INTRODUCTION

Introduction: Past, Present, and Future Care of Individuals With XXY

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XXY (Klinefelter syndrome) occurs one in 500–750 live male births, and while recognized more than 50 years ago, some of the most elementary aspects of this common but rarely diagnosed disorder are not well understood today. In the last 5 years, there has been a resurgence of interest in this chromosomal condition and its related disorders with the publication of numerous articles on the topic. Our title was chosen to highlight the myths of the past, the care of the present, and the needs of the future in XXY.

Although XXY was identified more than five decades ago, in many ways our understanding of the complexity of this disorder is quite primitive. Many questions persist: Does hormonal replacement effect brain function and to what degree? If so, when is it an ideal time for hormonal replacement to occur? What is the breadth and complexity to the phenotypic profile? What are the factors effecting the variability of the profile?

This issue of Seminars in Medical Genetics, *American Journal of Medical Genetics* Part C, will afford the most current information on XXY and related conditions by specialists in the diversified fields of medical genetics, neurology, endocrinology, neurodevelopment, immunology, orthopedics, neurosciences and obstetrics, and gynecology. Each article highlights various facets of XXY as well as the vital aspects of clinical care for these children. This issue also provides a window of opportunity to advance future areas of research in XXY and related disorders.

Dr. Margaret McCarthy describes the intricate relationship between brain development and hormones. She highlights the pervasive yet often unrecognized powerful influence which hormones exert across the lifespan in our neuroarchitecture, our neurodevelopmental progression as well as health and wellbeing. Her article encourages us to rethink the relationship between androgens, behavior and XXY.

Dr. Paduch and colleagues outlines the care and treatment of individuals with XXY. From an innovative perspective he and his colleagues provide the framework for the care and treatment of the child with XXY from birth through adulthood. This article affords insight into the relationship between androgens, psychosocial development and XXY. Their research focuses on the facilitation of appropriate pubertal development in XXY through hormonal manipulation resulting in increased strength, greater agility, and more muscle mass.

Dr. Samango-Sprouse and her colleagues further investigate the longstanding question to parents, researchers and clinicians, are the behavioral deficits a consequence of the additional X or the individual child? This article focuses on the complexity of the behavioral phenotype in XXY and begins to define the impact of familial learning disabilities (FLD). This article expands our understanding of novel attribute on the behavioral phenotype of XXY. It expands our comprehension of the phenotypic profile as well may account for some of the variability in 47,XXY.

In this issue, we have included three articles devoted to 49,XXXXY, which is a complex variant of 47,XXY. These articles report the largest cohort of patients and expand our understanding of this neurogenetic disorder from a neurodevelopmental, immunological, and orthopedic perspective.

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Andrea Gropman, M.D. is an Associate Professor of Neurology and Pediatrics at the George Washington University of the Health Sciences and an attending at the Children's National Medical Center in Washington, D.C. She is the Chief of the division of Neurogenetics and Neurodevelopmental Pediatrics. She is involved in clinical and molecular testing of patients with Neurogenetic conditions and her research is focused on neurological and neurodevelopmental phenotyping of genetic conditions. She also performs research using neuroimaging in children and adults with inborn errors of metabolism. She has overseen the care of children with X and Y Chromosomal Variations for over 15 years.

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Dr. Gropman and her associates outline a comprehensive description of the variability of neurodevelopmental skills in a large cohort of boys with 49,XXXXY. This article highlights the importance of the diverse cohort of patients with this uncommon disorder in order to appreciate the breath and complexity of their behavior. Gropman and Samango-Sprouse describe the components of multidisciplinary evaluations to assess the global impact of X chromosome imbalance on neuromotor and cognitive function as well as the individual variability of the child with 49,XXXXY.

Dr. Tosi and her colleagues describe for the first time in a large group of children with 49,XXXXY the musculoskeletal abnormalities. This article expands our understanding of the anomalies in the upper and lower extremities and identifies an increased incidence of Legg-Cavé-Perthes disease, radial ulnar synostosis, and other osseous disorders. This publication highlights the need for multidisciplinary approach to the musculoskeletal abnormalities in boys with 49,XXXXY.

Dr. Keller and associates describe immunology function in boys with 49,XXXXY. This article highlights the primary immunodeficiency in this disorder and reports a pattern of response that is highly suggestive of Specific Antibody Deficiency (SAD). This is novel finding in 49,XXXXY and has implications in routine well baby care as well as preventive care for these vulnerable and fragile boys.

Dr. Aksglaede and her colleagues provide detailed findings on individuals with XXY based on more than 40 years of care and research on 47,XXY. This group of researchers from Denmark has provided a wonderful and insightful experience from cradle to adulthood. They provide guidelines for the medical management of boys and men with this disorder. Their article supplies a multifaceted approach to the medical issues associated with XXY in a large and unbiased sample.

Drs Joe Leigh Simpson and Samango-Sprouse provide us with a current and comprehensive view of prenatal diagnosis and XXY. This is a rapidly changing field and provides an opportunity to identify XXY prenatally through noninvasive measures.

In conclusion, this issue of the Seminars in Medical Genetics addresses the complexity of XXY and related disorders from a multidisciplinary perspective with the goal of augmenting our comprehension of the disorder. With greater understanding of this genetic disorder, early detection can be increased with improved care and more targeted treatment for an under investigated and underdiagnosed population of children.

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