Down Syndrome

Originally described by John Langdon Down in 1866 (Down, 1866),Trisomy 21 was first reported in association with Down syndrome (DS) by Jérôme Lejeune, Raymond Turpin and Marthe Gautier in 1959 (1959).

Epidemiology

Incidence varies globally, in part due to choices surrounding prenatal testing. In the USA, 1 in approximately 800 live born children will have DS (de Graaf, Buckley, & Skotko, 2015). Ireland has the highest incidence in Europe (1 in 546 live births) (Ni She & Filan, 2014), In England and Wales, approximately 1 in 1000 live born children have DS (Wu & Morris, 2013) however in Iceland, no infants with DS have been born during a five year period (Wise, 2016).

The likelihood of having a child with DS increases with increasing maternal age: mothers aged 40 are 16 times more likely to have an affected pregnancy than mothers aged 25 (Wu & Morris, 2013).

Life expectancy has increased dramatically over the past 50 years, now reaching approximately 60 years of age (Englund, Jonsson, Zander, Gustafsson, & Annerén, 2013). While rare, it is not unheard of for some individuals to live past the age of 70. This means the numbers of individuals with DS are increasing, despite prenatal testing.

Genetics

DS is caused by a third copy of human chromosome 21 (Hsa21) (Lejeune et al., 1959). This is typically a full or partial trisomy of Hsa21, however translocation whereby a section of Hsa21 has attached to another chromosome (most commonly the long arm of Hsa21 to Hsa14 or Hsa22) or mosaicism, in which the third copy of Hsa21 is present in some, but not all of an individual's cells, account for around 4% and 1.3-5% of the DS population respectively (Flores-Ramírez et al., 2015; Morris, Alberman, Mutton, & Jacobs, 2012; Papavassiliou, Charalsawadi, Rafferty, & Jackson-Cook, 2015).

This excess of genetic material leads to a dysregulated expression of certain genes (Letourneau et al., 2014). 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 et al., 2014). The nuclear compartments of trisomic cells may also undergo modifications of the chromatin environment influencing the overall transcriptome (Letourneau et al., 2014).

230 coding, and 404 non-coding genes have been identified on Hsa21 (Ensembl, 2018). It remains a subject of on-going research whether DS specific phenotypes and disease susceptibility are the result of general dysregulation of the genome caused by the presence of aneuploidy, or whether they are related to gene-specific over expression. Some diseases, such as early onset Alzheimer's disease (AD), appear directly linked to the presence of an additional copy of a gene, in this case APP. Duplication of the *APP* gene in the absence of DS is known

to be sufficient to cause early onset AD (Sleegers et al., 2006). However, in mouse models it has been shown that triplication of other Hsa21 genes may also increase amyloid deposition (Wiseman et al., 2015, 2018).

The development of mouse models and induced pluripotent stem cells (iPSCs) has helped to shed light on the role of specific genes on chromosome 21 and their contribution to the DS phenotype. Models are used to show whether specific genes are necessary and sufficient to cause a certain phenotype.

Genes that have been identified which appear to contribute to the DS phenotype include dual specificity tyrosine-regulated protein kinase 1 (*DYRK1A*), *DSCR1*, *BACE 2* and *GATA 1*:

- *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 AD. When this over-expression is reduced in these mice, amyloid-beta and tau levels are reduced, as is cholinergic neurodegeneration (García-Cerro, Rueda, Vidal, Lantigua, & Martínez-Cué, 2017)
- *DSCR1* is overexpressed in AD 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 & Brown, 2010).
- *BACE 2* expression has been linked in some studies to the development of AD and age of onset in the DS population, although results have been inconsistent (Mok et al., 2014).
- Mutations in the *GATA1* gene have been associated with the development of transient myeloproliferative disorder and megakaryoblastic leukemia of DS in conjunction with trisomy 21 (Groet et al., 2003).

Physical and Mental Health

There is considerable variation in the penetrance of the phenotype associated with trisomy 21, however certain characteristics are more common. For example, intellectual disability is present to some degree in all patients with full trisomy 21, as is muscle hypotonia and AD neuropathology after the age of 35 years (Antonarakis, Lyle, Dermitzakis, Reymond, & Deutsch, 2004). Motor dysfunction is highly prevalent among individuals with DS, who can 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 (Dierssen, 2012). 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% of children with DS. 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.

Many DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44-71%) and cataracts are common in DS individuals of advanced age.

Obstructive sleep apnea is common in DS, and is increasingly being recognised as a cause of morbidity in this population. Prevalence is currently estimated between 54-90% (Simpson, Oyekan, Ehsan, & Ingram, 2018). Symptoms include loud snoring, heavy breathing, restless

nights and daytime sleepiness, as well as neurocognitive symptoms such as irritability, depression, paranoia, cognitive decline and behavioral problems.

About half of people born with DS have congenital heart defects (CHD), most commonly atrioventricular septal defect (42% of CHD in DS), ventricular septal defect (22%), and atrial septal defect (16%) (Bergström et al., 2016).

Epilepsy is present in 8% of children with DS, with a bimodal age of onset. One peak is before the age of 3 years, and the other occurs after the age of 30 (Roizen & Patterson, 2003). Infant onset has been associated with West Syndrome. Onset of epilepsy later in life is linked to the development of Alzheimer's disease (Gholipour, Mitchell, Sarkis, & Chemali, 2017).

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 (Alexander et al., 2016; Bittles, Bower, Hussain, & Glasson, 2007; Glasson, Dye, & Bittles, 2014). People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence).

People with DS have increased incidence of behavioural and mental health problems compared to the general population (Tassé et al., 2016). Depressive and anxiety disorders appear to be more prevalent . A small subgroup of adolescents and young adults with DS are observed to undergo acute regression, which has also been termed Down Syndrome Disintegrative Disorder, with loss of skills and independence compared to their previous levels of functioning. At present the cause of this decline is unknown, although often the decline appears to occur after exposure to emotional stressors (Mircher et al., 2017).

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.

Behavioural characteristics

DS is the most common genetic cause of intellectual disability with the majority of individuals with this syndrome classified in the mild – moderate range. Their cognitive profile demonstrates strengths in visual learning, but relative weaknesses in expressive language, verbal working memory, and episodic memory (Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). However, there is a wide range of cognitive function with variations in IQ, language, attention, memory and functional abilities (Karmiloff-Smith et al., 2016).

Fewer behavior problems compared to controls with cognitive disability have been described in DS but are 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).

People with DS may present with autism spectrum disorder (~10-15%) and attention deficit hyperactive disorder (ADHD ~6%). Clinical presentations may differ from the general population

and assessments may require input from specialists. They may also present with conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%).The stereotype of people with DS as happy, placid individuals with a gift for mimicry is therefore not always borne out by 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 until symptoms of dementia develop (Makary et al., 2014).

Cognitive characteristics

Intellectual disability (ID) is present in almost all patients with DS, but with individual ability varying widely, from borderline to profound ID (Karmiloff-Smith et al., 2016).

Most children and adults with DS function in the mild or moderate range, and cognitive abilities tend to be higher among people with mosaicism (Papavassiliou et al., 2015).

Early language milestones, such as babbling, are typically met within a similar period to typically developing infants. However, by school age a specific impairment in expressive language is evident in relation to most individuals' receptive language abilities (Grieco et al., 2015). Difficulties in syntax expression and comprehension are common throughout the lifespan, and verbal working memory is a noted weakness.

Visuo-spatial skills have historically been postited as a comparative strength for indivduals with DS, particularly in comparison to general verbal abilities and verbal memory, which is a particular weakness. However by compiling results from multiple studies, a more nuanced picture is seen. While spatial sequential memory skills are in line with general abilities, individuals with DS may show specific difficulties in wayfinding and spatial working memory (Yang, Conners, & Merrill, 2014).

Deficits in attention and executive functioning are seen at all ages. Individuals with DS show particular difficulties with inhibition but in terms of planning, for example, may take longer than mental-age matched controls, but can achieve similar levels of performance (Grieco et al., 2015).

There is increasing evidence that obstructive sleep apnoea, and disrupted sleep in general, may contribute to some of the cognitive problems in DS (Breslin et al., 2014; Chen, Spanò, & Edgin, 2013; Esbensen & Hoffman, 2018).

Alzheimer's disease and dementia

In adults with DS, neuropathological changes typical of Alzheimer's disease usually develop by the fourth decade of life, and dementia is now considered to be the leading underlying cause of death in older adults with DS (Hithersay et al., 2018). On post-mortem examination, almost all adults with DS over the age of 35 have the brain changes characteristic of Alzheimer's disease (i.e. amyloid plaques and neurofibrillary tangles) (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985).

Adults with DS are much more likely to develop dementia of Alzheimer type than the general population, with cumulative risk estimated to be in excess of 80% by age 65 (McCarron et al., 2017). However, age of dementia onset shows considerable variability. The average age of dementia diagnosis is typically in the mid-50's, yet a small number of individuals are reported to show decline before the age of 40, and several individuals live in to their 60's with their cognitive abiltiies relatively well preserved (Hithersay et al., 2018; Sinai et al., 2018). Further research concerning the factors that drive such variability is required, however it has been shown that earlier diagnoses are seen in those with early-onset epilepsy, and multiple health-comorbidities (Hithersay et al., 2018), and for women with DS, earlier dementia onset is associated with earlier menopause (Coppus et al., 2010).

While there is a clear association with *APP* and AD in DS (see above), non-chromosome 21 genes that are known to influence AD-onset in the non-DS populations, such at *APOE*, assert a similar influence in DS (Hithersay et al., 2018; Lai et al., 1999). Further, mouse-model studies have confirmed that triplication of genes on Hsa21 increase amyloid-beta deposition and cognitive deficits independently of *APP* (Wiseman et al., 2018).

Clinical signs and symptoms of AD in DS include early changes in memory and attention (Firth et al., 2018; Startin et al., 2019). Executive functioning, behavioural and personality changes may also be seen (Ball et al., 2006; Dekker et al., 2015; Lautarescu, Holland, & Zaman, 2017).

Baseline cognitive assessments are essential for tracking subtle changes in cognition at the earliest stages. Direct cognitive assessments are able to detect change before caregivers may be aware of any decline (Startin et al., 2019).

As dementia advances, neurological features become more apparent, with incontinence and Parkinsonian traits commonly seen (Strydom et al., 2010). Late-onset seizures develop in more than 40% of individuals with DS and AD, with seizures starting a median of 2-years after dementia diagnosis. Seizure development is associated with more rapid cognitive decline. In later stages, individuals will lose their ability to walk and talk and eventually become unresponsive.

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.

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