Oxidative Stress in Trisomy 13 and 18 Evaluation

Subjects: Obstetrics & Gynaecology

Contributor: Angelika Buczynska , Iwona Sidorkiewicz , Ahsan Hameed , Adam Krętowski , Monika Zbucka-Krętowska

Autosomal aneuploidies are the most frequently occurring congenital abnormalities and are related to many metabolic disorders, hormonal dysfunctions, neurotransmitter abnormalities, and intellectual disabilities. Trisomies are generated by an error of chromosomal segregation during cell division. Accumulating evidence has shown that deregulated gene expression resulting from the triplication of chromosomes 13 and 18 is associated with many disturbed cellular processes. Moreover, a disturbed oxidative stress status may be implicated in the occurrence of fetal malformations.

oxidative stress trisomy 18 syndrome trisomy 13 syndrome

1. Introduction

Trisomy 13 (T13), resulting in Patau syndrome, is a chromosomal condition with a prevalence rate of 1/5000 to 1/20,000 [1][2][3]. Trisomy 18 (T18), causing Edwards syndrome, is another frequent autosomal aneuploidy after Trisomy 21 (T21), affecting 1/6000 to 1/8000 live-birth fetuses [2][4]. The most frequent mechanism responsible for the apparition of complete homogenous T13 occurrence is the complete triplication of chromosome 13, generally resulted from maternal nondisjunction in meiosis. Additionally, less frequently, T13 occurs as a result of an unbalanced Robertsonian translocation and mosaicism formation [5]. T18 occurs most frequently as a result of complete 18 trisomy due to a maternal meiotic nondisjunction, which is the most common form (94%) [6]. Mosaic trisomy 18 is the second cause corresponding to fewer than 5% of occurrences, and fewer than 2% of cases are caused by an additional copy of long arm chromosome 18q [7]. These chromosomal aberrations generate many congenital abnormalities such as heart defects, gastrointestinal defects, tracheoesophageal abnormalities, endocrine disorders, vision and hearing disorders, and limb and nervous system anomalies [8][9][10]. Following the complexity of existing comorbidities, numerical chromosomal aberration, such as T13 and T18 are one of the main causes of miscarriage or stillbirth [11]. However, along with improvements in clinical management, an increasing survival rate of patients with these syndromes has been reported [4][12][13][14][15][16][17].

Recently, a broad range of genetic diseases have been investigated for the implications with oxidative stress and mitochondrial dysfunction in their pathogenesis [18]. Moreover, a growing number of studies have recently demonstrated that oxidative stress formation results from trisomy occurrence [19][20][21][22][23] and was observed to be responsible for the T21 phenotype [24][25][26]. T13 and T18 are the most frequently autosomal chromosome aberrations, excluding T21, where the pathogenesis of this chromosomal aberration is largely known, and

numerous studies have been conducted [5][7][27][28][29]. The pathogenic changes related to T13 and T18 may also be associated with oxidative stress with important causative genes being primarily involved in the redox balance regulation. Comprehensive studies concerning the evaluation of the trisomies' pathomechanism could explain the development of some malformations and the importance of oxidative stress, which can lead to a better understanding of the effects of the occurrence of these trisomies [4][30][31].

2. Oxidative Stress: An Overview

All biological processes constitute a redox equilibrium, i.e., balanced oxidation and reduction reactions, to ensure convenient homeostasis [32]. Oxidative stress occurs due to a reduction in antioxidant defense caused by defects in the defense mechanisms and/or increased reactive oxygen species (ROS) synthesis [33]. ROS generation is directly associated with oxidized damage in biological components such as proteins, lipids, and DNA [34]. These deteriorations are mostly caused by O_2^- (superoxide radical), OH^- (hydroxyl radical), and H_2O_2 (hydrogen peroxide) [35][36]. Recent studies have shown that mitochondrial dysfunction caused by oxidative stress plays an important role in neuronal damage and neurodegenerative diseases, which can be directly connected to the trisomic phenotype [34][37]. Mitochondrial respiratory chain complexes (MRCCs) play a key role in antioxidant defense by acting through the electron transport chain to oxidize hydrogen from the oxidation of organic acids with atomic oxygen to neutralize and expel hydrogen into water [34]. These complexes subsist as V cooperating units, which catalyze the phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Complex I is composed of nicotinamide adenine dinucleotide (NADH) coenzyme Q; complex II is composed of succinate dehydrogenase coenzyme Q; complex III is composed of coenzyme Q-cytochrome c reductase; complex IV is composed of cytochrome c oxidase; and complex V is composed of ATP synthase [38]. The MRCC is mostly exposed to oxidative stress through an increase in the possibility of oxidative damage caused to mitochondrial DNA (mtDNA), antioxidant proteins, and enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in this complex, which may result in a subsequent additional increase in the intensity of the oxidative stress [39].

3. Previously Established T13 and T18 Pathogenesis—An Indicator for Oxidative Stress Testing

It has been shown that the composition of amniotic fluid, which is produced daily by the fetal urinary and respiratory systems using products of fetal skin keratinization, is similar to that of fetal plasma at the end of the second trimester [40][41]. Consequently, the concentrations of fetal proteins in second-trimester amniotic fluid are directly correlated with the concentrations in fetal serum, the analysis of which would facilitate the discovery of trisomy 13 and 18 pathogeneses [42][43][44][45]. Due to this fact, amniotic fluid appears to be the most useful material for analyzing abnormalities occurring in T13 and T18 fetal development [46].

One of the first studies, performed by Vrachnis, focused on resistin and leptin evaluations and showed that their deregulation may be implicated in T13 and T18 pathogeneses [31]. Resistin is a 12.5 kDa polypeptide secreted by

adipocytes involved in insulin resistance development. Moreover, resistin is a potential marker of chronic inflammation associated with increased oxidative stress [47]. More interestingly, resistin can affect the function of nitric oxide synthase (eNOS) systems, resulting in a significant decrease in eNOS expression and nitric oxide (NO) production, thereby having antioxidative properties [31][48]. Leptin, a hormone released from the adipocytes, in addition to influencing the feeling of hunger, is also involved in antioxidant defense by decreasing ROS production [49].

Another study, performed by Hsu et al., aimed to evaluate T18 pathogenesis and was conducted on second-trimester amniotic fluid samples collected from six confirmed T18 pregnancies. The other six euploid pregnancies were enrolled as the control group [30]. The comparative proteomics analysis was performed using fluorescence-based two-dimensional difference gel electrophoresis (2D-DIGE) with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS). The concentration of amniotic fluid apolipoprotein A1 (ApoA1) was increased in the T18-delivered samples compared to the euploid fluid samples [30]. Furthermore, the study demonstrated the deregulation of four proteins in T18 pregnancies: alpha-1-antitrypsin (A1AT, also known as serpin 1), vitamin D-binding protein (VDBP), insulin-like growth factor-binding protein 1 (IGFBP-1), and transthyretin (TTR) [30] (**Table 1**). ApoA1 is frequently used as a biomarker to predict cardiovascular diseases [43]. Its involvement in T18 could be associated with impaired lipid metabolism due to cardiovascular and neurological comorbidities during T18 early fetal development [44][50][51]. Moreover, the dysregulated *ApoA1* expression could also correspond to the oxidative damage observed in trisomy 21-based studies [22][52]. Concluding, ApoA1 plays a meaningful role in the pathogenesis of ES. A1AT is involved in the protection of neurons and glial cells from oxygen and glucose deprivation [53]. VDBP is an important component of many biochemical processes, including the transport of vitamin D and its metabolites, ensuring proper homeostasis. VDBP also controls essential proteins for proper bone metabolism, binding fatty acids, sequestering actin, and modulating oxidative and immune defenses [54][55]. IGFBP-1 serves as a carrier protein for insulin-like growth factors 1 and 2 (IGF1 and IGF2)—important determinants of fetal growth during pregnancy [56]. *TTR* gene mapped on 18q12.1 encodes a serum- and cerebrospinal fluid-binding protein for thyroxine and retinol implicated in fetal development [57]. Using a biological network analysis of T18 pathogenesis, Hsu et al. showed that the protein expression profile is associated with a lipid- and hormone-disturbed metabolic processes, improper immune response mechanisms, and cardiovascular comorbidities potentially connected to increased oxidative stress [30] (**Table 1**).

Table 1. Disturbances in protein concentrations related to T13 and T18 pathogeneses [30][31].

Material	Protein	Full Name	Form of Dysregulation	Reference
Amniotic fluid T18 pregnancy	A1AT	alpha-1-antitrypsin	down	[30]
Amniotic fluid T18 pregnancy	ApoA	apolipoprotein A	up	[30]

Material	Protein	Full Name	Form of Dysregulation	Reference
Amniotic fluid T18 pregnancy	IGFBP-1	insulin-like growth factor-binding protein 1	down	[30]
Amniotic fluid T13 and T18 pregnancy	leptin	-	down	[31]
Amniotic fluid T13 and T18 pregnancy	resistin	-	down	[31]
Amniotic fluid T18 pregnancy	TTR	transthyretin	down	[30]
Amniotic fluid T18 pregnancy	VDBP	vitamin D binding protein	down	[30]

4. Genetic Basis of the T13 and T18 Pathogeneses

There are several genes mapped on chromosomes 13 and 18 recognized as the players in the maintenance of redox balance [58]. Chromosome 13 mapping demonstrated the presence of genes associated with copper transport (ATPase copper transporting beta; *ATP7B),* tumor suppression (breast cancer 2; *BRCA2),* the inhibition of cell cycle processes, chromatin remodeling (retinoblastoma transcriptional corepressor 1; *RB1),* chromosome stability maintenance and regulations of chromosome segregation in mitosis (chromosome alignment-maintaining phosphoprotein 1; *CHAMP1),* and oxidative mitochondrial processes (mitochondrial intermediate peptidase; *MIPEP),* all of which are relevant in T13 pathogenesis [59][60][61][62]. The proper expression of the *ATP7B* gene is implicated in copper homeostasis, the deregulation of which may result in the development of many pathologies, especially those related to metabolic, cardiovascular and neurodegenerative diseases, and cancer [63]. Interestingly, the proper expression of *ATP7B* is crucial for mitochondrial protection against increased oxidative stress conditions, being an essential micronutrient for proper SOD-1 and mitochondrial complex IV activities [64]. In this case, this gene triplication may lead to an increased possibility of mtDNA mutation, resulting in subsequent oxidative stress disturbances according to the lack of mitochondrial antioxidant defense [65]. The *BRCA2* gene is also responsible for oxidative stress homeostasis; its overexpression correlates with increases in oxidative stress-restricted mtDNA replication, resulting in a disturbed mitochondrial oxidative balance [66]. Moreover, alterations in *MIPEP* expression, involved in oxidative phosphorylation (OXPHOS)-related protein maturation, may additionally indicate a connection between mitochondrial dysfunction and T13 development [62][67]. Moreover, the study performed by Renaudin et al. showed that *BRCA2* deficiency impairs ribonuclease H1 (RNaseH1) function, which is required to ensure mtDNA maintenance [66]. Interestingly, other genes, such as *RB1* and *CHAMP1,* are also related to oxidative-stress-related processes. It has been suggested that disturbances in *RB1* gene expression are

involved in DNA damage sensor activity, forkhead box O (Foxo) transcription factors, and p38 mitogen-activated protein kinase processes, for which a disturbed expression affects cell-cycle progression, antioxidant capacity, mitochondrial mass, and cellular metabolism [68][69][70][71][72]. *CHAMP1* encodes a protein with a function in kinetochore–microtubule attachment and in the regulation of chromosome segregation. These properties are performed by their interaction and regulation of cell structure organization preceding mitosis, both of which are known to be important for proper fetal development [73][74]. Moreover, proper *MIPEP* expression is essential to maintain the normal level of mitochondrial sirtuin 3, which is considered a key regulator of oxidative stress by the deacetylation of the substrates involved in both ROS production and detoxification [75][76][77]. These mechanisms link oxidative stress to mitochondrial dysfunction and may be induced by the triplication of genes implicated in mitochondrial protective processes [78]. Referring to the fact that mitochondrial dysfunction is assumed to be one of the main T21-related symptoms [28][79], similar dysfunctions seem to be implicated in T13 development [59][66].

Furthermore, several important genes involved in intracellular cholesterol trafficking (Niemann–Pick C1 protein; *NPC1* gene), proper DNA transcription and signal transduction (mothers against decapentaplegic homolog; *SMAD),* and mitochondrial membrane function (ferrochelatase enzyme, coded by ferrochelatase; *FECH* gene) are mapped on chromosome 18 [80][81][82]. The *NPC1* gene encodes a crucial protein and affects the excitability of endosome and lysosome membranes, with characteristic mediation properties in intracellular cholesterol trafficking through cholesterol binding [80][83][84]. Interestingly, *NPC1* deficiency is related to neurodegenerative disease development due to oxidative damage. In this case, the *NPC1* gene's correct expression is essential for oxidative stress balance [85]. Moreover, SMAD proteins are signal transducers and transcriptional modulators involved in multiple signaling pathways, such as cell growth, apoptosis, morphogenesis, and immune responses [81][86][87]. Research conducted by Xui et al. showed that *SMAD* overexpression results in increased oxidative stress and a reduction in cell viability with subsequent induction of apoptosis [88]. The *FECH* gene, which encodes the ferrochelatase enzyme, essential for the proper catalyzation of the insertion of the ferrous form of iron into the protoporphyrin heme synthesis pathway, is also related to oxidative stress homeostasis [82][89][90][91] (**Table 2**).

Table 2. Gene expression related to T13 and T18 pathogeneses.

Gene Location	Gene	Full Name	Function
Chromosome 13	*ATP7B*	ATPase Copper Transporting Beta	copper transport
Chromosome 13	*BRCA2*	Breast Cancer 2	tumor suppression
Chromosome 13	*CHAMP1*	Chromosome Alignment-Maintaining Phosphoprotein 1	chromosome alignment maintenance with zinc finger protein regulations of chromosome

Gene Location	Gene	Full Name	Function
			segregation in mitosis
Chromosome 13	*MIPEP*	Mitochondrial Intermediate Peptidase	oxidative mitochondrial processes
Chromosome 13	*RB1*	Retinoblastoma Transcriptional Corepressor 1	inhibition of cell cycle processes, chromatin remodeling
Chromosome 18	*FECH*	Ferrochelatase	mitochondrial membrane function
Chromosome 18	*NPC1*	Niemann–Pick C1 Protein	intracellular cholesterol trafficking
Chromosome 18	*SMAD*	Mothers Against Decapentaplegic Homolog	transcription and signal transduction

ction and oxidative status. Therefore, a detailed evaluation of disturbed transcriptomic pathways related to T13 and T18 and the subsequent metabolic pathway disturbances may result in novel findings regarding trisomy-related abnormalities. Undoubtedly, studies may highlight deregulated pathways, and their detailed identification might become the basis for further research in T13 and T18 [45][92].

References

1. Satgé, D.; Nishi, M.; Sirvent, N.; Vekemans, M. A tumor profile in Edwards syndrome (trisomy 18). Am. J. Med. Genet. Part C Semin. Med. Genet. 2016, 172, 296–306.
2. Goel, N.; Morris, J.K.; Tucker, D.; De Walle, H.E.K.; Bakker, M.K.; Kancherla, V.; Marengo, L.; Canfield, M.A.; Kallen, K.; Lelong, N.; et al. Trisomy 13 and 18—Prevalence and mortality—A multi-registry population based analysis. Am. J. Med. Genet. Part A 2019, 179, 2382–2392.
3. McCaffrey, M.J. Trisomy 13 and 18: Selecting the road previously not taken. Am. J. Med. Genet. Part C Semin. Med. Genet. 2016, 172, 251–256.
4. Sifakis, S.; Anagnostopoulou, K.; Plastira, K.; Vrachnis, N.; Konstantinidou, A.; Sklavounou, E. Rare case of XX/XY mosaicism and trisomy 13 in early prenatal diagnosis. Birth Defects Res. Part A Clin. Mol. Teratol. 2012, 94, 245–248.

5. Kuznetsova, M.A.; Zaytseva, G.V.; Zryachkin, N.I.; Makarova, O.A.; Khmilevskaya, S.A. Patau Syndrome. Clin. Pract. Pediatrics 2021, 10, 90–93.
6. Cereda, A.; Carey, J.C. The trisomy 18 syndrome. Orphanet J. Rare Dis. 2012, 7, 81.
7. Balasundaram, P.; Avulakunta, I.D. Edward Syndrome; StatPearls Publishing: Treasure Island, FL, USA, 2021.
8. Pont, S.J.; Robbins, J.; Bird, T.; Gibson, J.B.; Cleves, M.A.; Tilford, J.M.; Aitken, M.E. Congenital malformations among liveborn infants with trisomies 18 and 13. Am. J. Med. Genet. Part A 2006, 140A, 1749–1756.
9. Peterson, J.; Kochilas, L.K.; Catton, K.G.; Moller, J.H.; Setty, S.P. Long-Term Outcomes of Children With Trisomy 13 and 18 After Congenital Heart Disease Interventions. Ann. Thorac. Surg. 2017, 103, 1941–1949.
10. Roberts, W.; Żurada, A.; Zurada-Zielińska, A.; Gielecki, J.; Loukas, M. Anatomy of trisomy 18. Clin. Anat. 2016, 29, 628–632.
11. Morris, J.K.; Savva, G.M. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. Am. J. Med. Genet. Part A 2008, 146A, 827–832.
12. Anderson, C.E.; Punnett, H.H.; Huff, V.; De Chadarévian, J.-P. Characterization of a Wilms tumor in a 9-year-old girl with trisomy 18. Am. J. Med. Genet. Part A 2003, 121A, 52–55.
13. Khan, F.; Jafri, I. Characterization of a 16-Year-Old Long-Time Survivor of Edwards Syndrome. Cureus 2021, 13, e15205.
14. Petek, E.; Pertl, B.; Tschernigg, M.; Bauer, M.; Mayr, J.; Wagner, K.; Kroisel, P.M. Characterisation of a 19-year-old “long-term survivor” with Edwards syndrome. Genet. Couns. 2003, 14, 239–244.
15. Zoll, B.; Wolf, J.; Lensing-Hebben, D.; Pruggmayer, M.; Thorpe, B. Trisomy 13 (Patau syndrome) with an 11-year survival. Clin. Genet. 1993, 43, 46–50.
16. Iliopoulos, D.; Sekerli, E.; Vassiliou, G.; Sidiropoulou, V.; Topalidis, A.; Dimopoulou, D.; Voyiatzis, N. Patau syndrome with a long survival (146 months): A clinical report and review of literature. Am. J. Med. Genet. Part A 2005, 140, 92–93.
17. Fogu, G.; Maserati, E.; Cambosu, F.; Moro, M.A.; Poddie, F.; Soro, G.; Bandiera, P.; Serra, G.; Tusacciu, G.; Sanna, G.; et al. Patau syndrome with long survival in a case of unusual mosaic trisomy 13. Eur. J. Med. Genet. 2008, 51, 303–314.
18. Arita, A.; Costa, M. Genetics and Genome Research Oxidative Stress and the Epigenome in Human Disease. J. Genet. Genome Res. 2014, 1, 2.
19. Rosa, R.F.M.; Rosa, R.C.M.; Zen, P.; Graziadio, C.; Paskulin, G.A. Trisomy 18: Review of the clinical, etiologic, prognostic, and ethical aspects. Rev. Paul. Pediatr. 2013, 31, 111–120.

20. Cammarata-Scalisi, F.; Lacruz-Rengel, M.A.; Araque, D.; Da Silva, G.; Avendaño, A.; Callea, M.; Stock, F.; Guerrero, Y.; Aguilar, E.; Lacruz, M.J.; et al. Mosaic trisomy 18. Series of cases. Arch. Argent. Pediatr. 2017, 115, e183–e186.
21. Abe, K.; Itoh, N.H.; Hirakawa, O.; Niikawa, N. Trisomy 13/trisomy 18 mosaicism in an infant. Clin. Genet. 1996, 50, 300–303.
22. Perluigi, M.; di Domenico, F.; Fiorini, A.; Cocciolo, A.; Giorgi, A.; Foppoli, C.; Butterfield, D.A.; Giorlandino, M.; Giorlandino, C.; Schininà, M.E.; et al. Oxidative stress occurs early in Down syndrome pregnancy: A redox proteomics analysis of amniotic fluid. Proteom.—Clin. Appl. 2011, 5, 167–178.
23. Laforgia, N.; Di Mauro, A.; Guarnieri, G.F.; Varvara, D.; De Cosmo, L.; Panza, R.; Capozza, M.; Baldassarre, M.E.; Resta, N. The Role of Oxidative Stress in the Pathomechanism of Congenital Malformations. Oxidative Med. Cell. Longev. 2018, 2018, 7404082.
24. Roper, R.J.; Reeves, R.H. Understanding the Basis for Down Syndrome Phenotypes. PLoS Genet. 2006, 2, e50.
25. Rafferty, K.; Archer, K.J.; Turner, K.; Brown, R.; Jackson-Cook, C. Trisomy 21-associated increases in chromosomal instability are unmasked by comparing isogenic trisomic/disomic leukocytes from people with mosaic Down syndrome. PLoS ONE 2021, 16, e0254806.
26. Perluigi, M.; Butterfield, D.A. Oxidative Stress and Down Syndrome: A Route toward Alzheimer-Like Dementia. Curr. Gerontol. Geriatr. Res. 2012, 2012, 724904.
27. Barone, E.; Arena, A.; Head, E.; Butterfield, D.A.; Perluigi, M. Disturbance of redox homeostasis in Down Syndrome: Role of iron dysmetabolism. Free Radic. Biol. Med. 2018, 114, 84–93.
28. Izzo, A.; Mollo, N.; Nitti, M.; Paladino, S.; Calì, G.; Genesio, R.; Bonfiglio, F.; Cicatiello, R.; Barbato, M.; Sarnataro, V.; et al. Mitochondrial dysfunction in down syndrome: Molecular mechanisms and therapeutic targets. Mol. Med. 2018, 24, 2.
29. Muchová, J.; Žitňanová, I.; Ďuračková, Z. Oxidative stress and Down syndrome. do antioxidants play a role in therapy? Physiol. Res. 2014, 63, 535–542.
30. Hsu, T.-Y.; Lin, H.; Hung, H.-N.; Yang, K.D.; Ou, C.-Y.; Tsai, C.-C.; Cheng, H.-H.; Chung, S.-H.; Cheng, B.-H.; Wong, Y.-H.; et al. Two-Dimensional Differential Gel Electrophoresis to Identify Protein Biomarkers in Amniotic Fluid of Edwards Syndrome (Trisomy 18) Pregnancies. PLoS ONE 2016, 11, e0145908.
31. Vrachnis, N.; Dalakli, E.; Zygouris, D.; Vlachadis, N.; Salakos, N.; Botsis, D.; Kalantaridou, S.; Drakoulis, N.; Mastorakos, G.; Creatsas, G.; et al. Altered Resistin Concentrations in Mid-trimester Amniotic Fluid of Fetuses With Trisomies 18 and 13: A Window onto the Pathophysiology of Trisomies 18 and 13. In Vivo 2019, 33, 433–439.

32. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. Oxid. Med. Cell. Longev. 2017, 2017, 8416763.

33. Buczyńska, A.; Sidorkiewicz, I.; Rogucki, M.; Siewko, K.; Adamska, A.; Kościuszko, M.; Maliszewska, K.; Kozłowska, G.; Szumowski, P.; Myśliwiec, J.; et al. Oxidative stress and radioiodine treatment of differentiated thyroid cancer. Sci. Rep. 2021, 11, 17126.

34. Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. Physiol. Rev. 2014, 94, 909–950.

35. Fernandez-Marcos, P.J.; Nóbrega-Pereira, S. NADPH: New oxygen for the ROS theory of aging. Oncotarget 2016, 7, 50814–50815.

36. Bartesaghi, R.; Haydar, T.F.; Delabar, J.M.; Dierssen, M.; Martínez-Cué, C.; Bianchi, D.W. New Perspectives for the Rescue of Cognitive Disability in Down Syndrome. J. Neurosci. 2015, 35, 13843–13852.

37. Lin, M.T.; Beal, M.F. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006, 443, 787–795.

38. Guo, C.; Sun, L.; Chen, X.; Zhang, D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen. Res. 2013, 8, 2003–2014.

39. Capone, G.; Kim, P.; Jovanovich, S.; Payne, L.; Freund, L.; Welch, K.; Miller, E.; Trush, M. Evidence for increased mitochondrial superoxide production in Down syndrome. Life Sci. 2002, 70, 2885–2895.

40. Laudanski, P.; Zbucka-Kretowska, M.; Charkiewicz, K.; Wolczynski, S.; Wojcik, D.; Charkiewicz, R. Maternal Plasma and Amniotic Fluid Chemokines Screening in Fetal Down Syndrome. Mediat. Inflamm. 2014, 2014, 835837.

41. Mange, A.; Desmetz, C.; Bellet, V.; Molinari, N.; Maudelonde, T.; Solassol, J. Proteomic profile determination of autosomal aneuploidies by mass spectrometry on amniotic fluids. Proteome Sci. 2008, 6, 1.

42. Underwood, M.A.; Gilbert, W.M.; Sherman, M.P. Amniotic Fluid: Not Just Fetal Urine Anymore. J. Perinatol. 2005, 25, 341–348.

43. Zbucka-Kretowska, M.; Charkiewicz, K.; Czerniecki, J.; Goscik, J.; Wolczynski, S.; Laudanski, P. Amniotic Fluid Angiogenic and Inflammatory Factor Profiling in Foetal Down Syndrome. Fetal Diagn. Ther. 2017, 44, 44–50.

44. Buczyńska, A.; Sidorkiewicz, I.; Ławicki, S.; Krętowski, A.; Zbucka-Krętowska, M. The Significance of Apolipoprotein E Measurement in the Screening of Fetal Down Syndrome. J. Clin. Med. 2020, 9, 3995.

45. Buczyńska, A.; Sidorkiewicz, I.; Trochimiuk, A.; Ławicki, S.; Krętowski, A.J.; Zbucka-Krętowska, M. Novel Approaches to an Integrated Route for Trisomy 21 Evaluation. Biomolecules 2021, 11, 1328.
46. Sheppard, O.; Wiseman, F.K.; Ruparelia, A.; Tybulewicz, V.L.J.; Fisher, E.M.C. Mouse Models of Aneuploidy. Sci. World J. 2012, 2012, 214078.
47. Laurikka, A.; Vuolteenaho, K.; Toikkanen, V.; Rinne, T.; Leppänen, T.; Tarkka, M.; Laurikka, J.; Moilanen, E. Adipocytokine resistin correlates with oxidative stress and myocardial injury in patients undergoing cardiac surgery. Eur. J. Cardio-Thoracic Surg. 2014, 46, 729–736.
48. Chen, C.; Jiang, J.; Lu, J.-M.; Chai, H.; Wang, X.; Lin, P.H.; Yao, Q. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. Am. J. Physiol. Circ. Physiol. 2010, 299, H193–H201.
49. Calió, M.L.; Marinho, D.S.; Ko, G.M.; Porcionatto, M. Antioxidant Effect of Leptin on Neurogenic Niches in a Model of Alzheimer's Disease. Free Radic. Biol. Med. 2016, 100, S159.
50. Chistiakov, D.A.; Orekhov, A.N.; Bobryshev, Y.V. ApoA1 and ApoA1-specific self-antibodies in cardiovascular disease. Lab. Investig. 2016, 96, 708–718.
51. Elliott, D.A.; Weickert, C.S.; Garner, B. Apolipoproteins in the brain: Implications for neurological and psychiatric disorders. Clin. Lipidol. 2010, 5, 555–573.
52. Perrone, S.; Longini, M.; Bellieni, C.; Centini, G.; Kenanidis, A.; De Marco, L.; Petraglia, F.; Buonocore, G. Early oxidative stress in amniotic fluid of pregnancies with Down syndrome. Clin. Biochem. 2007, 40, 177–180.
53. Buczyńska, A.; Sidorkiewicz, I.; Ławicki, S.; Krętowski, A.; Zbucka-Krętowska, M. Prenatal Screening of Trisomy 21: Could Oxidative Stress Markers Play a Role? J. Clin. Med. 2021, 10, 2382.
54. Nuszkiewicz, J.; Woźniak, A.; Szewczyk-Golec, K. Ionizing Radiation as a Source of Oxidative Stress—The Protective Role of Melatonin and Vitamin D. Int. J. Mol. Sci. 2020, 21, 5804.
55. Polidoro, L.; Properzi, G.; Marampon, F.; Gravina, G.L.; Festuccia, C.; Di Cesare, E.; Scarsella, L.; Ciccarelli, C.; Zani, B.M.; Ferri, C. Vitamin D Protects Human Endothelial Cells from H2O2 Oxidant Injury through the Mek/Erk-Sirt1 Axis Activation. J. Cardiovasc. Transl. Res. 2012, 6, 221–231.
56. Wiesli, P.; Zwimpfer, C.; Zapf, J.; Schmid, C. Pregnancy-induced changes in insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), and acid-labile subunit (ALS) in patients with growth hormone (GH) deficiency and excess. Acta Obstet. Gynecol. Scand. 2006, 85, 900–905.

57. Wang, Q.; Liu, C.; Zhang, Z. Transthyretin and Normal Human Pregnancy: Mini Review. Crit. Rev. Eukaryot. Gene Expr. 2016, 26, 273–277.
58. Brás, A.; Monteiro, C.; Rueff, J. Oxidative stress in trisomy 21: A possible role in cataractogenesis. Ophthalmic Paediatr. Genet. 1989, 10, 271–277.
59. Friedenson, B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 2007, 7, 152.
60. Salahuddin, P.; Rabbani, G.; Khan, R.H. The role of advanced glycation end products in various types of neurodegenerative disease: A therapeutic approach. Cell. Mol. Biol. Lett. 2014, 19, 407–437.
61. Dong, Y.; Shi, X.; Du, K.; Xu, R.; Jia, T.; Wang, J.; Wang, L.; Han, R. First Chinese patient with mental retardation-40 due to a de novo CHAMP1 frameshift mutation: Case report and literature review. Exp. Ther. Med. 2021, 22, 902.
62. Eldomery, M.K.; Akdemir, Z.C.; Vögtle, F.-N.; Charng, W.-L.; Mulica, P.; Rosenfeld, J.A.; Gambin, T.; Gu, S.; Burrage, L.C.; Al Shamsi, A.; et al. MIPEP recessive variants cause a syndrome of left ventricular non-compaction, hypotonia, and infantile death. Genome Med. 2016, 8, 106.
63. Balsano, C.; Porcu, C.; Sideri, S. Is copper a new target to counteract the progression of chronic diseases? Metallomics 2018, 10, 1712–1722.
64. Hartwig, C.; Zlatic, S.A.; Wallin, M.; Vrailas-Mortimer, A.; Fahrni, C.J.; Faundez, V. Trafficking mechanisms of P-type ATPase copper transporters. Curr. Opin. Cell Biol. 2019, 59, 24–33.
65. Yurkova, I.L.; Arnhold, J.; Fitzl, G.; Huster, D. Fragmentation of mitochondrial cardiolipin by copper ions in the Atp7b−/− mouse model of Wilson's disease. Chem. Phys. Lipids 2011, 164, 393–400.
66. Renaudin, X.; Lee, M.; Shehata, M.; Surmann, E.-M.; Venkitaraman, A.R. BRCA2 deficiency reveals that oxidative stress impairs RNaseH1 function to cripple mitochondrial DNA maintenance. Cell Rep. 2021, 36, 109478.
67. Chew, A.; Buck, E.A.; Peretz, S.; Sirugo, G.; Rinaldo, P.; Isaya, G. Cloning, Expression, and Chromosomal Assignment of the Human Mitochondrial Intermediate Peptidase Gene (MIPEP). Genomics 1997, 40, 493–496.
68. MacLeod, K.F. The role of the RB tumour suppressor pathway in oxidative stress responses in the haematopoietic system. Nat. Rev. Cancer 2008, 8, 769–781.
69. Hoskins, E.E.; Gunawardena, R.W.; Habash, K.B.; Wise-Draper, T.M.; Jansen, M.; Knudsen, E.S.; Wells, S.I. Coordinate regu-lation of Fanconi anemia gene expression occurs through the Rb/E2F pathway. Oncogene 2008, 27, 4798–4808.

70. Shaukat, A.; Shaukat, I.; Rajput, S.A.; Shukat, R.; Hanif, S.; Jiang, K.; Zhang, T.; Akhtar, M.; Ma, X.; Liu, J.; et al. Ginsenoside Rb1 protects from Staphylococcus aureus-induced oxidative damage and apoptosis through endoplasmic reticulum-stress and death receptor-mediated pathways. Ecotoxicol. Environ. Saf. 2021, 219, 112353.
71. Wang, A.-H.; Li, D.-W.; Zhou, F.-Z.; Sun, X.-C.; Li, S.-C.; Yang, J.-B.; Sun, H.-H. Ginsenoside Rb1 protects dopaminergic neurons from inflammatory injury induced by intranigral lipopolysaccharide injection. Neural Regen. Res. 2019, 14, 1814–1822.
72. Liu, X.; Gu, X.; Yu, M.; Zi, Y.; Yu, H.; Wang, Y.U.; Xie, Y.; Xiang, L. Effects of ginsenoside Rb1 on oxidative stress injury in rat spinal cords by regulating the eNOS/Nrf2/HO-1 signaling pathway. Exp. Ther. Med. 2018, 16, 1079–1086.
73. Hempel, M.; Cremer, K.; Ockeloen, C.; Lichtenbelt, K.D.; Herkert, J.C.; Denecke, J.; Haack, T.B.; Zink, A.M.; Becker, J.; Wohlleber, E.; et al. De Novo Mutations in CHAMP1 Cause Intellectual Disability with Severe Speech Impairment. Am. J. Hum. Genet. 2015, 97, 493–500.
74. Menarim, B.C.; Ali, H.E.-S.; Loux, S.C.; Scoggin, K.E.; Kalbfleisch, T.S.; MacLeod, J.N.; Dahlgren, L.A. Transcriptional and Histochemical Signatures of Bone Marrow Mononuclear Cell-Mediated Resolution of Synovitis. Front. Immunol. 2021, 12, 5042.
75. Kobayashi, M.; Takeda, K.; Narita, T.; Nagai, K.; Okita, N.; Sudo, Y.; Miura, Y.; Tsumoto, H.; Nakagawa, Y.; Shimano, H.; et al. Mitochondrial intermediate peptidase is a novel regulator of sirtuin-3 activation by caloric restriction. FEBS Lett. 2017, 591, 4067–4073.
76. Bause, A.S.; Haigis, M.C. SIRT3 regulation of mitochondrial oxidative stress. Exp. Gerontol. 2013, 48, 634–639.
77. Chen, Y.; Zhang, J.; Lin, Y.; Lei, Q.; Guan, K.-L.; Zhao, S.; Xiong, Y. Tumour suppressor SIRT3 deacetylates and activates manganese superoxide dismutase to scavenge ROS. EMBO Rep. 2011, 12, 534–541.
78. Renaudin, X.; Venkitaraman, A.R. A mitochondrial response to oxidative stress mediated by unscheduled RNA-DNA hybrids (R-loops). Mol. Cell. Oncol. 2021, 8, 2007028.
79. Izzo, A.; Manco, R.; De Cristofaro, T.; Bonfiglio, F.; Cicatiello, R.; Mollo, N.; De Martino, M.; Genesio, R.; Zannini, M.; Conti, A.; et al. Overexpression of Chromosome 21 miRNAs May Affect Mitochondrial Function in the Hearts of Down Syndrome Fetuses. J. Genom. 2017, 2017, 8737649.
80. Kallol, S.; Albrecht, C. Materno-fetal cholesterol transport during pregnancy. Biochem. Soc. Trans. 2020, 48, 775–786.
81. Andrabi, S.; Bekheirnia, M.R.; Robbins-Furman, P.; Lewis, R.A.; Prior, T.W.; Potocki, L. SMAD4 mutation segregating in a family with juvenile polyposis, aortopathy, and mitral valve dysfunction. Am. J. Med. Genet. Part A 2011, 155, 1165–1169.

82. MedlinePlus. FECH Gene: MedlinePlus Genetics. Available online: https://medlineplus.gov/genetics/gene/fech/ (accessed on 27 October 2021).
83. Ribeiro, I.; Marcão, A.; Amaral, O.; Miranda, M.C.P.S.; Vanier, M.T.; Millat, G. Niemann-Pick type C disease: NPC1 mutations associated with severe and mild cellular cholesterol trafficking alterations. Hum. Genet. 2001, 109, 24–32.
84. Hameed, A.; Mojsak, P.; Buczynska, A.; Suleria, H.A.R.; Kretowski, A.; Ciborowski, M. Altered Metabolome of Lipids and Amino Acids Species: A Source of Early Signature Biomarkers of T2DM. J. Clin. Med. 2020, 9, 2257.
85. Zampieri, S.; Mellon, S.H.; Butters, T.D.; Nevyjel, M.; Covey, D.F.; Bembi, B.; Dardis, A. Oxidative stress in NPC1 deficient cells: Protective effect of allopregnanolone. J. Cell. Mol. Med. 2009, 13, 3786–3796.
86. Qin, B.Y.; Chacko, B.M.; Lam, S.S.; de Caestecker, M.P.; Correia, J.J.; Lin, K. Structural Basis of Smad1 Activation by Receptor Kinase Phosphorylation. Mol. Cell 2001, 8, 1303–1312.
87. Shintani, M.; Yagi, H.; Nakayama, T.; Saji, T.; Matsuoka, R. A new nonsense mutation of SMAD8 associated with pulmonary arterial hypertension. J. Med. Genet. 2009, 46, 331–337.
88. Xiu, D.; Wang, Z.; Cui, L.; Jiang, J.; Yang, H.; Liu, G. Sumoylation of SMAD 4 ameliorates the oxidative stress-induced apoptosis in osteoblasts. Cytokine 2018, 102, 173–180.
89. Schneider-Yin, X.; Gouya, L.; Dorsey, M.; Rufenacht, U.; Deybach, J.-C.; Ferreira, G.C. Mutations in the iron-sulfur cluster ligands of the human ferrochelatase lead to erythropoietic protoporphyria. Blood 2000, 96, 1545–1549.
90. Gouya, L.; Schmitt, C.; Robreau, A.-M.; Austerlitz, F.; Da Silva, V.; Brun, P.; Simonin, S.; Lyoumi, S.; Grandchamp, B.; Beaumont, C.; et al. Contribution of a Common Single-Nucleotide Polymorphism to the Genetic Predisposition for Erythropoietic Protoporphyria. Am. J. Hum. Genet. 2006, 78, 2–14.
91. Ma, Y.-S.; Wu, S.-B.; Lee, W.-Y.; Cheng, J.-S.; Wei, Y.-H. Response to the increase of oxidative stress and mutation of mitochondrial DNA in aging. Biochim. Biophys. Acta (BBA)-Gen. Subj. 2009, 1790, 1021–1029.
92. Rogucki, M.; Buczyńska, A.; Krętowski, A.J.; Popławska-Kita, A. The Importance of miRNA in the Diagnosis and Prognosis of Papillary Thyroid Cancer. J. Clin. Med. 2021, 10, 4738.