MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

June 24, 1976

RECENT ADVANCES IN GENETIC COUNSELING

Joseph L. Goldstein, M.D.

OUTLINE

GENETIC PRINCIPLES - Brief Review

Pathogenesis of Disease
Molecular Basis of Gene Expression
Mutation
Cellular Mechanism by which Mutant Genes Produce Disease
Genetic Heterogeneity, Pleiotropism, and Variability

CATEGORIES OF GENETIC DISEASES

Chromosomal Disorders
Simply Inherited Disorders
  Autosomal Dominant
  Autosomal Recessive
  X-linked
Multifactorial Disorders

GENETIC COUNSELING

Objectives
Indications
Steps

CATEGORIES OF HIGH RISK FAMILIES

Risks Exceeding 50%
Risks of 25-50%
Risks of 10-25%
Risks of 1-5%

PRENATAL DIAGNOSIS

Procedure
Indications

EXAMPLES OF CASES REFERRED FOR GENETIC COUNSELING

Case #1 Marfan Syndrome in a 18 year old male with unaffected parents and grandparents

Case #2 Medullary Thyroid Carcinoma in a 36 year old male

Case #3 - Young couple at high risk to have child with neural tube abnormality

Case #4 - Risks to offspring of a young couple in whom both the husband and wife have Diabetes Mellitus

Case #5 - Prenatal diagnosis for Pompe's Disease (Glycogen Storage Disease)

Case #6 - 25 year old female whose brother had Duchenne form of Muscular Dystrophy

Case #7 - Kidney transplantation in hereditary forms of chronic renal disease

Case #8 - 38 year old female whose previous child had Down's Syndrome

EVALUATION OF GENETIC COUNSELING

Table 1

SOME RELATIVELY FREQUENT MENDELIAN DISORDERS

AFFECTING ADULTS

Autosomal Dominant Disorders

Familial hypercholesterolemia
Hereditary hemorrhagic telangiectasia
Marfan syndrome
Hereditary spherocytosis
Adult polycystic kidney disease
Huntington's chorea
Acute intermittent porphyria
Osteogenesis imperfecta tarda
von Willebrand's disease
Myotonic dystrophy
Hemochromatosis
Idiopathic hypertrophic subaortic stenosis (IHSS)
Noonan syndrome
Neurofibromatosis
Tuberous sclerosis

Autosomal Recessive Disorders

Deafness
Albinism
Wilson's disease
Sickle cell anemia
β-Thalassemia
Cystic fibrosis
Hereditary emphysema (α-1-antitrypsin deficiency)
Homocystinuria
Familial Mediterranean fever
Friedreich's ataxia
Phenylketonuria

X-linked Disorders

Hemophilia A
Glucose-6-phosphate dehydrogenase deficiency
Fabry's disease
Ocular albinism
Testicular feminization
Chronic granulomatous disease
Hypophosphatemic rickets
Color blindness

Table 2

EXAMPLES OF SIMPLY INHERITED DISORDERS THAT OCCUR WITH INCREASED FREQUENCY IN SPECIFIC ETHNIC GROUPS

ETHNIC GROUP	SIMPLY INHERITED DISORDER
African Blacks	Hemoglobinopathies, especially HbS, HbC, α- and β-Thalassemias Glucose-6-phosphate dehydrogenase deficiency
Armenians	Familial Mediterranean fever
Ashkenazi Jews	Abetalipoproteinemia Bloom syndrome Dystonia musculorum deformans (recessive form) Factor XI (PTA) deficiency Familial dysautonomia (Riley-Day syndrome) Gaucher disease (adult form) Neimann-Pick disease Pentosuria Tay-Sachs disease
Chinese	α-Thalassemia Glucose-6-phosphate dehydrogenase deficiency Adult lactase deficiency
Eskimos	Pseudocholinesterase deficiency Adrenogenital syndrome
Finns	Congenital nephrosis

French Canadians	Tyrosinemia
Japanese	Actalasemia
Mediterranean peoples (Italians, Greeks, Sephardic Jews)	β-Thalassemia Glucose-6-phosphate dehydrogenase deficiency Familial Mediterranean fever Glycogen storage disease, Type III
Northern Europeans	Cystic fibrosis
Scandinavians	α_1-Antitrypsin deficiency
South African Whites	Porphyria variegata

Data modified from V. A. McKusick, Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes. The Johns Hopkins University Press, Baltimore, 4th edition. pp. xv-lvi, 1975.

Table 3

METHODS FOR DETECTION OF ASYMPTOMATIC HETEROZYGOTES IN FREQUENTLY ENCOUNTERED DOMINANTLY INHERITED DISORDERS

Disorder	Method of Heterozygote Detection		Therapeutic Advantage of Early Diagnosis
	Physical Findings	Laboratory Tests	
GASTROINTESTINAL, LIVER, AND PANCREAS			
Hemochromatosis		Serum iron	Prevent cirrhosis, heart failure, and diabetes
Gilbert Disease		Serum bilirubin	Avoid confusion with more serious forms of liver disease
Peutz-Jeghers Syndrome	Melanin spots of lips, buccal mucosa, and digits	X-ray of small intestine	Clarify cause of gastrointestinal bleeding
Familial Polyposis		X-ray of colon; colonoscopy	Prevent colon carcinoma
Gardner Syndrome	Multiple sebaceous cysts; lipomas; fibromas; osteomos; dental abnormalities; desmoid tumors	X-ray of colon and small intestine; colonoscopy	Prevent colon carcinoma

METABOLIC AND ENDOCRINE			
Medullary Thyroid Carcinoma-Pheochromocytoma Syndrome		Serum calcitonin; measurement of blood pressure	Prevent thyroid carcinoma and complications of hypertension
Multiple Endocrine Adenomatosis	Multiple lipomas	Serum calcium, gastrin, blood sugar; x-rays of sella turcica and of stomach and small intestine	Prevent complication of hyperparathyroidism, hypoglycemia, peptic ulcer, metastatic cancer
Familial Hyperparathyroidism		Serum calcium, parathyroid hormone	Prevent renal damage and other complications of hypercalcemia
Familial Hypercholesterolemia	Tendon xanthomas, xanthelasma, arcus corneae	Serum cholesterol; LDL receptor activity of cultured fibroblasts	Prevent premature coronary heart disease
HEART AND VASCULAR			
Holt-Oram Syndrome	Abnormality of thumb and carpals; murmur of atrial septal defect	X-ray of hands; cardiac evaluation	Prevent complications of atrial septal defect
Noonan Syndrome	Hypertelorism; small chin; low-set ears; ptosis; pectus deformity; cryptorchidism; murmur of pulmonic stenosis	Cardiac evaluation; X-ray of skeleton; intravenous pyelogram (renal anomalies)	Prevent heart failure
Idiopathic Hypertropic Subaortic Stenosis (Asymmetric Septal Hypertrophy)	Presystolic gallop; characteristic carotid arterial pulse	EKG; echocardiogram	Prevent sudden death, syncope angina, heart failure

Dominantly inherited form of Atrial Septal Defect	Heart murmur	EKG showing first degree heart block, RBBB, RAD	Prevent complications of atrial septal defect
HEMATOLOGIC			
Hereditary Spherocytosis	Splenomegaly; jaundice	Blood smear; reticulocyte count; hemoglobin; osmotic fragility test	Prevent anemia, cholelithiasis
Hereditary Hemorrhagic Telangiectasia	Telangiectasia of tongue, lips, conjunctiva, ears, fingers; pulmonary AV fistula	X-ray of lungs	Clarify cause of nosebleeds and gastrointestinal bleeding
von Willebrand's Disease		Immunologic and functional assays of plasma AHG levels; bleeding time	Prevent gastrointestinal and urinary bleeding
CONNECTIVE TISSUE AND BONE			
Ehlers-Danlos Syndromes (Types I,II,III)	Loose-jointedness; fragile, stretchable, bruisable skin; subcutaneous calcified spherules		
Marfan Syndrome	Ectopic lens; mitral and aortic murmurs; excessive length of extremities	Slit-lamp exam; Metacarpal index by x-ray	Reduce risk of aortic dissection; prevent blindness
Osteogenesis Imperfecta	Multiple fractures; loose-jointedness; blue sclerae; deafness; aortic regurgitation	X-ray of bones	

RENAL			
Alport Syndrome	Nerve deafness; cataracts, lenticonus, spherophakia	Urinalysis; slit-lamp exam	Prevent uremia
Nail-Patella Syndrome	Dysplastic nails; absent patellas	X-ray of pelvis (iliac horns); urinalysis	Clarify cause of hematuria and azotemia
Polycystic Kidney Disease		Urinalysis; intravenous pyelogram; renal arteriogram; measurement of blood pressure	Prevent uremia and complication of hypertension
Renal Tubular Acidosis		X-ray of kidneys (nephrocalcinosis); urine pH, calcium; serum electrolytes, calcium	Prevent acidosis, osteoporosis, kidney stones
RESPIRATORY			
Hereditary Angioneurotic Edema		Serum level of C1 esterase inhibitor of complement	Reduce risk of sudden death caused by laryngeal edema and clarify cause of acute abdominal pain
DERMATOLOGIC			
Neurofibromatosis	Cafe-au-lait spots; neurofibromas; scoliosis		Prevent malignant degeneration of neurofibromas
Waardenburg Syndrome	Wide bridge of nose; frontal white blaze of hair; heterochromia iridis; white eye lashes; deafness		Clarify cause of deafness

Basal Cell Nevus Syndrome	Multiple basal cell carcinomas; jaw cysts; pits on palms and soles; skeletal defects (ribs, spina bifida, scoliosis)	X-rays of skull (calcification of falx cerebri) and skeleton	Removal of cutaneous cancers; provide cosmetic surgery
NEUROLOGIC			
Charcot-Marie-Tooth Disease	Pes cavus; atrophy of anterior tibial and calf muscles ("stork legs"); absence of deep tendon reflexes	Biospy of muscle and of sural cutaneous nerve	Improve walking by corrective shoes and orthopedic measures
Myotonic Dystrophy	Myotonia; muscle wasting of temporal and sternocleidomastoid muscles; cataracts; frontal baldness; signs of hypogonadism	Slit-lamp exam; electromyography; measurement of serum immunoglobulins; electrocardiogram	Anticipate complete heart block
Acute Intermittent Porphyria		Measurement of uroporphyrin synthetase activity in red blood cells	Reduce risk of neuropathic attacks by avoidance of aggravating drugs such as barbiturates
Tuberous Sclerosis	Adenoma sebaceum; cutaneous white macules; shagreen patch; periungal fibromas		Prevent seizures
Huntington's Chorea	Paranoia, other personality changes; choreic movements; dementia		

Periodic Paralysis Syndromes (Hypo-, hyper-, and normokalemic types)	Cold-induced myotonia	Electromyogram; serum potassium	Reduce frequency of attacks by avoidance of aggravating agents such as high-carbohydrate diet and exposure to cold
PHARMACOGENETIC			
Malignant Hyperthermia		Serum creatine phosphokinase	Prevent fatal episode of hyperthermia induced by general anesthesia

Table 4

APPROXIMATE PROPORTION OF PATIENTS AFFECTED BY NEW MUTATIONS IN SOME AUTOSOMAL DOMINANT DISORDERS

Disorder	Percentage
Achondroplasia	80%
Tuberous sclerosis	80%
Neurofibromatosis	40%
Marfan syndrome	30%
Myotonic dystrophy	25%
Huntington's chorea	4%
Adult polycystic kidney disease	1%
Familial hypercholesterolemia	Very Low

Table 5

EMPIRIC RISKS FOR SOME COMMON MULTIFACTORIAL GENETIC DISEASES AFFECTING ADULTS

Disorder in Index Case	Estimated Absolute Risk for First-degree Relatives
Cleft lip and/or palate	3%
Congenital heart disease	4%
Coronary heart disease	8% for male relatives 3% for female relatives
Diabetes mellitus	5%
Epilepsy	5%
Hypertension	10%
Manic-depressive psychosis	10-15%
Psoriasis	10-15%
Schizophrenia	15%
Thyroid disease (autoimmune disorders including hyperthyroidism, thyroiditis, primary myxedema, simple goiter)	10%

Table 6

INDICATIONS FOR PRENATAL DIAGNOSIS

1. Couples having a previous child with spina bifida or anencephaly (5% recurrence risk)

2. Couples having a previous child with a chromosomal aberration such as trisomy 21 form of Down's syndrome (1 to 2% recurrence risk)

3. Couples in whom either the husband or wife carries a balanced translocation chromosome for Down's syndrome (5-20% recurrence risk)

4. Couples at risk for having a child with a detectable inborn error of metabolism (25 to 50% recurrence risk)

5. Pregnant women 38 years of age and older who have a 1 to 2% chance of carrying babies with Down's syndrome

6. Women whose male fetuses have a 50% risk of being affected with a serious X-linked disorder such as Muscular Dystrophy or Hemophilia

Table 7

INBORN ERRORS OF METABOLISM FOR WHICH

PRENATAL DIAGNOSIS IS FEASIBLE

Lipidoses

Cholesteryl ester storage disease
Fabry disease
Gaucher disease
Krabbe disease (globoid cell leukodystrophy)
Metachromatic leukodystrophy
Neimann-Pick disease
Refsum syndrome
Tay-Sachs disease and other gangliosidoses
Wolman syndrome

Mucopolysaccharidoses

Hurler syndrome
Hunter syndrome
Sanfilippo syndromes
Scheie syndrome
β-glucuronidase deficiency

Amino Acid and Related Disorders

Argininosuccinic aciduria
Citrullinemia
Cysthationine synthase deficiency (homocystinuria)
Cystinosis
Histidinemia
Maple syrup urine disease
Methylmalonic aciduria

Disorders of Carbohydrate Metabolism

Fucosidosis
Galactosemia
Glucose-6-phosphate dehydrogenase deficiency
Glycogen storage diseases, types II, III, and IV
Mannosidosis

Miscellaneous Disorders

Adenosine deaminase deficiency
Familial hypercholesterolemia, homozygous form
Hypophosphatasia
I-cell disease
Lesch-Nyhan syndrome
Lysosomal acid phosphatase deficiency
Orotic aciduria
Sickle cell anemia
Testicular feminization
Thalassemia
Xeroderma pigmentosa

Data modified from A. Milunsky. The Prevention of Genetic Disease and Mental Retardation. W.B. Saunders Company, Philadelphia. pp. 239-241, 1975.

Table 8

HEREDITARY DISORDERS AFFECTING ADULTS

SUSCEPTIBLE TO TREATMENT

Method of Treatment	Disorder
Reduction of Toxic Food	
Lactose	Lactase deficiency
Galactose	Galactosemia
Fructose	Fructose intolerance
Neutral Fats	Familial lipoprotein lipase deficiency
Cholesterol and saturated fats	Familial hypercholesterolemia
Phytanic acid	Refsum syndrome
Phenylalanine	Phenylketonuria
Metabolic Supplementation	
Vitamin D and phosphate	Hypophosphatemic rickets
Gamma Globulin	Agammaglobulinemia
Factor VIII (AHG)	Hemophilia
Cortisol	Adrenogenital syndromes
Thyroxine	Familial goiters
Growth Hormone	Pituitary dwarfism
Removal of Toxic Product	
Cystine removal by D-penicillamine	Cystinuria
Copper removal by D-penicillamine	Wilson's disease
Iron removal by phlebotomy	Hemochromatosis
Surgery	
Splenectomy	Hereditary spherocytosis
Portacaval shunt	Glycogen storage disease, type I
Colectomy	Familial polyposis of the colon
Thyroidectomy	Medullary thyroid carcinoma syndrome
Organ Transplantation	
Kidney	Fabry disease
Kidney	Adult polycystic kidney disease

REFERENCES

CARTER CO: Genetics of common disorders. Br Med Bull 25: 52, 1972

CHILDS B, DER KALOUSTIAN VM: Genetic heterogeneity. New Eng J Med 279: 1205 and 1267, 1968

BROWN MS, GOLDSTEIN JL: New directions in human biochemical genetics: Understanding the manifestations of receptor deficiency disorders. Progress in Medical Genetics (Second Series) 1: 103, 1976

EPSTEIN CJ: Prenatal diagnosis of genetic disorders. Advances in Internal Medicine 20: 325, 1975

GOLDSTEIN JL, BROWN, MS: Genetic aspects of human disease. Chapter 64 in Harrison's Principles of Internal Medicine. Edited by G. Thorn, R. Adams, et al. 8th edition. McGraw-Hill Book Co., New York. In Press, 1976

GOLDSTEIN JL, BROWN MS: Prevention and treatment of genetic disorders. Chapter 65 in Harrison's Principles of Internal Medicine. Edited by G. Thorn, R. Adams, et al. 8th edition, McGraw-Hill Book Co., New York. In Press, 1976

HARRIS H: The Principles of Human Biochemical Genetics, 2nd edition, New York: American Elsevier, 1975

McKUSICK VA: Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes, 4th edition, Baltimore: John Hopkins, 1975

McKUSICK VA, CLAIBORNE R: Medical Genetics, New York: HP Publishing, 1973

MILUNSKY A: The Prevention of Genetic Disease and Mental Retardation. Philadelphia: WB Saunders, 1975

NORA JJ, FRASER FC: Medical Genetics: Principles and Practice. Philadelphia: Lea and Febiger, 1974

WATSON JD: Molecular Biology of the Gene, 3rd edition, New York: WA Benjamin, 1976

WORLD HEALTH ORGANIZATION TECHNICAL REPORT: Genetic Disorders; Prevention, Treatment, and Rehabilitation. Technical Report No. 497, 1972