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Genomic Imprinting: Review and Relevance to Human Diseases

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Since Gregor Mendel introduced the concept that hereditary transmission resulted from the inheritance of immutable factors, or genes, with equal effect from either parent, genetics has emerged as the central theme of biology. In retrospect, however, it seems likely that Mendel carefully selected a group of traits in peas that segregated neatly, while there are many other traits in peas (as in many other species) which do not show Mendelian inheritance. One of the important challenges of contemporary genetics is to explain those traits and conditions that do not mendelize. It is in that regard that the concept of genomic "imprinting" has assumed increasing importance, because it may provide an explanation for a remarkably diverse set of observations on conditions whose genetic transmission and expression does not conform to the predictions of single-gene inheritance. This paper explores the role of genomic imprinting in human inheritance, both normal and abnormal.

The term imprinting was probably first used in biology by Lorenz in the late 1930s to describe observations about animal behavior; for example, there are critical times during early life when behavior can be modified by particular exposures or experiences, as was seen when newly hatched goslings were imprinted to behave as if a dog were their mother if it was the first moving object they saw after hatching (Lorenz 1952). Imprinting is now also used to imply modification of all kinds of behavior because of particular experiences. Historically, the term imprinting was first used when referring to chromosomes to describe selective elimination of paternal chromosomes in *Sciara* (Crouse 1960; Sapienza 1989), and later to describe selective inactivation of paternally derived X chromosomes in extra embryonic membranes in mouse (Lyon and Rastan 1984). Most recently, genomic imprinting has been used to refer to the differential expression of genetic material, at either a chromosomal or allelic level, depending on whether the genetic material has come from the male or female parent (Surani 1986; Monk 1987, 1988; Solter 1987, 1988; Marx 1988). Genomic imprinting must involve modifications of the nuclear DNA of somatic cells in order to produce these phenotypic differences and thus is a concept which is quite contrary to the basic Mendelian tenet that the parental source of genetic information does not influence gene expression. In this context, the term imprinting is also meant to imply that something happens during a critical or "sensitive" period in development. In the case of genomic imprinting, the stage during which germ-line cells are formed may represent one critical period during which genetic information is "tagged" or marked, temporarily changing the genetic information to permit differential expression. Because this tagging is thought to occur during germ-line formation the term "germ-line imprinting" is sometimes used. Genomic imprinting appears to be a form of regulation, allowing another level of flexibility within the control and expression of the mammalian genome, and may explain why mutations in some parts of the mammalian genome function differently depending on whether they come from the father or the mother.

This paper will first examine the evidence concerning genomic imprinting which has been accumulated over the past few years and then explore how it may relate to human development and human diseases.

Evidence for Mammalian Genomic Imprinting

At this time six kinds of observations suggest the existence of genomic imprinting, some from studies on the mouse and some from studies on the human: (1) observations on the results of pronuclear transplantation-type experiments in mice, (2) the phenotypes of triploids in humans, (3) the expression of certain chromosomal disomies in mice and humans, (4) the phenotypic expression of chromosomal deficiencies in

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mice and humans, particularly in relation to specific chromosomal syndromes and malignant tumors, (5) the expression of transgene genetic material in transgenic mice, and (6) the expression of specific genes in mice and humans. At present, information is largely limited to placental mammals. Imprinting effects have not been observed in general for amphibians, reptiles, birds, or marsupials; however, they have been reported in some insects and plants (Sapienza 1989). The observations in nonmammals have recently been reviewed by Monk (1988) and Solter (1988) and, consequently, this paper will concentrate on the work done in mammals.

Pronuclear Transplantation

Pronuclear transplantation and parthenogenetic activation in mice is technically demanding; however, certain consistent observations have emerged (Surani 1986; Solter 1987, 1988). This work involves constructing zygotes in which all the nuclear genes (i.e., both sets of haploid chromosomes) have been derived entirely from either the mother or the father. There are a number of ways this can be achieved; the simplest to understand is the physical removal of either the paternal or the maternal pronucleus. The maternal and paternal pronuclei have different locations in the fertilized egg and are different in appearance, which in itself suggests different roles. They can be distinguished before the pronuclear membranes are lost, and each can be removed from the newly fertilized egg and replaced with a second pronucleus which has the same parental origin as the retained pronucleus. These reconstituted zygotes are then allowed to develop. Those with only paternally derived chromosomes (androgenetic) have relatively normal development of membranes and placentas but very poor development of embryonic structures; conversely, the gynogenetic zygotes (those with two sets of maternally derived chromosomes) have relatively good embryonic development but very poor development of the membranes and placentas. Both conditions are lethal and the failure to develop is caused by nuclear rather than cytoplasmic defects (Reik 1989). This type of pronuclear transplantation work suggests that *both* maternally and paternally derived chromosomes (and therefore at least parts of the genetic material carried on them) are necessary for normal embryonic development and make unique but complementary contributions to the embryo and placenta.

Human homologies to the pronuclear transplantation experiments in mice are the naturally occurring placental malformation, the hydatidiform mole, and the embryonically derived tumor, the teratoma. The complete mole is found in pregnancies without embryonic tissue. The complete mole has two paternally derived sets of haploid chromosomes—that is, it is androgenetic (Lawler et al. 1982; Jacobs et al. 1982; Sulzman and Surti 1984). Usually there has been a doubling of the chromosome complement of a normal 23X sperm, but occasionally moles are the product of dispermy. By contrast, teratomas are embryonic tumors with tissues from all three embryonic germ layers but no placental tissue. Ovarian teratomas have been demonstrated to have two maternal sets of haploid chromosomes—that is, they are gynogenetic (Linder et al. 1975).

Human Triploids

Human triploids are derived from twice the normal contribution from one parent and show differential functioning of maternal and paternal genetic material. Human fetal triploid tissue having two paternal and one maternal complement (diandry or android) typically is observed as a characteristic large cystic placenta (Lawler 1984) with partial molar changes. If a fetus is present it has usually survived by virtue of mosaicism and has the classic triploid fetus appearance with a relatively large head, small spindly body, severe intrauterine growth retardation and syndactyly (Kalousek 1988). Among early abortuses, two maternal haploid complements and one paternal complement (gynoid) may be present, and then only a small underdeveloped placenta without cystic changes is usually seen. There is a recent suggestion, however, that there may be a second fetal phenotype if the fetus is gynoid (D. McFadden, personal communication) which is markedly underdeveloped probably related to placental failure. These observations support the idea that paternal genetic information plays a particularly critical role in the development and maintenance of the placenta and membranes. Although the maternal contribution may be essential for early embryonic development in the case of human triploids, gynoid embryos probably are not able to grow well enough, in most cases, to survive long enough to be observed.

Uniparental Chromosomal Disomies

Uniparental chromosomal disomies (with deficiencies for the involved chromosome segment from the opposite sex parent) have been observed for almost all segments of the mouse genome. Using translocation constructs, Searle (Searle and Beechey 1978, 1985; Beechey and Searle 1987), Cattanach (1986; Cattanach and Kirk 1985), and Lyon (Lyon and Glenister 1977)

have produced mice that have received both copies of one specific chromosomal segment—often a chromosome arm in a mouse with a Robertsonian translocation or part of a chromosome arm with a reciprocal translocation—from one or the other parent. Thus, these mice have a balanced set of chromosomes, but both copies of the whole chromosome or part of the chromosome have been derived from one parent. By examining one chromosomal segment at a time it has been possible to determine which segments have phenotypic effects when there is a deficiency of the chromosomal material transmitted from one of the two parents. Seven mouse chromosome segments appear to have a major differential effect on growth, behavior, and survival. In some, the effect is only from maternal duplication with paternal deficiency, in others, from paternal duplication with maternal deficiency, and in still others, both types of constructs have phenotypic effects, which usually differ from one another. With two of the murine chromosomes (2 and 11), there seem to be pronounced opposite effects with paternal versus maternal uniparental disomy (large vs. small, hyperactive vs. hypoactive).

In the case of the mouse chromosome (nos. 2, 6, 7, 11, and 17, and possibly 8, although this seems less likely [Cattanach 1988, 1989]), when both sets or parts of both chromosomes are inherited from the mother, a different phenotype results, as compared to when they are both inherited from the father (Kirk and Searle 1988). It is not yet clear whether the effect is from a segment of a chromosome, from several genes in that segment, or even from a single gene carried in that segment. In addition, there may be strain differences in the phenotypes produced.

Besides these obvious phenotypic differences apparently produced by uniparental disomies for parts of the chromosomes, there are also distorted ratios in the expected numbers of offspring for several other mouse uniparental disomies (chromosomes 1, 4, 5, 9, 14, and 17), suggesting that early lethal effects may occur (Cattanach 1989 and personal communication).

Two cases of cystic fibrosis (CF) with uniparental disomy (Spence et al. 1988; Voss et al. 1988) appear to be a human situation which is similar to the mouse uniparental disomies. In both cases of CF the affected children have acquired both of their chromosomes 7 (or the major part of them) from their mothers; their fathers appear from the haplotypes not to be carriers of CF. Nonpaternity has been excluded through extensive DNA markers demonstrating that these children are the biological offspring of the purported fathers. The presence of apparently complete maternal isodisomy (identical copies of the same maternally derived chromosome) was demonstrated. Uniparental disomy has a number of noteworthy implications, but for the purposes of this paper it should be pointed out that both children (one a boy, one a girl) had moderate to severe intrauterine and postnatal growth retardation, which is reminiscent of the mouse disomy/deficiency observations. There are of course a number of other explanations, including the unmasking of another recessive condition. It seems natural, however, to speculate that uniparental disomy for chromosome 7 (without cystic fibrosis), and possibly for other chromosomes, may explain a variety of intrauterine, neonatal, and childhood growth problems. Uniparental disomy is also a possible explanation for occasional recessive disorders with the additional unexpected complications of disturbance in growth or development. Unusual segregation ratios have also been reported among the offspring of cystic fibrosis carrier parents (Kitzis et al. 1988) and transferrin C_3 carrier parents (Weitkamp and Schacter 1985) which may be similar to the unusual segregation ratios seen with some of the mouse uniparental disomies.

Chromosome Deficiency in Mice and Humans

When mouse uniparental disomies are produced by translocation, it is not clear whether the major phenotypic effects are because of the duplication (i.e., the presence of two chromosomes from one parent) or because of the deficiency (i.e., the lack of at least one chromosome/copy from one parent). Deficiencies of autosomes or parts of autosomes or even deficiencies of a single band (about a megabase at high resolution) are very poorly tolerated and are usually lethal in both the mouse and the human (Epstein 1985).

Syndromes.—The Prader-Willi syndrome has been recognized as a specific entity for over 30 years (Prader et al. 1956). It is characterized by hypotonia in infancy, obesity with hyperphagia beginning in early childhood, hypogonadotrophic hypogonadism, small hands and feet, mental retardation, and a specific facies. Nearly 10 years ago a chromosomal deletion of 15q11-13 was first noted in some patients (Ledbetter et al. 1981). Subsequently, more than half of affected individuals were found to have cytogenetically detectable deletions. More recently, with DNA markers, the deleted chromosome 15 has been determined to be paternally derived in most if not all cases (Butler et al. 1986; Knoll et al. 1989).

About 25 years ago, in first describing the syndrome which bears his name, Angelman (1965) used the desig-

nation puppet children because of the happy disposition, unusual and frequent laughter, and bizarre repetitive symmetrical ataxic movements seen in affected individuals. A specific facies, with a large mouth and red cheeks, and unusual seizures are also seen. About half the affected individuals have cytogenetically detectable deletions of 15q11-13 similar to those observed in some Prader-Willi patients. The deletions in Angelman syndrome typically involve the maternally inherited chromosome 15 (Magenis et al. 1987; Donlon 1988; Knoll et al. 1989; Pembrey et al. 1989).

At this time, it is not clear whether the deletions of chromosome 15 in Prader-Willi and Angelman syndromes are in exactly the same area, but DNA studies do suggest that there may be at least a common overlapping segment. Familial cases of Angelman syndrome may lack deletions (Pembrey et al. 1989); nevertheless, the evidence available clearly suggests that the difference in phenotype may well have to do with differential function of the q11-13 region of maternally versus paternally derived chromosome 15.

Nicholls et al. (1989) have recently observed several cases of the Prader-Willi syndrome in which no DNA deletion could be demonstrated but, instead, the two different chromosomes 15 in the affected individuals had both been inherited from the mother (i.e., uniparental disomy of chromosome 15). Both isodisomy 15 and heterodisomy 15 were observed. These cases strongly suggest that it is the lack of a paternal 15 chromosome (or at least a critical part of the 15q11-13 region) which leads to the Prader-Willi phenotype. Uniparental disomy for Angelman syndrome has not been demonstrated as yet, and may not exist, since the pathogenetic mechanism leading to the Angelman phenotype may be different. In Prader-Willi syndrome it seems likely that in most cases the nonviable condition of trisomy 15 was present at conception, and viability was achieved by loss of one chromosome 15 in a cell which then was able to outgrow the trisomy 15 cells and form the embryo. The ratio of Prader-Willi cases to Angelman syndrome cases may reflect the relative maternal versus paternal contributions to trisomy 15.

It becomes essential to ask the same kind of questions regarding other chromosome anomalies, now that DNA typing allows parental origin of a particular chromosome to be inferred. Are most deletions producing characteristic phenotypes the deletion of a particular parentally derived chromosome (4p-, 5p-, 18p-, 18q-, etc.)? Are the phenotypic differences within a specific chromosomal syndrome dependent on the parental origin of the affected chromosome? Do only some chromosomes or parts of chromosomes give these differential effects, or do all or specific segments of all chromosomes? Do the striking differences in frequencies of Down syndrome offspring born to maternal versus paternal 21- translocation carriers (and other Robertsonian translocations carriers) occur because of imprinting? Do duplications, trisomies, translocations, and small supernumerary marker chromosomes produce differing phenotypes depending on parental origin of the involved chromosome? Do some have no effect when inherited from the mother, but a severe effect when inherited from the father, or vice versa? When a child who is phenotypically abnormal is found to have a chromosomal translocation, and family studies reveal a parent who is apparently normal with the same apparently balanced translocation, could it be that the phenotypic abnormalities in the child are related to the sex of the transmitting parent?

These questions have not yet been systematically addressed because the DNA markers necessary to trace parental origin of a specific chromosome are only now becoming available. These markers can be used to define the size of mutations, chromosome changes, and the parent of origin. There are beginning to be hints that the particular parental origin of a specific chromosome is associated with or modifies the expression of some recognized syndromes: Miller-Diecker syndrome (17p-) may be primarily a paternal 17 deletion (vanTuinen et al. 1986; Schwartz et al. 1988). DiGeorge syndrome (22q-) (Greenberg et al. 1988) may be primarily a maternal 22 deletion; cri-du-chat (5p-) appears to be primarily a paternal deletion (Overhauser et al. 1989); and trichorhinophalangeal syndrome II (8q-) appears to be a maternal 8 deletion (Lüdecke et al. 1989) and primarily maternal in transmission when inherited (Haan et al. 1989). A different phenotype has been described (Fennell et al. 1989) with deletion of 8q in apparently the same banding area as trichorhinophalangeal syndrome II, suggesting, in this context, that the phenotypic differences associated with 8q deletions may represent differences in the parental origin of chromosome; 8 similar to those observed in 15q11-13 area.

Cancers.—The second class of chromosome deficiencies that is now recognized to have a nonrandom parental origin are the chromosomes lost during oncogenesis (Ponder 1988, 1989; Reik and Surani 1989; Sapienza 1989). Familial tumors usually behave as dominantly inherited traits with the loss of the wild-type allele occurring during development of the tumor. It has recently been recognized that in a large number of sporadic Wilms tumors there is loss of all or part of chromosome 11 (i.e., loss of heterozygosity). This was not a surprising observation, since Wilms tumors

have been seen in individuals with small deletions on chromosome 11 who also have other congenital anomalies—now known as WAGR deletions (Gessler et al. 1989). However, the striking finding, now that DNA markers allow identification of the parent of origin, is that the deletions or losses of chromosome 11 seen in sporadic Wilms tumors almost always involve the chromosome of maternal origin (Schroeder et al. 1987). These findings suggest the maternal chromosome 11 has some role in tumor suppression not compensated for by the paternal chromosome 11 (Wilkins 1988). Recent studies suggest that at least one gene responsible for familial Wilms tumor is not linked to chromosome 11 (Grundy et al. 1988; Huff et al. 1988). Family studies do suggest, however, that the predisposition to develop Wilms tumor is primarily transmitted through fathers, strongly suggesting a paternal origin for a different factor that is related to Wilms tumor but not mapped on the short arm of chromosome 11. Many other types of sporadic tumors also show loss of heterozygosity for 11p, suggesting that different tumor types can result from the loss of the same gene or chromosome segment, depending perhaps on the tissue type in which the loss occurs.

The relation of parental origin of chromosomes to tumorigenesis is complex. It has been known for some years from family studies of retinoblastoma that bilateral tumors are often transmitted as an autosomal dominant trait with a high degree of penetrance. Molecular work has confirmed that at least two steps are needed for the tumor to develop: first, inheritance or development of an abnormal gene; second, loss of the complementary normal gene (loss of heterozygosity) by one of several different molecular mechanisms, uncovering the abnormal inherited (or mutated) retinoblastoma gene (Ponder 1988; Dryja et al. 1989). The retinoblastoma gene has recently been isolated, and deficiencies or defects in it have been shown to play a role in the production of some other tumors including osteosarcomas. Examination of sporadic osteosarcomas (not those seen in retinoblastoma patients) indicates the preferential loss of the retinoblastoma locus on the maternal chromosome 13 (Toguchida et al. 1989). Further, on reexamination of families with retinoblastoma the few "skipped" individuals are usually the children of affected females (Scheffer et al. 1989). In nonfamilial retinoblastomas, the sporadic "somatic" cases may first have a mutation in the gene from either parentally derived chromosome 13, while new germ-line mutations (i.e., those giving rise to bilateral tumors and capable of being transmitted to offspring) appear to be primarily of the paternally derived chromosome 13 (Dryja et al. 1989; Zhu et al. 1989). These observations suggest that parentally derived modifications (imprinting) of the retinoblastoma gene in bone may be different from those in the retina and that new germ-line mutations may occur preferentially to the paternal chromosome (Ponder 1989). The parent of origin of the chromosome loss seen in other tumor tissue has not yet been determined, but is obviously of great interest. Many other tumors can be expected to have this kind of association. Most recently, familial glomus tumors have been shown to demonstrate an inheritance pattern compatible with imprinting (van der Mey et al. 1989).

Analysis of Transgene Expression

The analysis of transgene expression in transgenic mice has provided a powerful new approach for understanding the regulation and expression of specific genes. Several techniques and markers have been used to incorporate a specific gene into the genome of mice and then to follow expression of the "foreign" gene (transgene) in different tissues in different generations (Reik et al. 1987; Surani et al. 1988). A dramatic observation is that, for about one-fourth of transgenes examined, expression of the gene in subsequent generations depends on the sex of the parent transmitting the gene (Hadchouel et al. 1987; Reik et al. 1987; Sapienza et al. 1987; Swain et al. 1987). In these cases, the DNA has been integrated into the mouse genome, yet expression of the gene differs depending upon its parental origin. When the gene is inherited from a transgenic male mouse, for example, it is expressed in appropriate tissues, but when his expressing daughter transmits the same gene to her offspring they do not express it. Subsequently, however, her nonexpressing son's offspring will express the gene appropriately, but her daughter's offspring will not. This phenomenon does not appear to be related to the site of insertion, size of the transgene, number of copies incorporated, or size of the insert (i.e., the number of copies at the site of the insertion) (Surani et al. 1988). Nonexpression does, however, seem to be associated with methylation of the transgene. As the gene passes from one generation to another its methylation is reversed depending on the parental origin. For this reason it has been suggested that methylation may play a role in regulating the expression of genes involved in imprinting.

Expression of Specific Genes

The expression of specific genes when inherited from father versus when inherited from mother has not yet been evaluated in most human or mouse disorders. Bander (Bander et al. 1989) has demonstrated in mice

by extensive crossbreeding and cross-fostering that oocyte susceptibility to certain enzymes is a paternally imprinted phenotype and is strain dependent. Until recently, the assumption has been that the parental origin of a gene did not matter. Nevertheless, there are a number of human disorders where differences in phenotype, age of onset, and severity do seem to be related to the sex of the parent transmitting the gene. Myotonic dystrophy and Huntington disease are classic examples: in 10%–20% of affected families when the myotonic dystrophy gene is transmitted through the mother (and only through the mother), a severe, congenital form of the disease occurs (Harper 1975); in 5%–10% of families when the Huntington disease gene is transmitted through the father (and only through the father), a severe, rigid, juvenile form of the disease occurs (Reik 1988; Ridley et al. 1988). It is also worth noting that homozygous Huntington disease is apparently not more severe than the heterozygous disease, suggesting (among other possible explanations) that only one abnormal gene is functioning in the homozygous cases to produce the phenotype (Wexler et al. 1987; Myers et al. 1989).

There are several other relatively common disorders in which the severity (i.e., the phenotype) has been said to depend on inheritance from either father or mother: seizures (Ottman et al. 1988), spinocerebellar ataxia (Zoghbi et al. 1988), cerebellar ataxia (Harding 1981), Wiedemann-Beckwith syndrome (Lubinsky et al. 1974; Niikawa et al. 1986), neurofibromatosis I (Miller and Hall 1978), neurofibromatosis II (Eldridge 1981), familial glomus tumors (van der Mey et al. 1989) and fragile X (Laird 1987; Laird et al. 1987), but the question has not been asked for most other human genetic disorders. Even some X-linked proteins such as factor VIII may show differences in serum levels when the gene is inherited from mother versus father (C. H. C. Rizza, personal communication). There are also many disorders in which inheritance patterns are confusing and do not seem to follow normal Mendelian patterns or have "low penetrance" or "marked variability of expression": ectrodactyly (Spranger and Schapera 1988), hemochromatosis, manic-depressive illness, Gardner syndrome, polyposis coli, and polycystic ovary disease. With dimeric (e.g., hemoglobin) and trimeric (e.g., collagen) proteins there may be differential production of strands depending on parent of origin. If there are two loci for a disorder, as may be the case for tuberous sclerosis (Sampson et al. 1989) and adult polycystic kidney disease (Kimberling et al. 1988), then there may be two different types of imprinting and the question of effect of parental inheritance must be re-examined separately for the two forms.

There is another group of conditions in humans in which DNA techniques have permitted demonstration of distorted segregation ratios according to the sex of the transmitting parent: cystic fibrosis (Kitzis et al. 1988), insulin-dependent diabetes mellitus (Vanheim et al. 1986; Warram et al. 1984), HLA haplotypes, and transferrin alleles (Weitkamp and Schacter 1985). Blood-group effects have been observed in miscarriages and moles, but again these studies did not always take into account possible imprinting effects on the expression of the phenotype of the blood group from one parent versus the other. Chakraborty (1989) has suggested that this type of phenotype proportion (or disproportion) is what would be expected when a locus undergoes differential imprinting.

Taken together, these six types of observation suggest strongly that genomic imprinting (differential expression of maternally and paternally derived DNA) does occur in some parts of the mammalian genome and would be expected to play a role in human disease. It would appear that the marking or imprinting of DNA normally occurs during gametogenesis in some areas of the mammalian genome and is reversible; that is, it is not a mutation or permanent change, but rather a modification which can normally be "wiped off" or reestablished when germ cells are produced in the next generation (Hulten and Hall, in press).

Clues to Identifying Human Imprinting

The Oxford grid (Searle et al. 1989) helps to predict homologous areas of the human and mouse genome. If the imprinted mouse chromosome segments are conserved in the human, then one can extrapolate from the translocation uniparental disomies in mouse and predict that certain areas of the human genome may be susceptible to imprinting. There are many clinically relevant genes in these areas (table 1). Some genes suspected of demonstrating imprinting (e.g., the genes for Wiedemann-Beckwith syndrome, cystic fibrosis, and myotonic dystrophy) have already been shown to lie within these homologous areas.

Furthermore, if the segments of the human chromosomes where differential expression depending on the sex of the parent of origin has definitely been observed (e.g., for retinoblastoma, Wilms tumor, and Prader-Willi syndrome) are added, the chromosomal segments which should be considered as potentially involved in imprinting in humans include a large number of hu-

man disorders that do not conform to classical Mendelian inheritance or have puzzling manifestations. Obviously, the disorders in these areas need to be examined for the possibility of two contrasting phenotypes (i.e., contrasting in severity, type and number of complications, age of onset, etc.) depending on whether they are inherited from mother or father.

The Prader-Willi and Angelman phenotypes resemble in many ways the "opposite" phenotypes (hypotonic vs. hypertonic, active vs. inactive) seen in the translocation uniparental disomy of the distal areas of chromosome 2 in the mouse (Cattanach and Kirk 1985; Cattanach 1986) which is almost homologous. However, if the involved area of human chromosome 15 is syntenic to a region of the mouse chromosome 2 it is probably slightly more centromeric. Nevertheless, the phenotypic effect of paternal versus maternal deletion in some areas of the mouse and human genomes appears to be surprisingly similar.

Conservation of imprinting segments or genes may occur among mammals. However, since it is not yet clear whether single genes, clusters of genes, or whole chromosome segments are involved in the imprinting process, care must be taken in suggesting such homologies too strongly.

Examining a hypothetical pedigree of imprinting (fig. 1) helps in the visualization of what one should be looking for in family studies of human imprinting. An "imprintable" allele will be transmitted in a Mendelian manner, but expression will be determined by the sex of the parent transmitting the gene. Thus, in maternal imprinting, phenotypic expression of a normal or abnormal gene is affected in the mother's offspring of both sexes. This "silencing" or "turning off" of the gene occurs if offspring inherit the gene from the mother, but not when the same gene is transmitted by her father, brothers, or sons. When her nonmanifesting son transmits the gene, his offspring will express the gene if they inherit it, but her nonmanifesting daughter's children will not. Just the opposite is seen in paternal imprinting.

It should be noted that (1) equal numbers of affected or nonmanifesting males and females are seen in each generation in both maternal and paternal imprinting; (2) nonmanifesting (skipped or nonpenetrant) transmitting individuals are the clue to whether a trait is maternally or paternally imprinted (i.e., in maternal imprinting a male is the nonexpressing, nonmanifesting, or less manifesting carrier who transmits to manifesting offspring, and in paternal imprinting females are the nonmanifesting or nonexpressing carriers who transmit); (3) the pedigree of a gene which is imprintable can look like autosomal dominant, autosomal recessive, or multifactorial inheritance, depending on which part of the family is being observed (several models have been developed involving different types of modifiers of the imprinting mechanisms [Reik 1989; Sapienza 1989]; the hypothetical pedigrees with such models are even more complex); (4) the pedigree is quite different from that seen in mitochondrial or cytoplasmic inheritance in which none of father's children or grandchildren can be affected and all of mother's children are at risk.

It should be noted that these hypothetical pedigrees say nothing about the molecular mechanism, modifiers or alternative alleles involved in the imprinting process.

With knowledge of the possible imprinting effect on phenotype and expression, in any disorder that lacks a clear pattern of inheritance, the pedigree should be examined for evidence of imprinting (i.e., differential expression and phenotype when inherited from fathers vs. mothers). Many disorders which previously have been described as multifactorial, or as showing marked variability of expression, or with decreased penetrance, are particularly strong candidates for this type of effect. thus, pedigrees need to be systematically reexamined, particularly in disorders with unusual inheritance patterns. J. G. M. Shire (personal communication) has suggested that there is a great deal of information about imprinting waiting to be tabulated in mouse breeding logbooks, and, similarly, there is likely to also be a great deal of information waiting to be tapped in genetic clinic records.

In the case of adult polycystic kidney disease presenting in infancy and childhood (Gal et al. 1989), at first glance there are families with both paternal and maternal transmission. In any one family, however, the early-onset phenotype seems to be consistently transmitted only by a parent of one or the other sex, and since there are some linkage data to suggest that there are two or more linkage groups for dominant polycystic kidneys (Kimberling et al. 1988), one might predict the association of early onset of disease with maternal imprinting for one linkage group and with paternal imprinting for the other.

This type of hypothesis needs to be examined systematically for a variety of other human disorders. Experience in biology suggests strongly that nothing will be 100%. For example, only a small percentage of families seem to manifest differential effects in Huntington disease and myotonic dystrophy. Nevertheless, strong trends towards expression of a phenotype primarily when inherited from the parent of one sex or

Table I

Human Chromosome Areas Homologous to Mouse Chromosome Areas Involved in Imprinting

Human Homologous Chromosome Area	Mouse Chromosome Area Involved In Imprinting	Mouse Maternal vs. Paternal Imprinting Effects	Some Oncogenes, Growth Factors, and Human Tumor Genes in This Human Chromosome Area	Genes Mapped to This Area That Are Suspected on a Clinical Basis to be Imprinted	Genes or Diseases Which by Virtue of Location in This Area Should Be Considered Candidates for Imprinting
2p11-p13	6C	Maternal	Transforming growth factor alpha		Kappa light-chain gene cluster
4p16	None	Paternal	RAF2 oncogene	Huntington disease	
5q13.3-p33	11A	Maternal and paternal	Gardner syndrome/polyposis coli, granulocyte macrophage colony-stimulating factor 2, interleukins 3, 4, and 5, endothelial cell growth factor		Schizophrenia, campomelic dysplasia, susceptibility to diptheria, clotting factor XII, macrocytic anemia
6pter-p12	17A-D (T138Ca)	Paternal	Tumor necrosis factor (alpha and beta), PIMI oncogene	Insulin-dependent diabetes mellitus, spinocerebellar ataxia I, juvenile myoclonic epilepsy, transferrin	Atrial septal defect, H-Y antigen, major histocompatibility complex, heat-shock protein, 21-OH, hemochromatosis, Paget disease of bone, clotting factor XIII, prolactin, complement 2 and 4, phosphoglycerate-kinase pseudogene, orofacial cleft, preprogastrin, collagen IIA2, long QT syndrome, sialidosis
6q21-q7	17A	Paternal	Insulin-like growth factor 2 receptor	T complex	Macular dystrophy, apolipoprotein Lp(a), plasminogen, estrogen receptor, arginenemia
7p21-p14	6B-C	Maternal		HOX1	Craniosynostosis
7p14-p12	11A	Maternal and paternal	ERBB oncogene epidermal growth factor receptor, platelet-derived growth factor A chain, interferon beta 2, insulin-like growth factor		Myopathy due to PGAM deficiency, anemia due to BPGM
7q22-qter	6A-C (T7Ca)	Maternal	MET oncogene, INTI-related protein	Cystic fibrosis	Colorblindness-tritan, trypsinogen deficiency
9cen-q34	2A-C1 (T13H)	Maternal	ABL oncogene, chronic myeloid leukemia		Tuberous sclerosis, nail patella, fructose intolerance, familial Mediterranean fever (amyloid), adenylate kinase deficiency, torsion dystonia, complement 5, ABO blood goup, citrullinemia

(*continued*)

Table I (continued)

Human Homologous Chromosome Area	Mouse Chromosome Area Involved In Imprinting	Mouse Maternal vs. Paternal Imprinting Effects	Some Oncogenes, Growth Factors, and Human Tumor Genes in This Human Chromosome Area	Genes Mapped to This Area That Are Suspected on a Clinical Basis to be Imprinted	Genes or Diseases Which by Virtue of Location in This Area Should Be Considered Candidates for Imprinting
11pter-p15	None	Maternal	Rhabdomyosarcoma	Wiedemann-Beckwith	
11pter-p12	7B	Maternal	Adrenocortical carcinoma		Familial Mediterranean fever (amyloid)
11p13-p15.5	7F (T50H)	Maternal and paternal	Wilms, WAGR, RAS oncogene, insulin-like growth factor II, liver-cell carcinoma, T-cell leukemia	Maturity-onset diabetes	Manic depressive, persistent HbF, hypoparathyroidism, tyrosine hydroxylase, lactate dehydrogenase myopathy, beta hemoglobin locus, aniridia, hypoprothrombinemia, FSH, CI inhibitor
11q13-q21	7F (T50H)	Paternal and maternal	INT2 oncogene, multiple endocrine neoplasm, anal cell cancer, B-cell leukemia	Cerebellar ataxia	Tuberous sclerosis, albinism, pepsinogen A cluster, collagenase, ataxia-telangiectasia, apolipoprotein cluster
13q14.1-q14.2	None	Maternal	Retinoblastoma, osteosarcoma		Wilson disease
15q11-q13	None	Paternal and maternal	Prader-Willi/Angelman		Dyslexia, clotting factor XI
16pter-q13	11A (T30H)	Maternal and paternal			Hb alpha cluster, leukocyte-adhesion alpha cluster, polycystic kidney, HbH mental retardation
16q22.1-q248E....	8	Maternal			Urolithiasis, haptoglobin, LCAT, chymotrypsinogen B, tyrosinemia II
19p13.3-p13.2	8	Maternal	Insulin receptor		Leprechaunism, acanthosis, persistent müllerian duct
19cen-q13.32	7A-B	Maternal	Transforming growth factor beta Carcinoembryonic antigen MEL oncogene HKR oncogene	Myotonic dystrophy	Apolipoprotein cluster, pregnancy-specific glycoprotein, infertility due to LH deficiency, peptidase D, glucose-phosphate isomerase, polio susceptibility, P-450 family, B chain chorionic gonadotropin, Mannosidosis, anti-müllerian hormone, P-450 family II, PKG-2

(*continued*)

Table 1 (continued)

Human Homologous Chromosome Area	Mouse Chromosome Area Involved In Imprinting	Mouse Maternal vs. Paternal Imprinting Effects	Some Oncogenes, Growth Factors, and Human Tumor Genes in This Human Chromosome Area	Genes Mapped to This Area That Are Suspected on a Clinical Basis to be Imprinted	Genes or Diseases Which by Virtue of Location in This Area Should Be Considered Candidates for Imprinting
20q13.11	2H (T1Sn-T28H)	Maternal and paternal	Growth hormone releasing factor		Adenosine deaminase deficiency, diabetes insipidus, benign neonatal seizures, Albright hereditary osteodystrophy, Alagille syndrome, galactosialidosis
21q22.3	17B	Paternal	ERG oncogene		Crystallin A, homocystiuria, phosphofructokinase deficiency liver type
22q11.2-qter.....	11A	Maternal and paternal	Meningioma, Ewing sarcoma, Philadelphia chromosome	Neurofibromatosis II	Transcobalamin II, crystallin B2 and B3, thyroid-stimulating hormone receptor, Hurler-Scheie syndrome, cat's-eye syndrome, DiGeorge syndrome, immunoglobulemia, lambda light chain

NOTE.—Adapted from McKusick (1988).

the other certainly suggest a new kind of level of control of expression. Sapienza (1989) has suggested that imprinting is best described as a form of dominance modification in which different manifestations of an epigenetic allele-inactivation process that is dependent on the gamete of origin are occurring. Reik (1989) has suggested there may be many different types of modifiers and classes of imprinting. In view of these findings and suggestions, pedigrees need to be reexamined with this new agenda.

Why Should There Be Imprinting?

Perhaps the reason it has taken so long for human geneticists to recognize imprinting as a common biological phenomenon is the simplicity of the Mendelian dictum of equal parental effect and its validation over an extensive series of loci, including studies in plants, *Drosophila,* birds, and other animals, not to mention metabolic diseases and the well-established blood-group systems in humans. With accumulating evidence that imprinting does occur in mammals, the question is why? Many possibilities exist and some of the suggestions which have been put forward follow.

Imprinting may have been involved in the evolution of *placentation.* Among the pieces of evidence that there is differential function of maternally and paternally derived genetic material is the fact that the pronuclear transplantation work and the human triploidy work (see above) both imply a differential role for maternally versus paternally derived genetic information in both embryonic and placental growth and function. At the time in evolution when placentation was developing, the mother had to accept and tolerate the implantation of tissue which was half "foreign" and, second, restrain the growth potential of that tissue so that she was not sacrificed to its growth. There must be genes that are critical to this particular type of recognition process, and one would expect differences in functioning of the paternal genome within the placenta in order to accommodate the implantation. It is noteworthy that mice preferentially inactivate the paternal X in the placenta while humans have random X inactivation in the placenta (Migeon et al. 1985), both of which are just

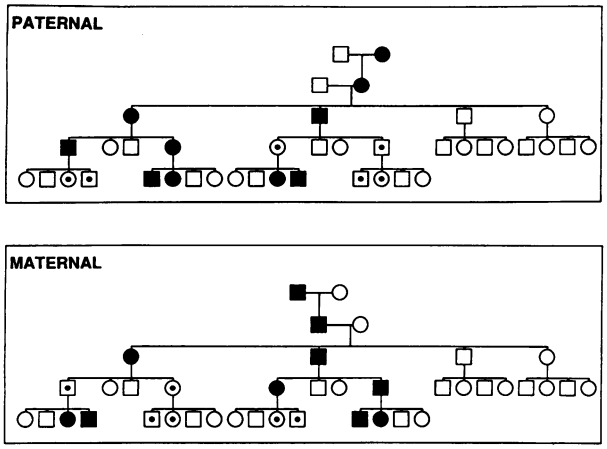

Figure 1 Idealized pedigrees for maternal and paternal imprinting. These figures are meant to diagram what a pedigree of human disease which had imprinting effects might look like. The term imprinting implies a modification in expression of a gene or allele. An imprintable allele will be transmitted in a Mendelian manner, but expression will be determined by the sex of the transmitting parent. In these idealized pedigrees the term maternal imprinting is used to imply that there will be no phenotypic expression of the abnormal allele when transmitted from the mother and paternal imprinting is used to imply that there will be no phenotypic expression when transmitted from the father. Because there will be a phenotypic affect only when the gene in question or chromosome segment in question is transmitted from one or the other parent, there are a number of nonmanifesting carriers. There are equal numbers of manifesting males and manifesting females or of nonmanifesting male and nonmanifesting female carriers for each generation.

the reverse of what might be expected from the pronuclear transplantation and triploid work. Further, when the zygote is implanted in the uterus some kind of limitation on its ability to invade the maternal tissue must be imposed if the mother is to survive the pregnancy. It can be anticipated, then, that a mechanism allowing placentation also involves differential functioning of maternal and paternally derived genetic information in the embryo and placenta. It also seems reasonable to suppose that some genes which by chance were linked to the genes involved in placentation but are uninvolved in placentation themselves might also be modified in an imprinting process.

Sexual reproduction has many advantages, but also has certain disadvantages. Thus, specific mechanisms for maintenance of sexual reproduction are probably required (Kelley et al. 1988). It seems likely that differential functioning of maternal and paternal genetic material could play an important role in maintaining sexual dimorphism and in maintaining sexual reproduction in an evolutionary sense. It has been suggested that imprinting would help to avoid the genetically deleterious effects of parthenogenesis—embryonic and fetal development in the absence of the male genetic contribution (Solter 1988). The work on imprinting suggests both maternal and paternal genetic contributions are necessary and complementary in mammals. Parthenogenesis has not been observed in mammals, although it has been reported in all vertebrates except mammals (Beatty 1957). The frequent occurrence of parthenogenesis in some birds, such as the turkey, suggests that imprinting may not be occurring on a regular basis in them.

A third possible explanation for imprinting as observed in mammals is that it has to do with gene control and flexibility during growth and development. There may be a need for alternative methods of dosage compensation and gene control—for example, to have genes in "reserve" for particularly critical cellular functions, particularly during cell division. By using only one copy of a particularly important gene, a reserve copy could be available for critical times of rapid growth, for function during cell duplication, or in case of a mutation or dysfunction of the other allele. Cell metabolism does not stop during DNA replication, and consequently a mechanism is needed to maintain certain functions. By having one allele of critical genes designated (or imprinted) in some way to be "late replicating," the other gene can replicate and be available for transcription while the imprinted gene replicates. This kind of imprinting (possibly using methylation) would involve an inactivation process which might render the gene active only at very specific times and, in this way, allow for the plasticity seen in early mammalian development. If this were true, critical genes for maintaining cell metabolism would be expected to be involved (Grant and Chapman 1988; Lyon 1988).

Still another explanation which has been suggested is that imprinting plays a role in the immunologic defense of the organism; that is, alternation of some of the presenting antigens (maternal versus paternal) every other generation or so might "confuse" the natural enemies or infectious agents in the environment. There is as yet no evidence for this type of mechanism in higher organisms (Huebner et al. 1989).

Sapienza (1989) has suggested that imprinting reflects a process of dominance modification. If this is true, it may have played an important role in evolution as well as in the mechanisms controlling embryonic development and tissue differentiation.

Finally, Chakraborty (1989) has suggested that genomic imprinting will mimic hybrid vigor and hetero-

zygote deficiency. Since these processes are thought to be important in evolution, the mechanisms of imprinting may produce similar results, but not take as long as natural selection.

When Does Imprinting Occur?

Imprinting would appear to be a process which can alter its form from one generation to the next; that is, it is not a permanent change or mutation in the DNA but, rather, a temporary alteration in the function of part of the DNA (albeit perhaps lasting the lifetime of an individual). The functional difference between the paternally derived genome and the maternally derived genome should have a molecular basis which can be defined. The mechanism of imprinting must involve (1) erasure or wiping off of any previous imprinting, (2) new modifications of the parental genome in the germ cells of each sex, (3) new imprinting or tagging of the chromosome as maternal or paternal (this may happen at the same time as new modifications of the genome), and (4) differential tissue-specific phenotypic expression of the new parental imprinting in the offspring (Hulten and Hall, in press).

Differential imprinting inherited from the parents must be erased or inactivated in the germ-cell lineage of every individual so that new appropriate imprinting can be introduced. In this sense, autosomal imprinting is reminiscent of X inactivation and may represent a similar process occurring in the autosomes (but probably only parts of the autosomes) which is not random but, rather, involves the genetic material inherited from one parent (Grant and Chapman 1988; Lyon 1988, 1989). Available evidence suggests that at least some part of the process which leads to differential expression of maternal and paternal genetic information in the embryo and fetus (and perhaps during later life) must occur during gametogenesis. The new modifications could occur during meiosis, the later stages of gamete maturation, or capacitation, or at the time of fertilization of the egg which will become the new individual. In other words, the process could begin as early as the in utero life of the parents who produce the eggs and sperm that form the individual or as late as the early life of the zygote. On the other hand, it is at pachytene that the two grandparentally derived chromosome homologues normally pair along their entire lengths, and this would be a logical time for some type of modification to occur. It may be a process related to the physical state of the chromosomes (stretched or condensed, methylated or unmethylated) during specific stages of gametogenesis, or it may be related to an active process such as the inactivation center(s) proposed for X inactivation. However, instead of spreading the length of the chromosome it seems to occur to specific parts of the autosomes, depending on parent of origin (Hulten and Hall, in press).

The preferential inactivation of the paternal X chromosome in the extra embryonic tissues of mice, rats, and marsupials is thought to be a form of imprinting (Solter 1988; Lyon 1989). On the other hand, X inactivation in human extra embryonic tissues appears to be random (Migeon et al. 1985). The possibility that expression of imprinting (as well as the manifestation of X inactivation) occurs only as tissues begin to differentiate is suggested by experiments in early mouse embryos (Monk and Harper 1979).

How Does Imprinting Occur?

The transgenic mouse work suggests that, in those cases where the transgene is imprinted, differential expression of the transgene is associated with methylation. Modification of DNA through methylation may give a means of determining whether a particular allele of a gene is inactivated at a particular time. In general, however, methylation appears to be a secondary phenomenon in gene regulation and may be secondary here as well. Sperm DNA is highly methylated, although specific genes may be spared (Monk et al. 1987). Transgenic mice are usually constructed by injecting transgenes into the paternal pronucleus in which the DNA is already highly methylated. Perhaps there is some relationship between the associated methylation seen with lack of expression in the transgenes of these mice and the original methylated state of the DNA when the transgene was inserted. The transgenes may be selectively inserted in unmethylated sites.

Of interest in this regard is the observation that methylated genes may be at increased risk for mutation by deamination of 5 methylcytosine. This predisposition to mutation of methylated genes may also be relevant to the somatic loss of genes involved in tumor suppression during mitosis and possibly meiosis (Holliday 1989). Perhaps newly unmethylated sites produced as part of the erasure of imprinting are particularly susceptible to mutation. It even seems feasible that methylation interferes with (or possibly even predisposes to) crossing-over during meiosis and is therefore related to the differential crossover rates of some segments of some chromosomes observed when male and female meioses are compared (in both humans and mice). Thus, the

differential methylation of cytosine (or whatever other process is utilized to tag the gametic chromosomes) could be related to the observed differences in crossover rates and possibly in mutation rates in specific areas of particular chromosomes. If that is true, the areas of differential crossover rates might also identify those areas at risk for imprinting of the genome. The molecular mechanisms for initiating, maintaining, and erasing imprinting are unknown, however.

Methylation may be the molecular mechanism involved in maintaining parent-of-origin information in some imprinting situations, but other epigenetic modifications must also be involved. There appear to be strain differences in imprinting of single genes in mice (Agulnik and Ruvinsky 1988; Bander et al. 1989). Many mechanisms leading to dominance modification have also been proposed in human tumorigenesis (Sapienza 1989). It is fair to say that the actual mechanism(s) involved in the imprinting phenomenon is totally unknown at this time.

Effects of Imprinting

The early differentiation in the phenotype of androgenetic and gynogenetic mouse zygotes suggests that the effects of imprinting appear at a very early stage. The early intrauterine death seen in some of the uniparental disomic mice suggests a very early effect as well. Later effects on growth and behavior are also seen in other mouse uniparental disomies, yet true malformations associated with imprinting have not been reported. Interspecies crosses also suggest that imprinting may have effects on the growth of different areas of the body. For instance, when the horse and donkey are crossed, clear differences are seen depending on whether the horse is the mother (hinny) or father (mule) (Chandley 1989).

It is not yet clear whether imprinting is maintained throughout life, in all tissues, in all individuals of a particular strain, or from one species to another in homologous areas (Lyon 1988; Reik 1989). Mouse work suggests there may be strain differences and tissue differences (Sapienza et al. 1987). The occurrence of a maternal effect in only 10%–20% of myotonic dystrophy families and a paternal effect in only 5% of Huntington families suggests that, if these are imprinting effects in humans, they do not occur in all families (strains), or between all chromosome parts.

Reversibility of imprinting from one generation to the next with the change of the sex of the parent has been observed in most of the mouse transgenes which demonstrate imprinting; however, in one gene (Hadchouel et al. 1987) the imprinting (i.e., the methylation and suppression of the gene) was not reversible after the gene "passed through" an ovary. This suggests that, in some rare cases, rare families, or rare situations, imprinting may be irreversible. Laird (1987; Laird et al. 1987) has suggested this to be the case in the human fragile X mental retardation syndrome (i.e., that the distal segment of the long arm of the X cannot be reactivated when continually passed through females, leaving the affected individual functionally aneuploid for that portion of the chromosome).

A second possible example of aberrant reversibility of imprinting is suggested by the observation that most monozygous twins with Wiedemann-Beckwith syndrome are discordant, with one twin affected and the other not (Litz et al. 1988; Olney et al. 1988). The syndrome appears to be determined by changes in a chromosome segment on 11p homologous to a mouse imprinting area (Koufos et al. 1989; Ping et al. 1989; Reik 1989). Furthermore, it fits the criterion of unusual inheritance patterns, often being transmitted in familial cases through an unaffected mother (Lubinsky et al. 1974; Niikawa et al. 1986; Aleck and Hadro 1989). It seems possible that something about monozygous twinning predisposes to loss of imprinting, or, conversely, that loss of imprinting in some cells of an embryo at a critical stage might lead to monozygous twinning.

In summary, compelling evidence has been accumulating that some areas of the genome (chromosomes, chromosome segments, and genes) function differently, depending upon the parent from whom they are inherited. This process appears to be normally reversible and thus involve a temporary DNA modification. The differential functioning of genes depending on which parent transmitted them may be ubiquitous and explain a variety of observations hitherto considered manifestations of atypical or inconsistent inheritance. Imprinting has been called an epigenetic process (Reik and Surani 1989); however, it would appear to be an integral part of normal genomic function during the development and maintenance of organisms. Reconsideration of family histories, expression patterns, and disease processes may reveal imprinting effects in many common inherited disorders. The observations reported here may be just "the tip of the iceberg." It is clear that mammalian development requires the functional and complementary presence of at least parts of both maternal and paternal genomes. Effects on embryonic and fetal growth and behavior have been observed; preferential involvement of paternal or maternal chromosomes is

seen with loss of heterozygosity in tumorigenesis. The challenge is to determine how many other childhood and adult disorders involve imprinting.

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