SSBP Syndrome Sheets

Down Syndrome

Originally described by John Langdon Down in 1866 (Down, 1866),Trisomy 21 was first reported in association with Down syndrome by Jérôme Lejeune, Raymond Turpin and Marthe Gautier in 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 Down syndrome (de Graaf, Buckley, & Skotko, 2015). In Europe there are an estimated 419,000 people with Down syndrome, as of 2015 (de Graaf, Buckley, Skoto, 2021). 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 Down syndome (Wu & Morris, 2013) however in Iceland, no infants with Down syndrome have been born during a five year period (Wise, 2016). In India approximately 21,000 babies are born with Down syndrome each year (Verma 2002).

The likelihood of having a child with Down syndrome 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 (Wiseman et al 2015; Coppus 2017). While rare, it is not unheard of for some individuals to live past the age of 70.

Genetics

Down syndrome is caused by a triplicationopy of human chromosome 21 (Hsa21) (Lejeune et al., 1959). This is typically a full or partial trisomy of Hsa21. In approximately 4% of individuals, Robertsonian translocation of the long arm of Hsa21(generally to Hsa14 or Hsa22) causes Down syndrome. Mosaicism, in which the third copy of Hsa21 is present in some, but not all of an individual's cells, accounts for between 1.3-5%.(Flores-Ramírez et al., 2015; Morris, Alberman, Mutton, & Jacobs, 2012; Papavassiliou, Charalsawadi, Rafferty, & Jackson-Cook, 2015).

Excess of genetic material leads to 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) and downstream stress-effects stemming from an inbalanced genome are reported (Li, Zhu, 2022).

221 coding, and 447 non-coding genes have been identified on Hsa21 (Ensembl, 2023). It remains a subject of on-going research whether the features and conditions associated with Down syndrome are the result of general dysregulation of the genome caused by the presence of an extra chromosome, or whether they are related to gene-specific over expression.

The development of mouse models of trisomy 21 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 Down syndrome phenotype. Models are used to show whether specific genes are necessary and sufficient to cause a certain phenotype.

A number of genes on chromosome 21 have been identified which appear to contribute to the Down syndrome phenotype or development of common health conditions, the most well-researched of these are Amyloid Precursor Protein (*APP)* and dual specificity tyrosine-regulated protein kinase 1 (*DYRK1A*). Other identified genes include Down syndrome critical region 1 (*DSCR1; also known as RCAN1)*, *BACE 2, SOD1, S100B,* while polymorphisms in the rest of the genome may also have an impact, such as *GATA1* and its associaton with leakaemia in children with Down syndrome.

- Triplication of *APP* is the primary driver for early-onset Alzheimer's disease (AD) observed in people with Down syndrome (Wiseman et al. 2015). Rare individuals with Down syndrome who have incomplete trisomy and only two copies of *APP* (disomy) do not appear to have the same AD risk (Doran et al., 2017). Triplication of *APP* leads to increased deposition and accumulation of amyloid-beta protein throughout life. Duplication of the *APP* gene in the absence of Down syndrome is known to be sufficient to cause early onset AD (Sleegers et al., 2006).

- *DYRK1A* is particularly expressed in the hippocampus, cortex, cerebellum, and heart—regions and overexpressed in fetal Down syndrome. Transgenic mice that overexpress *DYRK1A* show learning and memory deficits. It has been linked to impairments in angiogenesis and increased risk of developing pulmonary hypertension (Colvin et al 2017), Further, *DYRK1A* phosphorylates tau protein, and this change is known to be important in initiating the cascade of processes leading to AD. When this over-expression is reduced in mice, amyloid-beta and tau levels are reduced, as is cholinergic neurodegeneration (García-Cerro, Rueda, Vidal, Lantigua, & Martínez-Cué, 2017)

Phenotype

Trisomy 21 is associated with a number of common characteristics but there is considerable individual variation. Intellectual disability is present to some degree in all patients with full trisomy 21 but varies from mild disability to severe and profound. Motor dysfunction occurs frequently and individuals with Down syndrome can exhibit clumsy sequences of movements, with poor control of motor sequences, timing and force. Motor dysfunction in people with Down syndrome is accompanied by hyporeflexia and reduced muscular strength and tone (Antonarakis et al, 2020). Most adults with Down syndrome are of short stature (70%), with a characteristic facial appearance. Their eyes slope upwards and outwards as a result of alterations in the structure of the surrounding tissues ("upslanting palpebral fissures"). The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45% of children with Down syndrome. 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.

Physical Health

Many individuals with Down syndrome have significant hearing loss, usually of the conductive type. Sight problems (44-71%) and cataracts are common in Down syndrome individuals, the incidence increasing with age.

Obstructive sleep apnea (OSA) is common in people with Down syndrome, and is increasingly being recognised as an important condition to screen for and to manage. More than 1 in two of people with Down syndrome may have some degree of sleep apnoea. Symptoms include loud snoring, heavy breathing, restless nights and daytime sleepiness, as well as neurocognitive symptoms such as irritability, low mood, and difficulty with focus and attention or behavioral problems. General screening tools based on signs and symptoms may not be adequately sensitive to diagnose OSA and it is suspected that it remains under-diagnosed in this population (Simpson et al 2018).

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

Epilepsy is present in 8% of children with Down syndrome, 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).

Bowel problems including duodenal stenosis/atresia (250 times more commin in people with Down syndrome) and Hirschsprung disease (30 times more common) occur in babies with Down syndrome, while celiac disease and constipation may be more common in young people and adults, and can be overlooked, particularly in people with more severe intellectual disabilities.

Haematological malignancy, specifically acute megakaryocytic leukemia is 300-times more frequent in children with Down syndrome. Down syndrome is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis,

celiac disease and alopecia areata (Alexander et al., 2016; Bittles, Bower, Hussain, & Glasson, 2007; Glasson, Dye, & Bittles, 2014). In younger people the incidence of diabetes is up to 4 times that of people without Down syndrome, with onset of both type 1 and type 2 diabetes occurring at younger ages (Aslam et al 2022). People with Down syndrome are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence).

Health conditions associated with getting older, particularly bone disease including osteoporosis, obesity, cataracts, kidney disease and diabetes occur at earlier ages in people with Down syndrome compared to the general population. This includes Alzheimer's disease which is extremely common, with a rate nearly 95 times that of the general population. Other conditions including epilepsy, sleep disorders, and strokes occur around the same time as dementia onset and may be caused by the same disease pathways (Baksh, Pape et al 2023).

On the other hand, people with Down syndrome are less likely to have high cholesterol, high blood pressure, ischaemic heart disease, solid cancers, glaucoma or mental health disorders.

Mental Health

People with Down syndrome have increased incidence of behavioural and mental health problems compared to the general population (Tassé et al., 2016). Psychosis appears to be less common. In people with Down syndrome presenting to mental health services, depression and anxiety disorders are the most prevalent conditions.

An increasingly recognised condition is Down syndrome regression disorder. Adolescents and young adults present with loss of skills and independence compared to their previous levels of functioning. There is often withdrawl from activites and up to 90% of people show language regression. Features can appear similar to catatonia including stereotypes, reduced voilition and psychomotor slowing. It is estimated that around 50% of people make a partial or full recovery, with 35% stabilising at a poorer functioning level (Santoro et al, 2020). At present the cause of this decline is unknown, although it has been suggested that the decline can occur after exposure to emotional stressors (Mircher et al., 2017). An inflammatory or autoimmune aetiology has been suggested. There is often a poor response to anti-depressant and antipsychotic medication. Electro-convulsive therapy, steroids and intravenous immunoglobulins have been trialled with some sucess in subgroups of individuals, but many individuals do not fully recover.

Behavioural characteristics

Fewer behavior problems compared to controls with cognitive disability have been described in people with Down syndrome, but are more frequent than in sibling or in controls without intellectual disability. Children with Down syndrome may be at a lower risk for significant behavioral difficulties in that they show a lower profile of problem behaviors compared to children with other intellectual disabilities. However, in comparison to typically developing age-matched peers, children with Down syndrome can show higher rates of inattention and impulsivity (which may be associated with ADHD), and oppositional behaviors (Dykens, 2007).

People with Down syndrome 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 Down syndrome 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 relatively common, and many people with Down syndrome 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 adults with Down syndrome without dementia. This suggested a more positive pattern for ageing adults with Down syndrome until symptoms of dementia develop (Makary et al., 2014), although depressive symnptoms have been described prior to dementia onset.

Cognitive characteristics

Intellectual disability is present in almost all people with Down syndrome, but with individual ability varying widely, from borderline to profound (Karmiloff-Smith et al., 2016). Most children and adults with Down syndrome function in the mild or moderate range of abilities, 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). A distinct cognitive profile is described with particular weaknesses in processing verbal information (thought to be secondary to phonological loop deficits) and executive function, especially related to attention, processing speed, verbal working memory and set-shifting. Individuals with Down syndrome 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). Relative strengths are observed in non-verbal learning and memory (Hamburg et al 2019; Lanfranchi et al 2010).

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

Alzheimer's disease and dementia

In adults with Down syndrome, brain changes typical of Alzheimer's disease (AD) 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 Down syndrome (Hithersay et al., 2018). Intra-neuronal amyloid-beta deposition starts as early as the first decade, with extra- cellular diffuse plaques observed in adolescents with Down syndrome (Fortea et al 2021). On post-mortem examination, almost all adults with Down syndrome 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 Down syndrome 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 Down syndrome, earlier dementia onset is associated with earlier menopause (Coppus et al., 2010).

While there is a clear association with *APP* and AD in Down syndrome (see above), non-chromosome 21 genes that are known to influence dementia onset in sporadic AD, such at *APOE*, assert a similar influence in Down syndrome (Hithersay et al., 2018; Lai et al., 1999). Further, experimental 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 Down syndrome 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). The prodromal phase of Alzheimer's disease may present with depressive symptoms or behavioural and personality changes creating a potential diagnostic challenge for clinicians.

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 Down syndrome 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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The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation