Cytogenetic Evaluation: A Primer for Pediatric Nurse Practitioners

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ABSTRACT

Patients with genetic disorders require specific types of cytogenetic testing for accurate diagnosis and prognosis followed by prompt treatment. This primer will serve as a guide for pediatric nurse practitioners on the use of various cytogenetic testing for the diagnosis of genetic disorders. Knowledge of the latest cytogenetic technologies will facilitate diagnosis and counseling related to genetic abnormalities such as inherited disorders, mental retardation, developmental delay, and autism. This reference will enable pediatric nurse practitioners to help identify patients with various inherited genetic disorders and provide subsequent monitoring and treatment. J Pediatr Health Care. (2012) *27*, 426-433.

KEY WORDS

Cytogenetics, karyotyping, FISH, CGH, chromosomal microarrays

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Advances in genetic testing have important implications in clinical practice. Innovations in cytogenetic techniques and diagnostic capabilities have enabled earlier detection and diagnosis of genetic disorders. As a result, initiation of treatments and therapies occurs earlier, which may slow progression of the effects of the disease or enhance patient outcomes. This review will provide nurses with a basic background in genetics, which will enable them to assist children and their families who are affected by a genetic disorder or who are considering cytogenetic testing.

From a historical perspective, the field of human cytogenetics is relatively young, with less than 60 years between the first developments and present-day technologies. Cytogenetics is categorized into specific periods (Smeets, 2004; Therman & Susman, 1993) beginning with the "Dark Ages," the time prior to 1952, before the number of human chromosomes was determined (Hsu, 1979). During the Hypotonic Period (1952-1959), scientists discovered that hypotonic solution applied to cells caused swelling, which allowed for visualization of the chromosomes (Hsu, 1952). As a result, Tjio and Levan (1956) were able to determine that humans have 46 chromosomes. The Hypotonic Period led to the Trisomy Period (1959-1974), when trisomies 13, 18, and 21 were categorized. The Banding Era (1974-1989) followed Caspersson's 1970 development of Q-banding (fluorescent banding) and Yunis' 1976 development of Giemsa-Trypsin-Giemsa banding (G-banding; Caspersson, Zech, & Johansson, 1970; Yunis, 1974; see Box 1). These discoveries led to the ability to classify more accurately numerical and structural chromosome abnormalities. The Molecular Era began in 1989 when Pinkle and Grey (Pinkel et al., 1986) developed fluorescence in situ hybridization (FISH). FISH allows for faster, more reliable, and more precise methods of detecting a number of specific chromosome abnormalities. FISH does not detect all chromosome

BOX 1. Glossary

Array Comparative Genomic Hybridization: A solid platform on which deoxyribonucleic acid (DNA) is immobilized. Developed to circumvent resolution limitations of standard chromosome analysis and fluorescence in situ hybridization (FISH). It allows the analysis of hundreds to thousands of genes simultaneously. Gains and losses of DNA are measured by quantifying fluorochrome intensities by comparing patient DNA versus control DNA.
Copy number variants: Segments of DNA present in ≥ 1% of the population with no known clinical significance.
Cytogenetics: The science that combines the methods and findings of cytology and genetics.
Bacterial artificial chromosomes: Small pieces of DNA inserted into bacteria and used to spot the microarray.
Fluorescence in situ hybridization: Technique of using synthetic polynucleotide strands that bear sequences known to be complementary to specific target sequences at specific chromosomal sites.
Giemsa-Trypsin-Giemsa Banding (G-banding): Technique of treating chromosomes with trypsin and then staining them with Giemsa. Most euchromatin stains lightly, and most heterochromatin stains darkly under these conditions.
Karyotype: The chromosomal complement of a cell.
Nucleotides: Monomeric units from which DNA and ribonucleic acid polymers are constructed.
Oligonucleotides: Manufactured DNA sequences of known disease regions and genome sequences closely spaced across the genome.
Single nucleotide polymorphism: Small variations in DNA sequence in which at any given position a single nucleotide is replaced by one of the other three nucleotides.

Data from King, Stansfield, & Mulligan, 2006.

abnormalities. During this time, comparative and array comparative genomic hybridization (aGCH) techniques were developed (Still, Vince, & Cowell, 1997). Molecular techniques continue to evolve.

Using seminal and current research, the purpose of this review is to provide pediatric nurse practitioners (PNPs) with a cytogenetics primer. This primer will serve as a guide for PNPs on the use of various cytogenetic testing techniques for the diagnosis of genetic disorders. Clinical indicators for cytogenetic evaluation, cytogenetic techniques, and clinical applications will be discussed.

RED FLAGS AND CLINICAL INDICATORS FOR CYTOGENETIC EVALUATION

Referral for cytogenetic evaluation with the possibility of cytogenetic testing is dependent on prompt recognition of "red flags" that indicate a patient or family may be at risk for a genetic disorder. The health history and developmental and physical examination of a pediatric patient and family provide unique opportunities for the PNP to identify clinical indicators or genetic red flags that should prompt a referral for further evaluation. Syndromes are rare; phenotypes denoting a syndrome can be subtle; and some disorders such as autism have complex etiologies and therefore require that patients be referred for further evaluation. However, PNPs who are knowledgeable about red flags and clinical findings indicating a risk for a genetic disorder will be instrumental in making prompt referrals to a genetic specialist.

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FAMILY HISTORY

Obtaining a comprehensive family history is essential for identifying families at risk for genetic disorders. To obtain an accurate history, getting the history from *both* parents is preferable. To develop a complete historical picture, inclusion of information about three generations also is preferable. The National Coalition for Health Professional Education in Genetics (2011) developed a list of genetic red flags that may be useful in determining if a condition in a family has a significant genetic contribution (Box 2). The presence of one or more of these genetic red flags should prompt a referral to a genetics professional to interpret the family history and conduct a risk assessment.

PREGNANCY AND BIRTH HISTORY

The pregnancy and birth history provide important data for determining whether a patient is at risk for a genetic disorder. Although the index case, or affected individual, may provide the most relevant information, a history for all pregnancies and births should be obtained. The presence of one or more of the following genetic red flags should prompt the PNP to refer the family to a genetics professional: (1) maternal age younger than 15 years or age 35 years and older and paternal age younger than 20 years or age 40 years and older; (2) rapid sequential pregnancies; (3) poor reproductive history, including a previous unfavorable pregnancy outcome; (4) history or present use or abuse of substances, including drugs, alcohol, and/or cigarettes; (5) poor nutrition; (6) underweight or overweight;