Down Syndrome

Original description was by J. Langdon Down in 1886. Trisomy 21 was first reported in association with Down syndrome (DS) by Jérôme Lejeune and colleagues in 1959.

Incidence/prevalence
About 1 in 800 live born children have DS. The incidence increases with increasing maternal age, being about 1 in 1400 at maternal age 25 and 1 in 30 at maternal age 45.

Genetics
The presence of a complete or partial third copy of human chromosome 21 (Hsa21) is the cause of DS. Partial copy should include all or part of the long arm of Hsa21.This excess of genetic material leads to a dysregulated expression of certain genes. The functional impact of these changes could be a direct result of the action of the proteins expressed in excess by the Hsa21 genes, or indirectly, through the proteins that they regulate. In any case the effect will be different according to the protein involved (Fillat,2014). The nuclear compartments of trisomic cells undergo modifications of the chromatin environment influencing the overall transcriptome, and gene expression dysregulation domains may therefore contribute to some trisomy 21 phenotypes (Letourneau, 2014).

More than 450 genes have been identified on human chromosome 21. The development of new mouse models, either trisomic for different chromosome segments or for individual genes, has helped narrow the focus to those genes likely to be important contributors to the DS phenotype. Of particular interest are the findings relating to 2 genes located within the putative DS critical region of chromosome 21. These are dual-specificity tyrosine-regulated protein kinase 1 (DYRK1A) and DSCR1.

DYRK1A is particularly expressed in the hippocampus, cortex,cerebellum, and heart—regions affected in DS and overexpressed in fetal DS. Transgenic mice that overexpress DYRK1A show learning and memory deficits. Further, DYRK1A phosphorylates tau protein, and this change is known to be important in initiating the cascade of processes leading to amyloid formation in Alzheimer dementia.

DSCR1 is overexpressed in Alzheimer patients and causes abnormalities in synapse function in DS individuals. DYRK1A and DSCR1 act synergistically to regulate the transcription factor NFATc, which plays a critical role in the development of the central nervous system (Einfeld 2010).

The origin of supernumerary Hsa21 in free trisomy is in most cases the maternal meiosis. The risk of recurrence (not allowing for maternal age) is low. About 2% of DS results from an unbalanced translocation (material from one chromosome breaking off and "sticking to" another). This often involves chromosomes 21 and 14, and is usually a "one-off" event. In some cases a parent also has a (balanced) translocation (with no overall disruption of genetic material), and the risk of recurrence is high. 21 to 21 translocations also occur. Mosaicism is a term used to describe the presence of two (or more) cell lines within the body. In DS this means one cell line with trisomy 21 and one unaffected cell line. About 3% of DS probably results from mosaicism (many cases may not be diagnosed). The proportion of affected and

unaffected cell lines varies, as does the intellectual impairment. Transient myeloproliferative disorder and megakaryoblastic leukemia of DS are associated with mutations in the GATA1 gene in conjunction with trisomy 21.

Physical features

Two types of phenotypes are observed in trisomy 21: those seen in every patient and those that occur only in a fraction of affected individuals. For example, cognitive impairment is present in all patients with DS, so as muscle hypotonia and Alzheimer disease neuropathology after 35 years (Antonarakis,2004). Motor dysfunction is highly prevalent among individuals with DS, who exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierrsen 2012) On the contrary, congenital heart defect occurs only in ~40% and atrioventricular canal in ~16% of patients. Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, insulin dependent diabetes mellitus, celiac disease and alopecia areata. On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of most solid tumors, which are rarely reported in association with DS.

Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45%. Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms. People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence). Ninety percent of all DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44-71%) are common in DS of advanced age, and in a large percentage of the general population.

Obstructive sleep apnea occurs in over half of children with DS aged 2–4years and is related to otolaryngological problems associated with the disorder and to the atlantoccipital instability.

Life expectancy has improved markedly over the past 50 years, largely as a result of antibiotic treatment of respiratory tract infections. Survival into the 8th decade is unusual but not extraordinary. The presence of an AVSD often leads to heart and lung failure in early adult life. Although changes in blood cells are relatively common, leukaemia is not particularly common (affecting about 1%).

Behavioural characteristics

Fewer behavior problems compared to controls with cognitive disability have been described in DS but more frequent than in sibling or in controls with normal IQ. Children with DS may be at a lower risk for significant behavioral comorbidities in that they show a lower profile of maladaptive behaviors compared to children with other intellectual disabilities. However, in comparison to typically developing age-matched peers, children with DS show higher rates of inattention, oppositional behaviors, and impulsivity-(Dykens,2007.)

Seventeen six % of individuals with DS aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6·1%), conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%). Twenty five % of adults with DS present a psychiatric disorder, most frequently a major depressive disorder

(6·1%) or aggressive behaviour (6·1%).The dual diagnoses of DS and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7% and great delays in diagnosis. The stereotype of people with DS as happy, placid individuals with a gift for mimicry is not borne out by recent behavioural research. "Stubbornness" and obsessional features seem to be over-represented, and many people with DS react adversely in situations involving conflict.

No significant associations between age and the range or severity of any behavioural and emotional items were found in adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS than has been previously described (Makary 2014).

Cognitive characteristics

Cognitive disability is present in all patients with DS. Most children and adults with DS function in the mild or moderate range of intellectual disability. About 10% have a low average-borderline degree of intellectual disability. A minority have a severe or profound cognitive impairment. In DS patients, the average IQ score is around 50, with individual values ranging from 30 to 70 (Rachidi, 2007).

Almost all children with DS have a relatively specific expressive language impairment. Expressive language deficit in syntax is greater than expressive language deficit in the lexicon. Comprehension of words is typically more advanced than nonverbal cognition. Cognition deficits in verbal working-memory and delayed recall has been described.

Cognitive abilities tend to be greater among people whose DS is caused by mosaicism for trisomy 21.

In adults with DS, neuropathological changes typical of Alzheimer's disease usually develop by the fifth decade of life. Adults with DS are much more likely to develop dementia of Alzheimer type than the general population. On post-mortem examination, almost all adults with DS over the age of 35 have the brain changes characteristic of Alzheimer's disease but only about 45% of those over 45 years of age have clinically apparent dementia. The triplication of the amyloid precursor protein gene (APP) is a candidate for causing dementia in DS. However, additional Hsa21 genes may modulate the effects of APP triplication (Dierssen 2012).

Clinical signs and symptoms of Alzheimer's disease are noted in 75% of DS individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%). Seizures appear to be associated with rapid cognitive decline in demented individuals with DS. In any adult for whom the diagnosis of Alzheimer's disease is being considered, a complete medical assessment should be done to detect any treatable disorders such as thyroid disease or depression.

Updated by Annapia Verri, September 2014

References and suggested reading

Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S. (2004) Chromosome 21 and Down syndrome: from genomics to pathophysiology. Nat Rev Genet. 5(10):725-38.

Arque G, Casanovas A, Dierssen M (2013)Dyrk1A Is Dynamically Expressed on Subsets of Motor Neurons and in the Neuromuscular Junction: Possible Role in Down Syndrome PLoS One. 8(1):e54285

Block A, Dhanasekaran AR, Ahmed MM, Gardiner KJ. (2014)Abnormal Protein Profiles in Hippocampus of Mouse Models of Down Syndrome: Similarities with Alzheimer's Disease. J Alzheimers Dis Parkinsonism 4: 138.

Chapman RS, Hesketh LJ. (2000) Behavioral phenotype of individuals with Down syndrome. Ment Retard Dev Disabil Res Rev.;6(2):84-95.

Dierssen M. (2012) Down syndrome: the brain in trisomic mode. Nat Rev Neurosci.:844-58.

Dykens EM (2007) Psychiatric and behavioral disorders in persons with Down syndrome Ment. Retard. Dev. Disabil. Res. Rev., 13: 272–278

Einfeld SL, Brown R (2010) Down Syndrome—New Prospects for an Ancient Disorder JAMA 303(24):2525-2526

Epstein C. Down Syndrome1(1995) In: Scriver CR, Beaudet AL Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill 749-94.

Farriols Danés C (2012). Specific aspects of ageing in Down's syndrome. Rev Med Int Sindr Down. 16(1):3-10

Fillat C, Bofill-De Ros X., Santos M., Martín ED, Andreu N, Villanueva E, d'Amico D, Dierssen M, Altafaj X (2014) Identification of key genes involved in Down's syndrome pathogenesis by gene therapy. Rev Med Int Sindr Down 18(2):21-8

Gardiner K, Davisson MT, Pritchard M, Patterson D, Groner Y, Crnic LS,Antonarakis S, Mobley W (2005) Report on the 'Expert Workshop on the Biology of Chromosome 21: towards gene-phenotype correlations in Down syndrome', held June 11-14, 2004, Washington D.C. Cytogenet Genome Res.108(4):269-77.

Letourneau A,Santoni FA,Bonilla X, Sailani MR, Gonzalez D, Kind J, Chevalier C, Thurman R, Sandstrom RS, Hibaoui Y, Garieri M, Popadin K, , Falconnet E, Gagnebin M, Gehrig C, Vannier A, Guipponi M, Farinelli L, Robyr D, Migliavacca E, Borel C, Deutsch S, Feki A, Stamatoyannopoulos J A, Herault Y, van Steensel B, Guigo R & Antonarakis SE. (2014) Domains of genome-wide gene expression dysregulation in Down's syndrome. Nature 508 (7496):345-50

Lott IT (2012) Neurological phenotypes for Down syndrome across the life span. Prog Brain Res. 97: 101–121.

Makary A, Testa R, Einfeld SL, Tonge BJ, Mohr C, Gray KM (2014) The association between behavioural and emotional problems and age in adults with Down syndrome without dementia: Examining a wide spectrum of behavioural and emotional problems. Res Dev Disabil. 35(8):1868-77

Neri G, Opitz JM. (2009) Down syndrome: Comments and reflections on the 50th anniversary of Lejeune's discovery. Am J Med Genet Part A 149A:2647–2654

Nespoli L, Burgio GR, Ugazio AG, Maccario R (1993) Immunological features of Down's syndrome: a review. J Intellect Disabil Res. 37,543-51.

Oliver C, Crayton L, Holland AJ, Hall S. (2000). Acquired cognitive impairments in adults with Down syndrome: Effects on the individual, carers and services. AJMR, 105, 455-465.

Patterson D, Costa AC (2005) Down syndrome and genetics - a case of linked histories. Nat Rev Genet 6(2):137-47.

Rachidi M, Lopes C. (2007) Mental retardation in Down syndrome: from gene dosage imbalance to molecular and cellular mechanisms.Neurosci Res. 2007 Dec;59(4):349-69

Roizen NJ, Patterson D. (2003) Down's syndrome. Lancet 361(9365):1281-9

Ronan A,Fagan K, Christie L, Conroy J, Nowak NJ, Turner G.(2007) Familial 4.3 Mb duplication of 21q22 sheds new light on the Down syndrome critical region. J Med Genet.44(7):448-51

Shapiro BL (1994) The environmental basis of the Down Syndrome Phenotype. Developmental Medicine and Child Neurology, 36, 84-90.
