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Karl G. Sieg, M.D.

University of Kansas Medical Center

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Neurodevelopmental Disorders Associated with Chromosome 15

Karl G. Sieg, M.D.

Abstract

Chromosome 15 is a focus of increasing interest to both psychiatry and neurology. Several neurodevelopmental disorders are genetically associated with this autosome, including Prader-Willi syndrome, Angelman syndrome, Dyslexia, Autism, Hyperlexia, Ring 15 Chromosome syndrome, and Trisomy 15 syndrome. This report provides a review of the molecular biology of chromosome 15 and these associated disorders.

INTRODUCTION

Genetic research provides important information for the understanding of many disease entities. By defining an underlying genetic abnormality, a comprehensive understanding of the nature of certain disorders is possible. One particular autosome associated with a wealth of genetic research is chromosome 15. New advances in detecting chromosomal abnormalities have clearly related this autosome to several specific disorders characterized predominantly by pathologic neurodevelopment.

THE MOLECULAR BIOLOGY OF CHROMOSOME 15

Chromosome 15 is an acrocentric chromosome that comprises nearly 3% of the total human haploid genome (1). It is laden with satellite rich, heterochromatic, centromeric stalk regions which interfere with meiotic cross-over and preserve linkage groups in regions near the centromere (2). During meiosis, chromosome 15s pair like other D group chromosomes and form chiasmata in the proximal region of the long arm as well as at the telomere providing opportunities for unequal crossing over. Heterochromatic heteromorphisms are postulated to be the result of interspersed satellite DNAs composed of short repetitious sequences (3). The palindromic sequences contribute to instability of the region (4,5). The proximal long arm is thus commonly associated with translocations, small bi-satellited chromosomes (SBAs), and deletions. Addi-

Address correspondence to Dr. Sieg, Division of Child and Adolescent Psychiatry, University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS 66103.

tional research differentiates chromosome 15 from other morphologically similar acrocentric chromosomes on the basis of high levels of 5-methylcytosine-rich DNA (6). These sequences are uncharacteristically rich in adenine-thymine base pairs as highly methylated base pairs of other chromosomes are rich in guanine-cytosine base pairs. This gives chromosome 15 a unique chemical composition which accounts for its bright fluorescence after DA/DAPI staining (7). These features all likely contribute to the increased frequency of structural alterations during DNA replication.

As of 1990, 118 loci are assigned to chromosome 15, and 84 of these are regionally mapped (8). 47 are classified as genes with 37 restriction fragment length polymorphisms described in relation to the 71 DNA segments isolated from this chromosome. There is one aphidocolin-type fragile site at 15 q 22. A number of these genes are associated with specific medical disorders. The gene encoding the human cholesterol side chain cleavage enzyme cytochrome P450SSC is present (9). Abnormality of this enzyme is implicated in congenital lipid adrenal hyperplasia. A mitochondrial gene involved in electron transfer which codes for isovaleryl-CoA dehydrogenase is linked to the 15 q 14-q 15 segment (10). Deficiency of this gene is the primary lesion in glutaric aciduria type II. The alpha polypeptide of hexosaminidase A is mapped to 15 q 23-q 24 (11). Deficiencies of this enzyme result in GM2 ganglioside storage disease. Fumarylacetoacetate hydrolase deficiency is implicated in hereditary tyrosinemia (type 1), and a segment of the gene for this recessive disorder is at 15 q 23-q 25 (12). The mutation for xeroderma pigmentosa, complementation group F, is also assigned to chromosome 15 (13). Perhaps the most widely recognized gene on this chromosome is that for the Prader-Willi syndrome at the 15 q 11-q 13 region (5,14). Discussion of the chromosome 15-linked neurodevelopmental disorders begins with this complex syndrome.

PRADER-WILLI SYNDROME

The Prader Willi syndrome (PWS) consists of obesity, hypotonia, mental retardation, hypogonadism, short stature, small distal extremities and eating disturbances (15,16). Most PWS children are described as affectionate and happy until about age 3 when developmental delays become apparent in association with emotional lability and discontent (17). Mental retardation is common with the average IQ in the 50s (18). In nonmentally retarded children, learning disabilities are present (19). Particularly severe deficits occur with tasks that involve auditory information processing (20). Other data indicates some PWS children have more difficulty with arithmetic skills (21). Consequences of intellectual and learning problems include impaired social and daily living skills (21,22).

Other neuropsychiatric problems in PWS include impulsivity, aggressiveness, incessant skin picking and seizures (22,23). Adolescents develop emotional problems ranging from agitated depression to acute psychosis (22,23). Phobic behaviors and obsessive-compulsive disorders are also reported. Included in the

obsessive-compulsive characteristics of PWS are eating disturbances such as gorging and nocturnal feeding (22,23). PWS individuals demonstrate definite preferences for sweeter foods, and the strength of the food preference is directly related to the level of cognitive ability (24). The obesity can be very severe with associated abnormal glucose tolerance and frank diabetes.

Physical growth, maturational and sleep abnormalities are also prevalent. Shortness of stature contributes to disturbances of self-esteem (22,25). Primary and secondary sexual maturation delays are also detrimental to self-concept. Although a specific brain lesion has not been identified, clomiphene stimulation studies provide evidence for a hypothalamic role in PWS (26). Hypothalamic dysfunction would also explain sleep disturbances usually manifesting as excessive daytime somnolence (27,28). More recently, hypoventilation with obstructive sleep apnea leading to daytime somnolence is described (29,30). Some PWS subjects develop sleep onset rapid eye movement (REM) sleep (SOREM) which is unrelated to daytime somnolence (31). Hypothalamic dysfunction is postulated to alter the circadian rhythmicity of REM propensity leading to the appearance of SOREM. PWS characteristics such as hypotonia in association with synchronized electroencephalogram (EEG) patterns are also demonstrated in experimental hypothalamic lesions (32). Factors such as obesity and scoliosis may further complicate the growth and sleep abnormalities (33).

Oculocutaneous albinism is a PWS component resulting from a reduction of melanocytes in retinal and iris pigment epithelia of neuroepidermal origin (34). Misrouting of optic fibers with deviations 20 degrees or more at the chiasm with aberrant projections to the contralateral hemisphere are documented (35). The cortical cells do not receive normal binocular stimulation (36,37). These factors produce aberrant information in the visual cortex and lateral geniculate nucleus (38). Increased light scattering in the eye of an infant with hypopigmentation and poor visual feedback due to nystagmus aggravates strabismus (39). The melanin pigment is thus likely a prerequisite for normal development of the optic system during embryogenesis. Misrouting may be due to a timing error in ontogeny (38,40). This pigmentation defect may actually lie in the melanocyte-stimulating hormone receptors or post-receptor mechanisms involved in melanocyte-stimulating hormone action (41).

With the use of high resolution chromosome banding, various cytogenetic aberrations of PWS are identified in the 15 q 11-q 13 regions (7,14,42). More than 50% have a chromosome alteration involving these regions, most often a deletion, and less commonly a translocation. Cytogenetic findings in decreasing order of frequency in PWS include normal chromosomes, deletion 15 q 11-q 13, translocational deletion 15p and proximal 15q, balanced translocation involving 15, additional marker chromosome with resultant 15p and/or proximal 15q trisomy, tetrasomy, or pentasomy and mosaic deletion 15 q 11-q 13 (22). The failure of detection of chromosomal abnormality in 40% of PWS cases is likely due to a submicroscopic deletion or heterozygosity. Probes homologous to these regions from a fetal brain complementary DNA library indicate that the

deleted genes of this region are expressed in the brain and reflective of its normal development (43).

ANGELMAN SYNDROME

The Angelman or "Happy Puppet" syndrome is characterized by mental retardation, epilepsy, ataxia, a large mandible, protruding tongue, abnormal pigmentation, hypotonia, coarse motor movements and a euphoric disposition with paroxysms of laughter (44). General behavioral features of Angelman syndrome include psychomotor retardation and developmental delay (45). Aggressiveness, short attention span, self-stimulatory behavior, hypersensitivity to sound, speech delays and poor eye contact are prominent. Structural imaging techniques have demonstrated generalized cortical atrophy. Seizures demonstrate a peculiar, unusual EEG pattern recognized as a key diagnostic feature. This characteristic pattern includes persistent, generalized, large amplitude slow wave activity not associated with drowsiness, prolonged runs of very large amplitude rhythmic slowing often more prominent anteriorly with periodic associated ill-defined spike-wave complexes, and spikes/sharp waves mixed with large amplitude components mainly seen posteriorly and most prominent with eye closure (46).

The associated states of spontaneous laughter and euphoria are striking. Paroxysms of loud, driven laughter with associated increases in psychomotor tone are displayed for up to several minutes. One report indicates a mother remarking that the laughter "is that of a more mature child," not something expected from an infant (47). The laughter has not been directly attributed to EEG abnormalities, but it is possible that gelastic epilepsy may play some role in this affective disturbance (48). Seizure discharges in the limbic system and temporal lobe can lead to euphoric dispositions, and lesions of the hypothalamus are sometimes associated with convulsive laughter (49).

Angelman syndrome is associated with a chromosomal deletion in the 15 q 11-q 13 region in 40% of cases (50). The specificity of the deletion within this region is not clearly differentiated from that of PWS. Genetic imprinting defined as the differential modification of parental contributions to the zygote resulting in the differential expression of information inherited from parents is hypothesized in the inheritance determination of Angelman syndrome and PWS as the sex of the parent transmitting the specific deletion in chromosome 15 q 11-13 appears to have a major influence on the outcome. When the deletion occurs in the paternal chromosome, the result is PWS (51,52), while maternal transmission of the same deletion results in Angelman syndrome (53,54). The expression of a particular syndrome may not be entirely dependent on the presence of a deletion, but more importantly related to gene order and the consequent temporal expression of genes explaining why some cases lack evidence of a specific deletion (55). The presence of PWS with the lack of a deletion has also been explained by maternal heterodisomy where both copies of chromo-

some 15 are of maternal origin (56). Thus, the absence of a paternal contribution whether by deletion or uniparental disomy leads to PWS, and it is entirely possible that paternal disomy could result in Angelman syndrome. Specific mechanisms involved in genetic imprinting are correlated to the degree of gene methylation (57,58,59). It is not currently understood whether the sex-specific variations directly account for the imprinting mechanism or are merely reflective of an underlying process.

DYSLEXIA

Dyslexia is one of the most common conditions of childhood (60). Problems of dyslexic children include poor coordination, poor spatial reasoning, right-left confusion, poor temporal orientation, poor visual labelling, mixed cerebral dominance, linear tracking errors and failure to develop a leading eye (61,62,63,64). Dyslexic children often demonstrate psychiatric problems such as Attention Deficit Hyperactivity Disorder, antisocial behavior, Tourette Syndrome, affective disturbances and anxiety disorders (65,66).

Regional brain abnormalities are evident in certain dyslexics. An area on the posterior surface of the temporal lobe auditory cortex called the planum temporale has physically larger surface area on the left in 65% of normal nondyslexic subjects (67). In 25%, symmetry is apparent while 10% show asymmetry favoring the right temporal plane. The reversal of normal hemispheric asymmetry is correlated with poor verbal skills and developmental dyslexia as confirmed by MRI (68). The reversed asymmetry of dyslexic subject MRI's reflect smaller right anterior width, bilaterally smaller insular regions, and a smaller left planum temporale consistent with abnormalities in brain areas important in language (69). Dyslexics also demonstrate histopathologic abnormalities including cortical ectopias, cortical neuronal dysplasias and polymicrogyria (70). These anomalies are located primarily in the left hemisphere around the Sylvian fissure. EEG and brain electrical activity mapping (BEAM) also indicate findings that are consistent with left brain dysfunction in dyslexic subjects (71,72,73). Positron emission tomography (PET) correspondingly demonstrates hemispheric blood flow asymmetry, right flow greater than left (74).

Genetic analysis implicates chromosome 15 involvement in at least some familial reading disabilities. Linkage analysis of dyslexic subjects relates significantly to chromosome 15 short arm heteromorphisms (60,75,76). Less significant correlations exist between chromosome 15 and dyslexics with prominent visual and spatial skill deficits (dyseidetic dyslexia). The highest correlations occur with subjects who primarily manifest semantic and linguistic problems (dysphonetic dyslexia). Other data has produced no correlation between chromosome 15 and dyslexia (77). Currently, it is suggested that dyslexia is a heterogeneous disorder with at least 5 gene localizations (78). Thus, it is likely that only a subgroup of dyslexia derives from chromosome 15.

AUTISTIC DISORDERS

Autistic disorders are characterized by qualitative impairment in social interaction, verbal and nonverbal communication, and imaginative ability (79). They initially present in early childhood as disorders of delayed development which continue pervasively. Characteristics include isolation and withdrawal from emotional and social contact, severe language disability with muteness or bizarre nonfunctional language and obsessive preoccupation with certain objects or routines. Stereotyped behaviors such as rocking, flapping and clapping are also evident. Autism was initially described as an exclusively psychiatric disorder, but ongoing research is increasingly substantiating a neurologic basis leading to its redefinition as a heterogenous neuropsychiatric syndrome.

Neuroanatomical data in autistics provides glimpses of possible pathogenic mechanisms. Neurohistological studies are scant, but one report demonstrates abnormalities of the hippocampus, amygdala, and cerebellum (80). Brain imaging using pneumoencephalography shows bilateral ventriculomegaly (81) and enlargement of the left temporal horn reflecting flattening and atrophy of the hippocampus (82). Studies with computerized tomography (CT) and magnetic resonance imaging (MRI) support these findings, additionally demonstrating enlargement of the fourth ventricle, hypoplasia of the neocerebellar vermal lobules VI and VII, and forebrain, basal ganglia, brainstem and thalamic structural abnormalities, implying that anatomical aberrations are not specifically localizable in autism (83,84,85,86,87,88).

Electroencephalographic and evoked potential data also reflect abnormalities of brain function in autistic disorders. The average reported incidence of EEG abnormalities is 52% (89). These are usually diffuse abnormalities ranging from delta wave predominance to spike-wave complexes to hypersarrhythmic patterns, and these abnormalities reflect the associations of autism with epileptic disorders (90,91). Brainstem auditory evoked potentials demonstrate longer transmission times and left brain dysfunction (92,93). Auditory evoked potential P300's are abnormal, implicating processing defects in the limbic system (94,95).

Neurochemical research has focused on hyperserotonemia reported in approximately one third of autistics (96). Antibodies to serotonin receptors have been identified in autism (97), and they may play a role in aberrant synaptogenesis as serotonin inhibits neurite growth (98). Various endocrinologic and enzyme studies demonstrate nonspecific abnormalities (99,100). PET has demonstrated widespread metabolic aberrations in autistic brains consistent with impaired interaction of various brain regions (101,102).

Autism is likely caused by a multitude of factors both genetic and environmental leading to the presenting behavioral disturbances. Family studies demonstrate the incidence of autism in siblings of autistics is in excess of population rates (103,104). Twin studies are consistent with a genetic basis (105). Furthermore, cases that are discordant generally reflect a history of perinatal insult in the afflicted child implicating birth factors in the genesis of some autistic

disorders. Other medical disorders associated with autism include congenital viral or bacterial infections, meningitis, encephalitis, tuberous sclerosis, phenylketonuria, neurofibromatosis, Cornelia de Lange syndrome, histidinemia, Rett syndrome and Fragile X syndrome (106). This information reflects that autistic behavior can be the result of various insults as well as developing as a primary genetic disorder.

One of the genetic associations of autism is with chromosome 15 partial trisomy. Numerous case reports describe autistic patients with small bi-satellited derivatives of chromosome 15 (107,108,109,110,111,112). This abnormal structure has recently been postulated to derive from a replication error leading to the formation of a dicentric palindromic chromosome. Others have suggested that the structure represents an inverted duplication of regions 15 (pter-q13). Mechanisms such as parental inversion heterozygosity, translocation and U type exchange explain this hypothesis (111,113). Additional clinical features include facial dysmorphism, mental retardation, seizures, hypotonia, and strabismus. Structural brain abnormalities findings such as left temporal horn enlargement are described (114). Thus, evidence suggests at least one subgroup of autistic disorders derive from chromosome 15 partial trisomy.

HYPERLEXIA

The term hyperlexia relates to advanced reading ability without previous practice in the context of poor comprehension, expressive language deficits and poor social interactions (115). It is an ability frequently associated with autism usually identified as a savant skill (116). However, some cases do not present with autism, and it has been suggested that hyperlexia may represent an extreme form of developmental surface dyslexia (117). This postulation follows from data indicating specific comprehension inability to understand large units of meaning (118). Alternatively, hyperlexia may represent an independent brain syndrome.

Highly focused selective attention involving right hemispheric processes leading to neurological precocity is postulated to account for declarative memory enhancement with dysfunctional procedural memory (115). The neuroanatomical substrate derives from diencephalic and bitemporal brain regions. Recently, hyperlexia has been described in a PWS patient (119). Given the described associations of PWS, dyslexia and autism to chromosome 15, it is possible to speculate that hyperlexia may relate to a specific underlying genetic aberration explaining its overlapping and exclusivity with these chromosome 15 related disorders.

RING 15 CHROMOSOME SYNDROME

Individuals with ring 15 chromosome phenotypically present with growth deficiency, a triangular facies, digital anomalies, cafe au lait spots, microcephaly,

skeletal asymmetry and cardiac defects (120,121,122,123). Mental retardation in association with poor math skills and poor abstraction abilities are reported in conjunction with an observant, congenial, and euthymic affect in one patient (124). The chromosomal abnormality involves a deletion of the 15 q 26.2 to q terminal region. Ring 15 chromosome has certain phenotypic features similar to the Russell-Silver syndrome including growth deficiency, triangular facies, digital anomalies, asymmetry of growth and cafe au lait spots. In contrast, ring 15 chromosome patients are predominantly female while Russell-Silver subjects are predominantly male. Endocrinologic abnormalities such as growth hormone deficiency and hypopituitarism are more typical of the Russell-Silver syndrome (125,126). It is likely that the phenotype is caused by multiple factors which lead to a common pattern of intrauterine growth retardation. The frequency of asymmetry implies differential effects before laterality is established (127,128).

TRISOMY 15 SYNDROME

Duplication of 15 q results in a syndrome characterized by growth retardation, synophrys, down slanting palpebral fissures, beaked nose, high arched palate and low-set ears. Central nervous system features include mental retardation, seizures, hypertonicity or hypotonicity, and hyperactivity (129). Trisomy 15 falls under the category of group D chromosomopathies (130). Other features include developmental retardation, feeding difficulty, failure to thrive, apnea, and deafness. Multiple congenital defects are usually incompatible with survival, and few infants survive the first six months of life.

Cerebellar heterotopia is a frequent neuropathologic feature of trisomy 15 (131). Of the three types of heterotopic formations encountered in the cerebellum, the most distinctive is composed exclusively of primitive granule cells (132). The other heterotopias are found to a limited extent with a variety of cerebral malformations, particularly pachygyria. Two cases have demonstrated a shortened corpus callosum and absence of the olfactory tracts. Other findings include a horseshoe shaped cerebrum with the basal ganglia bulging into an unpaired ventricle roof bordered by a transparent membrane.

CONCLUSION

In reviewing chromosome 15-linked neurodevelopmental disorders, it is obvious that some are better characterized than others in terms of their relation to this chromosome and in terms of their neurobehavioral characteristics. With the recent mandate to completely map the human genome, more information regarding the nature of chromosome 15 and its derived syndromes is expected (133). Current difficulties include developing the technology to enable the project to proceed at a reasonable cost as well as perceiving the ethical and legal implications that will follow (134). One technique being developed to accelerate the mapping process uses sequence tagged sites (STSs) which may be useful in

rewriting all existing chromosome maps (135). More recently, investigators have narrowed the search for the Marfan syndrome gene to either chromosome 8 or 15 (136). With the additional advances that are expected to occur over the next decade, it is likely that a better understanding of the genetic mechanisms involved in chromosome 15-linked neurodevelopmental disorders will evolve.

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