

Human Genetics

Abstract

Why do offspring resemble their parents? Such resemblances are passed on relatively unaltered from generation to generation through a process called heredity. The units of heredity are deoxyribonucleic acid (Dna) segments called genes. Encoded in every gene are biochemical instructions that determine the characteristics or the traits of an organism. Genetics is the study of genes that is how they operate and how they are transmitted from parents to offspring

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Introduction

Heredity is the sum total of all biological processes by which particular characteristics are transmitted from their parents to their offspring. Among organisms they reproduce sexually, progeny are not exact duplicates of their parents but usually vary in many traits. Heredity and variation are the two side of the same coin, are the subject matter of the science of genetics. Genetics may be defined as the study of the way in which the genes which are the fundamental units of heritable material gets operated and transmitted in offspring from their parents. Modern genetics also involves the study of mechanism of gene action that is the way in which the genetic material affects the physiological reactions within the cell.

Genetics is often called the core science of biology. This does not necessarily mean that genetics is the most fundamental among the biological disciplines. It implies only that genetics impinges upon almost every kind of study of life. Anthropology, medicine, biochemistry, physiology, psychology, ecology, systematic, comparative morphology, and paleontology all have intersections with genetics. Like so many basic or theoretical sciences genetics has many potential and actual potential practical applications. The understanding and control of hereditary disorders and the breeding of improved crops and livestock are just two such applications.

History

Even before the beginnings of written history people were aware that certain traits could be passed from parent to offspring. By selectively breeding plants and animals, humans produced livestock and crops that could provide food, pull plows, and supply companionship and protection. But while farmers and breeders learned to control the transmission of the traits in agriculture the actual process of heredity remained at the mystery. Many theories were advanced. In ancient Greece, it was thought that the traits were transmitted through the blood, which is still often used to denote our ancestry. In the seventeenth century some biologists also believed that the female eggs contained miniature offspring whereas the male sperms activate the embryonic development. But some other biologists proposed the opposite that is the tiny formed offspring were present in the sperm.

By the Nineteenth century, three theories on heredity prevailed within the scientific community: pangenesis acquired characteristics, and blending inheritance. Pangenesis held that each and every cell produced gemmules that are the particles that embodied the cell's traits and which coalesced in the reproductive organs to form offspring. The theory of acquired characteristics stated that the traits acquired during an organism's life, such as increased muscle from exercise were passed on to the offspring. Blending inheritance proposed that the characteristics inherited in an organism are a blend of those characteristics present in their parents. For example an offspring of a fair white and a fair black individual would be of an intermediate complexion and the offspring of a tall and a short plant would be of medium height.

An English biologist Charles Robert Darwin in his book 'on the Origin of Species' (1859) had cited blending inheritance as a possible explanation for the variation observed in the nature. In Darwin's theory of Natural Selection the Variations in traits played a key role. Darwin had

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observed that the species can produce more number of offspring than they can survive upon, the given limited resources of the earth. The individuals with the traits providing an advantage in their surroundings are more likely to survive and reproduce than those individuals who lack these characteristics. If the environment changes or there is a drift, the species which contains the adaptive traits to that environment, would survive whereas the species who lack these adaptations would might become extinct or endangered.

Darwin did not know that what controlled heredity or how the trait passes to the offspring. However he knew that for Natural Selection to operate, there had to be a variable units of heredity, and that variations in the species arose through the accumulation of changes in these units over time. Darwin later revived interest in pangenesis, thinking that it had explained what he had observed.

Mendelian Classical genetics: In 1865 Gregor Mendel an Austrian Monk wrote a paper that laid the foundation for modern genetic. Mendel was the first to demonstrate experimentally the manner in which the specific traits are passed from one generation to next, and to use mathematics to analyze his data. He concluded that discrete, or distinct, hereditary units that passed from parent to offspring determined how traits were inherited. Mendel's findings were ahead of his time in which he described their significance and hereditary elements which were not understood until the early 1900s, when the units became known as genes.

16 years after Mendel's death his work was rediscovered independently by Hugo de Vries in Holland, Carl Erich Correns in Germany, Erich tschermak von seyseng in Austria. Like several investigators before him Mendel experimented on hybrids of different varieties of a plant. Mendel investigated a common pea plant (*Pisum sativum*). His methods differed in two essential respects from those of his predecessors. Firstly instead of trying to describe the appearance of a whole plants with all their characteristics, Mendel followed the inheritance of single easily visible and distinguishable traits such as round versus wrinkled seeds, yellow versus green seeds, purple versus white flowers etc. secondly he made exact count of numbers of plants bearing these traits; it was from such quantitative data that he deduced the rules governing inheritance.

Mendel crossed the pea plants by deliberately transferring the pollen of one variety to the pistils of another resulting in the first in the first generation hybrids denoted by symbol F1 then Mendel allowed the F1 hybrid plants to self pollinate and produce the second hybrid generation that is F2 Mendel concluded that the gametes of purple flowered plants carried some factor that caused the progeny to develop purple flowers and the gametes of white flowered plant carried the variant factor which induced the development of white flowers.

Mendel's experiment will illustrate how the genes are transmitted and in which particular ratio. Let R stands for the genes for the purple flowers and r for the gene for the white flower. Since each pea plant contains a gene dowment half of whose set is derived from the mother and from father, each plant has two genes for flower colour. If the two genes are alike for

instance, both having come from white flowered parents (rr), the plant is termed the homozygote. The union of gametes with different genes gives a hybrid plant termed a heterozygote (Rr). The gene R for purple is dominant over for white, the F1 generation hybrids will show purple flowers. They are phenotypically purple but their genotype contains both R and r genes and these alternative genes do not blend each other. Mendel inferred that when a heterozygote forms its sex cells, the allelic genes segregate and pass to different gametes. This is expressed in the first law of Mendel that is the law of segregation of unit genes. Equal number of gametes, ovules or pollen grains is formed that contain the genes (Rr).

Molecular Genetics: The data accumulated by the geneticists of the early 20th century provided compelling evidence those chromosomes and the carriers of the genes. But the nature of the genes themselves remained a mystery, as did the mechanism by which they exert their influence. Molecular genetics the study of molecular structure of the genes and the methods by which genes control the activities of the cell provided the answers to these fundamental questions.

Much of information in molecular genetics has come from the study of microorganisms, particularly the bacterium *Escherichia coli* (a common inhabitant of the human intestine) and its interactions with various bacteriophages. Bacteria have many features that make them especially useful in genetics research. For example, they have an extremely short life cycle, so that many generations can be raised in a brief period of time. Equally important, bacteria have only one basic function - to reproduce. Consequently, their genome is relatively limited. Furthermore, unlike higher organisms, bacteria are not diploid, so their genome does not include two alleles of each gene. This makes it easy to identify a bacterium that carries a mutant gene, as the effects of the mutation cannot be masked by a normal allele. Although they are not diploid, bacteria can and do occasionally exchange genetic information through a variety of processes. This genetic exchange feature has been important in certain lines of molecular genetics research. Viruses also have advantages in genetics studies. Although they can reproduce only in a living cell, they have the simplest form of genetic material and evidence both genetically controlled properties and the ability to mutate.

Because of the relative simplicity of gene action in microorganisms, their study profoundly influenced early understanding of molecular genetics. A study of the genetics of microorganisms involves the production of specific genes mutations and the examination of their biochemical effects. These studies have permitted the delineation of the metabolic pathways that produced the mutation in the experimental microorganism, as well as the isolation of the large molecules that contain the genetic information.

Although there are virtues to bacteria as experimental subjects in genetics research, it should

be pointed rather fundamental ways. In fact, bacteria (along with the cyanophytes or blue - green algae) are sufficiently distinct as to constitute their own kingdom, the Monera. Monerans, unlike protists, plants, and animals, are prokaryotic. This means that their cells lack a true, membrane enclosed nucleus, the cellular structure that contains the chromosomes, in all other organisms (which are known as eukaryotes). Perhaps more important in a discussion of genetics, the bacterial chromosome differs in composition from the chromosomes of eukaryotes, so much so that some authorities prefer to avoid the term chromosome in describing the genetic material of bacteria.

In eukaryotes, the chromosomes consist primarily of deoxyribonucleic acid (DNA) and a variety of proteins. Bacterial chromosomes have little protein, which proved to be an important clue in determining the chemical nature of the hereditary substance. Finally, all the progeny of a bacterium are identical; whereas the cell progeny of the fertilized egg of a complex, multicellular organism gives rise to many different tissues and organs whose component cells display specific patterns of different gene activities. This latter process is called differentiation.

Molecular Basis of Inheritance

DNA and Chromosomes: It has been discussed that each individual in sexually reproducing species inherits to alleles for each gene, one from each parent. When such an individual forms sex cells, each of the resultant gamete receives one member of each of allelic pair the formation of gametes occurs through a process of cell division called meiosis. It is also known as reduction division because the amount of hereditary material present in the gametes has been reduced by half. When gametes unite in fertilization the double dose of hereditary material is restored and a new individual is created. This individual is consisting at first of only one cell grows via mitosis a process of repeated cell divisions. Mitosis differs from meiosis in that each daughter cell receives a full copy of all the hereditary material found in the parent cell.

In 1869 a substance containing nitrogen and phosphorus was extracted from cell nuclei it was originally called nucleon but is now known as DNA. is the chemical component of chromosomes that is chiefly responsible for their staining properties in microscopic preparations. The chromosomes of eukaryotes contain a variety of proteins in addition to Dna. The nucleic acids or the proteins or the both together are the carriers of genetic information, which makes the gene of same organism or the different organisms specifically different. Until the early 1950s most biologists were inclined to believe that the proteins were the chief carriers of heredity nucleic acids contain only four different unitary building blocks, but proteins are made up of 20 amino acids which are different from each other. Hence proteins have a greater diversity o structures and the diversity of genes seemed at first likely to rest on the diversity of proteins.

Path of the Gene

The Watson and Crick model of the genetic material permit an explanation of the mechanism of precise replication of genes. The paired complementary strands of the DNA molecule may separate as a result of a breakage of the hydrogen

bonds between the paired nitrogenous bases. If the free nucleotides (base + sugar + phosphate) are present in the medium surrounding the gene, they might pair with the complementary bases of the single strands of DNA. An enzyme, the DNA polymerase functions to form the phosphate bonds between the sugars in the Dna backbone. It has been used in the synthesis of Dna in vitro, in cell-free systems. The enzyme is extracted from rapidly dividing cells of E. coli. A supply of the four nucleotides, A, T, G, and C, is provided, as well as a source of energy, adenosine triphosphate (Atp). To start DNA synthesis another key component is added- a trace of DNA to serve as a primer, or template. The kind of DNA that is synthesized depends on the primer. Even though the enzyme came from E. coli, if the primer is Dna of some quite different organism, such as cattle, the Dna that is synthesized is not E. coli but cattle DNA.

The DNA in one human cell is approximately two meters long when stretched out. It has been estimated that if the entire DNA in a human were stretched out, it would extend from the Earth to Sun and back again. For the large amount of Dna in one cell to fit, it obviously must be carefully and tightly packaged. About 140 base pairs of the DNA helix wind around a cluster of chromosome proteins (histones) to form a nucleosome, a structure similar to a bead on a string. Between the nucleosome beads is a string (linker region) of 20 to 100 DNA base pairs associated with another histone protein. This structure is flexible enough to permit the coiling and folding necessary to pack the DNA into the cell nucleus in a way that makes it readily available when it becomes genetically active.

DNA as an Information Carrier: Transcription and Translation of the Genetic Code

As has been stated, the Watson - Crick Model provides an explanation of how a gene can carry hereditary information in the form of a chemical code. This section will describe the genetic code and explain how it governs the biochemical processes of the cell.

Before turning to the language of the code, it is necessary to explain what it is that the code specifies. It is now known that genes encode instructions for the production of proteins which are largely responsible for the structure and function of the organism. Proteins are large, complex molecules consisting of one or more polypeptide chains that, in thru, are composed of amino acids linked together by peptide bonds, Proteins play many roles in organisms. Some proteins make up structural components of the organism; an example is the protein collagen in vertebrate animals. Others perform particular functions; for example, the protein hemoglobin transports oxygen in the blood of mammals, and the proteins of the immune system (immunoglobulins) protect against diseases in many members of the animal kingdom. Still other proteins regulate the rate of specific biochemical reactions in cells. This latter class of proteins, called enzymes, functions, as biological catalysts. Enzymes permit chemical reactions to occur with extreme rapidity at temperatures normal to living cells. Without these proteins, the molecular interactions would require much longer periods of time and much higher temperatures, and they would lose their specificity. It

is certainly no exaggeration to say life depends on enzymes.

The sequence of the genetic letters, A (adenine), T (thymine), C (cytosine) and G (guanine), in the Dna is first transcribed into the corresponding sequence of the letters A, U (uracil), C, and G in the messenger RNA. This occurs through the action of the enzyme RNA polymerase. This enzyme synthesizes RNA in a test tube from a mixture of the A, U, C, and G bases, but it does so only in the presence of a primer DNA. The sequence of the bases in primer copied in the RNA. The steps involved in this process are as follows: (1) The DNA double helix unwinds by breaking the hydrogen bonds between the corresponding bases in the paired strands; (2) The RNA polymerase forms the bonds between the Rna bases that are complementary to the bases in the DNA; and (3) The messenger Rna thus formed passes into the cytoplasm and becomes attached to a ribosome. Ribosome consists of proteins and another type of RNA (r RNA).

Protein synthesis translation. The process of protein synthesis is represented diagrammatically. The information contained in the sequence of the bases (letters) in the messenger RNA is then translated into a sequence of amino acids in a protein. This requires the presence of still another molecule that is capable of recognizing the code for a specific amino acid and selectively making the amino acid available at the right point in the protein synthesis, a soluble RNA fraction within cells that can bind amino acids. Soluble, or transfer, RNA (SRNA, or tRNA) is a single-stranded molecule that forms about 20 percent of the total cellular RNA. If amino acids and a source of energy (usually ATP) are added to a mixture to transfer RNA, reversible binding of amino acids to the RNA molecules occurs. Furthermore, each amino acid is bonded to a specific transfer RNA molecule by a specific activating enzyme.

There are at least 20 different kinds of transfer RNA's and activating enzymes that correspond to the 20 amino acids commonly found in proteins. The amino acid-transfer RNA complex becomes attached to the ribosome with its messenger RNA molecule; the addition of the amino acid to the growing polypeptide chain then occurs. A sequence of three nitrogenous bases (anticodon) on the transfer RNA molecule pairs with a complementary sequence (codon) on the messenger RNA molecule, which recognition has occurred, a peptide bond is formed between the amino acid bound to the transfer Rna and the growing polypeptide chain.

The accuracy of the model described has been confirmed by the achievement of protein synthesis in the test tube. This synthesis requires a DNA template (primer DNA), precursor nucleotide molecules, ribosome's, transfer RNA's amino acids, and a set of enzymes and certain other factors.

Reading the code. It is necessary to understand how the four letters - A, T, C, and G - specify, or code, for 20 different amino acids. If a single letter coded for an amino acid, only four amino acids could be specified. If two bases were needed to specify an amino acid, then 16 different combinations could be constructed, again an insufficient number (20 amino acids must be accounted for). Combinations of three letters allow 64

different words to be constructed, more than the necessary minimal number.

A three-letter, triplet, and code could be constructed in at least three different ways: (1) with words overlapping; (2) with words not overlapping and punctuated; and (3) with words not overlapping and not punctuated. An overlapping code is composed of words that overlap each other i.e., the letters of any given word may belong to one, two, or three words. The DNA might contain, for example, the sequence Agcgttacg; the first word is AGC, the second CGT, and so on. This type of code is improvable, because of the restrictions it would place upon the possible sequence of amino acids in protein. as the example above shows, if the first word is Abc, the second word must begin with C, etc. Examination of amino-acid sequences in a protein such as hemoglobin indicates that any amino acid can follow any other - possibility not allowed for by an overlapping code.

If the code is non-overlapping, a problem of distinguishing words from each other arises. Dna contains no spaces separating the words as in written sentences; therefore there must be other indications of specific starting points for messenger Rna synthesis. The base sequence AGC AGC AGC ... could be punctuated by the presence of a fourth base, T, between each AGC triplet. This would reduce the number of possible triplets to 27. that a punctuated code of this type is not realized is seen from the evidence of the degeneracy in the code for some amino acids. The degeneracy means that some amino acids are coded for by more than one triplet, and a punctuated code does not allow enough words. A second objection to this type of code comes from a consideration of the effects of mutation on the coding sequence. If one of the punctuation marks mutates to another base, or a coding base mutates to a punctuation mark, the resulting sequence will be complete non-sense functionally.

The third possibility is a no overlapping, non punctuated code, in which the reading starts from a specific point. In all organism studies in this respect this is the method of coding used. Knowledge of the base sequence in the messenger RNA and the resulting amino-acid sequence in protein reveals the code for each amino acid. The triplet Uuu, for example, is the code for the amino acid phenylalanine, corresponding to the sequence AAA in the DNA. Poly-A (AAA) and poly-C (CCC) are messenger RNA's codes for lysine and proline, respectively.

Mutations in the Code

The DNA content of the cell must accurately replicate itself prior to mitosis or meiosis. Given the complexity of the DNA molecule and the vast number of cell divisions that take place within the lifetime of a multicellular organism, it is obvious that copying errors are likely to occur. If unrepaired, such errors change the linear order of the unrepaired; such errors change the linear order of the DNA bases and produce mutations in the genetic code. Many mutations arise from unknown causes. In addition to these so-called spontaneous mutations, researchers have demonstrated that a variety of environmental agents - including ionizing radiation, toxic chemicals, and certain viruses - can induce mutations. The effects of

these mutagenic agents on human health are discussed below in the section Human genetics.

Kinds of mutations. The addition or deletion of one or more bases results in a frame-shift mutation, so named because the reading frame of the gene, and thus its message, is altered from that point forward. Suppose that a sage is altered from that a DNA message read from left to right reveals that triplets GAC, TCA, and TTA (which are transcribed in the RNA code as CUG, AGU and AAU). Deletion of the first T alters the reading frame so that triplets GCA, CAT, T alters the reading frame so that triplets GAC. CAT, TA... will be read. The first triplet is unchanged, but all the remaining triplets may specify wrong amino acids. The chemical addition of a based to the sequence likewise shifts the reading frame; such a mutant will also specify wrong amino acids beyond the point of the base addition. If an original mutant resulted from the deletion of a base at a point beyond the first mutation would restore the reading frame of the Dna sequence and would result in nearly normal function.

For example, assume that the original DNA sequence reads ACT, GGC, TAG, CTG, TCA, TCG ... Deletion of the C in the second triplet results in the following triplets being read: ACT, GGT, AGC, TGT, CAT, CG... The subsequent addition of a base (A) between the third and fourth mutant triplets results in the following sequence: ACT GGT AGC ATG TCA TCG... Note that the first, fifth, and sixth triplets are identical to those in the original sequence. Only the second, third and fourth triplets are altered, and the reading of the code from the fifth triplet on will be identical to that in the original message. Frequently, suppressor mutations occur in proximity to other mutations and restore the reading frame of the DNA sequence, thereby allowing a sequence of amino acids differing only slightly from the original one to be formed in the protein.

Mutations in which one base is exchanged for another are called base substitutions, or point mutations. A base substitution may result in the incorporation of one wrong amino acid into the polypeptide chain encoded by the gene. What effect this has on the functioning of the protein of which the chain is part depends on the type and position of the wrong amino acid. In many cases, the effects are minor, but there are exceptions. The human disease sickle-cell anemia, for example, is the product of a single base substitution inherited from both parents. Sometimes a base substitution results in a codon for an amino acid being changed to one of the termination triplets. This type of point mutation will cause premature termination of protein synthesis and, probably, complete loss of function in the finished protein.

Thus far distinctions have been made between mutations in terms of their effects on the nucleotide sequence of DNA. It is also useful to differentiate between mutations that affect germ cells (i.e., eggs and sperm) and those that affect somatic cells. When a mutation occurs in a germ cell, it can be passed on to offspring, where it will be carried in every cell of the new individual. Mutations in somatic cells, on the other hand, are not passed on to offspring, and they affect only a certain population of

cells (the original mutant cell and its mitotic descendants) within the affected individual.

Conclusion

The tools and techniques of human genetics are very much part of medicine in the 1990s and beyond. Man's motivation for self improvement has been an integral part of his make-up since time immemorial. The human desire for preserving the fittest and weeding out the worst remains the same since stone-age man practiced castration, coitus interruptus, mechanical contraception, urethral surgery, abortion, infanticide, infant cannibalism, delayed lactation and geronticide. During the intervening centuries there have been scores of attempts to develop dream states; at forced mass migration, or to protect social order by casting out the unwanted under various guises. For the first time we are catching a glimpse of the possibility of significantly altering our genetic constitution, supplying us with the tools to realize very deep seated instincts, but without adequate knowledge of all the dangers. It is foreseen that the law has an important contribution in maintaining the balance between seemingly conflicting interests of the individual, the community, and the state and genetic research scientists. There is a need for pro-active involvement in the author's opinion.

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