Human insulin-like growth factor I (IGF I) is an important mediator of balanced growth of most tissues of the body, the molecular structure has been established, and the genes have been sequenced. The gene for IGF I is situated at chromosome 12q23, and that for the receptor for this factor on chromosome 15. The gene for IGF II is situated at chromosome 11p15.5, and its receptor on chromosome 6q. But IGF I production is regulated also by dietary intake and nutritional status, apparently through alterations of the GH receptors and of post receptor responsiveness to GH.

c) Then there is the *platelet derived growth factor* (PDGF); its polypeptide chains are under separate genetic control. The alpha polypeptide is situated on chromosome 7, and the beta polypeptide on chromosome 22. As for the genes for the receptors, those of the alpha polypeptide are situated at chromosome 4q11–13 and for beta polypeptide at 5q33–35. PDGF is a potent mitogen for cells of connective tissue origin and plays a central role in controlling glial cell differentiation and division (Ross et al. 1986).

d) The *transforming growth factor* is now known to be heterogeneous. Transforming growth factor alpha is situated at chromosome 2p13, while transforming growth factor beta has several subdivisions, beta 1 being situated at chromosome 19q13.1 and beta 3 at chromosome 14q24. Perhaps the multiple functions formerly associated with this factor are subsumed by its different components. TGF beta stimulates or inhibits cell division, and positively or negatively controls cell differentiation; e.g. it induces chondrogenesis and squamous differentiation of bronchial epithelium but blocks myogenesis and adipogenesis.

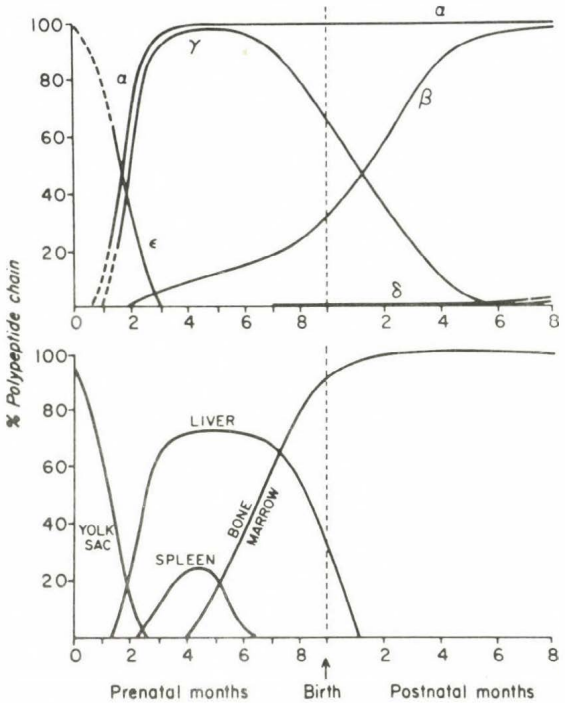

Fig. 1: Ontogeny of human hemoglobin chains and sites of blood formation at different stages of development. Note this close similarity in the time sequences of yolk sac and ε-chain, hepatosplenic and γ-chain, and bone marrow and β-chain erythropoiesis

Growth factors are so called because of their mitogenic effects, and with the availability of nucleotide sequence data many molecules that affect cell differentiation, induction, pattern formation, and that stimulate and inhibit cell division, are seen to cluster together into closely related growth factor families. The list of growth factors which have different effects during development is growing rapidly. The view that the division of a cell type and its effect on the growth of a particular tissue during development is under the control of a single, unique, locally produced growth factor is no longer tenable. The evidence is increasing that single growth factors have diverse functions, that embryonic cells respond to particular growth factors in different waqys, and that cells from the same region of the embryo may respond to the same growth factor differently at different times.

Genetic mechanisms

The genetic information controlling growth, as all other body characters, is the DNA transmitted on the parental chromosomes to the new organism at the moment of conception. Meticulously reproduced in subsequent cell divisions, it controls the structures of all the proteins making up and made by the new organism, regulates their synthesis and their interaction with other substances, to give the biochemical make up of each individual. The sequence of developmental differentiation, and individual variations in it, are consequences of differences in enzyme or protein synthesis. The

gene-controlled synthetic processes take place in the environment provided by the cell cytoplasm, where it is subject to other influences besides the genes.

Further instructions come from the highly organised cascade and cyclical chemical reaction systems, in which the product of one reaction forms the substrate of the next. The miracle of differentiation from the fertilised ovum of different kinds of cells, tissues and organs is brought about through a sequence of changing populations of cells organised in increasingly complex patterns. The delicacy of the process of cell division ensures that daughter cells contain virtually identical sets of genes. As division succeeds division, divergence of cells occurs until they have differentiated into types quite different in appearance and function e.g. muscle, pigment or nerve. These different cells behave almost as though they had been given different sets of genes, but this is clearly not so. It is not the genes or the chromosomes that are distributed unequally, instead the cell must be manifesting the effects of only a small fraction of its genes, in the differing chemical environments that have developed. The genetic potentialities of the cells are far greater than the actualities that they express.

The genetic control of embryonic and fetal development occurs as a result of (1) switch mechanisms, switching on and off the activity of particular genes, at (2) specific times in development, and producing (3) specific substances. Variations in fetal growth and development therefore may arise by (1) variation in efficiency or failure of the switch mechanism, (2) variation in its timing and (3) variation or errors in the substances synthesised. There is every reason to believe that similar control exists postnatally, with the switch being responsive to feedback from the body itself in response also to environmental stimulation. This model can be validated by examination of the variant substances or deficiency of substances, in association with fetal developmental stages (Roberts 1986). Such studies show

1. There is tissue specificity of isoenzymes;
2. There is subcellular localisation;
3. There is temporal variation in isoenzymes, both quantitative and qualitative;
4. The tissue changes are asynchronous.

But there are other mechanisms that bring about selective expression of gene products, in addition to sequential activation by switching. In the normal process by which a cell acts on genetic instructions there are a number of points of control. There may be gene amplification by differential replication, giving multiple copies so that the number of RNA molecules produced per unit time is increased. There may be different rates of transcription, giving altered rates of synthesis of RNA. There may be changes in the rate of passage of the RNA from the nucleus to the cytoplasm. The messenger RNA once synthesised may function a number of times before being degraded, and so enhance the synthetic activity of the cell. There may be regulation of the activity of the DNA in the cytoplasm, to change the rates of protein synthesis. There may be differences in the rate of degradation of some enzymes. The messenger RNA may be stored in an inactive form, accumulating in preparation for periods when bursts of activity are required. Hormones of fetal origin become differentially available during prenatal life, stimulation of mRNA synthesis therefore varies, and since they are all organ-specific they may be a factor in the variation in isoenzyme activity that occurs between organs in fetal life.

Finally there may be epigenetic modification of structure after polypeptide chain production.

This discussion has been essentially in terms of biochemical studies and mainly with reference to fetal growth. Another extremely important and informative area of research has been the analysis of quantitative characters, and apart from birth weight, has concerned postnatal growth.

Birth Weight

Birth weight, which represents the culmination of fetal growth and the beginning of the postnatal phase, is the only measure of fetal growth in size where attempts at genetic analysis have been made. Yet it is an artifical entity, for it represents what amounts to an arbitrary point in a continuum, since babies are born at different gestational ages and at different stagees of maturation, so that individuals being compared are not in fact comparable in many respects. The existence of genetic influence is shown by the fact that birth weight of some babies is grossly affected by genetic disease, both single gene and chromosomal – fibrocystic disease, galactosaemia, the Bloom syndrome, Down syndrome, the Turner syndrome and many others. The earlier genetic studies of "normal" birth weight may or may not have excluded such extreme abnormalities, but certainly could not have excluded the less obvious.

Birth weight is a biometric character, so the methods of quantitative genetic analysis can be employed, based on the fact that relatives of different degrees have different proportions of their genes in common. Thus whereas third degree relatives of babies of high or low birth weight are very similar in mean birth weight to the general population, second degree relatives deviate slightly towards the level in the propositi, and first degree relatives do so conspicuously (Ounsted 1968). This is a usesful first step in suggesting some genetic effect in high and low birth weight. The classic study partitioning birth weight variance into its components was that of Penrose (1954). He showed that the contribution of the fetus' own genes in determining its size when it is born is small, and the contribution of maternal factors – both environmental and genetic – is overwhelming. This predominance of maternal factors presumably is a selective effect allowing small mothers to survive the birth of infants from large fathers. Then after birth such strong prenatal influences upon growth are gradually neutralised, the individual's own genes begin to reassert their influence, and postnatal growth moves firmly in a direction determined genotypically, and the individual is back on genetic target by the age of 2–3 years. A child may depart from its genetic channel of growth as a result of extraneous influences or disease, or can be brought back to or near it by appropriate treatment.

Postnatal growth

Quantitative studies provide the principal evidence on genetic control of postnatal growth (Roberts 1981):

1. *Genetic control* operates throughout the whole process of growth

a) Genetic syndromes affect postnatal growth

b) There are positive correlations between relatives at the age at which they reach peak velocity of growth in height, and in attained height. Inbreeding effects on height, sitting height, arm and hand length and other measurements show the directional dominance compatible with the genetic influence demonstrated by familial correlations.

c) Data on the rate of skeletal maturation (appearance of ossification centres) show familial correlations. There are race differences in ossification timing, even allowing for environmental factors.

d) Rate of physiological maturation as assessed by menarcheal age shows fairly high positive correlations, and the heritability of menarcheal age has been estimated at 72–98%.

e) The pattern of development of the different tissues shows family similarity, not only where the more rapid skeletal maturation occurs in the earlier or later years of infancy, but also in the shapes of the velocity curves of maturation.

f) Dental development shows strong genetic control, with high heritabilities of tooth formation time, ages at eruption of particular teeth, and the order in which they calcify. racial differences provide further evidencve.

It seems likely, that for given environmental circumstances, the genetic control of growth processes extends down to many of the details of the velocity and acceleration curves, but few family studies using the neessary curve fitting to individual records have yet been reported.

2. The *genes are independent.* The genes controlling the rate of growth are partly independent of those controlling final size, and the genes controlling postnatal growth exert relatively slight effect on the size attained at birth. Here the evidence consists of the steady increase in the correlation coefficients between child and parent with the age of child.

3. *Developmental polymorphisms.* Though genetic control over most aspects of normal growth, with very few exceptions, is multifactorial stricter for some growth features than for others, a line of evidence is accumulating from longitudinal records of children's growth that polymorphisms (i.e. single loci), are important in development. These polymorphisms refer to:

a) The sequence in which the developmental milestones occur.

b) The sequence of onset of ossification centres in the hand and wrist.

c) The sequence of eruption of the mandibular second premolar and second molar.

d) The HLA system, for diabetic children with HLA B8 appear to grow more slowly than patients without.

4.The genes controlling postnatal growth are widely distributed over the human chromosomes. This is illustrated from the many chromosomal aberrations that are now known, and from the productive current work on gene localisation.

Summary

From the many studies of growth from different view points, a series of principles can be derived summarising the genetic control of growth. For fetal growth, knowledge is obtained indirectly and shows the complexity of genetic control.

1. There are many genes involved;
2. Many of these are pleiotropic;
3. There is interaction of quantitative and qualitative control;
4. Switch mechanisms, activating and inactivating a succession of genes, is the principal mechanism of genetic control;
5. Genetic effects are tissue specific;
6. Genetic effects are time specific;
7. Temporal variations do not coincide in all tissues;
8. Intracellular mechanisms also modify the implementation of genetic instructions.

For postnatal growth there is more direct evidence deriving from quantitative analyses in family studies and indirect evidence from population comparisons.

1. Genetic control operates throughout the whole process of postnatal growth, but is stricter for some features than for others.
2. It is largely multifactorial, though there are some single locus effects.
3. Genes controlling rates of growth are independent of those controlling final size.
4. Different groups of genes operate at different times during growth.
5. Genes controlling growth are widely distributed across the chromosomal array.

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