R.C.P.U. NEWSLETTER

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Chromosome microdeletions and microduplications – New syndromes identified by new technologies.

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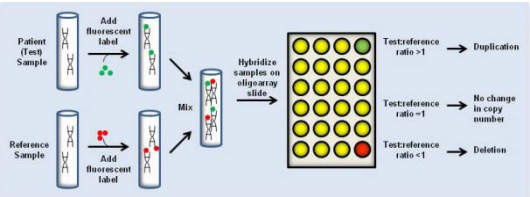
Introduction:

Array comparative genomic hybridization (array CGH) has revolutionized the cytogenetic testing available for patients with learning disabilities who have "chromosomal" phenotypes with dysmorphic features and multiple anomalies. Screening large patient cohorts with mental retardation by array CGH has recently lead to the characterization of many novel microdeletion and microduplication syndromes, initially according to the shared cytogenetic aberrations, with secondary characterization of the corresponding phenotypes. This review provides a detailed clinical and molecular cytogenetic description of several of the most common of these aberrations.

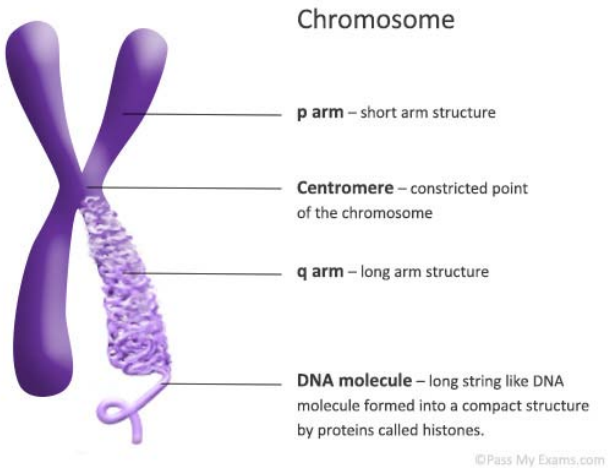
As will be noted in reading this information, the conditions resulting from these smaller deletions and duplications are not as distinctive in either physical or behavioral presentation as are the previously reported whole chromosome conditions such as Down syndrome, or larger microdeletion syndromes such as Williams syndrome, Prader Willi syndrome, or Smith Magenis syndrome. Additionally, unlike these previously reported cytogenetically visible conditions, not all individuals who present with one of these microdeletions will show any identifiable problems at all. The presence of "nonpenetrance" of phenotype in these microdeletion and microduplication conditions results in an additional layer of complexity in the provision of genetic counseling to affected families.

Figure 1: Chromosome Microarray Analysis



Larsen et al., www.intechopen.com/pdfs-wm/43450.pdf

Figure 2. Chromosome structure



1q21 deletion

The 1q21 deletion is associated with learning difficulties in approximately 75% of affected individuals. Motor skills tend to be more affected than cognitive skills and intellectual disabilities are typically in the mild range. Characteristic physical features are mild but include: prominent forehead, large rounded nasal tip, long philtrum (upper lip), high arched

palate. Other features include microcephaly (small head size), short stature, hearing loss and cataracts. Heart defects and abnormalities of the genitalia or urinary tract have also been reported. Neurological problems include hypotonia and seizures, with psychiatric and behavioral problems in a minority of patients. Autism spectrum disorder, ADHD and sleep disturbances are also frequently reported.
This deletion is frequently inherited and can be inherited from a "normal" parent. The typical size of this deletion is 1.35Mb. This typically involves 9 genes. Larger deletions are reported and result in an increased risk for cardiac and other birth defects. The deletion is inherited in approximately half of all cases. The deletion is variable in expression and parents are frequently milder than their affected children. About 1 in 4 individuals with the deletion show no overt symptoms and appear clinically asymptomatic.

1q21 duplication

The counterpart of the 1q21 deletion is the 1q21 duplication, and the phenotype is quite similar. Children with this condition present with variable intellectual disabilities and often have features of autism spectrum disorder. However, unlike the 1q21 deletion syndrome, individuals with the duplication display macrocephaly (large head size) rather than the microcephaly frequently reported in the deletion condition. Much like the deletion, the duplication is frequently inherited from a parent who may or may not express complications related to the duplication.

9q22.3 deletion

Individuals with this deletion have delays in motoric development that generally improve over time. Intellectual disabilities are present in some individuals and occasionally seizures are reported. About 20% of people with this deletion have prenatal overgrowth and this can continue into childhood. Metopic craniosynostosis has been reported and has hydrocephalus. Dysmorphic facial features include a prominent forehead, vertical skin creases, slanting palpebral fissures, long philtrum, short nose. Additionally, due to the deletion of the PTCH1 gene, individuals will have features of Gorlin (Basal Cell Nevus Syndrome). This condition results in benign tumors of the jaw (keratocysts), large head size, prominent forehead, skeletal anomalies of the spine, ribs and skull. The classic features include small pits in the skin of the palms of hands and soles of feet, large head size, increased risk for basal cell carcinoma and a risk for medulloblastoma (a childhood onset brain cancer.
The typical deletion is 352kb in size, but deletions can be much larger and have been reported to be as large as 20.5Mb. The number of genes included in the deletion is from 2 to 270 and with the variable size comes variable presentation. Features of Gorlin syndrome come about as the result of deletion of the PTCH1 gene. This gene is a tumor suppressor and deletion of one copy of this gene means that a somatic mutation in one cell in the other copy of the gene is sufficient to allow for cell proliferation and features of Gorlin syndrome.

9q34.3 deletion – Kleefstra syndrome

This condition results from deletion at chromosome 9q34.3. This condition results in intellectual disabilities with severely limited or absent speech, hypotonia, microcephaly, brachycephaly. Facial features are distinctive including: synophrys (continuous eyebrow), hypertelorism (widespaced eyes), midface hypoplasia (flattened midface), anteverted nares, prognathism with everted lips and macroglossia (large tongue).
Developmental problems described in this condition are often in the autism or autism spectrum with significantly decreased communication and social interactions. Large birth weight and childhood obesity are frequently reported. Brain anomalies, congenital heart defects, genitourinary abnormalities, seizures and respiratory infections are reported with increased frequency. Adolescents are reported to exhibit apathy and catatonia.
The gene EHMT1 has been determined to be the critical gene in this condition, and mutations in this gene are also noted to result in Kleefstra syndrome. Inheritance of the 9q34.3 is not common and this condition typically results from either a new mutation or an unbalanced chromosome anomaly.

15q13.3 deletion

The phenotype of this deletion is highly variable and individuals frequently have this deletion without identifiable phenotype. Approximately half of individuals will express intellectual deficiency that is of mild to moderate degree. Speech and language skills are frequently affected, and

seizures are the most major medical complication associated with the deletion with about 1/3 of individuals with the deletion having reported seizures or epilepsy. Psychiatric and behavioral problems including: schizophrenia, ADHD, impulsivity, aggression and hyperactivity have been reported. In the minority of affected individuals, heart defects and dysmorphic features have been reported.
The incidence of the 15q13.3 deletion is estimated to be 1 in 40,000 individuals. The deletion occurs much more frequently in individuals with epilepsy, schizophrenia or autism spectrum disorder. The typical deletion is 2Mb. The microdeletion is inherited in about 75% of individuals, and this may be either from an affected or non-affected parent.

15q24 deletion

This deletion is quite variable in size from 1.7-6.1Mb although there is a common 1.2Mb deletion present in all individuals. It is associated with mild-moderate intellectual disability and delayed speech development. Other features include short stature, hypotonia, hyperextensible joints. Males can have micropenis and distinctive facial features include: high front hairline, broad eyebrows, widely spaced eyes, downslanting palpebral fissures (eyelids), broad nasal bridge, full lower lip, smooth phitrum (upper lip).
This deletion has not been reported to be inherited from a parent, and there have been no major gene effect identified for this condition.

16p11.2 deletion

One of the most significant conditions identified by the new technology of chromosome microarray studies is the 16p11.2 microdeletion and microduplication syndromes. The deletion condition is typically associated with intellectual disabilities and frequently with behaviors in the autism spectrum. It is characterized by more significant expressive delays than receptive delays and impairs communication and socialization skills. Although initially there were distinctive physical features reported to be associated with this condition, it is currently felt that there is not a distinctive appearance of the 16p11.2 deletion.
The microdeletion typically deletes about 600kb of genetic information that comprises about 25 genes. It is uncertain which gene(s) plays the most significant role in the phenotype associated with the deletion.
The 16p11.2 deletion is frequently inherited and can come from either parent. Interestingly, many individuals who carry the deletion do not display the developmental concerns that have been linked to this deletion. It has been suggested that the microdeletion itself is not sufficient to cause developmental concerns and that there must be an additional factor to trigger developmental issues.

17p11.2 duplication – Potocki Lupski syndrome

This condition is the counterpart of a much better known condition, the 17p11.2 deletion or Smith Magenis syndrome. Despite the relative frequency of SMS, Potocki Lupski syndrome is less frequent and is estimated to occur in approximately 1 in 20,000 individuals. Although the size of the duplication is variable, the typical duplication is of 3.7Mb in size.
Some manifestations of this condition are similar to those seen in SMS, and 80% of children display intellectual disabilities and autism spectrum disorder. Heart defects, sleep apnea, short stature and failure to thrive are reported in this condition.

17q11.2 duplication

There is significant variation between individuals reported with this duplication. Facial features reported include: microcephaly, long midface with thin upper lip, sparse eyebrows and premature baldness. Intellectual disabilities are also widely variable.
The significant gene in this region is the Neurofibromin gene that results in Neurofibromatosis type 1 when either deleted or mutated.

Deletion 17q21.31 – Koolen de Vries syndrome

This condition imparts mild-moderate intellectual deficiency and is often associated with a cheerful, sociable affect. Children present with hypotonia and about 50% will have a seizure disorder. Characteristic facial features are reported in this condition and include: blepharophimosis (narrow eye openings), ptosis (drooping eyelids), high forehead, upward slanting palpebral fissures (eyelids), bulbous nose and prominent ears. Males often have cryptorchidism (undescended testicles), and heart, kidney and skeletal anomalies are also frequently described.
The incidence of this deletion is reported to be 1 in 16,000 although it is felt to likely be underdiagnosed. The deletion is typically 500kb in size and the major gene in this condition is the KANSL1 gene. The microdeletion is typically not inherited. However, frequently one of the parents is a carrier for a 900kb inversion on chromosome 17 that is seen in approximately 20% of individuals of European and middle Eastern descent. This inversion is known as the H2 lineage and does not convey any medical concerns but may predispose to an increased risk for the 17q21.31 deletion in offspring.

Resources for families:

Although there are specific support groups and informational resources for some of these conditions, the main resource for families seeking information about their chromosome abnormality is the Chromosome Deletion Outreach.

Chromosome Deletion Outreach
PO Box 724
Boca Raton, FL 33429-0724
Helpline: (561)395-4252

www.info@chromosomedisorder.org

About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent

of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate intellectual disabilities through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of intellectual disabilities. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

Acknowledgments:

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