HUMAN GENETICS

Ichiro Matsuda
Ezuko Institution for Developmental Disabilities, Kumamoto City, Japan

Keywords: genetic disease, genetic service, genetic testing, gene therapy, bioethics

Contents

Summary

Recent progress in human genetics has advanced our knowledge of the role of inheritance in health and diseases. Studies related to medical genetics have led to a better understanding of: mechanisms of genetic disorders, progress in genetic testing using molecular biotechnology, and to mass-screening programs for newborn infants, and effective treatment. The potential for gene therapy for monogenic and other diseases is being given much attention. The main goal of medical genetics is to aid persons with a genetic disorder, and their families, to live as normal a life as possible, to make informed choices about all genetic services, and to obtain relevant medical or social support systems. Genes contribute not only to the cause of severe single-gene disorders but also cause a predisposition to a wide range of common diseases. Only when the gene-related information is applied (as based on evidence of safety and effectiveness, and general principles of biomedical ethics), will these persons and

families be benefited. The genome is not only an individual's property; blood-related members possibly share it. Genetic information can affect an entire family and genetic choice can affect future generations. Thus, questions in medical genetics extend beyond the traditional boundaries of biomedical ethics and the physician–patient relationship.

1. Human Genetics and Medical Genetics

Human genetics is one part of human biology. This subject includes the study of human variability in terms of causes and effects, environmental effects on human heredity, twin studies, pharmacogenetics, forensic medicine, clinical genetics, and so on. Medical genetics is synonymous with clinical genetics, and is explained by McKusick as "the aspect of human genetics that is concerned with the relation between heredity and diseases." Recent advances in human genetics, especially molecular and cell biology, have revolutionized our knowledge of the role of inheritance in health and diseases. However, to date (2002), treatments of choice are limited for the majority of inherited disorders. Therefore, as the WHO defined it in 1998, the main goal of medical genetics is as follows:

1) Helping people with a genetic disadvantage and their families to live and reproduce as normally as possible, 2) making informed choice in reproductive and health matters, 3) assisting people to obtain access to relevant medical services or social support systems, and 4) helping them adapt to their unique situation and to become informed on relevant new developments.

Current advances in medical genetics represent progress in the molecular analysis of genetic information applied to genetic counseling for a family carrying risk factors, mass-screening programs for newborn infants related to early effective treatment, the development of several medicaments using recombinant technology (for example, human growth hormone), and the potential for gene therapy for monogenic and other diseases. Genes determine the cause of catastrophic single-gene disorders. Genetic variants (alleles) may also predispose people to diseases such as cancers, coronary artery disease, hypertension, diabetes mellitus, psychiatric disorders, and even to some infectious diseases. Knowledge of genetic factors, when used properly, may be of benefit to subjects and families with genetic burdens worldwide. However, such advances will be respected only when they are applied with due regard to general principles of biomedical ethics. As the genome is the property of an individual, and is shared in part with blood-relatives, genetic information can affect an entire family and all related decisions and treatments can affect future generations. For this reason, the unique issues of medical genetics can challenge the traditional ethics of medical care and the physician–patient relationship.

2. Historical Aspects of Human Genetics

The rule of heredity was first noted in plant breeding experiments, as reported by G. Mendel in 1865 (see *Mendelian Genetics and its Development*). Six years earlier C. Darwin had published *On The Origin of Species.* Between them, Darwin and Mendel laid the foundations for the development of current human genetics. In 1869, F. Galton (1869), a cousin of Darwin, published a book proposing the hereditary improvement of

humans using methods of selective breeding, and coined the word "eugenics." The idea, which was based on an immature concept of biology (in terms of the current knowledge of human genetics), did carry some weight in the early twentieth century in Europe and the United States, until being discredited when the Nazis adopted it (see *Eugenics*). Mendelism remained unrecognized until 1900, when W. Bateson translated Mendel's paper from German into English and published it in an English language journal. Immediately after this, there were intensive efforts to find applications to humans. In 1902, A.E. Garrod described cases of alkaptonuria in four families, where affected individuals were the offspring of consanguineous marriages. Garrod applied Mendel's theory to explain his finding, and called it "an inherited disease." He suggested that genes dominate the synthesis of the enzymes in the body, errors in which could produce a disturbance in biochemical metabolism and relevant clinical features. Garrod's theory, which was apparently the beginning of biochemical genetics, was supported by the experiments of G.W. Beadle and E.L. Tatum using the bread mold *Neurospore.* Based on their results, they proposed "the one gene–one enzyme theory" in 1941.
Another approach to clarification of genetic mechanisms in humans is the use of chromosomal analysis (cytogenetics). In 1956, J.H. Tijo and A. Levan demonstrated that there were 46 human chromosomes (46, XY in males, 46, XX in females), rather than 48 as had been believed. A most exciting finding, made by J. Lejenue in 1959, was that patients with Down syndrome have one additional chromosome 21 (trisomy).

Biochemical genetics and cytogenetics had belonged to different research fields until the disease-causing genes were cloned and identified on the specific loci of chromosomes. Novel approaches to gene mapping were developed using advanced molecular biotechnology, and members of families affected with inherited diseases were identified. The principles of biotechnology were based on the double helical structure of DNA (deoxyribonucleic acid) found by J.D. Watson and F.H. Crick in 1953, recombinant DNA technology developed by P. Berg and co-workers in 1972, and DNA sequencing methods established by F. Sanger with his co-workers, and by A.M. Maxam and W. Gilbert in 1977 (see *The Human Genome*). D. Comings, editor of the *American Journal of Human Genetics*, described his reaction to the new technology as follows: "since the degree of departure from our previous approaches and the potential of this procedure are so great, one will not be guilty of hyperbole in calling it *New Genetics*."

3. Genetic Diseases

Genetic diseases are classified into three groups: (1) chromosomal disorders, (2) inherited single-gene disorders, and (3) disorders due to multifactorial inheritance. A fourth category, *birth defects*, can be identified to cover congenital abnormalities with chromosomal, monogenic, polygenic, environmental, and unknown etiology. Cancers seem to be common to all four categories. One must understand that *genetic* and *hereditary* are not synonymous. All hereditary conditions where a mutant gene or chromosomal abnormality is transmitted from one or both parents are genetic in origin, but not all genetic conditions where a gene or chromosome abnormality is involved in the development of disorder are necessarily hereditary. Somatic mutations (not inherited) play a role in disease, especially cancers. The term "familial" is not synonymous with either of the others. Generally, hereditary conditions may be responsible for familiar occurrences, but also non-genetic factors such as toxins,

teratogenic agents, infection, and other environmental factors may contribute to familiar occurrences.

3. 1. Chromosomal disorders

The somatic cell and zygote consists of 46 chromosomes (22 pairs of autosomes plus XX and XY sex chromosomes in females and males), known as diploid (2N). Recent advances in chromosomal analysis are banding and high-resolution banding methods supported by molecular genetic techniques, including fluorescence *in situ* hybridization (FISH). These methods have been used to differentiate individual chromosomes, to clarify parental origin of a chromosome in question, to specify the precise origin of a translocated chromosomal fragment, and to achieve gene mapping.

Chromosomal aberrations are found at a frequency of at least 0.5% (1/200) of the live-born, and account for a significant proportion of the causes of mental retardation and congenital structural defects. Studies of spontaneous abortion indicated that generally, 50% to 60% of abortuses have detectable chromosomal abnormalities, of which 49% to 52% are autosomal trisomies, 18% to 23% monosomy X (45,X), 15% to 20% triploidy, 4% to 6% tetraploidy, 3% to 7% structural rearrangements, and 3% to 5% other abnormalities. Therefore, nature exercises selection, as only a small proportion of abnormal conceptuses survive to term. In live-born infants with chromosomal errors, autosomal trisomies (for example, trisomies 21, 18, and 13) account for about 25%, sex chromosomal abnormalities (e.g., 45,X, 47,XXX, and 47,XXY) for about 35%, and structural rearrangements (for example, translocations, and deletions) for about 40%. Thus, the major chromosomal abnormalities are numerical.

The common mechanisms of chromosomal aberrations are meiotic errors (for instance, non-disjunction of chromosome) during oogenesis and spermatogenesis. In addition, mitotic errors after fertilization also occur, resulting in somatic mosaicism. Meiosis is a reduction division of 2N (diploid) germ cells, resulting in gametes with a haploid set (N) of chromosomes. If non-junction occurs in meiosis, the chromosomes fail to separate properly into the daughter cells and both chromosomes of a homologous pair are taken into the daughter cells, leading a gamete with 24 (N+1) chromosomes and a gamete with 22 (N-1) chromosomes. When such a gamete is fertilized by a normal counterpart gamete, a trisomic (for example, trisomy 21) or monosomic zygote (for example, 45, X) is produced. Albeit rare, other chromosomal errors (for instance, balanced and unbalanced translocation, deletion, partial duplications, and ring chromosome) can also occur in meiotic cells, and the gametes are affected *de novo*.

Generally speaking, chromosomal disorders arise spontaneously, and only some of these instances are heritable. Such inherited chromosomal errors may occur when a parent, albeit with a normal appearance, carries a balanced translocation. The possibility of a child with or without an unbalanced chromosomal aberration depends on how meiotic segregation occurs in this parent, who may contain balanced or unbalanced translocated chromosomes in the gamete. Thereby, when a balanced translocation is present in a family, such an abnormality can pass from generation to generation, and individuals will inherit an unbalanced chromosome. One of commonly encountered familial

translocations is that in Down syndrome (for example, 46 XX, or XY, der (14) t (14; 21); an additional chromosome 21 on an unbalanced translocated chromosome 14).

Down syndrome (trisomy 21) is the most common numerical chromosomal disorder, the prevalence being about 1/1000 live births (Table 1).

Abnormality	Frequency/1000 births
Numerical	
Autosomal	
Trisomy 21	1.0-1.5
Trisomy 18	0.1- .2
Trysomy 13	0.1-0.3
Others	0.2
Sex chromosomes	
45X	0.1-0.4
47XXX	0.8-1.2
47XXY	1.0-2.0
47XYY	1.0-1.2
Others; male	0.08
Others; female	0.3
Structural	
Balanced translocation	2.1
unbalanced translocation	0.5

Source for Table 1 Weatherall DJ(1991): The New Genetics and Clinical Practice, 3rd edition,Oxford University Press. and Lashley FR(1998): Clinical Genetics in Nursing Practice,2nd edition,Springer Publishing Company

Table 1. Prevalence of some selected chromosomal disorders in live-birth infants

The typical IQ score of such affected individuals is approximately 40 to 50, with some individuals achieving a low normal IQ. Mortality related to respiratory infections has been reduced and most of these affected subjects live to mid-adulthood. The extra chromosome 21 is of maternal origin in approximately 90% of the patients. The prevalence of Down syndrome depends on maternal age, the rate per 1000 live-births being 0.65 at age 20 years, 2.28 at age 35 years, and 10.68 at age 40 years, because the

rate of non-junction at oogenesis increases as maternal age is advanced. Prenatal screening for Down syndrome is available for pregnant subjects of advanced age. In most developed countries, except Japan, the prevalence decreased by about 30% to 40% during the last half of the twentieth century, mainly because of reproduction control in women of advanced age.

With regard to another chromosomal abnormality, the concept of "contiguous gene syndrome" was introduced to better understand the clinical association of manifestations, such as in Langer–Giedion syndrome. This syndrome combines mental retardation with characteristics of two or more dominant disorders: multiple cartilaginous exostosis and tricho-rhino-phalangeal syndrome type . A deletion of one chromosome 8q24 band destroys these two contiguously located genes, and consequently "haploinsufficiency" (where the haploid allele(s) is not enough for normal expression) leads to Langer–Giedion syndrome.

3.2. Inherited Single-gene (Monogenic) Disorders

(See *Molecular Genetics of Inherited Disorders*)

Humans have 30 000 to 40 000 nuclear genes on haploid chromosomes. Although there are several exceptions (so-called "non-Mendelian genetics"), monogenic disorders are inherited through mutated single genes by the Mendelian rule. Judging from the appearance of clinically abnormal individuals in an affected family, monogenic disorders are categorized as inherited traits: autosomal dominant, autosomal recessive, and X-linked traits. In case of autosomal dominant inheritance, the disorder occurs in a heterozygous individual, and the same abnormality will be observed in one of the parents, usually with equal numbers of males and females affected in the family. The risk of recurrence in future offspring of such parents is 50%. Sometimes in case of autosomal disorders, members of only one sex are affected. The term "sex limitation" is used in such cases to distinguish from X-linked traits, especially when only males are affected. However, father-to-son transmission is never observed in the case of a X-linked trait. In an affected family with autosomal dominant disorders, it is possible to find that the expression or severity of phenotype differs even in the same affected family, a phenomenon known as "expressivity." Another phenomenon is "penetrance," which is defined as the proportion of individuals of a specified genotype that show the expected phenotype under a defined set of environmental conditions. For example, if all individuals carrying a dominant mutant gene show the mutant phenotype, the gene is said to show complete penetrance.

A new germ line mutation in one of the parents, possibly related to advanced paternal age, is another cause of the disorder in autosomal dominant inheritance (for example, achondroplasia). In autosomal recessive inheritance, disorders occur when the mutant gene is present in the homozygous state, and both parents are heterozygotes carrying one copy of the mutant allele concerned (carrier state). The risk of recurrence for future offspring of such parents is 25%. Theoretically, they produce 50% of carrier offspring and 25% of normal offspring. Unlike autosomal dominant disorders there is usually no family history, especially with a small family size and in the absence of consanguinity. The risk of a recessive disorder occurring is increased greatly if there is parental

consanguinity. It is evident that some genetic disorders (for example, PIT-1 deficiency, isolated growth hormone deficiency, and von Willebrand disease), even resulting from mutations in the same gene, show either dominant inheritance or recessive inheritance, depending on the specific mutation. For example, a dominant negative effect of the mutant gene (a mutant allele product disturbs the function of a normal allele product) would cause dominant inheritance, and no product or much less of a product of mutant allele (loss of function) would cause recessive inheritance (see *Gene Action in Inheritance*). In X-linked recessive disorders, only males are affected, and the disorders are transmitted through female carriers (heterozygote) who are generally free of clinical symptoms, because females have two X chromosomes while males have one. A female carrier passes the disorder to half the number of her sons, producing affected males, and to half the number of her daughters, producing the carriers. One of the two X chromosomes in females is randomly inactivated in somatic cells at an early stage of development, according to Lyonization; therefore, heterozygous females can occasionally show some features of the condition, depending on the degree of inactivation of the mutant gene. It must be noticed that 20% to 25% of male patients of X-linked recessive disorders (for example, Duchenne muscular dystrophy) are due to new mutations. Some X-linked dominant conditions are lethal in males carrying the mutant gene (hemizygote) and in the families affected there will be fewer males than usual (for example, Rett syndrome) (see *Patterns of Heredity*).

The incidence of rare recessive disorders is not equal in all races or ethnic groups (Table 2). For example, the incidence of Tay-Sachs disease is 0.2–0.4 per 1 000 in Ashkenazi Jews, but only 0.001–0.003 per 1 000 in Sephardi Jews. Such a high frequency possibly reflects the genetic drift or a founder effect, but the precise mechanisms are unclear. Presumed increased resistance in hetrozygotes may account for several genetic disorders, such as malaria in Sickle cell disease, β-thalassemia, and G6PD deficiency, whose incidence is prominent in the malaria-dominant area covering the equator (see *Population Genetics*). Sickle cell disease and thalassemia are most common in monogenic disorders. WHO estimates suggested about 7% of the world's population as carriers of theses disorders in the year 2000. It is evident that there are two types of mutation. First, the same genomic mutation is common in certain diseases in the general population, such as Sickle cell disease (single amino acid substitution, valine for glutamic acid at position 6 of hemoglobin S) and achondroplasia (single amino acid substitution, arginine for glycine at position 380 of fibroblast growth factor receptors). Second, mutations are individual (private mutation) in each affected family, such as Duchenne muscle dystrophy and hemophilia A. Gene analysis is easily feasible in the former cases, but not in the latter, in terms of effectiveness related to time and expense. Needless to say that there are many private mutations, and analysis at the protein level may be more efficient (for example, the same functional abnormality may occur, and be detected, for hundreds of different mutations).

Diseases	Nations/Regions/Ethical Group	Frequency/1000 birth
Phenylketonuria		
	USA, England,France	0.08-0.1

	Germany,Belgium,	0.15-0.16
	Finland	0.01
	Japanese	0.01
	North Chinese	0.1
Galactosemia		
	USA	0.016
	England	0.014
	Japanese	0.008
Thalassenia		
	Mediterranean, Orientals	10-20
	Japanese	<0.001
Sickle-cell disease		
	Africans	10-20
	Japanese	0
Cystic fibrosis		
	European	0.4-0.5
	Afro-Americans,Orientals	0.01
Adrenogenital syndrome		
	Yupik Eskimos	2
	USA	0.02
	Japanese	0.07
Huntington disease	Tasmania	0.017
	Japanese	0.07

Source for Table 2 Weatherall DJ(1991) The New Genetics and Clinical Practice,3rd edition,Oxford University Press. ,ScriverCR, Beudet AL,Sly WS, Valle D, (1989) The metabolic Basis of Disease, 6th edition,McGraw-Hill,New York, Maternal Child Health Statistics of Japan(1998),and personal communication of Drs Y Fukumaki and K Aoki

Table 2. Race differences in frequency of genetic diseases

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Bibliography

Ad hoc Committee on Genetic Counseling (1975). Genetic counseling. *American Journal of Human Genetics* **26**, 240–244. [Describing still available and indispensable concepts of genetic counseling.]

American Academy of Pediatrics (2000). Serving the family from birth to medical home. A report from the newborn screening task force convened in Washington DC, May 10-11,1999. *Pediatrics* **100**, 383–427. [The purpose of the Task Force is to review issues and challenges for the newborn screening system. Readers will understand a blueprint for the future of the newborn screening and new bioethical issues including potential uses of residual blood samples.]

American Society of Clinical Oncology (1996). Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. *Journal of Clinical Oncology* **14**, 1730–1736. [The real meaning of genetic testing for cancer can be understood clearly when reading this article.]

American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure (1998). Professional disclosure of familial genetic information. *American Journal of Human Genetics* **62**, 474–483. [Useful ideas as to how to disclose genetic information within affected family members is addressed in detail. Readers will understand how this issue is discussed internationally.]

ASHG/ACMG Report (1995). Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *American Journal of Human Genetics* **57**, 1233–1241. [Children have a special position in genetic testing, since they may not be competent to make decisions. Parents or guardians contribute to maximum benefits and minimum risks for their minors. Readers will comprehend how, and on what, parents or guardians (instead of minors), should make a decision concerning genetic testing, including neonatal screening, susceptibility testing, especially without reliable prevention or treatment.]

Lashley F.R. (1998) *Clinical Genetics in Nursing Practice*, 2nd edn. Springer.

McKusick V.A. (1998). *Mendelian Inheritance in Man: A Catalog of Human Genetics and Genetic Disorders*, 12th edn. pp x x viii-I x iii. Baltimore: Johns Hopkins University Press. [The Bible of the study of human genetics. The article addresses basic but recent, important concepts and knowledge of human genetics. Most recent information is available through <http://www.ncbi.nlm.nih.gov/Omim/>.]

Scriver C.R., Beudet A.L., Sly W.S., and Valle D., (1989). *The Metabolic Basis of Disease*, 6th edn. New York: McGraw-Hill.

Shiloh S., Avdor O., and Goodman R.M. (1990). Satisfaction with genetic counseling: dimensions and measurement. *American Journal of Medical Genetics* **37**, 522–529. [Probably the first report concerning the assessment of genetic counseling. Traditional non-directive genetic counseling must be evaluated carefully from the viewpoint of the person being counseled.]

Weatherall D.J. (1991): *The New Genetics and Clinical Practice*, 3rd edn. Oxford University Press

World Health Organization Human Genetics Programme (1998). *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic* Services. pp. 1-15 [Compact description of the internationally acceptable purpose and goal of medical genetics, and ethical principle of genetic testing and genetic services. This publication will be most helpful for medical and co-medical professionals involved in medical genetics.]

Further reading

Andrews L.B., Fullarton J.E., Holtzman N.A., Motulsky A.G. (1994). *Assessing Genetic Risks. Implications for Health and Social Policy.* National Academy Press. Washington, DC. [Authors present principles for policy recommendations and bioethical key issues in genetic testing and screening. This is a most recommendable book for readers interested in clinical application of genetic testing.]

British medical Association (1998), *Human genetics, choice and responsibility*. Oxford University Press, Oxford. [This book deals the most authoritative and up-to-date assessment of the ethical, legal and professional issues raised by human generics in clinical practice.]

Harper PS, Clarke AJ (1997). *Genetics, Society and Clinical Practice*. BIOS Scientific Publisher. Oxford. [This is one of the most eminent books, discussing potential issues of biomedical ethics relevant to human genetics. Key issues are carefully described in detail so that readers will understand what is acceptable or unacceptable ethically, in decision making in health care science.]

Hodgson SV, Maher ER (1999). *A Practical Guide to Human Cancer Genetics*. 2_{nd} edition, Cambridge University Press, Cambridge, UK [This book presents the principles of cancer genetics and introduces the basic concepts and mechanisms of tumorigenesis and inherited predispositions to cancer.]

Holtzman NA, Watson MS (1998). *Promoting Safe and Effective Genetic Testing in the United States, Final Report of the Task Forces on Genetic Testing.* Johns Hopkins University Press, Baltimore. [This is the final report of the Task Force on Genetic Testing created by Working Group on Ethical, Legal, and Social Implications of Human Genome Research at the National Institutes of Health, reviewing genetic testing in the United States and making recommendations to ensure the development of safe and effective genetic tests. All persons interested in human genetics must read this report, to learn what are rational and desirable measures to provide genetic testing in clinical practice.]

National Bioethics Advisory Commission (1999). *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance.* Rockville, Maryland. [Most recent concepts when dealing with human samples/specimens for genetic research is discussed in detail from the bioethical viewpoint and a dictum validate for genetic research is proposed.]

Strachan T, Read AP (1999). *Human Molecular Genetics*. 2^{nd} edition, BIOS Scientific Publisher, Oxford [This is one of the most outstanding textbooks addressing basic description of structure and function of human genes and chromosomes to molecular diagnosis and gene therapy.]

Walters L, Palmer JG (1998). *The Ethics of Human Gene Therapy*. Oxford University Press, Oxford [The authors describe the science of gene therapy and focus on controversial ethical and public policy issues. They also address not only somatic cell gene therapy, but also germ line gene therapy, and genetic enhancements.]

Biographical Sketch

Professor Ichiro Matsuda graduated from Hokkaido University School of Medicine in 1957, and the Postgraduate School of Hokkaido University in 1962. He received research training at McGill University School of Medicine in 1963–1965 and at Johns Hopkins University School of Medicine in 1972–1974. He became Professor and Chairman of the Department of Pediatrics, Kumamoto University School of Medicine at 1976, Professor Emeritus of Kumamoto University at 1998, and Visiting Professor at Genetics and Public Policy Studies, Johns Hopkins Medical Institute, in 1998. At present, he is Professor of the Postgraduate School of Hokkaido Health Science University, and Director of the Ezuko Institution for Developmental Disabilities, President of Japan Society of Human Genetics, and President of Japan Society of Mass-Screening. The Japan Society of Human Genetics awarded the Society Prize and The Purple Ribbon Medal to Professor Matsuda in 1994 and by the Japanese Government in 1999, in connection with the successful investigations on Human Genetics.