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Volume 1

# MEDICAL

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Volume 2

# MEDICAL SURGICAL NURSING

THIRD EDITION

*With 2 Free Companion Books:*
- Practice Workbook
- Handbook of Medical Surgical Nursing

BT BASAVANTHAPPA



# Contents

## Volume 1


1. **Brief History of Medicine and Nursing in India** 1
   - Traditional Medicine and Surgery in India *2*
   - Golden Period of Indian Medicine *2*
   - Hindu Writings on Diagnosis and Treatment *2*
   - Hindu Surgery *3*
   - Chronological Events of Health Science *3*
   - Nursing in India *4*
   - Registration of Nurses *7*
   - The Nurses' Responsibility for the Future of Nursing *7*

2. **Nursing Process Application** 10
   - Nature of Nursing Process *10*
   - Definition of Nursing Process *11*
   - Steps of Nursing Process *12*
     - Assessment *12*
     - Nursing Diagnosis *14*
     - Planning *18*
     - Implementation *20*
     - Evaluation *21*
   - Health Assessment *22*
     - Health History *22*
     - Physical Assessment *25*
   - Positions for Physical Examination *25*
   - Techniques of Physical Examinations *26*
   - Symptom Analysis *28*
   - Physical Examination Instruments *29*
   - Guideline for Head-to-Toe Approach to Physical Examination *30*
   - An Advice to Public by Nurses for their Care *37*
   - Nursing Care Plan of Fever–Samples of Nursing Care Plan *39*

3. **Common Problems of Adult Patient** 61
   - Stress and its Management *61*
   - Pain and its Management *68*
   - Management of Fluid, Electrolyte and Acid-Base Imbalances *85*
   - Regulation of Fluids and Electrolytes or Homeostatic Mechanism *87*
   - Organs that Maintain Homeostasis *89*
     - Fluid Imbalances *89*
     - Electrolytes and their Imbalance *91*
     - Acid-Base Imbalances *100*

4. **Human Genetics and Genomic Nursing** 104
   - Scope of Genomic Nursing *105*
   - Heredity in Health Problems *107*
   - Congenital Malformations *116*
   - Causes of Chromosome Defects *117*
   - Autosomal Inheritance Patterns *120*
   - Role of Nurses in Applications of Genetics in Health Care *128*

5. **Immunological Problems and Nursing** 136
   - Review Immune System *136*
   - Types of Immunity *137*
   - Primary Immune Aberrations and Disease *145*
     - Immunodeficiencies *145*
     - Gammopathies *149*
     - Hypersensitivities *151*
     - Autoimmunity *166*
     - Human Immunodeficiency Virus Infection *168*

6. **Perioperative Nursing** 192
   - Scope of the Perioperative Nursing *193*
   - Classification of Surgical Procedure *195*
     - Role of Nurse in Perioperative Care *195*
     - Preoperative Nursing *197*
     - Intraoperative Nursing *206*
   - Anesthesia *213*
     - Postoperative Nursing *221*
   - Discharge from the POCU *232*
     - Operation Theater Instruments *235*
   - Infection Control *240*
   - Host-specific Defense Mechanisms against Infection *242*

- Blood-borne Viruses and the Perioperative Environment *242*
- Obtaining and Maintaining a Sterile Field *244*
- Personal Protective Equipment *246*
- Equipment *252*
- Fumigation of Operation Theater *254*

**7. Critical Care Nursing 256**

- Evolution of Critical Care Nursing *256*
- Classification of Critical Care Units *257*
- Types of Critical Care Unit/ICU *257*
- Principles of Critical Care Nursing *258*
- Critical Care Unit/ICU *259*
- Patient Monitoring in Critical Care Unit *271*

**8. Oncological Nursing 273**

- Cancer *273*
- Pathophysiology of Cancer *274*
- Etiology of Cancer *276*
- Classification of Cancer *278*
- Diagnosis of Cancer *283*
- Management of Cancer *284*
- Surgery *284*
- Radiation Therapy *287*
- Chemotherapy *289*
- Nursing Responsibilities in Oncological Emergencies *300*

**9. Respiratory Nursing 313**

- Assessment of Respiratory System *313*
- Diagnostic Studies of Respiratory System *317*
- Disorders of Nose and Sinuses *319*
  - Epistaxis (Nosebleed) *325*
  - Acute Pharyngitis *326*
  - Chronic Pharyngitis *327*
  - Acute Follicular Tonsillitis *328*
  - Acute Laryngitis *329*
- Acute Bronchitis *336*
  - Pneumonia *337*
  - Tuberculosis *341*
  - Bronchiectasis *344*
  - Empyema *346*
  - Lung Abscess *347*
  - Occupational Lung Diseases *348*
- Lung Cancer *350*
- Nursing Management in Thoracic Surgery *352*
- Chest Trauma and Thoracic Injuries *356*
  - Rib Fractures *357*
  - Flail Chest *358*
  - Pneumothorax *359*
  - Tension Pneumothorax *361*
  - Hemothorax *361*
  - Pleural Effusion *362*
  - Pleurasy *364*
  - Interstitial Lung Diseases *365*
  - Vascular Lung Disorders *365*
  - Pulmonary Embolism *365*
  - Pulmonary Hypertension *369*
  - Lung Transplantation *372*
  - Pulmonary Contusion *373*
- Obstructive Lung Diseases *374*
  - Chronic Bronchitis *374*
  - Emphysema *375*
  - Asthma *378*
  - Cystic Fibrosis *383*
  - Respiratory Failure *384*

**10. Gastrointestinal Nursing 473**

- Diagnostic Studies in Gastrointestinal System *478*
  - Problems of Mouth *482*
  - Oral Infections and Inflammations *483*
  - Oral Cancer *484*
  - Nausea and Vomiting *487*
  - Gastroesophageal Reflux Disease *490*
  - Hiatal Hernia *493*
  - Achalasia *495*
  - Esophageal Carcinoma *498*
  - Gastritis and Dyspepsia *500*
  - Chronic Gastritis *504*
  - Upper Gastrointestinal Bleeding *505*
  - Peptic Ulcer Disease *513*
  - Cancer of the Stomach *523*
- Irritable Bowel Syndrome *524*
- Diarrhea *525*
  - Fecal Incontinence *529*
- Constipation *530*
  - Acute Abdomen *532*
  - Abdominal Trauma *534*
  - Appendicitis *535*
  - Peritonitis *537*
  - Diverticulitis *538*
- Inflammatory Bowel Disease *540*
  - Ulcerative Colitis *541*
  - Crohn's Disease *544*
  - Intestinal Obstruction *545*
  - Colorectal Cancer *550*
  - Ostomy Surgery *552*
  - Anorectal Disorders *555*
- Nasogastric/Nasointestinal Intubation *560*

**11. Hepatobiliary Pancreatic Nursing** 570

- Jaundice *570*
- Hepatitis *571*
- Cirrhosis of Liver *574*
- Problems of Gallbladder *580*
  - Cholelithiasis *580*
  - Acute Pancreatitis *586*
- Chronic Pancreatitis *595*
- Assisting with Percutaneous Liver Biopsy *612*

**12. Cardiovascular Nursing** 614

- Cardiovascular Assessment *614*
- Physical Examination *615*
- Diagnostic Studies of CVS *617*
  - Hypertension *622*
- Nursing Management *627*
  - Coronary Artery Disease *630*
  - Angina Pectoris *632*
- Nursing Management *635*
  - Myocardial Infarction *636*
  - Shock *648*
  - Cardiogenic Shock *666*
  - Heart Failure *669*
- Inflammatory Heart Disease *699*
  - Pericarditis (Cardiac Tamponade) *699*
  - Myocarditis *703*
  - Infective Endocarditis *704*
  - Rheumatic Heart Disease *707*
- Valvular Heart Disease *708*
  - Mitral Stenosis *708*
  - Mitral Regurgitation *709*
  - Mitral Valve Prolapse *711*
  - Aortic Stenosis *712*
  - Tricuspid Valve Disease *713*
  - Pulmonic Valve Disease *714*
  - Cardiac Surgery *714*
- Vascular Problems Arterial Disorders *742*
  - Aneurysms *742*
  - Chronic Arterial Occlusive Disease *749*
  - Buerger's Disease *750*
  - Raynaud's Disease *751*
- Amputation and its Management *753*
- Venous Disorders/Disorders of Veins *753*
- Varicose Veins *757*
  - Venous Stasis Ulcer *758*
  - Pulmonary Embolism *758*


## Volume 2


**13.Orthopedic Nursing** 773

- Common Abnormalities of Musculoskeletal System *779*
- Diagnostic Studies of the Musculoskeletal System *780*
  - Soft Tissue Injuries *783*
  - Dislocation and Subluxation *785*
  - Carpal Tunnel Syndrome *786*
  - Repetitive Strain Injury *787*
  - Rotator Cuff Injuries *787*
  - Meniscus Injury *787*
  - Bursitis *788*
  - Muscle Spasms *789*
  - Fractures *789*
  - Reduction of Fractures *794*
  - Traction *794*
- Fracture Immobilization *797*
  - Casts *797*
- Internal Fixation *801*
  - Complications of Fracture *802*
- Inflammatory and Degenerative Disorder: Musculoskeletal System *804*
  - Rheumatoid Arthritis *804*
  - Gout/Gouty Arthritis *818*
- Septic Arthritis *820*
  - Lyme's Disease *821*
  - Seronegative Arthropathies *822*
  - Psoriatic Arthritis *824*
  - Reiter's Syndrome *824*
- Systemic Lupus Erythematosus *824*
  - Systemic Sclerosis *826*
  - Crest Syndrome *827*
  - Sjögren's Syndrome *827*
  - Polymyositis/Dermatomyositis *827*
  - Fibromyalgia Syndrome *828*
- Infectious Bone Diseases *829*
  - Osteomyelitis *829*
  - Low Back Pain *832*
  - Acute Low Back Pain *832*
  - Degenerative Disorders of Spine *836*

- Surgical Management of Surgery *837*
  - Scoliosis *839*
- Common Hand and Foot Problems *840*
  - Hand's Problem *840*
  - Foot Problem *840*
  - Musculoskeletal Tumors *842*
- Metabolic Bone Diseases *845*
  - Osteomalacia *845*
  - Paget's Disease (Osteitis Deformans) *847*
  - Osteoporosis *848*

**14. Neurological Nursing 858**

- Assessment of the Nervous System *858*
- Diagnostic Studies of the Nervous System *867*
- Intracranial Problems *869*
  - Altered Level of Consciousness *869*
  - Increased Intracranial Pressure *874*
  - Hematoma Formation *884*
- Infections and Inflammation of Brain *897*
  - Meningitis *897*
  - Encephalitis *901*
  - Brain Abscess *901*
  - Intracranial Tumors *902*
  - Spinal Cord Tumors *905*
  - Intracranial Surgery *906*
- Cerebrovascular Accident/Stroke *907*
- Epilepsy/Seizure Disorder *932*
  - Headache *937*
  - Multiple Sclerosis *941*
  - Parkinson's Disease *945*
  - Myasthenia Gravis *951*
  - Alzheimer's Disease *955*
  - Guillain-Barré Syndrome *960*
- Cranial Nerve Disorders *965*
  - Bell's Palsy *966*
- Spinal Cord Injury *967*
  - Spinal Cord Syndrome *968*
  - Spinal Shock *970*
- Nursing Management of Spinal Cord Injury *973*

**15. Hematological Nursing 992**

- Assessment of the Hematological System *993*
- Hematological Disorders *998*
- Disorders of Erythrocytes *998*
  - Anemia *998*
  - Iron Deficiency Anemia *1001*
  - Thalassemia *1004*
  - Aplastic Anemia *1005*
  - Hemolytic Anemias *1006*
  - Hereditary Spherocytosis *1008*
  - Enzyme Deficiency Anemia *1008*
  - Sickle Cell Disease *1008*
- Erythrocytosis/Polycythemia *1012*
  - Polycythemia Vera *1012*
- Anemia Caused by Blood Loss *1013*
- Disorders of Hemostasis *1014*
  - Thrombocytopenia *1014*
- Thrombocytosis *1017*
- Disorders of Coagulation *1018*
  - Hemophilia *1018*
  - Vitamin K Deficiency *1020*
- Disorders of WBCS (Leukocytes) *1023*
  - Neutropenia *1023*
  - Neutrophilia *1024*
  - Leukemias *1024*
  - Lymphedema *1027*
- Lymphomas *1028*
  - Hodgkin's Disease *1028*
  - Non-Hodgkin's Lymphoma *1031*
  - Infectious Mononucleosis *1032*
  - Multiple Myeloma *1032*

**16. Endocrinological Nursing 1040**

- Assessment of the Endocrine System *1041*
- Disorders of Pituitary Gland *1043*
  - Hyperpituitarism *1043*
  - Prolactin Hypersecretion *1045*
  - Growth Hormone Hypersecretion *1045*
  - Hypopituitarism *1046*
- Diabetes Insipidus *1052*
- Disorders of the Thyroid Gland *1057*
- Hyperthyroidism *1058*
  - Ophthalmopathy in Graves' Disease *1060*
- Hypothyroidism *1074*
  - Cancer of the Thyroid Gland *1077*
- Disorders of Parathyroid Gland *1078*
  - Hyperparathyroidism *1078*
  - Hypoparathyroidism *1080*
- Disorders of Adrenal Gland *1083*
  - Cushing's Syndrome *1083*
  - Iatrogenic Cushing's Syndrome *1087*
  - Aldosteronism *1088*
  - Adrenocortical Insufficiency *1089*
- Disorders of Adrenal Medulla *1097*
  - Pheochromocytoma *1097*
- Disorders of Pancreas *1098*
  - Diabetes Mellitus *1098*

- Complications of Diabetes Mellitus *1108*
- Hyperglycemic Hyperosmolar Non-ketonic Coma *1119*
- Chronic Complications of DM *1119*
  - Hypoglycemia in DM *1120*
  - Hypoglycemia in Non-DM *1121*
  - The Diabetic Foot *1124*

**17. Urological and Renal Nursing (Renourological) 1127**

- Assessment of Urinary System *1127*
- Urine Studies *1128*
- Inflammatory Disorders of Urinary System *1134*
  - Urinary Tract Infections *1134*
  - Cystitis *1137*
  - Pyelonephritis *1138*
  - Urethritis *1139*
  - Renal Tuberculosis *1140*
  - Chemical-induced Nephritis *1140*
  - Glomerulonephritis *1141*
  - Chronic Glomerulonephritis *1143*
  - Nephrotic Syndrome *1144*
  - Goodpasture's Syndrome *1146*
  - Renal Artery Stenosis *1147*
  - Renal Vein Thrombosis *1147*
  - Nephrosclerosis *1147*
  - Obstructive Uropathies *1148*
  - Hydronephrosis *1149*
  - Renal Calculi (Stones) *1151*
  - Strictures *1156*
  - Renal Tumor *1157*
  - Wilm's Tumor *1158*
  - Bladder Cancer *1158*
  - Urinary Retention *1159*
  - Urinary Incontinence *1160*
  - Reno-ureteral Surgery *1165*
  - Urinary Diversion *1166*
  - Acute Renal Failure *1168*
  - Chronic Renal Failure *1178*

**18. Reproductive Health Nursing 1194**

- Assessment of the Male and Female Reproductive System *1195*
- Diagnostic Studies of Reproductive System *1202*
- Reproductive Problems of Females/Women *1206*
  - Vaginitis *1206*
  - Cervicitis *1208*
  - Bartholinitis (Bartholin's Cysts) *1209*
  - Pelvic Inflammatory Disease *1209*
  - Problems of Menstruation *1212*
  - Premenstrual Syndrome *1212*
  - Dysmenorrhea *1213*
  - Amenorrhea *1215*
  - Dysfunctional Uterine Bleeding *1216*
  - Endometriosis *1217*
  - Uterine Prolapse *1218*
  - Fistulas *1221*
- Neoplasms of the Female Reproductive Tract *1222*
  - Cervical Polyps *1222*
  - Cervical Cancer *1222*
  - Uterine Leiomyoma (Fibroids) *1225*
  - Endometrial Cancer *1226*
  - Ovarian Cysts *1227*
  - Ovarian Cancer *1228*
  - Vulvar Cancer *1229*
- Surgeries of the Female Reproductive System *1230*
  - Infertility *1231*
- Problems of the Breast *1233*
  - Cystic Breast Disease *1235*
  - Fibroadenoma *1237*
- Breast Infections *1238*
  - Mammary Duct Ectasia *1238*
  - Acute Mastitis and Abscess *1238*
  - Breast Cancer *1239*
- Nursing Management of the Patient Undergoing Mastectomy *1242*
- Male Breast Problems *1245*
  - Gynecomastia *1245*
  - Male Reproductive Problems *1245*
  - Epididymitis *1247*
  - Orchitis *1249*
  - Testicular Torsion *1249*
  - Testicular Cancer *1251*
- Problems of Prostate *1252*
  - Prostatitis *1252*
  - Benign Prostatic Hyperplasia *1254*
  - Cancer of the Prostate *1258*
- Problems of the Penis *1259*
  - Congenital Problems *1260*
  - Phimosis and Paraphimosis *1260*
  - Cancer of the Penis *1260*
  - Erectile Dysfunction/Impotence *1261*
- Sexually Transmitted Diseases *1264*
  - Gonorrhea *1264*
  - Syphilis *1265*
  - Herpes Genitalis *1266*
  - Chlamydial Infections *1268*
  - Lymphogranuloma Venereum *1269*
  - Chancroid *1269*

- Trichomoniasis *1271*
- Bacterial Vaginosis *1271*
- Hepatitis B Virus *1271*
- HIV Infection and AIDS *1272*

**19. Dermatological Nursing or Integumentary Nursing 1281**

- Health Promotion Practices of Skin Problems *1289*
- Common Skin Problems *1290*
- Parasitic Infections *1290*
  - Pediculosis (Lice Manifestation) *1290*
  - Scabies *1290*
- Fungal Infections *1291*
  - Candidiasis *1291*
  - Dermatophytoses *1293*
- Bacterial Infections *1294*
  - Impetigo *1294*
  - Folliculitis *1295*
  - Furuncles and Carbuncles *1295*
  - Erysipelas *1296*
- Viral Infections of the Skin *1297*
  - Herpes Simplex *1297*
  - Herpes Zoster *1297*
  - Verruca Vulgaris *1298*
  - Warts *1298*
- Allergic Conditions of the Skin *1298*
  - Contact Dermatitis *1299*
  - Urticaria *1300*
  - Drug Reaction *1300*
  - Atopic Dermatitis *1300*
  - Other Type of Dermatitis *1301*
  - Pruritus *1302*
  - Skin Reactions *1302*
- Lupus Erythematosus *1304*
- Papulosquamous Diseases *1304*
  - Psoriasis *1305*
  - Pityriasis Rosea *1307*
- Acne *1307*
  - Acne Vulgaris *1307*
  - Acne Rosacea *1308*
- Bullous Diseases *1308*
  - Pemphigus Vulgaris *1308*
- Tumors of the Skin *1310*
  - Benign Tumors *1310*
  - Premalignant Lesions *1311*
  - Malignant Lesions *1312*
- Nursing Management of Dermatological Surgery *1313*
  - Pressure Ulcers *1314*
  - Burns *1317*
  - Types of Burns *1317*
  - Pathophysiology of Burns *1318*
  - Burn Location *1322*
  - Management of Burns *1322*
- Responsibilities of Nursing Personnel on Burn Patient *1338*
- Rehabilitation of Burn Person *1340*

**20. Ophthalmic and Otological Nursing 1342**

- Ophthalmic Nursing [Nursing the Visual Disorder] *1342*
- Assessment of the Visual System *1342*
  - Visual Impairment *1348*
  - Eye Trauma and Injury *1352*
  - Glaucoma *1355*
  - Congenital Glaucoma *1357*
  - Cataract *1358*
  - Retinal Detachment *1361*
  - Strabismus *1362*
  - Eye Tumors *1363*
- Procedures Used in Ophthalmology *1364*
- General Procedures/Treatment Modalities *1365*
- Otologic Nursing [Nursing the Disorder of Ear] *1370*
  - Assessment of Auditory System *1370*
  - Hearing Impairment *1373*
- Problems of Middle Ear and Mastoid *1379*
  - Otosclerosis *1379*
  - Mastoiditis *1380*
  - Otitis Media *1382*
- Problems of Inner Ear *1385*
  - Acoustic Neuroma *1385*
  - Meniere's Disease *1385*
  - Other Vestibular Disorders *1388*

**21. Organ Transplantation and Nursing 1390**

- Organ Sources *1390*
- Role of Nurses in Donation Process *1391*
- Kidney Transplant *1395*
- Heart Transplant *1396*
- Liver Transplant *1398*
- Lung Transplantation *1399*
- Pancreas Transplantation *1400*
- Bone Marrow Transplantation *1401*
- Cornea Transplant *1402*

**22. Nursing the Poisoned Client 1403**

- Assessment of the Poison Victim *1403*
- Pathophysiology and Mechanisms of Toxicity *1407*

- Treatment of Poisoned Victim *1408*
- Case Study with Sample Care Plan: Patient with Acute Poisoning *1411*

***Appendices***

- Appendix I: Cardiopulmonary Resuscitation *1421*
- Appendix II: Index of Normal Values *1431*
- Appendix III: Diets in Health and Illness *1438*
- Appendix IV: Terminology Used in the Text *1450*
- Appendix V: Prefixes and Suffixes Used in the Text *1467*
- Appendix VI: Abbreviations Used in the Text *1469*

*Index* *1471*

CHAPTER

4

# Human Genetics and Genomic Nursing

JAYPEE BROTHERS

## INTRODUCTION

Genomics is the branch of molecular biology concerned with the structure function, evolution, and mapping of genomes. Genotype is the genetic constitution of an individual organism. Genomic is the complete set of genetic material of an organism.

The term 'genetics' has been derived from Greek word "gene" which means "to grow into" or "to become", "Gene" is a unit of heredity, which is transferred from a parent to offspring and is held to determine some characteristics of offspring, in particular, a distinct sequence of DNA forming part of chromosome. The terms 'Genetic' was introduced by **Bateson** in 1906.

Genetic is the scientific study of heredity in which it deals with how specific traits or predispositional one transmitted from parents to offspring. 'Genome' is the total genetic compliment of an individual genotype. Genotype is the genes and variations there in than a person inherits from his or her parents. "Genomics" is the study of human genome including gene sequencing mapping, and function.

Human genetics is the study of the human condition as it is influenced by inherited factors that affect and determine growth and development and that can be transmitted from generation to generation. Furthermore, genetic factors extend beyond the limited view of solely distinct genetic syndromes to encompass influences on health, the occurrence of complex disorders, individual biologic responses to illness, potential treatment and medical management approaches, and strategies for prevention or cure.

Advances in genetic science raise questions as to what is normal and abnormal, when variation is called disease; and when variation should be treated, prevented, or both. Cultural perspectives on when to consider a variation a disease are a source of potential conflict among population group in a diverse world. As knowledge of human variation increases care must be taken to ensure that human rights are not violated.

This tremendous realization is readily apparent through the accomplishments of the Human Genome Project (HGP). One significant goal is to identify the 50,000 to 100,000 human genes. These advances and the associated knowledge will continue to significantly impact the delivery of health care and nursing practice. Genetic evaluations, screening, testing, guided treatment, family counseling, and related legal, ethical, and psychosocial issues will become daily practice for nurses.

Human genome discoveries have ushered in a new era of medicine, genomic medicine, which recognizes that multiple genes work in concert with environmental influences to cause disease. Genomic medicine aims to improve predictions about a persons susceptibility to diseases; the time of onset, extent and eventual severity of diseases; and the treatments or medications likely to be most effective or most harmful. New gene-based strategies for disease detection, management, and treatment have been created, allowing health professionals to tailor care to a person's particular genetic makeup.

Genomic nursing will be a challenging of nursing, in which nurses study and recognize the pattern of inheritance, understand the new technologies of testing and management of gene-based health care services, and applying genetic principles in respective clinical areas of nursing for assessment. diagnosis, planning and intervention of genetic related health needs of the client.

To meet the challenges of genomic nursing, nurses must understand the new technologies and treatments of gene-based health care. Nurses also must recognize that they are a vital link between the patient and health care services; patients often turn to nurses first with questions about a family history of risk factors, genetics information, and genetic tests and interpretations. The incorporation of genetics into nursing means bringing a genetic framework to health assessments, planning, and interventions that supports identification of and response to the changing genetics-related health needs of people.

When obtaining family and health histories, nurses must learn to recognize patterns of inheritance and understand when it is appropriate to consider new gene-based testing and treatment options. The clinical application of genetics principles in medical and surgical nursing, outlines the nurses role in genetic counseling and evaluation, addresses important ethical issues, and provides genetics resources for nurses and patients.

## SCOPE OF GENOMIC NURSING

Now genetics is called the new central science of health care. Knowledge about molecular biology is necessary for future health care professionals to understand innovations in diagnosis, treatment and prevention of disease based on genetic information. Nursing with its tradition of holistic care, offers a unique contribution to patients and family trying to make sense of new genetic information for making health decisions. Because nurses serve people throughout the lifespan and across setting, they are in key position to integrate knowledge of genetics influences into health care.

The unique contribution of nursing to genomic medicine is its philosophy of holism. Nurses are ideally positioned to incorporate genetics into the care of patients at all ages and stages of life and in all settings. The holistic view that characterizes nursing takes into account each person's intellectual, physical, spiritual, social, cultural, biopsychologic, ethical and esthetic experiences while addressing genetic information, gene-based testing, diagnosis, and treatment. Thus, knowledge of genetics is basic to nursing practice.

Integrating genetics into nursing practice includes a philosophy of care that recognizes when genetic factors are playing a role or could play a role in a person's health. This means using family history and the results of genetic tests effectively, informing patients about genetics concepts, understanding the personal and societal impact of genetics information, and valuing the privacy and confidentiality of genetics information.

A person's responses to genetics information, genetic testing, or genetics-related conditions may be either empowering or disabling. Genetics information may stigmatize people if it affects how they view themselves or how others view them. Nurses can help individuals and families learn how genetic traits and conditions are passed on within families and how genetic and environmental factors influence health and disease.

Nurses facilitate communication among family members, the health care system, and community resources, and they offer valuable support by virtue of their continuity of care with patients and families. All nurses should be able to recognize when a patient is asking a question related to genetics information and should know how to obtain genetics information by gathering family and health histories and conducting physical and developmental assessments. Being able to recognize a genetics concern allows nurses to provide appropriate genetics resources and support to patients and families.

Essential to a genetic in nursing is the awareness of one's attitudes, experience, and assumptions about genetics concepts and how these are manifested in one's own practice.

The information from HGP about the 3 billion base pairs of the human genome will open the possibility of changes in every aspect of biology and medicine and have a major impact on health care in the future. Much effort is being focused on identifying gene variations. Although as a human species we are 99.9% alike, it may be the 0.1% variation that will help us understand the genetic risk for illnesses. It is hoped that treatment strategies can be devised that are specific to an individuals disease mutation. Another new field of study created by the HGP is the study of how inheritance affects the body's responses to drugs, called *pharmacogenetics*. The hope is that better, safer, and in some cases more powerful drugs can be developed. The information from HGP may influence more areas than we can currently imagine. Because of this, it has focused on issues such as genetic discrimination, privacy, and education. It will continue to look at new issues generated by information about our human genome.

Nurses will increasingly be faced with interpreting genetic information in client histories and diagnostic testing, and with assuming responsibility for protecting client privacy. To better counsel families and to participate likely problems, the nurses needs a fundamental understanding of the principles of genetics and the importance of heredity and the parental environment as etiologic factors in diseases and disorders of childhood. **Key terms for understanding genetics are defined as given below:**

*Allele:* Any one of two or more alternate forms of a gene at the same location. An allele for each gene is inherited from each parent. Alternative forms of a gene occupying same locus on homologous chromosomes.

*Association:* Nonrandom cluster of malformations without a specific etiology (e.g. CHARGE or VATER association).

*Autosome:* Chromosome other than a sex (X or Y) chromosome; in normal human cells there are 22 pairs of autosomes and 2 sex chrosomes.

*Carrier:* Person who possesses one copy of affected gene and one copy of unaffected gene and is clinically unaffected; however, may have clinically affected offspring because of expansion of mutation, X-linked expression, or recessive paring with the another.

*Chromosome aberration:* Addition, loss, or structural abnormality of a chrosome; detectable by cytogenetic analysis.

*Congenital:* Condition present at birth, although may not be apparent; causes may be genetic, nongenetic, environmental, or multifactorial.

*Cytogenetics:* Study of relationship of microscopic appearance of chrosome and their behavior during cell division to genotype and phenotype of individual.

*Deformation:* Fetal abnormalities due to extrinsic factors (e.g. uterine position); may also show subsequent defects.

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*Deoxyribonucleic acid (DNA):* Two-stranded molecule that contains the genes or blueprints responsible for the structure and function of living organisms and allows the transmission of genetic information from one generation to the next.

*Nuclear DNA (nDNA):* Located in the nucleus of the cell; it contains blueprints for the cells that make up the body.

*Mitochondrial DNA (mtDNA):* Located in the mitochondria or powerhouse of each cell.

*Diploid:* The number of chromosomes normally present in somatic cells. For humans, that number is 46.

*Dominant:* A genetic trait that is normally expressed when a person has a gene mutation on one of a pair of chromosomes and the "normal" form of the gene is on the other chromosome.

*FISH analysis:* Fluorescent in suit hybridization (FISH), a process by which chromosomes or portions of chromosomes are painted with fluorescent molecules; technique is useful for identifying chromosomal microdeletions.

*Gamete:* One of two cells produced by a gametocyte, male (spermatozoon) and female (ovum), whose union in sexual reproduction initiates development of a new individual.

*Genes:* Genetic material (DNA) responsible for programming body's physiologic functions and characteristics.

*Genome:* Complete genetic information of an organism, usually described as total number of base pairs, human genome contains 3 billions base pairs.

*Genotype:* Genetic constitution that determines the physical and chemical characteristics of an individual.

*Germ cell:* Sperm or ovum with DNA complement of 23 unpaired chromosomes.

*Genetics:* The scientific study of heredity; how specific traits or predispositions are transmitted from parents to offspring.

*Genome:* The total genetic complement of an individual genotype.

*Genomics:* The study of the human genome, including gene sequencing, mapping and function.

*Genotype:* The genes and the variations therein that a person inherits from his or her parents.

*Haploid:* The number of chromosomes present in egg or sperm (gametes); in humans, this is 23.

*Human genome project:* An international research effort aimed at identifying and characterizing the order of every base in the human genome.

*Human genome project:* International research project to map each human gene and sequence the human genome.

*Imprinting:* Phenomenon in which an allele at a given locus is altered or inactivated, depending on whether it is inherited from mother or father; implies a functional difference in genes inherited from the two parents and explains some variation in expression.

*Inherited (heritable, hereditary):* Genetic transmission of a particular quality or trait from parent to offspring.

*Malformation:* Morphogenic defect of organ, part of organ, or larger region of the body resulting from intrinsically abnormal developmental process.

*Major malformation:* Structural abnormality with serious medical, surgical, or cosmetic consequences.

*Minor malformation:* Has no serious consequences or is normal variation (e.g., extra nipple or umbilical hernia).

*Meiosis:* Cell division that results in reproductive cells (gametes) containing a complement of 23 unpaired chromosomes.

*Meiosis:* The reduction division of diploid egg or sperm (germ cells) resulting in haploid gametes (having 23 chromosomes each).

*Mitosis:* Cell division occurring in somatic cells that normally results in daughter cells with the same number of chromosomes – 46 (diploid).

*Mitosis:* Cell division resulting in two daughter cells identical to parent cell in chromosome complement (23 pairs) and genetic information.

*Monosomy:* Missing one of a chromosome pair in normally diploid cells (For example, 45, X females have only one X chromosome).

*Mutation:* A heritable alteration in the genetic material.

*Nondisjunction:* The failure of a chromosome pair to separate appropriately during meiosis, resulting in abnormal chromosome numbers in reproductive cells (gametes).

*Mitochondrion:* Part of the cell that is responsible for converting nutrients into energy as well as many other specialized tasks; own separate and unique DNA; mtDNA is inherited exclusively from the mother.

*Monogenetic:* Genetic disease caused by single-gene mutation.

*Monosomy:* Chromosome abnormality in which one chromosome of a pair is missing; most monosomies are nonviable.

*Mosaicism:* Condition in which an individual harbors two or more genetically distinct cell lines (generally, one cell line is normal and one is abnormal); results from a genetic change after formation of a zygote (i.e. postzygotic event).

*Multifactorial:* Complex interaction of both genetic and environmental factors that produces an effect on individual.

*Mutation:* Structural or chemical alteration in genetic material that when changed remains changed and is transmitted to future generations; usually occurs naturally **(spontaneous)**, or can be **induced** by a variety of external agents, or **mutagens**, including temperature, certain chemicals, and radiation.

*Mutation:* **Hereditary** changes in genetic material; can be either change in single gene or change in chromosome characteristics,

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gene mutations can be passed from parent to offspring or can be new mutation in an individual, which is then heritable in offspring.

*Nondisjunction:* Failure of two chromatids or two homologous chromosomes to separate during cell division, so that both members of a pair pass to new cell, resulting in trisomy of that chromosome pair, or monosomy in cell that does not receive chromosome.

*Pedigree:* Diagram of genetic family tree.

*Penetrance:* Frequency with which a heritable trait is manifested in individuals carrying gene.

*Phenotype:* Clinically exhibited physical or chemical characteristics of individual; produced by interaction of environment with genotype.

*Polygenic:* Inheritance involving many genes at separate loci whose combined, additive effects produce a given phenotype.

*Polymorphism:* A genetic variation with two or more alleles that is maintained in a population.

*Population screening:* The application of a test or inquiry to a group to determine if persons in the group have an increased likelihood of a genetic condition or a mutation in a specific gene (e.g. cholesterol screening for hypercholesterolemia).

*Predisposition testing:* Testing that is used to determine the likelihood that a healthy person with or without a family history of a condition will develop the disorder. Having the gene mutation would indicate that the person has an increased susceptibility to the disorder, but this is not a diagnosis. One example is DNA mutation testing for hereditary breast/ovarian cancer.

*Prenatal screening:* Testing that is used to identify whether a fetus is at risk for a birth defect such as Down syndrome or spina bifida (e.g. multiple marker maternal serum screening in pregnancy).

*Presymptomatic testing:* Genetic testing that is used to determine whether persons with a family history of a disorder, but no current symptoms, have the gene mutation. An example of this would be Huntington's disease.

*Proband (index case):* Affected individual (regardless of sex) through whom family comes to attention of investigator.

*Recessive:* Refers to a gene that produces its effect (is expressed) only when it is present in homozygous state.

*Recessive:* A genetic trait that is expressed only when a person has two copies of a mutant autosomal gene or a single copy of a mutant X-linked gene in the absence of another X-chromosome.

*Somatic cell:* Body tissue cells with DNA complement of 46 chromosomes.

*Sporadic:* Birth defect or disorder occurring as a new case in a family and not inherited.

*Syndrome:* Recognized pattern of malformations with a single, specific etiology (e.g. Down syndrome).

*Translocation:* Transfer of all part of a chromosome to a different chromosome following chromosome breakage; can be balanced, producing no phenotypic effects, or unbalanced, producing severe or lethal effects.

*Transcription:* The process of transforming information from DNA into new strands of messenger RNA.

*Trisomy:* Condition in which there are three, rather than two, copies of one chromosome in same cell.

*Trisomy:* The presence of one extra chromosome in an otherwise diploid chromosome complement—for example, trisomy 21 (Down syndrome).

*Variable expression:* Variation in the degree to which a trait is manifested; clinical severity.

*X-linked:* Located on the X chromosomes.

*X-inactivation (Lyon hypothesis):* In normal female most of genes on one of X-chromosomes are inactivated during early embryonic development, such that alleles on active chromosome are allowed full expression.

*X-linked:* Refers to gene located on X-chromosome and to specific mode of inheritance of such genes.

*Zygote:* Conjugation of male and female gametes.

## HEREDITY IN HEALTH PROBLEMS

Scientists and philosophers have long speculated about heredity and developed theories to explain how traits are transmitted to offspring. Developments in technology and research have increased understanding of genetics, resulting in better understanding of relatively rare diseases such as phenylketonuria (PKU) or hemophilia that are related to mutations of a single gene inherited in families. New technologies and tools allow scientist to characterize inherited metabolic variations that interact over time and lead to common diseases such as cancer, heart disease, and dementia. This transition from genetics to genomics highlights how understanding of single genes and their individual functions has evolved to understanding how multiple genes act and control biologic processes. Most health conditions are now believed to be the result of a combination of genetic and environmental influences.

Contained within the nucleus of every somatic cell in the human body are approximately 35,000–70,000 genes, the genetic material responsible for programming the body's physiologic process and characteristics. These genes are composed of segments of DNA (deoxyribonucleic acid) and are organized into structures called chromosomes, which are visible only during certain stages of cell division. Alterations of a whole chromosome, a part of a chromosome, or even a single gene can manifest as a genetic disorder. Important to this concept is that this alteration or mutation may have been passed from one or both parents and previous generations, or it may be a new alteration in that individual. It is misleading to regard all genetic disorders as having been "passed through the family".

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There is probably a genetic component in all disease processes. In some disorders the genetic defect is known; in others the precise nature of the genetic component is more obscure. In some the disorder is apparent at birth; in others the manifestations do not appear for weeks, months, or years (Table 4.1). Some diseases and disorders are determined by the genetic constitution of the individual, such as muscular dystrophy, Marfan's syndrome, and Down syndrome. Other diseases, although genetically determined, do not become clinically apparent until environmental factors precipitate the onset of symptoms. For instance, phenylketonuria is a disorder in which the enzyme to metabolize the protein phenylalanine is lacking. Deleterious effects in the infant are exhibited subsequent to sufficient ingestion of phenylalanine—containing substances, such as milk. Also, the acute symptoms of sickle cell disease are precipitated by certain conditions such as lowered oxygen tension, infection or dehydration.

Another area in which this interplay of genetic and environmental factors is being investigated is cancer genetics. All cancer is genetic in the sense that cancer cells result from a "sporadic" gene malfunction (acquired mutation). However, only 5 to 10% of all cancers are inherited, which means the gene mutation that pre-disposes to cancer development was present in the germline. Therefore the individual is prone to cancerous development much earlier in life.

**TABLE 4.1:** Characteristic age of onset for manifestations of some genetic disease

| Age of onset | Condition |
|---|---|
| Lethal during prenatal life | Some chromosome aberrations<br>Some gross malformations |
| Birth | Congenital malformations<br>Chromosome aberrations (e.g. Down's syndrome)<br>Some forms of adrenogenital syndrome<br>Some forms of deafness |
| Soon after birth | Phenylketonuria<br>Galactosemia<br>Cystic fibrosis (sometimes)<br>Maple-syrup urine disease |
| Infancy | Sickle cell anemia (sometimes later)<br>Tay-Sach's disease<br>Werding-Hoffman's disease |
| Early childhood | Cystic fibrosis<br>Duchenne muscular dystrophy<br>Fragile X-syndrome |
| Near puberty | Limb-girdle muscular dystrophy<br>Some forms of adrenogenital syndrome<br>Turner's syndrome |
| Young adulthood | Acute intermittent porphyria<br>Hereditary juvenile glaucoma |
| Variable-onset age | Diabetes mellitus (0 to 80 years)<br>Huntington chorea (15 to 65 years)<br>Myotonic dystrophy (birth to old age) |

Other disorders result primarily from environmental factors. These include most infectious diseases and trauma. Development of the disease depends on environmental contact with the etiologic agent, but there is strong evidence to indicate a decided genetic element in the susceptibility to most disease (e.g. tuberculosis, poliomyelitis, and measles in some population).

Genetic diseases can usually be classified into one of the following broad categories according to the hereditary factors that produce the observed effect—cytogenetic, mitochondrial, monogenetic, or multifactorial. Prenatal environmental influences, such as alcohol exposure and placental abnormalities, are also regarded as being within the realm of genetics because these effects can produce congenital structural, functional, or growth defects. In such cases the chromosomes would be normal although anomalies produced might be indistinguishable phenotypically from a genetically determined anomaly. The important difference is that the defects would not be inheritable because they would not have been caused by a genetic mutation.

Genes are central components of human health and disease. Specific genes are associated with specific genetic conditions makes diagnosis possible, even in the unborn. Research demonstrates that many common conditions have genetic causes. Many more associations between genetics, health, and disease are likely be identified with refinement of human genome mapping and sequencing.

## Genes and Chromosomes

A persons unique genetic constitution, called a **genotype**, is made up of some 30,000 to 40,000 genes. A person's **phenotype**, the observable characteristics of his or her genotype, includes physical appearance and other biologic, physiologic, and molecular traits. Environmental influences modify every persons phenotype, even phenotypes with a major genetic component.

Human growth, development, and disease occur as a result of both genetic and environmental influences and interaction. The contribution of genetic factors may be large or small. For example, in a person with cystic fibrosis or PKU, the genetic contribution is significant. In contrast, the genetic contribution underlying a persons response to infection may be less important.

A single gene is conceptualized as a unit of heredity. A gene is composed of a segment of **deoxyribonucleic acid (DNA)** that contains a specific set of instructions for marking the protein or proteins needed by body cells for proper functioning. Genes regulate both the types of proteins made and the rate at which proteins are produced. The structure of the DNA molecule is referred to as the double helix. The essential components of the DNA molecule are sugar-phosphate molecules and pairs of nitrogenous bases. Each **nucleotide** contains a sugar (deoxyribose), a phosphate group, and one of four nitrogenous bases: adenine (A), cytosine (C), guanine (G), and thymine (T), a number of nucleotides. The strands are held together by hydrogen bonds between pairs of bases (Figs 4.1 to 4.10).

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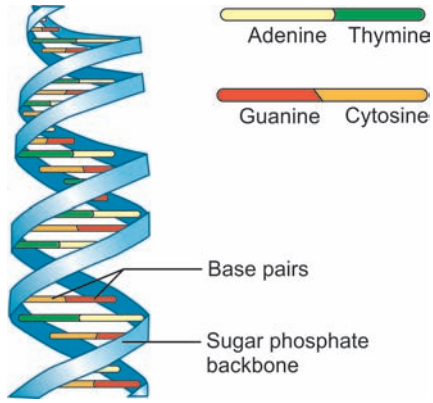


**FIG. 4.1:** DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone. DNA carries the instructions that allow cells to make proteins. DNA is made up of four chemical bases

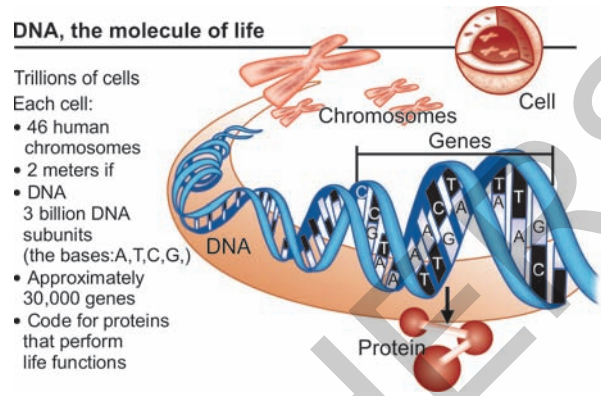


**FIG. 4.2:** DNA: The molecule of life. Illustrates the embedding of protein codes in base pair sequences of genes on DNA strands of chromosomes in the nucleus of the cell

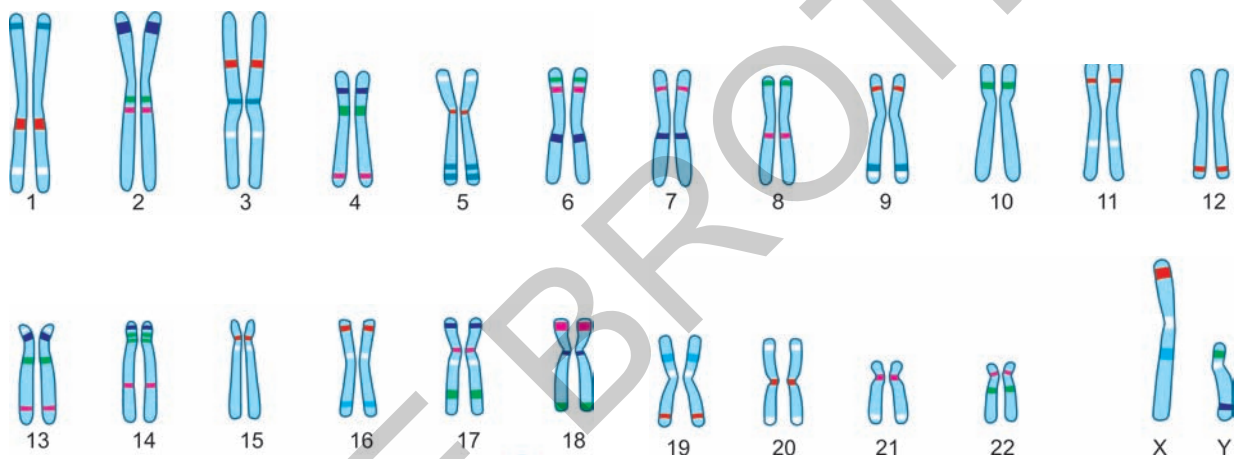


**FIG. 4.3:** Each human cell contains 23 pairs of chromosomes, which can be distinguished by their size and unique banding patterns. This set is from a male, because it contains a Y chromosome. Females have two X chromosomes

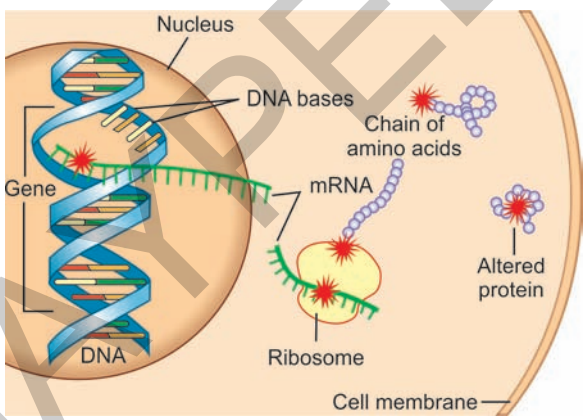


**FIG. 4.4:** When a gene contains a mutation, the protein encoded by that gene is likely to be abnormal. Sometimes the protein is able to function, although it does so imperfectly. In other cases, it is totally disabled. The outcome depends not only on how the mutation alters the protein's function but also on how vital that particular protein is to survival

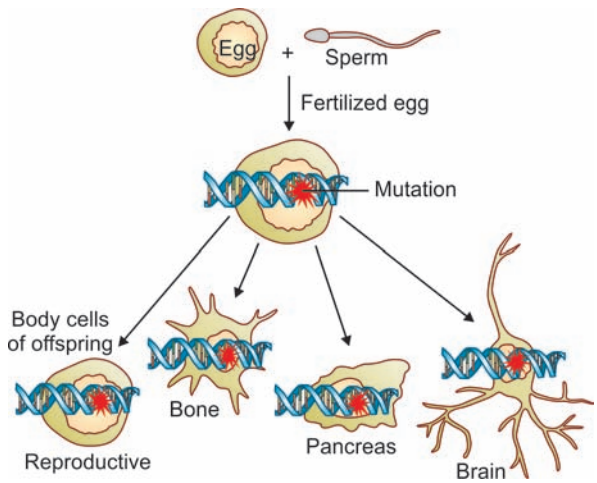


**FIG. 4.5:** Hereditary mutations are carried in the DNA of the reproductive cells. When reproductive cells containing mutation combine to produce offspring, the mutation is present in all of the offspring's body cells

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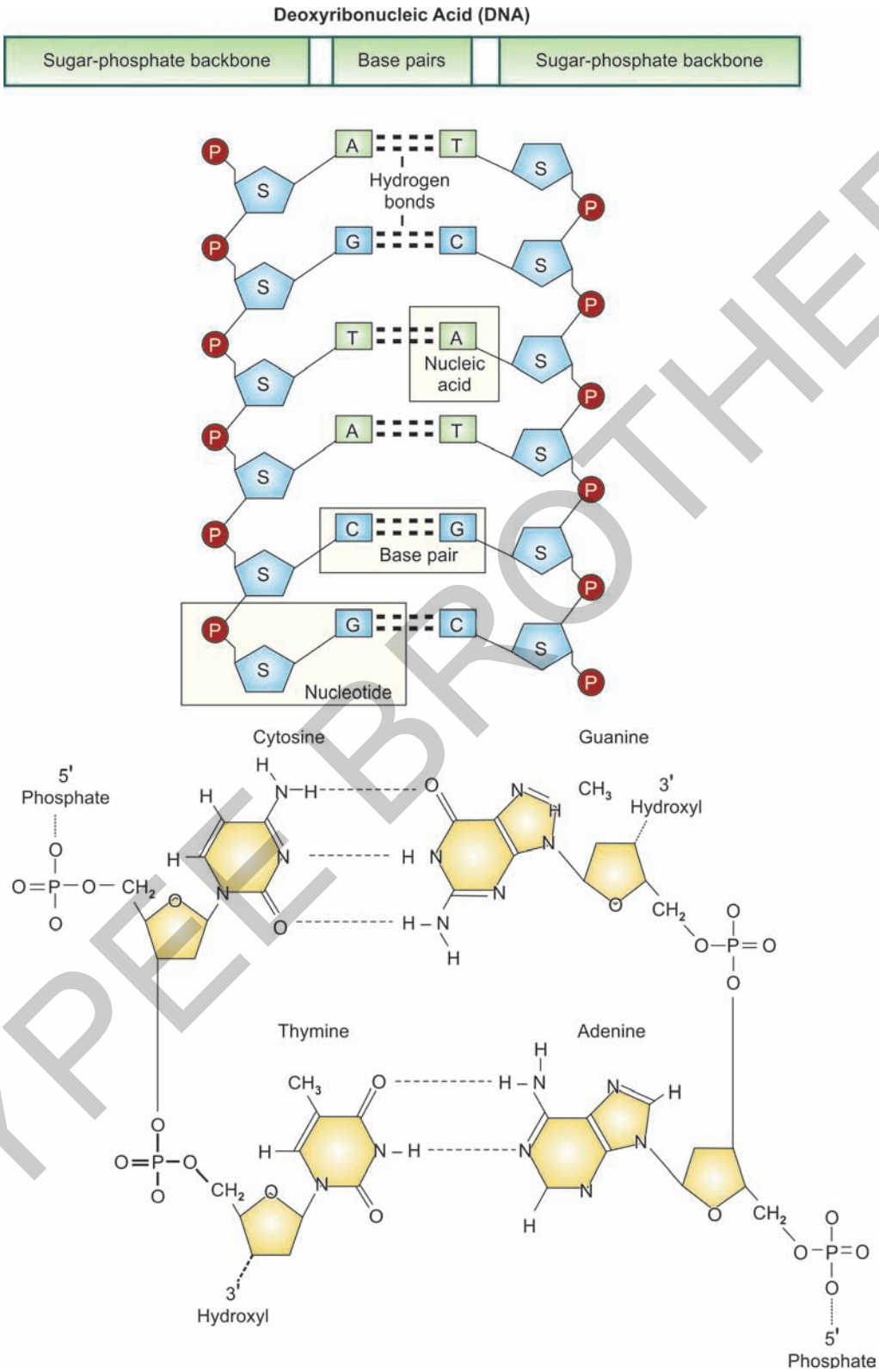


**FIG. 4.6:** Base pairs of DNA include A, adenine pairs with T, thymine; G, guanine pairs with C, cytosine; P, phosphate; S, sugar

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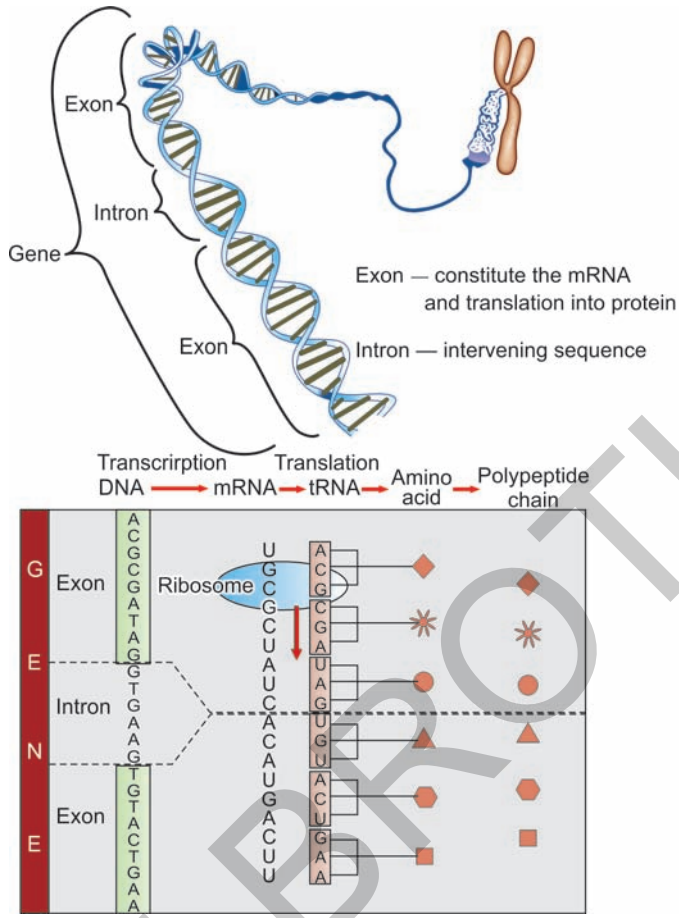


**FIG. 4.7:** Diagram of genetic components that produce amino acid chains using the script from the DNA base pairs. Messenger RNA carries directions from part of the gene to cell ribosomes where one of 20 possible amino acids are created. Amino acids form proteins. mRNA, messenger ribonucleic acid; tRNA, transfer RNA; A, adenine; G, guanine; C, cytosine; T, thymine; U, uracil

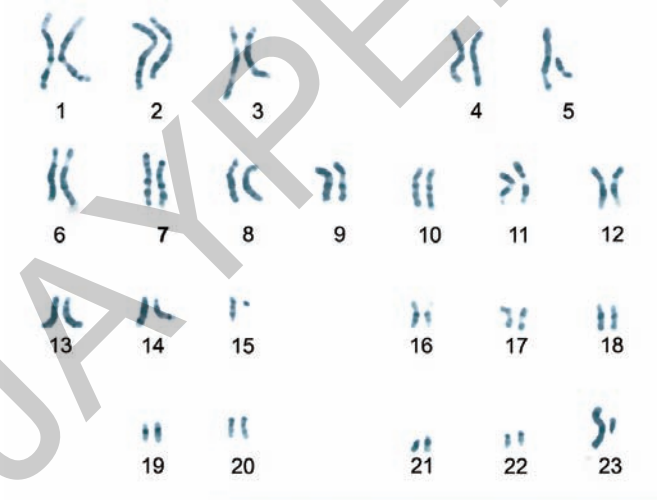


**FIG. 4.8:** Karyotype. Visual display of the 22 pairs of chromosomes and male sex chromosomes

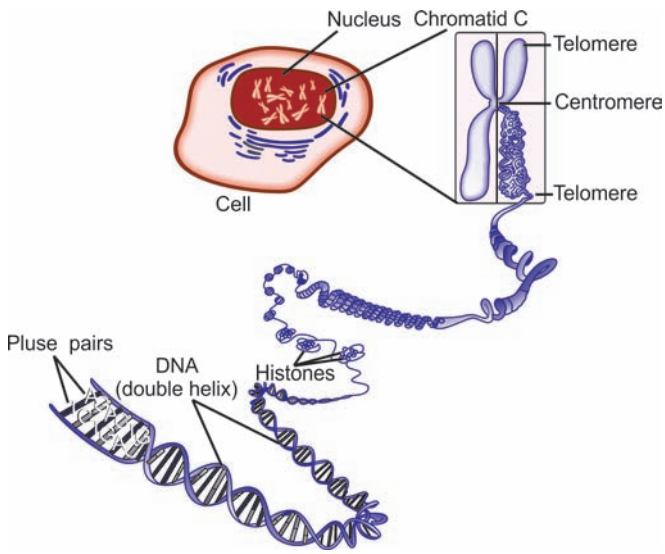


**FIG. 4.9:** Chromosome structure in increasing detail from nucleus to base pairs

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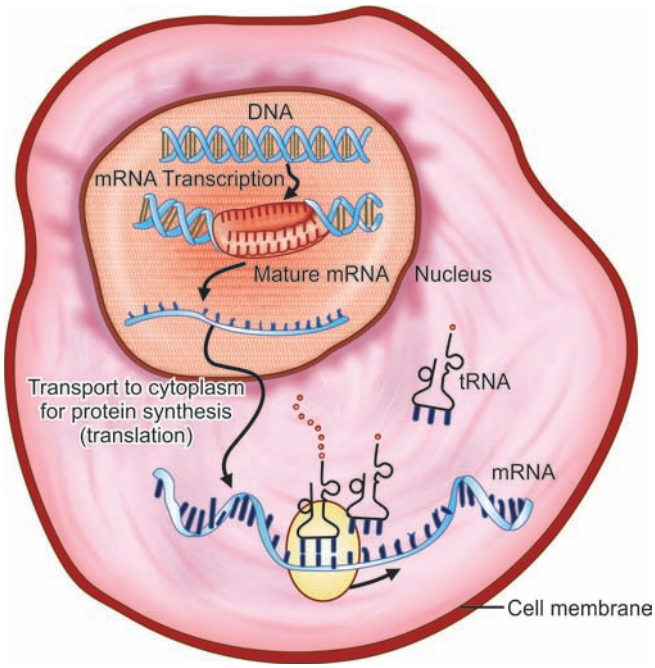


**FIG. 4.10:** Messenger ribonucleic acid (mRNA); tRNA, transfer RNA

Genes are packaged and arranged in a linear order within **chromosomes**, which are located in the cell nucleus. In humans, 46 chromosomes occur in pairs in all body cells except oocytes (eggs) and sperm, which each contain only 23 chromosomes. Twenty-two pairs of chromosomes, called autosomes, are the same in females and males.

The 23rd pair is referred to as the sex chromosomes. A female has two X-chromosomes, whereas a male has one X- and one Y-chromosome. At conception, each patient normally gives one chromosome of each pair to his or her children. As a result, children receive half of their chromosomes from their father and half from their mother (Fig. 4.3).

Careful examination of DNA sequences from many people shows that these sequences have multiple versions in a population. These different versions, or sequence variations, are called **alleles**. Sequences found in many forms are said to be polymorphic, meaning that there are at least two common forms of a particular gene.

### *Cell Division*

The human body grows and develops as a result of the process of cell division. Mitosis and meiosis are two distinctly different types of cell division.

Mitosis is involved in cell growth, differentiation, and repair. During mitosis, the chromosomes of each cell duplicate. The result is two cells, called daughter cells, each of which contains the same number of chromosomes as the parent cell. The daughter cells are said to be diploid because they contain 46 chromosomes in 23 pairs. Mitosis occurs in all cells of the body except oocytes and sperm.

Meiosis, in contrast, occurs only in reproductive cells and is the process by which oocytes and sperm are formed. During meiosis, a reduction in the number of chromosomes, takes place, resulting in oocytes or sperm that contain half the usual number, or 23 chromosomes. Oocytes and sperm are referred to as **haploid** because they contain a single copy of each chromosome, compared to the usual two copies in all other body cells. During the initial phase of meiosis, as the paired chromosomes come together in preparation for cell division, portions cross over, and an exchange of genetic material occurs before the chromosomes separate. This event, called recombination, creates greater diversity in the makeup of oocytes and sperm.

During meiosis, a pair of chromosomes may fail to separate completely, creating a sperm or oocyte that contains either two copies or no copy of a particular chromosome. This sporadic event, called **nondisjunction**, can lead to either a **trisomy** or a monosomy. Down syndrome is an example of trisomy. People with Down syndrome have three copies of chromosome number 21. Turner's syndrome is an example of monosomy. Girls with Turner's syndrome usually have a single X-chromosome, causing them to have short stature and infertility.

## Gene Mutations

Within each cell, many intricate and complex interactions regulate and express human genes. Gene structure and function, **transcription** and translation, and protein synthesis are all involved. Alterations in gene structure and function and the process of protein synthesis may influence a persons health. Changes in gene structure, called **mutations**, permanently change the sequence of DNA, which in turn can alter the nature and type of proteins made (Figs 4.11 and 4.12).

Some gene mutations have no significant effect on the protein product, whereas others cause partial or complete changes. How a protein is altered and its importance to proper body functioning determine the impact of the mutation. Gene mutations may occur in hormones, enzymes, or other important protein products, with significant implications for health and disease. Sickle cell anemia is an example of a genetic condition caused by a small gene mutation that affects protein structure, producing hemoglobin S. A person who inherits two copies of the hemoglobin S gene mutation has sickle cell anemia and experiences the symptoms of severe anemia and thrombotic organ damage resulting from hypoxia.

Other gene mutations may be larger, such as a deletion (loss), insertion (addition), duplication (multiplication), or rearrangement (translocation) of a longer DNA segment. Duchenne muscular dystrophy, an inherited form of muscular dystrophy, is an example of a genetic disorder caused by structural gene mutations such as deletions or duplications in the dystrophin gene. Another type of gene mutation, called a

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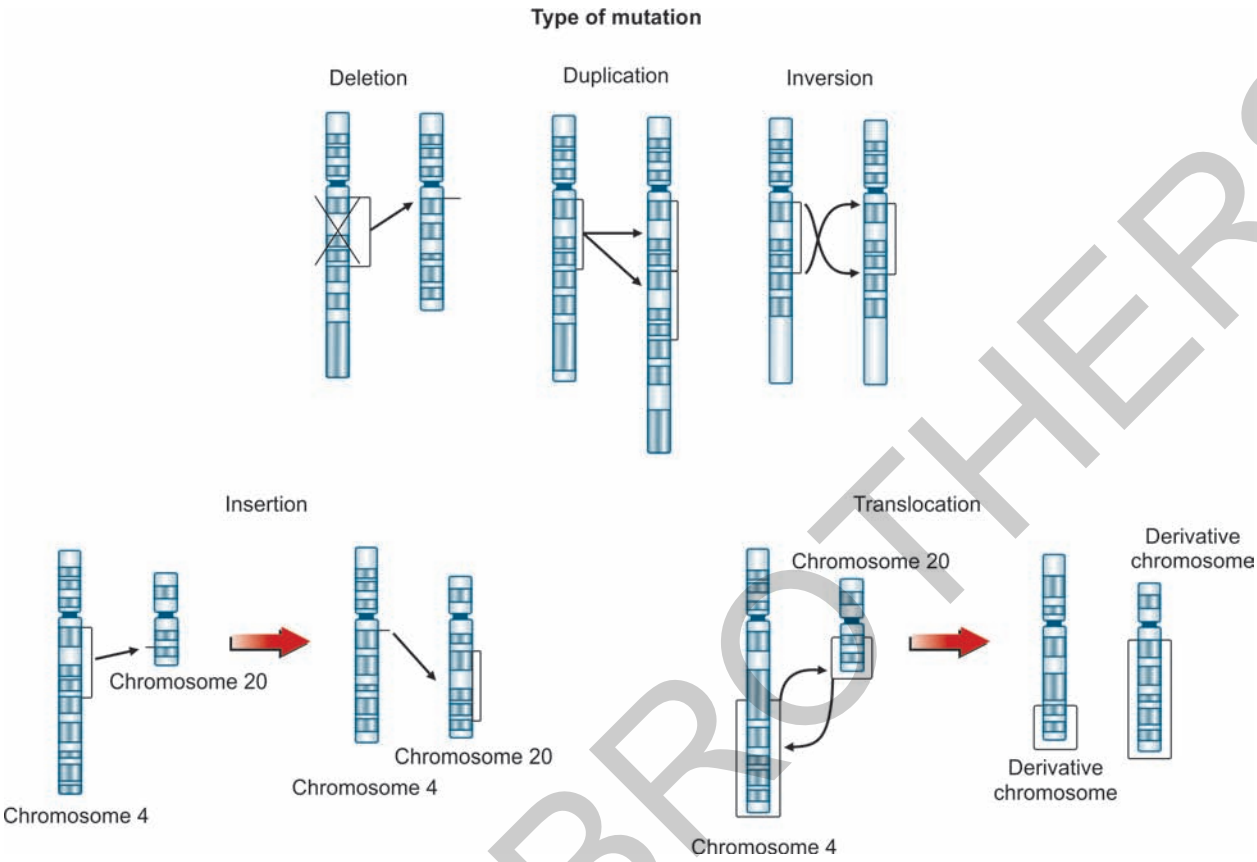


**FIG. 4.11:** Main types of chromosome mutation

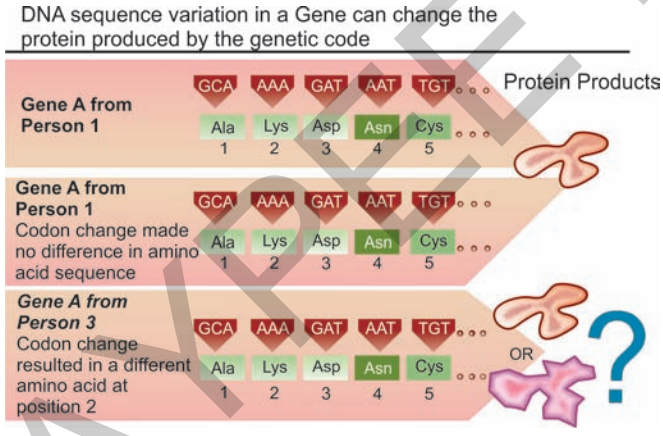


**FIG. 4.12:** DNA sequence variation. Base pairs include A, adenine, pairs with T, thymine; G, guanine, pairs with C, cytosine. Amino acids illustrated include Ala, alanine; Asp, aspartic acid; Asn, asparagines; Cys, cystenine; Lys, lysine

triplet or trinucleotide repeat, involves expansion to more than the usual number of copies of a triplet repeat sequence within a gene. Myotonic dystrophy, Huntington disease, and fragile X syndrome are examples of conditions caused by this type of gene mutation.

Gene mutations may be inherited or acquired. Inherited or germline gene mutations are present in the DNA of all body cells and are passed on in reproductive cells from parent to child. Germline mutations are passed on to all daughter cells when body cells replicate (Fig. 4.12). The gene that causes Huntington is one example of a germline mutation.

Spontaneous mutations take place in individual oocytes or sperm at the time of conception. These mutations are not inherited in other family members. However, a person who carries the new "spontaneous" mutation may pass on the mutation to his or her children. Achondroplasia, Marfan syndrome, and neurofibroma-tosis type 1 are examples of genetic conditions that may occur in a single family member as a result of spontaneous mutation.

Acquired mutations take place in somatic cells and involve changes in DNA that occur after conception, during a person's lifetime. Acquired mutations develop as a result of cumulative changes in body cells other than reproductive cells (Fig. 4.13). Somatic gene mutations are passed on to the daughter cells derived from that particular cell line.

Gene mutations occur in the human body all the time. Cells have built in mechanisms by which they can recognize mutations

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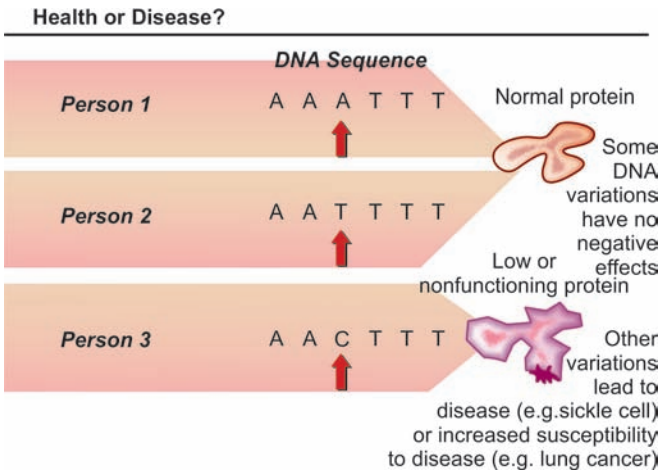


**FIG. 4.13:** Health or disease. A, adenine, pairs with T, thymine: G, guanine, pairs with C, cytosine. The substitution of one base pair can change the protein produced and lead to disease

in DNA, and in most situations they correct the changes before they are passed on by cell division. However, over time, body cells they may lose their ability to repair damage from gene mutations, causing an accumulation of genetic changes that may ultimately result in diseases such as cancer and possibly other conditions of aging, such as Alzheimer's disease.

## Genetic Variation

Research is ongoing to sort out the genetic components of complex conditions (e.g. heart disease, diabetes, common cancers, psychiatric disorders) that result from the interaction of environment, lifestyle, and genetic effects. New studies of genetic variation in humans are underway to develop a map of common DNA variants. Genetic variations occur among people of all populations. *Polymorphisms* and single nucleotide polymorphisms (SNP's, or "snips") are the terms used for common genetic variations that occur most frequently throughout the human genome. Some SNP's may contribute directly to a trait or disease expression by altering function. SNP's are becoming increasingly important for the discovery of DNA sequence allows clinicians to subclassify diseases and adapt therapies to individual patients. For example, a polymorphism or SNP can alter protein or enzyme activity, and thereby affect drug efficacy and safety, if it occurs in proteins that are targets of medication regimens or that are involved in drug transport or drug metabolism.

A number of variables have been observed that explain or modify basic inheritance patterns and the effects of chromosome abnormalities. Some of these variations have been recognized for some time; others are newly discovered phenomena that explain some apparent contradictions in the established patterns of inheritance. Some of the variations involve individual genes, and others involve whole-chromosome behavior but will still affect manifestation of single-gene disorders. Also, some disorders have been reported to follow more than one inheritance pattern in different families (e.g. a classically recessive disorder may occasionally be reported as following a dominant or X-linked pattern in other families).

The most notable of these gene variations is mutation. A **mutation** is any heritable change in the DNA sequence of a gene. Mutations can be a deletion, duplication, or alteration in the base pair sequence. A mutation may cause the protein made by that gene to be produced in an altered, less functional form; to be produced in a decreased amount; or to be entirely absent. A gene mutation may have occurred generations ago and be passed down unchanged until it dies out because an individual does not reproduce, or a new gene mutation can occur spontaneously in an individual. Certain disease-producing gene mutations are known to be "old" mutations, such as the mutation that causes fragile X-syndrome, and new mutations are seldom if ever identified. Other disease known to have a high new mutation rate, such as the 30 to 50% rate for neurofibromatosis and Duchenne muscular dystrophy. This type of definitive determination of a gene mutation is possible only for those single-gene disorders in which the gene site has been located and characterized. Some disorders previously described as exhibiting sporadic occurrence (e.g. Williams syndrome) not attributable to a traditional inheritance pattern may be new mutations with effects such that the individual does not reproduce and the mutation is not passed on to offspring.

**Variable expression** is an important concept that describes differences in the extent and severity of manifestations of genetic diseases. There is a continuum of expression for any affected person from undetectable (mild) to severe clinical manifestation. Therefore a phenotypically normal person may still possess the mutant gene. This situation most often applies to autosomal dominant disorders; for example, a parent of a child with neurofibromatosis may exhibit only a couple of café-au-lait spots. Genomic imprinting and X-inactivation, discussed later in this section, may account for some variation in expression and penetrance, a term used less often as these new discoveries explain variation in phenotypic manifestation.

The discovery of a new type of mutation in some genetic disorders has helped explain their variation in inheritance patterns and clinical expression. Within genes are sequences **DNA nucleotide repeats**. A normal gene has a certain number of these repeats; for example, in the fragile X syndrome gene there are about 30 to 50 repeats. Some persons, however, have additional repeats of from 50 to 200, which have been termed **permutations**. These permutations in females are unstable and during meiosis can undergo amplification, expanding to hundreds more repeats, thereby becoming a full mutation and causing the offspring to be affected. Because fragile X is an X-linked disorder, females are less likely to be affected because of the tempering effect of the second X chromosome. These expanding repeats have also been found to occur in myotonic

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dystrophy, Huntington's disease, and spinocerebellar ataxia, which are autosomally transmitted disorders. This expanding-gene discovery exhibits the old concept of **genetic anticipation**, in which certain dominantly inherited disorders tend to worsen or have an earlier age of onset with succeeding generations. It is believed that additional disorders may be discovered to exhibit this type of mutation. In fact, the first recessively inherited disorder to exhibit an expansion mutation is Friedreich ataxia. This disorder usually demonstrates an onset in puberty or early adulthood, depending on the repeat size of the smaller of the two expansion alleles. Recent evidence suggests genetic anticipation may be a factor for the presence of father-son testicular tumors.

Genomic imprinting and uniparental disomy are two genetic phenomena that consider the parental origin of genetic information (i.e. maternally or paternally derived). The concept of *genomic imprinting* refers to modification, in some instances, of genetic material, resulting in phenotypic differences based on whether the genes/chromosomes were from the mother or the father. Genomic imprinting is exhibited during pregnancy, when paternally derived chromosomes seem to positively influence placemental development and maternally derived chromosomes seem to positively influence fetal development. It has also been shown to be a factor in some genetic disorders, most classically Prader-Willi and Angelman syndrome. In both of these disorders, about two thirds of affected individuals have a deletion of the same segment of chromosome 15. However, the clinical manifestations of Prader-Willi and Angelman syndromes are markedly different. If the deletion occurs on the paternally derived chromosome 15, the child exhibits Prader-Willi's syndrome; if the deletion occurs on the maternally derived chromosome 15, Angleman's syndrome is manifested.

**Prader-Willi syndrome** is characterized by central hypotonia, cognitive dysfunction, dysmorphic appearance, behavioral disturbances, hypothalamic hypotonadism, short stature, and obesity, as well as abnormal low body temperature, an increased tolerance to pain, and diminished salivation. In contrast, **Angelman's syndrome** (also called happy puppet syndrome) includes severe mental retardation, characteristic facies, abnormal (puppet like) gait, and paroxysms of inappropriate laughter. Children with Angelman's syndrome are usually nonverbal, although they may vocalize.

In some cases both copies of a chromosome pair are determined to have come from one parent, either the mother or the father, instead of one from each, a phenomenon called uniparental disomy. An other example of **uniparental disomy** has been reported with cystic fibrosis, in which both chromosomes, each with a mutant recessive gene, came from the carrier mother; the father was not a carrier. In cases that appear to be nonpaternity, uniparental disomy may be a factor. One of the several theories about uniparental disomy is that the chromosome pair was originally a trisomy and the father's chromosome was randomly expelled, leaving two copies of the mother's chromosome. Because the chromosomes appear as a normal "pair", diagnosis of this situation is only possible with molecular (DNA) techniques. Uniparental disomy has also been reported with Beckwith-Weidemann syndrome, which is characterized by overgrowth and hypoglycemia at birth.

## Mitochondrial Disorders

Mitochondrial DNA mutations also account for nontraditional inheritance patterns. Mitochondria are components of the cell cytoplasm involved in energy production. They perform many different functions in different tissues of the body. They are the only cellular organelles to have their own DNA distinct from nDNA and inheritance is exclusively maternal. A defect in the mtDNA can lead to altered functions of the proteins in some or all of the cells. Because the mitochondria perform so many different functions in the body, when a mutation has occurred, the spectrum of symptoms is enormous. Individuals with the same mtDNA mutation may be symptom free or severely affected with seizures, pancreatitis and metabolic disease. Even within the same family, different manifestations of the mitochondrial condition are seen. Mutations may be inherited or occur spontaneously. It is now believed that mitochondria are responsible not only for diseases occurring in childhood, such as Leigh disease (with symptoms of hypotonia, seizures, and failure to thrive), but they can be responsible for many common diseases associated with aging such as diabetes, parkinsonism, and dementia. Because there is such variability of expression with mitochondrial disorders, it can be very confusing to determine the diagnosis. However, when a child has an unexplained constellation of symptoms, a mitochondrial disorder should be considered.

Diagnosis of a mitochondrial disorder can be very difficult and therefore genetic counseling may be possible only in a small number of cases. Nuclear DNA mutations can also cause disorders of the mitochondria, and, with the advances in the detection of nDNA mutations, accurate diagnosis and therefore accurate information about recurrence risk and prenatal diagnosis is possible. Currently, treatment for these disorders is symptomatic and some patients show benefits from vitamin and cofactor supplementation. Referral to mitochondrial support groups can be very helpful to parents.

All cancers are "genetic". In DNA, cellular maintenance and repair genes inhibit abnormal cell growth that may become malignant. To lose this function, mutations must occur in both alleles of one of these genes. These mutations usually result from exposure to carcinogens, with exposure occurring over a lifetime. Only 5 to 10% of cancer occurs as a single gene abnormality, and in these hereditary cancer syndrome a person is born with a mutation already existing in one of the alleles. For this reason the cancer is much more likely to develop earlier in life. One of the cardinal clues to an inherited cancer syndrome is early onset.

Some of the inherited cancer syndromes for which DNA testing is available and medical surveillance and intervention is indicated in children include retinolblastoma, medullary

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- Number of relevant colored figures are provided for better understanding of certain concept related to certain disorders
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