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Phenotypes Associated with Down Syndrome and Causative Genes

Fatma Söylemez

Abstract

Down syndrome (DS) is the most common chromosomal condition associated with mental retardation and is characterized by a variety of additional clinical findings. It occurs in approximately 1 of 800 births worldwide. DS is associated with number of phenotypes including heart defects, leukemia, Alzheimer's disease, hypertension etc. Individuals with DS are affected by these diseases to variable rates, so understanding the reason for this variation is an important challenge. Multiple genes located both on chromosome 21 and other regions of the genome such as the polymorphism of the amyloid precursor protein (APP) gene contribute to clinical variations. Information on these genetic variations allows early diagnosis and treatment of phenotypes associated with DS. In this chapter, an overview of disease management will be provided by reviewing the genes or miRNAs that cause DS-associated phenotypes.

Keywords: Down syndrome, disease, phenotypes, genes, variation

1. Introduction

Down syndrome is one of the best-recognized and most common chromosome disorders caused by the presence of a third copy of chromosome 21 (Trisomy 21). It is the most common genetic cause of mental retardation. The incidence of Down syndrome is approximately 1/800 newborns [1, 2]. The risk for having a child with Down syndrome increases with maternal age. There are several features that occur in the entire DS population, including learning disability, craniofacial abnormality, and hypotonia [3]. In addition to learning difficulties, Down syndrome patients face a variety of health problems, including congenital heart disease, Alzheimer's diseases (AD), leukemia, cancers and gastrointestinal defects. The 200 to 300 genes on chromosome 21 have been identified as causatives to clinical features of the syndrome. Multiple genes such as polymorphisms of the Down syndrome cell adhesion molecule (DSCAM) and APP gene, both on chromosome 21 and other regions of the genome, are known to contribute to variation in clinical manifestations [4].

2. Down syndrome genetics and typical features

The most common reason for having a baby with DS is the presence of an extra copy of chromosome 21 that results in trisomy. Trisomy 21 (47,XX,+ 21 or 47,XY,+ 21) is caused by a failure of the chromosome 21 to separate during egg or sperm development (**Figure 1**). The other causes can be Robertsonian translocation and isochromosomal or ring chromosome [5]. Robertsonian translocation occurs in only 2–4%

Figure 1.
47,XX,+21. Down syndrome karyotype demonstrating trisomy 21 (female) (Karyotype prepared by Fatma Soylemez).

of cases and occurs when the long arm of the 21st chromosome is attached to another submetacentric chromosome. Mosaicism occurs as a result of an error in cell division or a false division after fertilization. This is why people with mosaic DS have two cell lines in their tissues, one containing a normal number of chromosomes and the other an extra chromosome 21 [5]. Mosaicism of trisomy 21 and partial trisomy 21 are other genetic diagnoses and are usually associated with fewer clinical features of DS. Trisomy 21 and partial trisomy 21 mosaicism are generally associated with less clinical features of DS [4].

DS has high genetic complexity and phenotype variability [6, 7]. DS individual has some physical characteristics like a small chin, slanted eye, poor muscle tone, a flat nasal bridge, a single crease of the palm, big toe, short fingers and large tongue [8]. DS patients may have an increased dosage or copy number that can lead to an increase in gene expression in Hsa 21 [8]. Specific genes such as Hsa21 or subsets of genes are able to control specific DS phenotypes [9]. In addition, phenotypic analyzes were performed on individuals with partial trisomy for Hsa21. It has been determined that a 3.8–6.5 Mb region called “Down syndrome critical regions” (DSCR) is responsible for most of the Down syndrome phenotypes at 21q21.22 [9]. With the sequencing of Hsa 21, more information was learned about DS-associated genotype–phenotype correlations and characterization of DSCR regions [3]. It has been suggested that the dual- specificity tyrosine phosphorylation-regulated kinase (DYRK1A), the regulator of calcineurin 1 (RCAN1) and Down syndrome cell adhesion molecule (DSCAM), play a critical role in brain development and the occurrence of heart defects in DS patients [10]. In particular, DSCAM plays a very important role in neuron differentiation, axon guidance and neural networks formation. Disruption of these processes contributes to the DS neurocognitive anomalies. All studies have shown that there is not a single critical gene region sufficient to cause DS phenotypes, and there must be a large number of critical regions or critical genes contributing to a DS-associated phenotype or phenotypes.

3. Various pheotypes associated to Down syndrome

The various clinical phenotypes associated with DS are Alzheimer’s disease, heart defects, leukemia, hypertension and gastrointestinal problems (**Figure 2**).

Figure 2.
 Various phenotypes associated with Down's syndrome with its responsible genes (GI: Gastrointestinal).

The pathogenesis mechanism of these phenotypes associated with DS should be studied together with their causative agents to better understand the disease.

3.1 Alzheimer disease

It has been determined that the risk of early onset Alzheimer Disease (AD) is high in DS patients. After the age of 50, the risk of developing dementia increases up to 70% in patients with DS [11]. In the past decade, substantial progress has been made in the search for genetic risk factors for dementia in people with DS, and in understanding the neuropathological similarities and differences between AD with DS and without DS. For people with DS over the age of 40, dementia development has a similar progression to that of AD [12–14]. However, if dementia occurs in younger individuals (30–40 years of age), it manifests itself as personality and behavior changes such as increasing impulsivity and onset of apathy [10]. The most conspicuous parallel between AD and AD in DS are characteristic neuropathologies such as amyloid- β accumulation [15]. Results from post-mortem neurochemistry studies have showed a significant loss of choline acetyltransferase and noradrenaline in people with DS, which is similar to the changes seen in Alzheimer's disease [16]. Results obtained from studies, the cholinergic dysregulation in DS is controlled by the DYRK1A gene [17]. DYRK1A is a serine–threonine protein kinase. DYRK1A is involved in tau phosphorylation, and its up-regulation may contribute to early onset formation of neurofibrillary tangles. In addition, the results obtained from microarray studies, pointed out that there is an up-regulation of the α 2 sub-unit and down-regulation of the α 3 and α 5 subunits of GABA_A receptor [18].

There are several genes known to cause early onset AD. The most important of these genes are APP (amyloid precursor protein), BACE2 (beta secretase 2), PICALM (Phosphatidylinositol binding clathrin assembly protein) and APOE (Apolipoprotein E) [19, 20]. APP is an integral membrane protein concentrated in the synapse of neurons. It is thought that the trisomy of this protein may contribute significantly to the increased frequency of dementia in individuals with DS. It has been shown that trisomic of APP along with Hsa 21 in non-DS individuals is associated with early onset AD. In a preliminary study, a tetranucleotide repeat, ATTT, in

intron 7 of the amyloid precursor protein, was associated with the onset of AD in DS [20]. It is also known that BACE2, encoding the enzyme beta secretase 2, plays a role in AD. Like APP, the BACE 2 gene is located on chromosome 21. The results of the studies are that the haplotypes in BACE2 are associated with AD [21]. A genome wide study, an important relationship was found between variants in BACE2 and age of onset of dementia in DS, with the rs2252576-T allele being associated with an earlier onset by 2–4 years [22]. However, there are other studies that reported no significant relationship between BACE2 and the age of onset of dementia [23]. There is still some uncertainty about the relationship between BACE2 variants and the development of dementia in DS.

In addition to the APP and BACE2 genes, other genes such as PICALM and APOE were found to be associated with early onset AD in DS [24]. PICALM, the other candidate risk gene for AD and DS were examined. PICALM is present in enlarged endosomes in early developing AD [25]. In a DS genome wide study, a relationship has been verified between the variation in the PICALM region of chromosome 11 and the age of onset of AD [26]. Three SNPS in this study, rs2888903, rs7941541 and rs10751134 has been associated with an earlier age of onset. The ϵ 4 allele of the APOE gene, located on chromosome 19, is the most important genetic risk factor for late-onset Alzheimer's disease [27]. The APOE ϵ 4 allele, known to be associated with increased amyloid burden and cholinergic dysfunction, is probably the most studied genetic risk factor. In individuals with DS, the presence of the APOE ϵ 4 allele has been shown to increase the risk of Alzheimer's disease [28, 29]. Also, A β accumulation DS individuals carrying the APOE ϵ 4 allele are increased [30].

3.2 Heart defects

The frequency of heart defects in newborns with DS is up to 50% [31]. The defect called atrioventricular cushion defect is the most common heart defect affecting 40% of DS patients. Ventricular septal defect (VSD) also affects 35% of patients [31]. In atrioventricular septal defect (AVSD), there is a common atrioventricular junction in contrast to normal heart. Other defects include muscular and membranous atrioventricular septum defects and an oval shape of the common atrioventricular junction. Pulmonary arterial hypertension occurs in 1.2 to 5.2% of people with DS [32]. Early repair of heart defects minimizes the risks of heart failure and irreversible pulmonary vascular disease [33]. Observation of specific anatomical patterns of heart defects that can be seen in DS showed that a locus on chromosome 21 plays a role in the development of cardiac malformations [34, 35]. Although up-regulation of genes mapped on chromosome 21 is thought to be related to heart defects, the molecular basis that regulating existence and anatomy of heart defects are still unclear [34]. It has been suggested that type VI collagen (COL6A1, COL6A2) is involved in the pathogenesis of AVSD in Down syndrome, in a similar way to other genes mapping on chromosome [36].

Apart from chromosome 21, other genes localized on different chromosomes have also been studied as the cause of heart defects in DS. Among these genes, the CRELD1 gene has been evaluated as increasing susceptibility to AVSD [31]. Mutations in the CRELD1 (Cysteine-rich EGF-like domain1) gene has been found to contribute to the development of AVSD in DS [37]. CRELD1 gene is located on chromosome 3p25 and contains 11 exons spanning approximately 12 kb [38]. This gene encodes a cell surface protein that functions as a cell adhesion molecule and is expressed during cardiac cushion development. There are studies suggesting that the CRELD1 gene probably plays a major role in the causation of the AVSD phenotype in DS individuals [39, 40]. Two heterozygous missense mutations (p.R329C

and p.E414K) were identified with two subjects in DS and AVSD [31]. They also included 39 DS with complete AVSD and found the same mutations. No such mutation was detected in DS individuals without heart defects [37]. The R329C mutation reported in a person with sporadic partial AVSD and has also been detected in an individual with DS with AVSD. Although the mutation is the same in DS patients AVSD heart defect has created a more serious condition. Therefore, it has been suggested that the CRELD 1 mutation contributes to the pathogenesis of AVSD heart defects occurring in DS individuals.

3.3 Hypertension

Individuals with DS may have an increased risk of developing pulmonary hypertension (PH), in part due to congenital heart defects. Other factors such as upper airway obstruction, lung hypoplasia with DS, gastroesophageal reflux, abnormal pulmonary vascular function may play a role in increasing the risk of PH in DS. Findings from a study with DS in Mexico City (high altitude) showed that % 40 had congenital heart disease and 80% had PH [41, 42]. On the other hand, a reduced incidence of hypertension has been reported in individuals with DS [43, 44].

Some of the Hsa21-encoded miRs have been shown to be overexpressed in cells and tissues of DS patients. The direct cause of the overexpression of miRs in DS appears to be the extra copy of HSA21, whose miRs are at their normal chromosomal location [45]. It has been reported that trisomy of Hsa21 microRNA hsa-miR-155 causes this low incidence [45]. An allele of the type-1 angiotensin II receptor (AGTR1) gene is the specific target of HsamiR-155. In this study of twins (one twin was unaffected, and the other had a trisomy 21) to evaluate the expression of MiR-155 in trisomy 21, both twins are homozygous for the 1166A AGTR1 allele and therefore AGTR1 Reported to be the target of miR-155 [46]. This receptor has a vasopressor effect and regulates aldosterone secretion. It is an important factor controlling blood pressure and volume in the cardiovascular system. In this way, it is suggested that it contributes to the decrease of the risk of hypertension by reducing the expression of AGTR1. More studies are needed to validate these thoughts and to determine whether other genes could also protect DS people against hypertension.

3.4 Leukemia

Hematological abnormalities are common in patients with DS. Patients with DS have a wide risk of malignancy including leukemia. The first leukemia report in a DS patient was in 1930 [47]. It has been reported that leukemia may develop in DS individuals with subsequent systemic studies. Studies have shown that DS patients have an approximately 10–20 times higher risk of leukemia, with a 2% risk by age 5 and 2.7% at age 30 [48]. DS individuals account for about 2% of all childhood acute lymphoblastic leukemia (ALL) and about 10% of acute myeloid leukemia (AML).

Somatic mutations such as GATA 1 gene play a role in the development of acute megakaryoblastic leukemia (AMKL) in DS patients [49]. GATA 1 is a transcription factor localized on the X chromosome, which plays a role in erythroid and megakaryocytic differentiation. Mutations in GATA 1 cause a shorter GATA 1 protein to be expressed and consequently uncontrolled proliferation of immature megakaryocytes [49, 50]. Transient abnormal myelopoiesis, a form of myeloid preleukemia that occurs in about 10% of newborns with DS, is also caused by mutations in GATA1 [4]. A mutation in GATA1 in individuals with DS has been reported to cause transient myeloproliferative disorder (TMD) [51]. They thought it was likely that trisomy 21 and GATA1 causing hyperplasia of the fetal liver in some DS individuals to induce perinatal TMD.

Another mutation that has been suggested to play a role in ALL cases occurring in DS is in the Janus Kinase 2 (JAK 2) gene and is present in approximately 30% of ALL cases in DS [52]. Mutations in the JAK–STAT pathway are at high risk for the development of ALL in individuals with DS [53]. JAK2 is a non-receptor tyrosine kinase and a member of the Janus kinase family. It has been implicated in signaling by members of some receptor families (e.g. interferon receptors and interleukin receptors) [54]. Mutations in JAK2 have been associated with polycythemia vera, essential thrombocythemia, myelofibrosis, and other myeloproliferative disorders. Also, it has been reported that the JAK1, JAK2 and JAK3 genes are mutated in AMKL patients with DS [55–57].

3.5 Gastrointestinal defects

Individuals with DS consist about 12% of Hirschprung disease (HD) cases. HD is an intestinal obstruction caused by the absence of normal myenteric ganglion cells in part of the colon [58]. In this gastrointestinal (GI) defect, peristaltic waves do not pass through the aganglionic segment and cause obstruction as there is no normal defecation. Other GI defects that can be seen in individuals with DS are duodenal stenosis (DST) and imperforate anus (IA). They are seen 260 and 33 times more respectively in DS [59]. In newborns with duodenal blockage or DST, bilious vomiting occurs in the early neonatal period. If left untreated, there is a risk of death due to severe dehydration and electrolyte imbalance. IA is a birth defect that causes rectal malformation and is associated with the increase of some other specific anomalies such as tracheoesophageal fistula and esophageal atresia.

It has been suggested that changes in genes unrelated to Hsa21 play a role in these diseases. DSCAM has long been viewed as a candidate gene explaining the increased prevalence of this GI defect in HD patients with DS. DSCAM is Down syndrome cell adhesion molecule and plays a crucial role in the development of DS. It is a trans-membrane protein and a member of the immunoglobulin (Ig) superfamily of cell adhesion molecules. It is expressed in the developing nervous system with the highest level of expression occurring in the fetal brain. When over-expressed in the developing fetal central nervous system, it leads to Down syndrome. DSCAM gene is expressed in neural crest that gives rise to enteric nervous system. The overlapping critical region is defined for both DST and IA [58]. Alterations in the DSCAM gene have been shown to play a role in HD development. In connection with HD, two SNPs, rs2837770 and rs8134673, spanning a 19 kb exon-free region of the DSCAM gene was identified [60].

4. Conclusions

DS, the most common chromosomal abnormality among newborns, is associated with a number of congenital malformations, primarily mental retardation caused by the trisomy of chromosome 21. In addition to its own characteristics, DS can be accompanied by different phenotypes. Different theories such as “gene dosage” have been considered to understand the interactions between phenotype and genotype. The DS phenotype is mainly due to the dosage imbalance of genes located on human chromosome 21 (Hsa 21). The most common cause of DS is presence extra copy chromosome 21. A critical region in 21q22 is thought to be responsible for various DS phenotypes such as craniofacial abnormalities, congenital heart defects, clinodactyly and mental retardation. The health problems and life period of DS people are quite complex and are associated with many different medical, psychological and social problems from infancy to adulthood. In this chapter, it is

to reveal the common genes involved in DS related phenotypes such as APP, BACE2, PICALM, APOE, GATA 1, JAK 2.

The association of DS with various clinical phenotypes requires continuous following of these patients with a multidisciplinary approach. For example, there are numerous epidemiological and molecular studies linking the pathological changes observed in the brains of individuals with Down syndrome and the neurodegeneration seen in Alzheimer's disease. Knowing the genes and pathology associated with such changes is very important for a good clinical follow-up of DS patients. Due to the insufficient knowledge of the molecular pathogenesis of DS, an effective therapeutic intervention is unlikely to be found yet. The situation is further complicated by the complex phenotypes accompanying DS. It may be a good option to use pharmacological approaches to key target molecules that are crucial for dysregulated metabolic pathways or phenotypic characteristics. In conclusion, elucidating the phenotypic consequences of gene dose imbalance in DS and knowing the genes that cause accompanying phenotypes may provide new opportunities for therapeutic interventions.

Author details

Fatma Söylemez
Department of Food Processing, Vocational School of Technical Sciences,
Mersin University, Mersin, Turkey

*Address all correspondence to: soylemez_fatma@yahoo.com

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References

- [1] Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*, 13: 221-227, 2007.
- [2] Soylemez F. Double Aneuploidy in Down Syndrome. *Health Problems in Down Syndrome*. InTechOpen, Chapter 6, 101-123, 2015.
- [3] Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S. Chromosome 21 and Down syndrome: from genomics to pathophysiology. *Nat Rev Genetics*, 5: 725-738, 2004.
- [4] Bull MJ. Down Syndrome. *The New England Journal of Medicine*, 382: 2344-2352, 2020.
- [5] Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S. Down syndrome: an insight of the disease. *Journal of Biomedical Science*, 22: 41-50, 2015.
- [6] Mégarbané A, Ravel A, Mircher C, Sturtz F, Grattau Y, Rethoré MO, Delabar JM, Mobley WC. The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. *Genet Med*, 11: 611-616, 2009.
- [7] Prandini P, Deutsch S, Lyle R, Gagnebin M, Delucinge Vivier C, Delorenzi M, Gehrig C, Descombes P, Sherman S, Bricarelli FD, Baldo C, Novelli A, Dallapiccola B, Antonarakis SE. Natural gene-expression variation in Down syndrome modulates the outcome of gene-dosage imbalance. *Am J Hum Genet*, 81: 252-263, 2007.
- [8] Patterson D. Genetic mechanisms involved in the phenotype of Down syndrome. *Ment Retard Dev Disabil Res Rev*, 3: 199-206, 2007.
- [9] Pritchard MA, Kola I. The “gene dosage effect” hypothesis versus the “amplified developmental instability” hypothesis in Down syndrome. *J Neural Transm Suppl*, 57: 293-303, 1999.
- [10] Holland AJ, Hon J, Huppert FA, Stevens F. Incidence and course of dementia in people with Down’s syndrome: findings from a population based study. *J Intellect Disabil Res*, 44: 138-146, 2000.
- [11] Janicki MP, Dalton AJ. Prevalence of dementia and impact on intellectual disability services. *Ment Retard*, 38: 276-288, 2000.
- [12] Ballard C, Mobley W, Hardy J, Williams G, Corbett A. Dementia in Down’s syndrome. *Lancet Neurol*, 15: 622-636, 2016.
- [13] Holland AJ, Hon J, Huppert FA, Stevens F, Watson P. Population-based study of the prevalence and presentation of dementia in adults with Down’s syndrome. *Br J Psychiatry*, 172: 493-498, 1998.
- [14] Oliver C, Crayton L, Holland A, Hall S, Bradbury J. A four year prospective study of age-related cognitive change in adults with Down’s syndrome. *Psychol Med*, 28: 1365-1377, 1998.
- [15] Mann DM, Royston MC, Ravindra CR. Some morphometric observations on the brains of patients with Down’s syndrome: their relationship to age and dementia. *J Neurol Sci*, 99: 153-164, 1990.
- [16] Godridge H, Reynolds GP, Czudek C, Calcutt NA, Benton M. Alzheimer-like neurotransmitter deficits in adult Down’s syndrome brain tissue. *J Neurol Neurosurg Psychiatry*, 50: 775-778, 1987.

- [17] Hijazi M, Fillat C, Medina JM, Velasco A. Overexpression of DYRK1A inhibits choline acetyltransferase induction by oleic acid in cellular models of Down syndrome. *Exp Neurol*, 239: 229-234, 2013.
- [18] Bhattacharyya A, McMillan E, Chen SI, Wallace K, Svendsen CN. A critical period in cortical interneuron neurogenesis in down syndrome revealed by human neural progenitor cells. *Dev Neurosci*, 31: 497-510, 2009.
- [19] Myllykangas L, Wavrant-De Vrieze F, Polvikoski T, Notkola IL, Sulkava R, Niinisto L. Chromosome 21 BACE2 haplotype associates with Alzheimer's disease: a two-stage study. *J Neurol Sci*, 236 (1-2): 17-24, 2005.
- [20] Jones EL, Ballard CG, Prasher VP, Arno M, Tyrer S, Moore B, Hanney ML. An Intron 7 polymorphism in APP affects the age of Dementia in Down Syndrome. *Int J Alzheimers Dis*, 2011: 1-5, 2010.
- [21] Myllykangas L, Wavrant-De Vrieze F, Polvikoski T, Notkola IL, Sulkava R, Niinisto L. Chromosome 21 BACE2 haplotype associates with Alzheimer's disease: a two-stage study. *J Neurol Sci*, 236 (1-2): 17-24, 2005.
- [22] Mok KY, Jones EL, Hanney M, Harold D, Sims R, Williams J, Ballard C, Hardy J. Polymorphisms in BACE2 may affect the age of onset Alzheimer's dementia in Down syndrome. *Neurobiol Aging*, 35: 1513-1518, 2014.
- [23] Yu Y, Jia J. Lack of association between the polymorphisms of beta-site APP-cleaving enzyme 2 (BACE2) 5'-flanking region and sporadic Alzheimer's disease. *Brain Res*, 1257: 10-15, 2009.
- [24] Jones EL, Mok K, Hanney M, Harold D, Sims R, Williams J. Evidence that PICALM affects age at onset of Alzheimer's dementia in Down syndrome. *Neurobiol Aging*, 34 (10): 244, 2013.
- [25] Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. *Am J Pathol*, 157: 277-286, 2000.
- [26] Jones EL, Mok K, Hanney M, Harold D, Sims R, Williams J, Ballard C. Evidence that PICALM affects age at onset of Alzheimer's dementia in Down syndrome. *Neurobiol Aging*, 34: 2441, 1-5, 2013.
- [27] Roses AD, Saunders AM, Corder EH, Pericak-Vance MA, Han SH, Einstein G, Hulette C, Schmechel DE, Holsti M, Huang D. Influence of the susceptibility genes apolipoprotein E-epsilon 4 and apolipoprotein E-epsilon 2 on the rate of disease expressivity of late-onset Alzheimer's disease. *Arzneimittel-Forschung*, 45: 413-417, 1995.
- [28] Cedazo-Minguez A. Apolipoprotein E and Alzheimer's disease: molecular mechanisms and therapeutic opportunities. *J Cell Mol Med*, 11: 1227-1238, 2007.
- [29] Deb S, Braganza J, Norton N, Williams H, Kehoe PG, Williams J, Owen MJ. APOE epsilon 4 influences the manifestation of Alzheimer's disease in adults with Down's syndrome. *Br J Psychiatry*, 176: 468-472, 2000.
- [30] Hyman BT, West HL, Rebeck GW, Buldyrev SV, Mantegna RN, Ukleja M, Havlin S, Stanley HE. Quantitative analysis of senile plaques in Alzheimer disease: observation of log-normal size distribution and molecular epidemiology of differences associated with apolipoprotein E genotype and

- trisomy 21 (Down syndrome). *Proc Natl Acad Sci USA*, 92: 3586-3590, 1995.
- [31] Maslen CL, Babcock D, Robinson SW, Bean LJ, Dooley KJ, Willour VL, Sherman SL. CRELD1 mutations contribute to the occurrence of cardiac atrioventricular septal defects in Down syndrome. *Am J Med Genet*, 140: 2501-2505, 2006.
- [32] Weijerman ME, van Furth AM, van der Mooren MD, van Weissenbruch MM, Rammeloo L, Broers CJM, Gemke RJB. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. *Eur J Pediatr*, 169: 1195-1199, 2010.
- [33] Martin T, Smith A, Breatnach CR, Kent E, Shanahan I, Boyle M, Levy PT, Franklin O, El-Khuffash A. Infants born with Down syndrome: burden of disease in the early neonatal period. *J Pediatr*, 193: 21-26, 2018.
- [34] Versaccia P, Di Carloa D, Digiliob MC, Marino B. Cardiovascular disease in Down syndrome. *Current Opinion in Pediatrics*, 30 (5), 616-622, 2018.
- [35] Korenberg JR, Bradley C, Disteche CM. Down syndrome: molecular mapping of the congenital heart disease and duodenal stenosis. *Am J Hum Genet*, 50: 294-302, 1992.
- [36] Gittenberger-de Groot AC, Bartram U, Oosthoek PW, Bartelings MM, Hogers B, Poelmann RE, Jongewaard IN, Klewer SE. Collagen type VI expression during cardiac development and in human fetuses with trisomy 21. *Anat Rec A Discov Mol Cell Evol Biol*, 275: 1109-1116, 2003.
- [37] Rup PA, Fouad GT, Egelston CA, Reifsteck CA, Oslon SB, Knosp WM, Glanville RW, Thornburg KL, Robinson SW, Maslen CL. Identification, genomic organization and mRNA expression of CRELD1, the founding member of a unique family of matricellular proteins. *Gene*, 293: 47-57, 2002.
- [38] Sheffield VC, Pierpont ME, Nishimura D, Beek JS, Burns TL, Berg MA, Stone EM, Patil SR, Lauer RM. Identification of a complex congenital heart defect susceptibility locus by using DNA pooling and shared segment analysis. *Hum Mol Genet*, 6: 117-121, 1997.
- [39] Asim A, Agarwal S, Panigrahi I, Sarangi AN, Muthuswamy S, Kapoor A. CRELD1 gene variants and atrioventricular septal defects in Down syndrome. *Gene*, 641: 180-185, 2018.
- [40] Ghosh P, Bhaumik P, Ghosh S, Ozbek U, Feingold E, Maslen C, Sarkar B, Pramanik V, Biswas P, Bandyopadhyay B, Kumar Dey S. Polymorphic haplotypes of CRELD1 differentially predispose Down syndrome and euploids individuals to atrioventricular septal defect. *Am J Med Genet A*, 158A (11): 2843-2848, 2012.
- [41] Beghetti M, Rudzinski A, Zhang M. Efficacy and safety of oral sildenafil in children with Down syndrome and pulmonary hypertension. *BMC Cardiovascular Disorders*, 17: 177-186, 2017.
- [42] Espinola-Zavaleta N, Soto ME, Romero-Gonzalez A, Gomez-Puente, Gómez-Puente LDC, Munoz-Castellanos L, Gopal AS, Keirns C, Lupi-Herrera E. Prevalence of congenital heart disease and pulmonary hypertension in Down's syndrome: an Echocardiographic study. *J Cardiovasc Ultrasound*, 23: 72-77, 2015.
- [43] Draheim CC, McCubbin JA, Williams DP. Differences in cardiovascular disease risk between nondiabetic adults with mental retardation with and without Down

syndrome. *Am J Ment Retard*, 107: 201-211, 2002.

[44] Sethupathy P, Borel C, Gagnebin M, Grant GR, Deutsch S, Elton TS, Hatzigeorgiou AG, Antonarakis SE. Human microRNA-155 on chromosome 21 differentially interacts with its polymorphic target in the AGTR1 3' untranslated region: a mechanism for functional single-nucleotide polymorphisms related to phenotypes. *Am J Hum Genet*, 81: 405-413, 2007.

[45] Farroni C, Marasco E, Marcellini V, Giorda E, Valentini D, Petrini S, D'Oria V, Pezzullo M, Cascioli S, Scarsella M, Ugazio AG, De Vincentiis GC, Grimsholm O, Carsetti R. Dysregulated miR-155 and miR-125b Are Related to Impaired B-cell Responses in Down Syndrome. *Front Immunol*, 9: 2683-2695, 2018.

[46] Sethupathy P, Borel C, Gagnebin M, Grant GR, Deutsch S, Elton TS, Hatzigeorgiou AG, Antonarakis SE. Human microRNA-155 on Chromosome 21 Differentially Interacts with Its Polymorphic Target in the AGTR1 3 Untranslated Region: A Mechanism for Functional Single-Nucleotide Polymorphisms Related to Phenotypes. *The American Journal of Human Genetics*, 81 (2): 405-413, 2007.

[47] Brewster HF, Cannon HE. Acute lymphatic leukemia: Report of a case in eleventh month mongolina idiot. *New Orleans Med Surg J*, 82: 872-873, 1930.

[48] Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumors in individuals with Down's syndrome. *Lancet*, 355: 165-169, 2000.

[49] Wechsler J, Greene M, McDevitt MA, Anastasi J, Karp JE, Le Beau MM, Crispino JD. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down

syndrome. *Nat Genet*, 32 (1): 148-152, 2002.

[50] Shivdasani RA, Fujiwara Y, McDevitt MA, Orkin SH. A lineage-selective knockout establishes the critical role of transcription factor GATA-1 in megakaryocyte growth and platelet development. *EMBO J*, 16 (13): 3965-3973, 1997.

[51] Marshall GM, Carter DR, Cheung BB, Liu T, Mateos MK, Meyerowitz JG, Weiss WA. The prenatal origins of cancer. *Nat Rev Cancer*, 14 (4): 277-289, 2014.

[52] Kearney L, Gonzalez De Castro D, Yeung J, Procter J, Horsley SW, Eguchi-Ishimae M, Bateman CM, Anderson K, Chaplin T, Young BD, Harrison CJ, Kempinski H, So CWE, Ford AM, Greaves M. Specific JAK2 mutation (JAK2R683) and multiple gene deletions in Down syndrome acute lymphoblastic leukemia. *Blood*, 113 (3): 646-648, 2009.

[53] Mateos MK, Barbaric D, Byatt SA, Sutton R, Marshall GM. Down syndrome and leukemia: insights into leukemogenesis and translational targets. *Transl Pediatr*, 4 (2): 76-92, 2015.

[54] Brooks AJ, Dai W, O'Mara ML, Abankwa D, Chhabra Y, Pelekanos RA, Gardon O, Tunny KA, Blucher KM, Morton CJ, Parker MW, Sieracki E, Gambin Y, Gomez GA, Alexandrov K, Wilson IA, Doxastakis M, Mark AE, Waters MJ. Mechanism of activation of protein kinase JAK2 by the growth hormone receptor. *Science*, 344 (6185): 703-717, 2014.

[55] Yoshida K, Toki T, Okuno Y, Kanezaki R, Shiraishi Y, Sato-Otsubo A, Sanada M, Park M, Terui K, Suzuki H, Kon A, Nagata Y, Sato Y, Wang R, Shiba N, Chiba K, Tanaka H, Hama A, Muramatsu H, Hasegawa D, Nakamura K, Kanegane H,

- Tsukamoto K, Adachi S, Kawakami K, Kato K, Nishimura R, Izraeli S, Hayashi Y, Miyano S, Kojima S, Ito E, Ogawa S. The landscape of somatic mutations in Down syndrome-related myeloid disorders. *Nature Genetics*, 45 (11): 1293-1299, 2013.
- [56] Blink M, Buitenkamp TD, van den Heuvel-Eibrink MM, Danen-van Oorschot AA, de Haas V, Reinhardt D, Klusmann JH, Zimmermann M, Devidas M, Carroll AJ, Basso G, Pession A, Hasle H, Pieters R, Rabin KR, Izraeli S, Zwaan CM. Frequency and prognostic implications of JAK 1-3 aberrations in Down syndrome acute lymphoblastic and myeloid leukemia. *Leukemia*, 25: 1365-1368, 2011.
- [57] Hama A, Muramatsu H, Makishima H, Sugimoto Y, Szpurka H, Jasek M, O'Keefe C, Takahashi Y, Sakaguchi H, Doi S, Shimada A, Watanabe N, Kato K, Kiyoi H, Naoe T, Kojima S, Maciejewski JP. Molecular lesions in childhood and adult acute megakaryoblastic leukaemia. *Br. J. Haematol*, 156: 316-325, 2012.
- [58] Amiel J, Sproat-Emison E, Garcia-Barcelo M, Lantieri F, Burzynski G, Borrego S, Pelet A, Arnold S, Miao X, Griseri P, Brooks AS, Antinolo G, de Pontual L, Clement-Ziza M, Munnich A, Kashuk C, West K, Wong KY, Lyonnet S, Chakravarti A, Tam PKH, Ceccherini I, Hofstra RMW, Fernandez R. Hirschsprung disease, associated syndromes and genetics: a review. *J Med Genet*, 45: 1-14, 2008.
- [59] Berrocal T, Lamas M, Gutiérrez J. Congenital Anomalies of the Small Intestine, Colon, and Rectum. *Radiographics Radiol Bras*, 19: 1219-1236, 1999.
- [60] Jannot AS, Pelet A, Henrion-Caude A, Chaoui A, Morel M, Arnold S, Sanlaville D, Ceccherini I, Borrego S, Hofstra RMW, Munnich A, Bondurand N, Chakravarti A, Clerget-Darpoux F, Amiel J, Lyonnet S. Chromosome 21 Scan in Down Syndrome Reveals DSCAM as a Predisposing Locus in Hirschsprung Disease. *PLoS One*, 8 (5): 1-8, 2013.