Preventive Management for Children with Genetic Conditions: Providing a Medical Home

This unique source of reference and clinical guidance provides health professionals with an invaluable, structured approach to the preventive care of children with congenital disorders. Over 120 conditions ranging from cerebral palsy to Down syndrome are discussed. For each disorder there is an introductory summary of key information, followed by more detailed listing of general pediatric and speciality concerns, all structured to provide an integrated approach to patient care. For 32 common disorders or disease categories, preventive management checklists are provided: these checklists provide an ongoing record for the child’s medical complications and progress and they are designed to be copied and placed in the medical record.

The text provides details of medical complications and preventive recommendations supported by key literature and web resources for parents and professionals. The introductory chapters provide an overview of the approach to genetic/metabolic disease and developmental disabilities, and a useful glossary is also included.

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Preventive Management for Children with Genetic Conditions: Providing a Medical Home

Second Edition

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and

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For SHAMUS WILSON and the physicians who care for special children.

GNW

For my wife, SEDDON SAVAGE, who is, among other more important things, the best physician I know.

WCC
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Preface

How to use this book

This book is designed as a reference in which health professionals can review complications and design preventive management for common congenital anomalies or syndromes. Over 250 disorders are discussed, including 29 disorders and 3 syndrome families that are described in detail with standardized flow sheets for preventive care (e.g., see the general checklist at the end of this preface). These preventive management checklists are meant to be copied and placed in the medical record. By checking off the appropriate boxes and entering notes, the practitioner can assemble an ongoing record of key concerns, evaluations, and referral/counseling measures. The appended general checklist can be used for less common disorders summarized in this book or elsewhere; complications can be listed and management considerations written in as the child is followed.

A new checklist format of four pages is provided for this second edition. The first page includes a succinct description of the disease and summarizes its complications in a standardized organ-system format. The second and third pages include age-specific recommendations with evaluations and key concerns in the first column and management considerations in the second. The third column has room for physician notes, with occasional reminders for high-risk problems. Below the columns are succinct summaries of disease-specific risks as well as general genetic or social risk factors for that child (e.g., coronary artery disease, prematurity, nutritional deprivation). The presence of general and disease-specific risks on the same flow sheet provides the practitioner with a comprehensive, on-going summary of patient care. The last page contains parent-oriented information on the disorder that may be copied and provided to families.

The more common disorders have longer discussions organized as sections on terminology, etiology, differential diagnosis, genetic/family counseling, complications, and preventive management strategies. The less common disorders have a more succinct format listing complications by region/organ system with management
considerations. It is envisioned that most users will turn to the book with a specific disorder in mind and focus on the relevant medical problems and management suggestions. A detailed table of contents and index are available for this purpose.

Since the first edition, an enormous amount of general and disease-specific information about disabilities has appeared on the Internet. With each disorder are included Internet addresses for parent support groups or medical information sites with physician- and parent-oriented information. This wealth of web information has allowed condensation of references to standard textbooks for background – particularly Gorlin et al. (2001) and Jones (1997) – and a few recent articles. The Online Mendelian Inheritance in Man database (search on OMIM or go to www.ncbi.nlm.nih.gov/entrez), plus its linked Entrez databases like PubMed, will provide updated references on most of the disorders in this book. Searching on disease names like cerebral palsy or Down syndrome will provide information on conditions that are not caused by single genes.

Another use of the book is to read more broadly about the approach to children with developmental disabilities and genetic disease. Because of rapid progress in the field of medical genetics, certain terms or concepts encountered in the chapters may be unfamiliar. For this reason, introductory chapters on the approach to genetic disease and developmental disabilities have been provided (Part I, Chapters 1 and 2). These sections review categories of disease and the specialized tests that are available for diagnosis of syndromes and congenital anomalies. Familiarity with the diagnostic approach allows generalists to be informed participants in the evaluation and management of congenital disorders. A glossary is also provided to aid with specialized terminology.

**Which disorders are included?**

The more common congenital anomalies and syndromes were selected for detailed discussion, with emphasis on those requiring chronic management due to mental and physical disability. To qualify as a “more common” disorder, an incidence above 1 in 25,000 births was required, since that number makes it probable that the disorder will come to the attention of the average pediatric practitioner. If the disorder is rarely encountered by practitioners, or if there are limited strategies for preventive care, then the discussion is limited to a succinct summary without inclusion of a checklist. The general checklist in this preface can be used for these rarer disorders after appropriate entry of their disease-specific complications. The rationale for preventive management strategies is discussed in Chapter 3.

It should be noted that hydrocephalus and spina bifida are isolated anomalies rather than syndromes, and that cerebral palsy is a functional description of brain injury or developmental anomaly. However, their congenital origin and requirements
for chronic management justify coverage in this book. It is expected that the developmental pediatrician will provide specialty expertise for the latter disorders, while the pediatric geneticist will be more actively involved with patients having malformation syndromes.

Some common metabolic disorders are also discussed in this book, although it is recommended that metabolic specialists be continuously involved in their care. The frequent laboratory measurements and dietary modifications required by acute metabolic disorders are not adequately conveyed by a checklist approach, but the frequency of developmental disabilities in these children justifies attention to preventive management in other areas. Checklists are definitely useful for some chronic metabolic conditions, exemplified by the mucopolysaccharidoses discussed in Chapter 19.

Rationale for preventive guidelines

For those interested in the rationale for particular management guidelines, reading of Chapter 3 is recommended. The central rationale is that each syndrome or anomaly places the patient at higher risk for particular complications as compared to the general population; preventive screening or evaluation for these complications is then justified by criteria of efficiency (selection of high-risk patients) and ethics (improved quality of life). This strategy of ameliorating complications is one of secondary or tertiary rather than primary prevention, since few congenital disorders can be prevented or cured (see Chapter 3). A list of complications is the basis for preventive management guidelines, and is rendered in a standard format according to anatomic location or organ system. General complications are listed first (e.g., increased mortality, feeding problems), followed by a standard sequence of body regions and systems.

The Committee on Genetics, American Academy of Pediatrics (1995a, b, 1996a, b, 2001a, b) has published consensus recommendations for the health care supervision of children with, achondroplasia, neurofibromatosis-1, Marfan, fragile X syndrome, Turner, and Down syndrome. These recommendations are certainly followed in this book, and their spirit is extrapolated to other disorders for which consensus guidelines are not yet formulated.

Although there is a clear rationale for alerting practitioners to the complications of a disorder, the nature and timing of intervention often require clinical judgment. Some children with severe dysfunction may benefit more from palliative care than the inconveniences of medical intervention. Decisions about screening measures become particularly difficult when anesthesia is required (e.g., brain imaging), or when a positive result has controversial significance (e.g., cervical spine radiographs for atlantoaxial instability in Down syndrome). Such recommendations are often
footnoted in the checklists, with the reminder that clinical judgment must always be used.

Types of preventive guidelines

The United States Surgeon General has recommended that all families know their family history, and columns for risk factors ascertained from family background or prenatal history are included on the checklists. Social and environmental concerns can also be listed, providing a summary of general and disease-specific risks that will remind practitioners of age-related concerns. In Chapter 3, the effectiveness of checklists in improving preventive care is documented.

“Family Support” appears frequently under management considerations in the second column of the checklists. This is a prompt to the primary care physician to inquire about the general impact of the child’s condition on family life. Questions should routinely be raised about specific family stresses, school issues, the status of siblings, access to information, contact with others affected by the same condition, and financial pressures. Eligibility for benefits such as Medicaid, Supplemental Security Income (SSI), Title V, and respite care should be considered and followed with appropriate referrals. Some families may need to consider the financial planning issues related to income taxes, trusts, and estate planning when individuals with developmental disabilities are involved. Many states have family support programs for families of children with disabilities which may include the services of a family support coordinator. All eligible families should be referred to such programs. Birthdays, anniversaries of the initial diagnosis, and life transitions (e.g., preschool to elementary school; school to work/adult life) are particularly difficult times for families during which extra support may be needed. Included on the checklists and with text discussions are websites for parent support groups and parent information that can be invaluable for negotiating times of crisis.

Validation of preventive management guidelines

Having stated that the preventive management guidelines are based on disease complications, it must again be emphasized that the invasiveness and frequency of preventive screening may be subject to dispute. Judgments about screens (e.g., echocardiography for all infants with Down syndrome) versus a wait for symptoms (e.g., echocardiography for a heart murmur) are often difficult, and practitioners should keep in mind that consensus guidelines are available for few disorders. Certainly practitioners should feel free to modify the guidelines based on their experience and style.
Preface

In summary, this book should be used to enhance the health care of patients with congenital anomalies and syndromes by considering preventive management guidelines. It is certainly not intended to impose unwanted advice on experienced physicians or to add new burdens to the already busy routines of those involved in patient care. However, anyone observing the improved outcomes for patients with Down syndrome over the past few decades must award some merit to preventive management. While congenital disorders may not be cured, the attentive physician can almost always heal by enhancing the quality of life of children with developmental or genetic disorders.

Acknowledgements

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## Congenital anomalies

General preventive medical checklist for congenital anomalies or syndromes

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluations: key concerns</th>
<th>Management considerations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Neurologic problems, anomalies</td>
<td>□ Imaging; □ specialists; □ family support</td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td>Hearing, vision, feeding</td>
<td>□ ABR; □ ophthalmology; □ video swallow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Airway, jaw, neck: obstruction, mobility</td>
<td>□ Radiology; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>Growth, development, feeding</td>
<td>□ Consider ECI; □ family support; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>Hearing, vision, feeding, sleep</td>
<td>□ ABR; □ ophthalmology; □ sleep study; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Internal defects: heart, kidneys, gut</td>
<td>□ Cardiology; □ urology; □ GI</td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td>Growth, development, school transition</td>
<td>□ Family support; □ ECI; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>9 years</td>
<td>Hearing: vision, sleep</td>
<td>□ Audiology; □ ophthalmology; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>Growth, hearing, vision</td>
<td>□ ENT; □ ophthalmology; □ school progress, IEP; □ vocational, behavioral counseling; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>15 years</td>
<td>Diet, activity, exercise, sleep</td>
<td>□ Dietician; □ sleep study; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>16 years</td>
<td>Puberty, behavior</td>
<td>□ Vocational, behavioral counseling; □ ENT; □ anesthesia precautions</td>
<td></td>
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<tr>
<td>18 years</td>
<td></td>
<td>□ Dietician; □ sleep study; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>19 years</td>
<td>Adult care transition</td>
<td>□ Vocational, behavioral counseling; □ ENT; □ anesthesia precautions</td>
<td></td>
</tr>
<tr>
<td>23 years</td>
<td>Diet, activity, exercise, behavior</td>
<td>□ Dietician; □ behavior therapy; □ ENT; □ anesthesia precautions</td>
<td></td>
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<tr>
<td>Adult</td>
<td></td>
<td>□ Vocational, behavioral counseling; □ ENT; □ anesthesia precautions</td>
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<tr>
<td></td>
<td>Adult care transition</td>
<td>□ Vocational, behavioral counseling; □ ENT; □ anesthesia precautions</td>
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<tr>
<td></td>
<td>Diet, activity, exercise</td>
<td>□ Dietician; □ behavior therapy; □ ENT; □ anesthesia precautions</td>
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</table>

### Disease-specific concerns

<table>
<thead>
<tr>
<th>Disease-specific concerns</th>
<th>Other concerns from history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Family history/prenatal</td>
</tr>
<tr>
<td></td>
<td>Social/environmental</td>
</tr>
</tbody>
</table>

Guidelines for the neonatal period should be undertaken at whatever age the diagnosis is made; ABR, auditory brainstem evoked response; ECI, early childhood intervention; IEP, individualized educational plan; GI, gastrointestinal; infants with unexplained delays or multiple anomalies should have pediatric developmental, genetic, and neurologic assessment; consider karyotype and/or cranial sonogram/head MRI for anomalies; by practitioner; as dictated by clinical findings; if suspected disability, consider parent group, family/sib, financial, and behavioral issues; if disability, early intervention and preschool program; monitor individual education plan, educational testing, balance of special education and inclusion, academic progress, behavioral differences, later vocational planning; inoring, pause in breathing, daytime sleepiness, unusual sleep positioning.
Glossary of genetic and molecular terms

These brief definitions should be supplemented by consulting the texts recommended in the Preface.

*Acrocentric chromosome*: Chromosome with small short (p) arms as opposed to metacentric chromosomes with approximately equal short and long (q) arms.

*Allele*: Alternative gene structure (e.g., S and A alleles of the β-globin gene).

*Agenesis*: Absence of a part of the body caused by an absent anlage.

*Aneuploidy*: Abnormal chromosome number that is not an even multiple of the haploid karyotype (i.e., 47,XX,+21 or 90,XX).

*Anlage, primordium, blastema*: Embryonic precursor to a tissue, organ or region.

*Anomaly*: Any deviation from the expected or average type in structure, form and/or function which is interpreted as abnormal.

*Anticipation*: Worsening of phenotype with subsequent generations.

*Aplasia*: The absence of a body part resulting from a failure of the anlage to develop.

*ASO*: Allele-specific oligonucleotides used for DNA diagnosis.

*Association*: Any non-random occurrence in one or more individuals of several morphologic defects not identified as a sequence or syndrome. Associations represent the idiopathic occurrence of multiple congenital anomalies during blastogenesis.

*Atavism*: A developmental state that is normal in phylogenetic ancestors, but abnormal in their descendants.

*Atrophy*: Decrease in a normally developed mass of tissue(s) or organ(s) due to decrease in cell size and/or cell number.

*Base pairs (bp)*: Adenine–thymine (A–T) or guanine–cytosine (G–C) pairing in DNA; also the basic unit for DNA strand length.

*Blastogenesis*: Stages of development from karyogamy and the first cell division to the end of gastrulation (stage 12, days 27–28).

*Candidate gene*: A gene implicated in pathogenesis based on protein function, chromosomal location, or sequence homology.
Glossary of genetic and molecular terms

**Chromosomal rearrangements**: Aberration where chromosomes are broken and rejoined as opposed to numerical excess or deficiency.

**Chromosome painting**: Use of repetitive DNA FISH probes to fluoresce entire chromosomes or chromosome regions.

**Contiguous gene deletions**: Deletion encompassing neighboring genes to produce a composite phenotype.

**Crossover**: Breakage and reunion of chromosomes that realign parental loci.

**Cytogenetic notation**: Formal nomenclature describing karyotypes and chromosome location, that is:

- 47,XY+11: Extra chromosome 11 (Trisomy 11)
- 45,XY−11: Absent chromosome 11 (Monosomy 11)
- 46,XY,11q−: Terminal deletion of chromosome 11
- 46,XY,11q+: Extra material of unknown origin on 11q
- 46,XY.del(11p11p13): Interstitial deletion between bands p11 and p13 of chromosome 11

**DNA cloning**: Isolation of a DNA segment by insertion into a simple genome (plasmid, bacteriophage) and production of multiple copies.

**DNA diagnostic techniques**: Use of DNA modifying enzymes, hybridization, and size separation technologies for diagnosis of identity, genetic disease, or predisposition.

**DNA hybridization**: Rejoining (reannealing) of complementary DNA or RNA stands.

**DNA marker**: DNA segment, often anonymous, that exhibits sufficient sequence variation to be useful in genetic linkage and DNA diagnosis.

**DNA sequence**: Order of nucleotides in a DNA segment, usually displayed from the 5'-triphosphate (5' end) to the 3'-hydroxyl (3' end) nucleotides.

**Empiric risks**: Recurrence risk based on epidemiologic survey of affected families.

**Exon**: Portion of gene that encodes protein.

**First-degree relative**: Those with 50% of genes in common (child, parent, sibs).

**FISH**: Fluorescent in situ hybridization, a technique by which flourochromes are attached to DNA probes and hybridized with cytogenetic or cell preparations.

**Functional cloning**: Isolation of gene segments based on gene function; that is, using antibodies to a characterized protein or expression assays where traits are deleted or restored to cultured cells.

**Gene map**: Order of genes within a chromosome or entire genome.

**Genetic heterogeneity**: Multiple loci where mutations can produce a similar phenotype, such as autosomal-dominant or X-linked Charcot–Marie–Tooth disease.
Glossary of genetic and molecular terms

Genetic mapping: Use of genetic linkage to produce a relative gene order based on recombination distances (centimorgan = approximately 1 megabase).

Genome: Complete set of genes (DNA) in an organism.

Genomic DNA: DNA isolated from an organism or tissue, containing transcription signals and introns that will be absent from cDNA.

Genomics: The study of function and disease based on gene structure and organization.

Genotype: Genetic constitution, often with reference to particular alleles at a locus.

Germinal mosaicism: Mosaicism within the germ line, whereby a fraction of eggs or sperm may contain a particular mutation or chromosome aberration.

Heteroplasmy: Different mitochondrial genomes in the same cell, a mechanism by which the proportions of altered mitochondria may increase in specific tissues to cause disease.

Heterozygote: Individual with different alleles at a locus.

Homeobox: A DNA sequence shared by several Drosophila segmentation genes.

Homeotic mutations: Mutations altering segment identity in Drosophila. In a broader sense, a developmental switch analogous to that replacing one homologous insect segment with another.

HOX, hox: Gene clusters in humans and mice that exhibit homology to the structure and expression of Drosophila homeotic loci.

Hyperplasia: Overdevelopment of an organism, organ, or tissue resulting from a decreased or increased number of cells.

Hypertrophy: Increase in size of cells, tissue, or organ.

Hypoplasia: Underdevelopment and overdevelopment of an organism, organ, or tissue resulting from a decreased or increased number of cells.

Hypotrophy: Decrease in size of cells, tissue, or organ.

IGF: Insulin-like growth factor.

Incomplete penetrance: Absence of phenotypic expression in a person known from a pedigree to have an abnormal genotype.

Interstitial deletions: Chromosomal deletion removing regions between termini.

Isochromosomes: Duplicate long or short chromosome arms that result in deficiency (i.e., Turner syndrome patients with i(Xq) are monosomic for Xp).

Karyotype: A standard number and arrangement of chromosomes as obtained from human blood or tissue specimens. A normal karyotype is 46,XX for females and 46,XY for males.

Kilobases (kb): Unit of DNA/RNA length = 1000 bp; megabase = 1 million bp.

L1CAM: L1 cell adhesion molecule implicated in X-linked hydrocephalus.

Linkage: The tendency for neighboring genes to segregate together in families.
Glossary of genetic and molecular terms

Locus: Unique location of a gene on a chromosome.

Major anomaly: Anomaly with cosmetic or surgical consequences.

Malformation: A morphologic defect of an organ, or larger region of the body, resulting from an intrinsically abnormal developmental process.

Maternal inheritance: Inheritance mechanisms that exhibit maternal transmission based on abnormal mitochondria or maternal RNAs.

Meiosis: The process of germ cell division that randomly allots one chromosome of each pair to gametes.

Mendelian inheritance: The classical autosomal dominant, autosomal recessive, and X-linked inheritance mechanisms derived from Mendel’s observations in peas.

Microdeletions: Chromosome deletions requiring prometaphase banding for visualization.

Minor anomaly: Anomaly of no medical but considerable diagnostic significance.

Mitosis: The process of somatic cell division that produces identical genomes in daughter cells.

Morphogenesis: A developmental process that includes the stages of blastogenesis and organogenesis.

Morphology: Discipline of zoology that concerns itself at once with the form, formation, and transformation of living beings.

Mosaicism: Variation in DNA sequence or chromosome constitution among different cells of an organism.

Multifactorial determination: Dependence of traits on multiple genes plus the environment.

Multipoint linkage: Linkage analysis that examines multiple traits or markers in a pedigree and orders them relative to one another.

Normal variant: Deviation from expected or average type in structure, form or function that is more frequent (arbitrarily >4% of population) and more innocuous than an anomaly.

Obligate carrier: Carrier deduced by pedigree structure.

Oligonucleotide: Short nucleotide sequence often obtained by chemical synthesis.

Organogenesis: A developmental process that extends from late stage 13 (day 28) until the end of stage 23 (day 56) when the major organs and body parts are formed.

Paired box: A DNA sequence motif found in the paired gene of the fruit fly.

PAX: Genes in mice and humans containing paired boxes.

PCR: Polymerase chain reaction by which individual gene segments are amplified through sequential cycles of polymerization, heat denaturation, and reannealing.

Phenotype: Individual traits or characters.

Physical mapping: Gene order based on actual physical measurements in terms of chromosome bands or DNA base pairs.

Pleiotropy: Multiple traits determined by a single cause, often a gene mutation.
**Glossary of genetic and molecular terms**

*Point mutations*: Nucleotide substitutions.

*Polymorphism*: Multiple alleles at a locus, producing amino acid or DNA sequence variation.

*Polypeptide chains*: Proteins or, in the case of multiple subunits, components of proteins formed by peptide bonds between amino acids.

*Polyploidy*: Abnormal chromosome number that is a multiple of the haploid karyotype (e.g., 69,XXY or 92,XXXX).

*Positional cloning*: Isolation of gene segments based on chromosome location.

*Primary relative*: First-degree relative (i.e., those sharing 50% of genes).

*Primer*: Oligonucleotide used to begin nucleic acid polymerization at a particular site on a DNA strand (e.g., with PCR or reverse transcriptase).

*Proband*: Individual bringing family to attention, indicated by arrow in pedigrees.

*Prometaphase analysis*: Karyotype prepared from synchronized cells arrested in early prophase; these studies require prior notice to the laboratory.

*Propositus*: Same as proband.

*Protein polymorphism*: Products of alternate alleles at a locus exemplified by the ABO or HLA systems.

*Quantitative traits*: Incremental phenotypes such as height or blood pressure.

*Recombinant DNA*: Chimeric DNA molecules produced by joining of segments from different species, often using the complementary “sticky ends” produced by restriction endonucleases.

*Recombination*: Breakage and reunion of DNA strands.

*Repetitive DNA*: DNA sequences that have multiple copies in a genome.

*Restriction endonuclease*: A bacterial enzyme designed for defense against bacteriophage that recognizes and cleaves at specific nucleotide sequences.

*Reverse genetics*: Genetic analysis proceeding from chromosomal location to cloned gene; positional cloning is now the preferred term.

*Robertsonian translocations*: Joining of two acrocentric chromosomes at their short arms to produce a single translocation chromosome.

*Sequence*: A cascade of primary and secondary events that are consequences of a single primary malformation or a disruption.

*Somatic mosaicism*: Variation in DNA sequence or karyotype among different somatic cells of an organism.

*Sporadic*: Isolated case, often implying lack of inheritance or genetic causation.

*Submicroscopic deletion*: Small chromosome deletions that can be visualized only by DNA analysis.

*Syndrome*: Multiple anomalies thought to be pathogenetically related and not representing a sequence.

*Syndrome variability*: Differing phenotypic manifestations among individuals with the same syndrome.
Targeting sequences: Amino acid regions that direct proteins to particular cellular locations.

Teratology: The study of abnormal development, particularly with regard to the disruptive influence of drugs, chemicals, and physical agents.

Threshold: A theoretical barrier at which an individual’s combination of genes and environmental exposure crosses from predisposition to actual defect.

Translocation breakpoint: The region of recombination between two chromosomes.

Translocation carriers: Individuals with “balanced” translocations that have no extra or missing chromosome material.

Triplet repeat amplification: Increased number of tandemly repeating 3-bp units that can alter gene expression, as in Fragile X syndrome or mytonic dystrophy.

Trisomies/monosomies: Karyotypes with extra or missing entire chromosomes.

Uninformative: Genetic linkage study where parental alleles and therefore the risk for disease transmission cannot be distinguished.

Uniparental disomy: Two copies of a chromosome pair derived from one parent.

Variable expressivity: Variable symptoms among affected individuals in a family.

Zygotic expression: Synthesis of gene products from zygotic DNA rather than maternal RNA molecules.