R.C.P.U. NEWSLETTER

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R.C. Philips Research and Education Unit

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An Update on Down Syndrome

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Introduction:

Down syndrome, also known as trisomy 21, is familiar to most individuals in the medical community and the general public. Approximately one in 700 babies are born with Down syndrome in the United States every year, making it the most common chromosome abnormality identified in humans. This article provides general information about Down syndrome and updates readers on recent advances and ongoing research in the field.

Down syndrome was named after an English physician, John Langdon Down, who in 1866 published the first description of Down syndrome as a distinct condition. Dr. Jerome Lejeune was the first to identify Down syndrome as caused by an abnormality in chromosomes in 1959. In 2000, the 329 genes on chromosome 21 were identified and catalogued by an international team of scientists.

Figure 1: Facial features in a child with Down syndrome. Source: CDC - https://www.cdc.gov/ncbddd/birthdefects/downsyndrome.html

Down Syndrome in Children:

The features of Down syndrome are well-recognized – a flat appearance to the face, an upward slant to the eyes, short neck, small ears, small hands and feet, a single crease on the palms of the hand, low muscle tone (hypotonia), and intellectual disability, amongst other characteristics. Children with Down syndrome are at an increased risk for several medical complications including heart defects and gastrointestinal abnormalities present at birth, hearing loss, vision problems, hypothyroidism, celiac disease, and obstructive sleep apnea. Children with Down syndrome also have a small increase in risk of developing leukemia in childhood. It is important to monitor for conditions that occur more frequently among children with Down syndrome, and for this reason, the American Academy of Pediatrics has developed guidelines for health supervision for children with Down syndrome. This allows pediatric healthcare providers to know what testing to be performed at what ages so that these conditions can be identified early and treated appropriately. http://pediatrics.aappublications.org/content/128/2/393 For example, since nearly half of babies with Down syndrome are born with a congenital heart defect, such as an atrioventricular canal, an echocardiogram is recommended for all newborns diagnosed with Down syndrome so that these babies can be treated with medications or surgery as needed.

Children with Down syndrome also have varying degrees of cognitive impairment. Prompt referral to early intervention services (Early Steps in Florida) http://www.floridahealth.gov/alternatesites/cms-kids/families/early_steps/early_steps.html is recommended so that children with Down syndrome can reach their full potential.

Down Syndrome in Adults:

Life expectancy of persons with Down syndrome has increased substantially in recent years. Whereas the average age at death for persons with Down syndrome in 1983 was 25 years, life expectancy is now into the 60s. We are learning more about what to expect in adulthood as persons with Down syndrome age. Adults with Down syndrome are at risk for certain medical problems including early onset of cataracts, conductive hearing loss, hypothyroidism, obstructive sleep apnea, early onset of Alzheimer disease, and increased risk for mental health disorders, such as depression and obsessive-compulsive disorders. Persons with Down syndrome develop Alzheimer disease up to two decades earlier than is typically seen in persons who do not have Down syndrome. http://www.ndss.org/wp-content/uploads/2017/11/Aging-and-Down-Syndrome.pdf It appears that genes on chromosome 21 predispose persons to an earlier onset of Alzheimer disease. Better understanding of these genes could lead to preventive and therapeutic options for persons with Alzheimer disease, both with and without Down syndrome.

While many studies have focused on conditions for which persons with Down syndrome are at increased risk, some conditions are less likely amongst individuals with Down syndrome. Several studies in recent years have suggested that persons with Down syndrome are at a lower risk of developing solid tumors, such as breast, prostate, and colon cancer. This suggests that a gene or genes on chromosome

21 might lead to a decreased risk of these common cancers, and studies in mice have identified a gene that may be responsible.(Sussan et al., 2008)

Genetics:

Down syndrome results from having three copies of the genetic material on chromosome 21, rather than two copies, and this can occur in three ways: Trisomy 21, translocation Down syndrome, and mosaic Down syndrome. Chromosome analysis (or a karyotype) is needed to identify which type of Down syndrome an individual patient has. Trisomy 21, the most common type of Down syndrome, is due to an error in the formation of the sperm or egg (called nondisjunction) that results in the presence of an extra chromosome. The risk for a nondisjunctional event increases with maternal age. A 35-year-old woman has a 1/350 chance of having a child with Down syndrome, and that risk increases to 1/30 in mothers at 45 years of age. Translocation Down syndrome occurs when a full or partial extra copy of chromosome 21 attaches to another chromosome, usually chromosome 14. This form can be inherited from a parent who has a balanced translocation, but does not have Down syndrome. Thus, when a child is identified as having Down syndrome due to a translocation, it is important that chromosome analysis is performed on his or her parents to determine the risk of recurrence. In mosaic Down syndrome, children have some cells in their bodies with three copies of chromosome 21 and other cells with the typical number (two) of chromosome 21s. Children with mosaic Down syndrome might have more mild features of the condition, given that not all cells have an extra chromosome, although in most cases, children with mosaic Down syndrome cannot be distinguished from Trisomy 21 without chromosome analysis.

Prenatal Diagnosis and Screening:

Prenatal diagnosis (amniocentesis) for Down syndrome first became available in the 1970s. Amniocentesis is conducted in the second trimester of pregnancy; a needle in inserted through a pregnant woman's abdomen into the uterus to obtain a sample of the amniotic fluid that surrounds the fetus. The amniotic fluid contains cells from the fetus that can be tested to determine if the fetus had Down syndrome. Amniocentesis remains the primary method for prenatal ***diagnosis*** of Down syndrome. However, because amniocentesis introduces a small risk of miscarriage, screening tests (tests that identify pregnancies at increased risk for having Down syndrome) have become available. Testing for certain markers in a pregnant woman's blood can be combined with information on the mother's age with fetal ultrasound looking at the thickness of the back of the neck (nuchal folds) of the fetus to provide an estimate of the risk for Down syndrome in a particular pregnancy.

In recent years, another screening test (noninvasive prenatal screening using cell-free DNA) has become available. This test, performed at around 9-10 weeks of pregnancy, looks at fragments of genetic material circulating in the mother's blood. This material

originates from the placenta, the tissue that connects the blood supplies of the mother and the fetus. This genetic material can be used to screen a pregnancy for Down syndrome and other chromosome abnormalities. While the accuracy of this screening test for Down syndrome is higher than that for other screening tests, it remains a ***screening*** test, with both false negatives and false positive results. A positive noninvasive prenatal screening test needs to be confirmed with a diagnostic test for Down syndrome (that is, amniocentesis during pregnancy or testing the baby's blood after birth).

National Institutes of Health's (NIH's) INCLUDE Initiative

In June of 2018, the National Institutes of Health (NIH) launched the INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to understand Down syndromE) Project. This project focuses on understanding critical health and quality-of-life needs for individuals with Down syndrome. The project has three parts: (1) to conduct high-risk, high-reward basic science studies on chromosome 21, (2) to assemble a large study population of persons with Down syndrome (a cohort) that can be followed over time, and (3) include persons with Down syndrome in clinical trials that address conditions that are common in Down syndrome. The NIH has committed $22.2 million for the INCLUDE project in 2018, with further support expected in future years.

Selected Resources:

- American Academy of Pediatrics: http://pediatrics.aappublications.org/content/128/2/393
- Centers for Disease Control and Prevention: https://www.cdc.gov/ncbddd/birthdefects/downsyndrome.html
- Down Syndrome: Health Issues http://www.ds-health.com/
- Global Down Syndrome Foundation: www.globaldownsyndrome.org
- Lettercase Resources: http://understandingdownsyndrome.org/
- National Down Syndrome Society: https://www.ndss.org/
- National Down Syndrome Congress: https://www.ndsccenter.org/
- National Institutes of Health: https://www.nih.gov/include-project

References:

ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med 2013;15(5), 395-398.

American Academy of Pediatrics. Health supervision for children with Down syndrome. Pediatrics. 2011;128(2):393-406.

Ballart C, Mobely W, Hardy J, Williams G, Corbett A. (2016). Dementia in Down's Syndrome. Lancet 2016;15, 622-636.

Hasle H, Friedman JM, Olsen JH, Rasmussen SA. Low risk of solid tumors in persons with Down syndrome. Genet Med.

2016;18(11):1151-1157.

Sussan TE, Yang A, Li F, Ostrowski MC, Reeves RH. Trisomy represses Apc(Min)-mediated tumours in mouse models of Down's syndrome. Nature. 2008; 451(7174):73-5.

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 mental retardation 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 mental retardation. Staff members are available for consultation and for educational programs for health.

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