Acta Genet Med Gemellol 45: 15-16 (1996)

Prader-Willi and Angelman Syndromes and the Implications of Genomic Imprinting in Their Etiology

S.B. Cassidy

Case Western Reserve University and the Center for Human Genetics, University Hospitals of Cleveland, Ohio, U.S.A.

The unfolding of the genetic story of Prader-Willi and Angelman syndromes provided the first recognition of human genomic imprinting. These disorders, which are clinically very distinct, are related through their genomic proximity and the inverse direction of the imprinting which affects them. Both are interesting disorders in themselves, especially in that both have distinctive behavioral patterns among their clinical features that may teach us much about normal human behavior.

Prader-Willi syndrome (PWS) is a complex multi-system condition whose major features include infantile hypotonia with decreased arousal, poor suck and failure-to-thrive; characteristic dysmorphic facial features; hypopigmentation; childhood onset of obesity due to lack of satiety; hypogonadotropic hypogonadism with genital hypoplasia and delayed and incomplete puberty; short stature for genetic background; developmental delay and usually mild mental retardation; and a characteristic behavioral disturbance with temper tantrums and obsessive-compulsive behavior. PWS occurs in about 1/15,000 people. Since its first description in 1956, it has been apparent that many of these features arise from insufficient function of the hypothalamus, and recent identification of neurosecretory growth hormone insufficiency and temperature and sleep regulation abnormalities support this. However, no visible gross or microscopic abnormalities of the hypothalamus are seen on neuropathology. The finding of a chromosome 15q11-13 deletion in a proportion of patients with PWS by Ledbetter and colleagues in 1981 was the first window to the exciting genetic discoveries of the past decade, including recognition (initially by Butler and Palmer) that the deletion is always on the paternally-derived chromosome 15 in PWS, and the finding by Nicholls and coworkers that the vast majority of the remainder of patients had normal chromosomes but had maternal uniparental disomy (UPD). Nearly all patients with clinically typical PWS have either 15q deletion (about 75%) or maternal UPD (about 25%). This is the first human disorder that was recognized to result from uniparental disomy, and lead to many insights into imprinting.

Angelman syndrome (AS) is also an interesting disorder. Described first in 1965, and

occurring at about the same frequency as PWS, our understanding of this condition is less far advanced. It shares with PWS the presence of infantile hypotonia, mental retardation, and partial hypopigmentation. However, it has much more severe mental retardation with nearly absent speech, milder hypotonia eventually changing to hypertonia, and less systemic hypopigmentation. Affected patients exhibit, in addition, microcephaly, distinctive facies, stiff and uncoordinated movements, and a significant seizure disorder. A " happy " disposition with nearly constant smiling and frequent unprovoked bursts of laughter, as well as hyperactivity, is quite different from the sometimes aggressive and controlling behavior seen in the very verbal patients with PWS. The pattern of anomalies seen in AS was recognized among the patients who had a chromosome 15q deletion but did not have PWS, and with the advent of molecular genetic techniques it was recognized by Knoll and coworkers that in AS the deletion had occurred on the maternally-derived chromosome 15. While approximately the same percent of patients have 15q deletions in PWS and AS, only 3%-5% of patients with AS have paternal uniparental disomy. This probably reflects the differing frequencies of maternal versus paternal nondisjunction. Approximately 35% of patients with AS have neither deletion nor UPD, and it is within this group that we are likely to learn the most about the mechanisms of imprinting.

While a number of other human disorders have subsequently been recognized to occur because of the existence of genomic imprinting, it is Prader-Willi syndrome and Angelman syndrome, these two very different but equally fascinating clinical disorders, that have given us the greatest insight into the complex human consequences of imprinting.

Correspondence: S.B. Cassidy, Case Western Reserve University and the Center for Human Genetics, University Hospitals of Cleveland, Ohio, USA.