Lipodystrophy-associated progeroid syndromes

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Abstract

With the exception of HIV-associated lipodystrophy, lipodystrophy syndromes are rare conditions characterized by a lack of adipose tissue, which is not generally recovered. As a consequence, an ectopic deposition of lipids frequently occurs, which usually leads to insulin resistance, atherogenic dyslipidemia, and hepatic steatosis. These disorders include certain accelerated aging syndromes or progeroid syndromes. Even though each of them has unique clinical features, most show common clinical characteristics that affect growth, skin and appendages, adipose tissue, muscle, and bone and, in some of them, life expectancy is reduced. Although the molecular bases of these Mendelian disorders are very diverse and not well known, genomic instability is frequent as a consequence of impairment of nuclear organization, chromatin structure, and DNA repair, as well as epigenetic dysregulation and mitochondrial dysfunction. In this review, the main clinical features of the lipodystrophy-associated progeroid syndromes will be described along with their causes and pathogenic mechanisms, and an attempt will be made to identify which of López-Otín's hallmarks of aging are present.

Introduction

Aging is a natural process associated with a decline in structure and function of body systems, alterations in repair and maintenance systems, a reduction in reproductive capacity, and an increase in susceptibility to disease and increased odds of mortality [1].

Raoul Hennekam has established the physical features and medical conditions that characterize the elderly (Table 1) [1]. Most of these characteristics are clearly identifiable external signs, with most being related to the skin and its appendages, as well as to mesenchymal tissues. These tissues, embryologically derived from the mesoderm, include adipose tissue, muscle, bone, cartilage, tendons, mesothelium, and endothelium. On the other hand, mesenchymal stem cells (MSC), originating in bone marrow, adipose tissue, muscle, and cord blood, are present in all of the tissues, playing a critical role in regeneration of the injured or damaged tissues thanks to their capacity to migrate to affected areas and repair them [2].

In 2013, López-Otin et al. [3] defined the hallmarks of aging. These mechanisms correspond to nine molecular alterations that include genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient-sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication. These hallmarks are not independent mechanisms, but, instead are intertwined and influence each other, contributing in a specific manner to the complex pathogenesis of different aging-associated disorders [3].

Progeria means accelerated aging. Classically, progeroid syndromes have been divided into unimodal progeroid syndromes, i.e., those in which only one tissue is affected (as in familial Alzheimer's disease or familial Parkinson's disease) and segmental progeroid syndromes, in which more than one tissue is involved [4]. This review will deal only with the latter. In this sense, it must be clarified that the concept of "progeroid" is not equivalent to the meaning that can be applied to, for example, the “Cushingoid” or “acromegaloid” phenotypes, in which only the phenotype mimics Cushing's syndrome or acromegaly, but without chronic hypercortisolism or excessive GH secretion. The concept of progeroid syndrome refers to clinical conditions in which the underlying molecular mechanisms lead to progressive and accelerated aging that affects certain organs or tissues, and which could theoretically lead to premature death.

In 2020, Raoul Hennekam concluded that in order to consider a nosological entity as a progeroid syndrome, it must meet at least 40% of the 34 signs that define old age (Table 1) [5]. According to

this criterion, the author selected a total of 17 Mendelian syndromes. Interestingly, in 15 of these 17 conditions, lipodystrophy was present in varying degrees of severity. It therefore seems clear that lipodystrophy is a recurrent disorder in accelerated aging processes.

Although the definition of lipodystrophy syndromes refers to those conditions in which there is a lack of adipose tissue once causes of hypercatabolism or caloric deprivation have been excluded, in some partial forms there may be abnormal fat accumulation [6]. However, in progeroid syndromes, lipodystrophy generally refers to a loss of adipose tissue, although the extension of the lack of fat is variable in each syndrome [6]. It is, on the other hand, important to highlight that whereas lipoatrophy is a well documented and relevant sign in many of these conditions, as concerns others, there are no studies on a putative energy dysbalance or else there are only limited references to adipose tissue deficiency.

In order to expand, if possible, the list of these disorders, a systematic search in PubMed and OMIM was performed using the words “progeria,” “progeroid, and “lipodystrophy”, applying Hennekam’s criteria to the new conditions [5]. On the basis of this approach, another five syndromes were included in the list (Table 2).

These disorders are extremely rare and, concerning several subtypes, only half a dozen cases or fewer have been reported. Among those cases that have been reported, the majority concern Cockayne syndrome and Werner syndrome. In most of these disorders, the onset of the phenotype begins in childhood, and the diagnosis is based on external clinical manifestations, such as developmental delay, skin and skin appendage manifestations, musculoskeletal abnormalities, and a gestalt facies. These are the clues that usually guide the diagnosis, apart from a subsequent molecular confirmation. Although the pathogenetic mechanisms are extremely diverse, alterations in the nuclear envelope, DNA damage, and defects in DNA repair are the most frequent.

In this review, a description will be provided of the causes and the most notable clinical features of progeroid syndromes associated with lipodystrophy, including their pathogenetic mechanisms. Likewise, and as far as possible, an attempt will be made to provide a critical view of what these disorders represent as manifestations of accelerated aging for a deeper understanding of the physiological aging process.

General clinical features of lipodystrophy-associated progeroid syndromes

Apart from lipoatrophy, the most relevant signs are shown in Fig. 1. One hundred percent of these disorders present anomalies in the skull and face. They present cutaneous signs as well as musculoskeletal and joint anomalies. Growth retardation, short stature, and dental abnormalities are also frequent features. Regarding the cardiovascular system, 43% of these syndromes will present some type of alteration, although, strikingly, atherosclerotic cardiovascular disease is present in only 19% of these disorders. Other conditions that characterize the phenotype of the elderly, such as cognitive disorders, metabolic derangements, or predisposition to neoplasms, have only been reported in some syndromes. Interestingly, a reduction in life expectancy has been reported only in 45% of these diseases. Particularly interesting is the fact that, in addition to lipoatrophy, most of the signs seen in these syndromes are related to other mesenchymal tissues (Fig. 2).

Lipodystrophy-associated progeroid syndromes according to their molecular bases

1. Alterations in nuclear lamina proteins

These syndromes are related to variants in the *LMNA* gene, which encodes the lamin A/C protein, and in other genes that encode proteins involved in lamin A maturation, such as *ZMPSTE24*, or that encode proteins that are closely related to the nuclear lamina, such *BANF1*. So, *LMNA*-associated syndromes would be considered primary laminopathies and the others secondary laminopathies [7]. Lamin A and C are intermediate filament proteins and constitute the main components of the nuclear lamina, a protein mesh intimately attached to the inner nuclear membrane to which heterochromatin is tightly bound, and which has a close relationship with other proteins, such as BAF, lamin-associated polypeptides, emerin, MAN1, lamin B receptor, nesprins, and SUN domain proteins, and with nuclear pore complexes [8]. For correct assembly of lamin A in the nucleus, immature prelamin A requires post-translational processing which encompasses C-terminal farnesylation, enzymatic cleavage of the last three amino acids by the ZMPSTE24 endoprotease, methylation of the terminal cysteine and, finally, enzymatic cleavage of the terminal 15 amino acids including the farnesylated cysteine by ZMPSTE24 [8].

Nuclear lamina participates in the maintenance of the nuclear structure, chromatin organization, DNA replication, and gene expression in such a way that it is not surprising that any alteration of its

structure and/or function is closely related to the processes of physiological aging and to the progeroid syndromes related to it [9].

1.1. Progeroid primary laminopathies

1.1.1. Hutchinson-Gilford progeria syndrome

The classical form of **Hutchinson-Gilford progeria syndrome (HGPS) (MIM#176670)** is caused by certain variants in exon 11 of the *LMNA* gene leading to cryptic splicing resulting in the loss of 50 amino acids from lamin A giving rise to an aberrant protein called progerin. This process involves the loss of the cleavage site for ZMPSTE24. In this way, the progerin is permanently farnesylated at the C-terminal end, which causes a stable association with the inner nuclear membrane [10, 11]. The molecular bases of HGPS are related to the accumulation of farnesylated progerin at the nuclear rim. This process alters the integrity of the nuclear lamina, causing severe abnormalities that include lobulation of the nuclear envelope, thickening of the nuclear lamina, loss of peripheral heterochromatin, and disorganization of nuclear pores. This damage leads to misregulated gene expression, genomic instability, defects in DNA repair, accelerated telomere attrition, changes in epigenetic marks, mitochondrial dysfunction, and premature senescence [12].

According to the Progeria Research Foundation, the estimated prevalence of this syndrome is one case per 20 million inhabitants (www.progeriaresearch.org). These children are born healthy and the onset of the phenotype usually occurs at the end of the first year of life. The most notable clinical characteristics are a marked delay in weight and height development, hair loss, nail dystrophy, skin hypo/hyperpigmentation, loss of skin elasticity, micrognathia, prominent eyes, dental crowding, beaked nose, high-pitched voice, hearing loss, severe generalized lipoatrophy, muscular atrophy, acroosteolysis affecting the distal phalanges and clavicles, osteopenia, coxa valga, joint stiffness, and contractures (Fig, 3A-D). Cognitive development is otherwise normal. The cardiovascular system is severely affected, with a loss of medial smooth muscle cells, secondary maladaptive vascular remodeling, intimal thickening, ruptured elastin fibers, and extracellular matrix deposition [13]. Metabolic involvement is not usually severe. Life expectancy is 14.5 years [14], with the most frequent causes of death being acute myocardial infarction and stroke.

1.1.2. Type A mandibulocacral dysplasia (MIM#248370)

MADA is an autosomal recessive disorder related to missense variants in the *LMNA* gene [15]. Although the molecular mechanisms responsible for this syndrome are not entirely understood, it seems that the initial disorder consists of the accumulation of the farnesylated lamin A precursor, which is detected at the nuclear rim and in intranuclear aggregates [16]. This abnormal accumulation leads to peripheral disorganization, and heterochromatin loss [16] and a redistribution of different nuclear envelope proteins like LBR, SUN2 and emerin. It has been suggested that a general mechanism of nuclear positioning depending on SUN proteins and the LINC complex may play a role in the pathogenesis of MADA [16], suggesting a process of accelerated cellular senescence. In MADA cells, cellular differentiation is hampered due to impaired import of transcription factors that are required for adipogenic gene activation or stress response [17]. Moreover, MADA osteoblasts produce elevated levels of TGFbeta 2 which activates a non-canonical pathway of osteoclast differentiation [17]. In addition, the mammalian target of rapamycin (mTOR) complex seems to be related with MADA pathogenesis, as TGFbeta 2 accumulation appears to be part of a mechanism aimed at degradation of mutated lamin A through the TGFbeta 2-dependent activation of Akt-mTOR axis [18].

The onset of the phenotype occurs in childhood [19]. These patients have normal cognitive development. The most frequent clinical manifestations are acroosteolysis in distal phalanges, lipodystrophy in the extremities, skin mottled pigmentation, mandibular and clavicular hypoplasia, growth retardation and short stature, progressive stiffness or contractures of joints, and a beaked nose. Less frequent manifestations include prominent cheeks and eyes, dental crowding, and persistently wide cranial sutures. Alopecia is a minor disease sign reported in only half of the patients to date [19]. Metabolic alterations include hyperinsulinemia [15] and low HDL-cholesterol [20]. At the present time, the life expectancy of these patients is not known.

1.1.3. *LMNA*-associated atypical progeroid syndromes

***LMNA*-associated atypical progeroid syndromes (APS)** constitute a group of disorders caused by missense variants in the *LMNA* gene. The pathogenetic mechanisms of these atypical forms of *LMNA*-associated progeria are not known. In some cases, nuclear deformities or accumulation of prelamin A have been demonstrated, but not in others. Several proposed mechanisms of allelic

heterogeneity include changes in heterochromatin formation in the nuclear envelope, disruption of gene silencing programs, and modulation of interactions between lamins and the histone H2A/H2B dimer. Other researchers have also suggested that a loss of interaction between lamin A/C and various splicing factors may be responsible for the tissue-specific effects of lamin A/C variants [21-23].

The onset of the phenotype usually occurs during childhood or early adulthood [24,25]. Although the clinical manifestations are heterogeneous, the majority of these patients present with lipodystrophy, which may be generalized or partial, more severe metabolic disorders than those observed in HGPS and MADA, and various progeroid signs, among which are raised mottled skin pigmentation, sclerodemiform lesions, prominent eyes, micrognatia, dental crowding, high-pitched voice, beaked nose, sensorineural deafness, early graying, contractures and joint stiffness, osteoporosis, and low muscle mass. Unlike HGPS and MAD, acroosteolysis is absent or mild and affects only the distal phalanges, with the same being true for clavicular hypoplasia [22]. The cognitive development of these subjects is generally normal. Although their life expectancy is not known with certainty, it is clearly longer than that of subjects with HGPS.

In particular, two recurrent variants have been described, p.(Thr10Ile) and p.(R349W), which present specific symptoms. Thus, the p.(Thr10Ile) variant causes generalized lipodystrophy-associated progeroid syndrome [21], which is characterized by generalized lipodystrophy, short stature, progeroid signs, severe metabolic complications in early life, and dilated cardiomyopathy (Fig. 3E). The p.(R349W) variant gives rise to multisystem progeroid syndrome [24,25] and is characterized by a loss of adipose tissue affecting limbs and face together with over-accumulation of fat in the dorsocervical region, as well as progeroid features. Metabolic complications and hepatic steatosis are frequent. Most patients have proteinuric nephropathy. Cardiovascular involvement, such as coronary artery disease, valvular disease, atrial fibrillation and other arrhythmias and cardiomyopathy, is also common. Hearing loss appears in two-thirds of these patients.

1.2. Progeroid secondary laminopathies

1.2.1. Type B mandibuloacral dysplasia

Type B mandibuloacral dysplasia (MADB) (MIM#608612), an autosomal recessive disorder, is due to variants in the *ZMPSTE24* gene, which encodes zinc metalloproteinase STE24. The pathogenetic mechanisms responsible for this syndrome are superimposable on MADA, the presence of accumulation of farnesylated prelamin A in fibroblasts also being observed [17]**.**

The clinical picture begins in early childhood and is more severe than that of MADA [26]. Unlike MADA, lipodystrophy is generalized and is usually associated with insulin resistance, diabetes mellitus and hypertriglyceridemia. The most outstanding clinical features are mandibular hypoplasia, delayed closure of cranial sutures, dental crowding, premature tooth eruption, clavicular resorption, acroosteolysis, absent or sparse hair, generalized sclerodermic skin, mottled pigmentation, hypoplastic nails, and short stature. The patients also present other skeletal abnormalities such as breaking of vertebrae, calcified skin nodules, and severe osteoporosis [17,27]. Regarding the cardiovascular system, these patients do not present relevant disorders and cognitive development is normal, while the presence of focal segmental glomerulosclerosis is a distinguishing feature. [28]. The life expectancy of these patients is not known, although it is longer than that noted in HGPS [27].

1.2.2. Nestor-Guillermo progeria syndrome

Nestor-Guillermo Progeria syndrome (NGPS) (MIM#614008) is an autosomal recessive disorder caused by variants in the *BANF1* gene, which encodes BAF (barrier-to-autointegration factor), a small non-specific DNA-binding protein that functions as a dimer by binding to the phosphate backbone of DNA, compacting the DNA in a looping process. BAF is a critical component of the nuclear envelope and is involved in the maintenance of chromatin structure and genome stability, being essential for the assembly and disassembly process of the nuclear envelope during mitosis [29,30].

BAF is crucial for the maintenance of cellular homeostasis, and particularly for the integrity of the nuclear envelope and the organization of chromatin. While the links between BAF, DNA repair, and the aging process are not known in depth, it has been confirmed that these are closely related to genomic instability. In this regard, it has been shown that BAF controls the DNA damage response to oxidative stress via regulation of poly [ADP-ribose] polymerase 1 (PARP1) and, consistent with this, cells from NGPS patients have defective PARP1 activity and impaired repair of oxidative

lesions. Recent in vitro studies have shown that variants in *BANF1* alter its DNA binding capacity [30].

To date, three cases of NGPS have been reported [31, 32]. The children were born healthy and the phenotype began in early childhood. From the onset, they presented growth retardation, generalized lipodystrophy, widely open cranial sutures, sparse hair on the scalp, prominent eyes, convex nasal ridge, small retrognathic chin due to marked osteolysis, dental crowding, acroosteolysis, absence of clavicles, severe osteoporosis and scoliosis, articular stiffness, and dystrophic nails. Their skin was thin, dry, and atrophic with small light-brown spots. Regarding the cardiovascular system, these patients presented moderate tricuspid insufficiency, severe mitral regurgitation, and pulmonary hypertension, although they did not show signs of ischemia or atherosclerosis. Cognitive development was normal and there were no relevant metabolic alterations. Their life expectancy is not known, although it is clearly superior to that of HGPS.

2. DNA damage and defects in DNA repair

The integrity and stability of DNA, which are critical for cellular homeostasis, can be affected by endogenous factors, including errors in DNA replication, spontaneous hydrolytic reactions, and ROS that can lead to different types of genomic lesions. To minimize the impact of these injuries, organisms have developed a complex network of damaged DNA repair mechanisms in order to guarantee the stability of the genome. During the physiological process of aging, there is progressive accumulation of genetic damage. It should not be surprising, therefore, that pathogenic variants in certain genes directly involved in DNA replication and DNA repair mechanisms can give rise to premature aging syndromes [33].

2.1. Werner syndrome

Werner syndrome (WS) (MIM#277700) is an autosomal recessive disorder caused by variants in the *RECQL2* gene: the latter encodes an ATP-dependent helicase which is a multifunctional enzyme with magnesium and ATP-dependent helicase activity and exonuclease activity towards double-stranded DNA. It binds to DNA substrates with alternative secondary structures, such as replication forks or Holliday junctions, and also participates in the dissociation of DNA molecules produced by homologous recombination or in DNA repair, relieving polymerase stalling at the sites of DNA lesions [34]. Consequently, it is involved in a number of critical processes in healthy cells, such as DNA

repair, replication, recombination, and telomere maintenance. It therefore plays a fundamental role in maintaining genomic integrity [35].

The pathogenetic mechanisms of WS are related to genomic instability, senescence, changes in nuclear morphology and heterochromatin, telomere shortening, and stem cell exhaustion [36,37]. Recent studies in animal models of WS and in cell and blood samples from WS patients point to the involvement of impaired mitophagy, NAD+ depletion, and accumulation of damaged mitochondria [35].

The onset of the phenotype is usually during the second decade of life. These patients usually present short stature compared to that expected based on the height of the parents. Between 20-30 years of age, skin atrophy, hair loss, and graying become evident. Lipodystrophy is partial, mainly affecting the extremities. Over time, the loss of muscle mass becomes evident (Fig. 3F). These patients generally present with cataracts and osteoporosis, as well as a high-pitched voice, diabetes mellitus, hypertriglyceridemia, hypogonadism, neoplasms, and atherosclerosis. On the other hand, cognitive development is normal. The median age of death is 55 years, usually related to malignancy or myocardial infarction. WS confers a strong predisposition to a variety of neoplasms, of which two-thirds are thyroid neoplasms, melanoma, meningioma, soft tissue sarcomas, leukemias, and primary bone neoplasms [38].

2.2. Bloom syndrome

Bloom syndrome (BS) (MIM#210900) is an autosomal recessive disorder caused by variants in the *RECQL3* gene, which encodes the Bloom syndrome protein, an ATP-dependent DNA helicase with different functions, such as unwinding dsDNA, dissolving Holliday double junctions, and processing complex DNA structures including G-quadruplexes and hairpins during DNA replication and transcription and at telomeres. This protein functions in multiple DNA repair pathways [34].

The pathogenetic mechanisms of BS have been related to chromosome instability, excessive homologous recombination, and a greatly increased number of sister chromatid exchanges [34]. Likewise, there is evidence of senescence in the adipose lineage [39], and of an adaptive response to oxidative stress and increased ROS levels as well as mitochondrial damage, with these mitochondrial alterations being secondary to defects in DNA repair [40].

BS is a pediatric-onset disorder characterized by prenatal and postnatal growth deficiency with short stature. These patients' faces are long and narrow, with prominent ears, retrognathia/micrognathia, malar flattening, and scant facial fat. In fact, during childhood these subjects have notably sparse adipose tissue, which gives them an emaciated appearance, although in adulthood central obesity could be developed. As BS patients age, they may develop an erythema of the face, hands, and forearms, which is exacerbated by sun exposure. Cognitive development is normal. These patients may present with carbohydrate metabolism abnormalities, insulin resistance, and susceptibility to diabetes, dyslipidemia, and hypothyroidism. Women with BS have delayed puberty and early menopause. Men with BS have normal progression of pubertal development, although cryptorchidism or testicular atrophy is common and they are invariably infertile. Cancer is the most frequent medical complication and is the most common cause of death. The distribution of cancers is similar to that of the general population, although the cancers occur at younger ages. Leukemia and lymphoma are the most common types of cancer. Unfortunately, BS patients are short-lived (less than 30 years) [41].

2.3. A and B Cockayne syndromes

A and B Cockayne syndromes (CS) (MIM#216400, #133540) are autosomal recessive disorders caused by variants in the *ERCC8* (type A) and *ERCC6* (type B) genes. The former encodes the DNA excision repair protein ERCC-8 (CSA), while the latter encodes DNA excision repair protein ERCC-6 (CSB). CSA is a substrate-recognition component of the CSA complex, a ubiquitin-protein ligase complex involved in transcription-coupled nucleotide excision repair (TC-NER) [42]. CSA complex promotes the ubiquitination and subsequent proteasomal degradation of CSB in a UV-dependent manner. It is also needed to remove RNA polymerase II-blocking lesions from the transcribed strand of active genes and plays a role in the repair of DNA single and double-strand breaks (DSBs). On the other hand, CSB is also involved in TC-NER, promotes homologous recombination-mediated repair of DSBs, and acts as a chromatin remodeler [43,44].

Regarding pathogenic mechanisms, UV radiation is not involved in most of the clinical complications observed in people affected by CS and these patients do not have an increased risk of cancer, which is usually seen in DNA repair-deficient syndromes. Many aspects of CS cannot be explained by deficient NER. Therefore, there must be other endogenous transcriptional blocking lesions that are

substrates for TC-NER or CS proteins that have additional functions outside of DNA repair. As for the latter possibility, there is certainly evidence that CS proteins play an important role in regulating transcription. Thus, in CS, the defect in the removal of transcription-blocking lesions causes that persistently stalled RNAPs would activate cell death responses, which would lead to UV sensitivity and degenerative phenotypes, without predisposition to cancer. Furthermore, mitochondrial dysfunction may play a role in the pathogenesis of CS through PARP1 activation, which leads to sirtuin inactivation and consequently to an increase in ROS. Decreased repair, stalled transcription, and mitochondrial dysfunction all contribute to neurodegeneration in CSB patients [42,45] .

Approximately 70% of CS-affected individuals harbor a genetic variant in the *ERCC6* gene. No obvious genotype-phenotype correlation can be drawn between the *ERCC8* and *ERCC6* variants and clinical phenotypes due to overlapping symptoms. The clinical manifestations of CS begin in childhood and lead to death before the age of 12 years on average. Its approximate prevalence is 2.5 cases per million inhabitants. The typical phenotype includes growth impairment, severe mental retardation, wrinkled skin, lipodystrophy, beaked nose, and stooped posture. The most striking clinical characteristics are the neurological manifestations, which are related to a progressive process of demyelination. There is severe atrophy of cerebral white matter, which leads to microcephaly, a characteristic sign of this disorder. Severe involvement of the nervous system leads to cognitive dysfunction and mental retardation. People with CS develop motor dysfunction and have difficulty walking. Sensorineural hearing loss has been considered a cardinal feature of CS. These patients may present with cataracts even before 3 years of age. Retinal dystrophy is common. CS patients present dental anomalies, hepato-splenomegaly, osteoporosis, kyphosis, and limited joint mobility. The cardiovascular system shows advanced atherosclerosis for their age. There may be accelerated hypertension, while metabolic disorders are rare [46].

2.4. Ruijs-Aalfs syndrome

Ruijs-Aalfs syndrome (MIM#616200) is an autosomal recessive disorder caused by variants in the *SPRTN* gene [47], which encodes the DNA-dependent metalloprotease SPRTN that mediates the proteolytic cleavage of covalent DNA-protein cross-links (DPCs) during DNA synthesis, thereby playing a key role in maintaining genomic integrity. Proteins can be accidentally and covalently linked with DNA molecules. This covalent, irreversible binding of protein to DNA, a DNA–protein cross-link,

is considered a type of DNA damage representing an impediment for replication, repair, and transcription. If not repaired in a timely manner, DPCs are a source of genomic instability and cancer [48].

Severe proliferation defects with concomitant sensitivity toward genotoxic agents and chromosomal instability have been observed in fibroblasts from these patients. SPRTN dysfunction leads to sustained DNA replication stress and consequent replication-related DNA damage, especially DSBs, which are transferred to the next cell generation due to a leakage of the G2/M checkpoint and, consequently, lead to cancer or aging [47].

To date, only three patients with Ruijs-Aalfs syndrome have been reported [47,49]. These children have developmental delay, premature graying of scalp hair, frontal bossing, triangular face, small deep-set eyes, bilateral cataracts, bulbous nose with high nasal bridge, and micrognathia. They also present with mild lipodystrophy, muscle atrophy, delayed bone age, thoracic kyphoscoliosis, mild pectus excavatum, and mild joint restrictions. All of the patients developed early onset hepatocellular carcinoma, two of them dying before the age of 18 years.

2.5. Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome

Mandibular hypoplasia, deafness, progeroid features and lipodystrophy syndrome (MDPL) (MIM#615381) is a disorder caused by *de novo* variants in the *POLD1* gene, which encodes the p125 subunit of DNA polymerase delta, which is the catalytic component of the Pol-delta3 and Pol-delta4 complexes, playing a crucial role in high-fidelity genome replication. It possesses both 5' to 3' polymerase and 3' to 5' exonuclease activity, the latter enabling proofreading during DNA replication [50].

In MDPL patients, polymerase activity is impaired [51]. This results in an increase in stalled replication forks, which are associated with DSBs, genomic instability, cell cycle checkpoint response, and cell senescence and death [51]. Studies carried out on fibroblasts have shown severe abnormalities of the nuclear envelope, accumulation of prelamin A, impaired cell growth, cellular senescence, decreased ability to repair DSBs, the presence of micronuclei, and a higher rate of telomere shortening [50]. On the other hand, it seems that telomere shortening may also influence mitochondrial activity leading to mitochondrial dysfunction [52].

To date, 26 patients with MDPL have been reported [50]. These children were born healthy, the clinical manifestations appearing in childhood. There is no data that life expectancy is reduced. Many MDPL patients have been described as having short stature. Lipodystrophy is generalized and progressive, appearing in late childhood, although there is a marked increase in visceral adipose tissue [51]. They present growth retardation, mandibular hypoplasia, beaked nose with bird-like facies, prominent eyes, narrow mouth with dental crowding, and a high-pitched voice. Hearing loss appears in the second decade of life. Their skin is thin and atrophic. Patients also frequently present with joint contractures, premature osteoporosis, thoracic kyphosis, scoliosis, and wasting muscle. They also usually present alterations in glucose metabolism, with insulin resistance, hypertriglyceridemia, and fatty liver. Women with MDPL have poor breast development, although fertility is apparently not compromised. Affected males show cryptorchidism with hypergonadotropic hypogonadism. These patients do not seem to have a greater predisposition to cancers [50].

2.6. Wiedemann-Rautenstrauch syndrome

Wiedemann-Rautenstrauch syndrome (WRS) (MIM#264090) is an autosomal recessive disorder caused by variants in the *POLR3A* gene [53], which encodes the DNA-directed RNA polymerase III subunit RPC1, the largest subunit of the DNA-dependent RNA polymerase III. This polymerase synthesizes small RNAs, such as 5S rRNA, tRNAs, and ncRNA. Some of these ncRNAs, such as 7SL and 7SK RNAs, regulate the activity of DNA-dependent RNA polymerase II; hence, *POLR3A* variants can also affect levels of polymerase II-transcribed genes. It also has been shown that POLR3A is important for the proper functioning of the nucleolus, for ribosome assembly, and for protein translation determining the metabolic state of the cell [54].

The mechanisms through which certain biallelic variants in the *POLR3A* gene lead to a clinical phenotype remain unclear [55]. Although certain biallelic loss-of-function variants in *POLR3A* can cause 4H syndrome, hypomyelination cannot be said to be a characteristic of WRS. Báez-Becerra et al. [56] have carried out studies on fibroblasts, finding changes in the morphology of the nucleus in these cells, premature senescence, an increased number and area of nucleoli, increased DNA damage, telomere shortening and the activation of P53. All these changes may cause a serious defect in ribosome biogenesis and protein translation, which could contribute to the WRS phenotype.

There are at present no clinical criteria that define WRS. These patients have a varied lifespan, ranging from a few months to many years into adulthood, although many of them die before the age of 6. They present a serious deficiency of pre- and postnatal growth, generalized lipodystrophy, sparse scalp hair and prominent forehead veins, relative macrocephaly, large fontanelles, prominent forehead, triangular face with mandibular hypoplasia, hypertelorism, small palpebral fissures, broad nasal root and pointed nasal tip, low-set ears, small mouth, natal teeth, and a pointed chin. In general, cognitive development is normal. Abnormalities in glucose metabolism or dyslipidemia have not been reported and cardiac alterations are rare [55].

3. Mitochondrial dysfunction

Mitochondria are critically involved in the aging process. These organelles are the main intracellular source of ROS. Therefore, dysfunctional mitochondria can cause rising amounts of ROS, consequently determining DNA and protein damage. Excessive ROS production, caused by telomere shortening, can regulate the DNA damage response and maintain persistent cellular senescence [3].

3.1. Fontaine progeroid syndrome

Fontaine progeroid syndrome (FPS) (MIM#612289) is a disorder caused by *de novo* variants in the *SLC25A24* gene [54], which encodes the calcium-binding mitochondrial carrier protein SCaMC-1. This protein is a calcium-dependent mitochondrial solute carrier that mediates the reversible exchange of Mg-ATP or Mg-ADP against phosphate ions, catalyzing the net uptake or efflux of adenine nucleotides across the inner mitochondrial membrane. This protein is likely to favor the formation of calcium phosphate precipitates in the mitochondrial matrix, buffering its calcium levels, reducing oxidative stress and, therefore, protecting cells from the death it induces [57].

The pathogenetic mechanism of FPS is related to mitochondrial dysfunction. Enlarged, swollen mitochondria and abnormal cristae have been observed in fibroblasts from these patients [58,59]. The involvement of mitochondrial morphology suggests an impact on oxidative phosphorylation via decreased ATP synthesis. This creates conditions under which cell proliferation is hampered [58].

FPS is characterized by pre- and postnatal developmental delay, short stature, generalized lipodystrophy, sparse scalp hair, wrinkled skin with prominent veins, hypertrichosis, large anterior

fontanelle, craniosynostosis, broad forehead, triangular facies with micrognathia, midface hypoplasia, wide and convex nasal bridge, microphthalmia, low-set dysplastic ears, conductive hearing impairment, oligodontia or microdontia, and small nails and distal phalanges. Some of the patients who managed to live longer presented delayed speech with normal outcome or delayed motor development due to muscle weakness. No metabolic alterations have been reported. Most of these patients die before 8 months [59], although cases with a longer life (15 years) have been reported [58].

3.2. Mandibuloacral dysplasia progeroid syndrome

Mandibuloacral dysplasia progeroid syndrome (MDPS) (MIM#619127) is an autosomal recessive disorder caused by variants in the *MTX2* gene, which encodes metaxin 2, a protein that interacts with the mitochondrial membrane protein metaxin 1. It is thought that the encoded protein is peripherally associated with the cytosolic face of the outer mitochondrial membrane and that it is involved in the import of proteins into the mitochondrion [60].

Studies in the fibroblasts of these patients have shown a fragmentation of the mitochondrial network, decreased oxidative phosphorylation, resistance to apoptosis, increased senescence and autophagy, and reduced proliferative capacity. In addition, dysfunctional metaxin 2 severely affects nuclear morphology [61].

To date, seven patients have been reported, with an onset of the phenotype between 1 and 2 years of age. These children presented developmental delay, short stature, gradual loss of hair, small viscerocranium with mandibular hypoplasia, beaked nose, high-pitched voice, acroosteolysis of the hands and feet, clavicular hypoplasia, lipodystrophy, altered skin pigmentation, nail dystrophy, severe hypertension in most cases, focal renal glomerulosclerosis, cardiac disorders, hypotonia, and hepatic steatosis in some cases. They did not present alterations in glucose metabolism. All of the patients had normal cognitive development [61]. Although some of the patients died early, life expectancy is unknown.

3.3. Cutis laxa progeroid types

Cutis laxa progeroid types include two disorders caused by an alteration in the mitochondrial proline cycle, cutis laxa autosomal dominant 3 (ADCL3) (MIM#616603) [62], and cutis laxa autosomal recessive type IIB (ARCL2B) (MIM#612940) [63]. ADCL3 is an autosomal dominant disorder caused

by *de novo* variants in the *ALDH18A1* gene, which encodes the mitochondrial enzyme delta-1-pyrroline-5-carboxylate-synthetase (P5CS), a bifunctional enzyme that catalyzes the first common step in proline and ornithine biosynthesis. This enzyme catalyzes the conversion of glutamate to gamma-glutamyl semi-aldehyde, which spontaneously converts to pyrroline-5-carboxylate (P5C). ARCL2B is an autosomal recessive disorder caused by variants in the *PYCR1* gene, which encodes the mitochondrial enzyme pyrroline-5-carboxylate reductase 1 (P5R1), which metabolizes P5C to proline [64].

The pathogenetic mechanisms of these syndromes are still unclear. In the case of ARCL2B, variants in the *PYCR1* gene have been linked to altered mitochondrial morphology, membrane potential, and increased apoptosis rate upon oxidative stress [63]. P5R1 could have a possible role in cell growth regulation [63], while in ADCL3 patients, cell studies have shown altered submitochondrial distribution and reduced enzymatic activity [62].

In ADCL3 syndrome, the phenotype begins at birth. Patients have intrauterine and postnatal growth restriction, with less than ten cases having been reported between the ages of 1 and 13. All affected individuals showed moderate intellectual disability, hypotonia with brisk muscle reflexes, triangular face, prominent and broad forehead, cataracts or corneal clouding, prominent low-set ears, lipodystrophy, lax and thin skin with visible veins, joint hyperlaxity, and clenched fingers [62].

ARCL2B with progeroid features due to variants in the *PYCR1* gene was initially reported by Reversade et al. [63], being similar to ADCL3, with some differences such as less frequent brain abnormalities and cataracts.

4. Other causes of lipodystrophy-associated progeroid syndromes

4.1. SHORT syndrome

SHORT syndrome (MIM#269880) is an autosomal dominant condition caused by variants in the *PIK3R1* gene [65], which encodes the p85a, p55a, and p50a regulatory subunits of class IA phosphatidylinositol 3 kinases (PI3Ks), which are dimers composed of a p110 catalytic subunit and a p85 regulatory subunit. PI3K leads to the activation of the AKT1 signaling pathway and is involved in multiple cellular functions, such as cell growth, proliferation, migration, metabolism, angiogenesis, survival, and apoptosis [66].

The mechanisms responsible for the associated SHORT syndrome phenotype are not well understood. Insulin resistance is a consequence of decreased PI3K activity [65] and other signs such as bone demineralization and teething delay, are consistent with decreased PI3K-AKT signaling, a critical pathway for bone development and growth [67]. There is some evidence supporting the role of this gene in the aging process [68].

SHORT is an acronym for Stature, Hyperextensibility of joints or inguinal hernia or both, Ocular depression, Rieger anomaly and Teething delay; however, not all patients with this disorder have all of these signs. The onset of the phenotype occurs in childhood and it is unknown whether it can reduce life expectancy, with patients up to 79 years of age having been reported [69]. These patients are characterized by intrauterine growth retardation, low birth weight, short stature, lipodystrophy mainly affecting the face, upper extremities and buttocks, triangular face, prominent forehead, micrognathia, mild midface hypoplasia, hypoplastic alae nasi or beaked nose, large low-set ears, hyperopia, hypertelorism, hearing loss, thin wrinkled skin, acanthosis nigricans, delayed bone age, ovarian cysts, and insulin resistant diabetes mellitus [65, 69]. Cognitive development is usually normal.

4.2. Penttinen syndrome

Penttinen syndrome (PS) (MIM#601812) is an autosomal dominant condition caused by variants in the *PDGFRB* gene [70], which encodes the platelet-derived growth factor receptor beta (PDGFR-β), a membrane-bound receptor tyrosine-protein kinase that plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis, and migration [71]. PDGFR-β engages several well-characterized signaling pathways (e.g., Ras-MAPK, PI3K, and PLC-γ) which are known to be involved in multiple cellular and developmental responses [72].

The pathogenic mechanisms of PS are not known but have been related to deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [5]. Studies in fibroblasts from these patients have shown alterations in their morphology, senescence, and apoptosis. It seems that these processes are related to an increase in PDGFR-β autophosphorylation and the consequent phosphorylation of proteins such as STAT1, PLCγ1, PTPN11-Y580, and AKT [70].

Only eight cases of PS have been reported to date [73]. The phenotype starts during infancy with patients soon showing features of premature aging, although their growth may be normal or accelerated. These patients present acroosteolysis, progressive joint contractures, kyphoscoliosis, and generalized lipoatrophy. Skull anomalies range from open fontanelle to multiple craniosynostosis. Hair on the scalp is sparse. Their skin is particularly thin, dry and translucent with nodular keloid-like lesions at pressure sites. Premaxillary and maxillary retraction lead to pseudoprognathism and palpebral malocclusion. There is corneal opacity due to neovascularization. They may present muscle atrophy, although their strength is normal. Intellectual functions are preserved. Metabolic complications such as arteriosclerosis or diabetes mellitus are absent. Although exact life expectancy is not known, death may occur in the second decade of life [70].

4.3. Keppen-Lubinsky syndrome

Keppen-Lubinsky syndrome (KLS) (MIM#614098)is an autosomal dominant condition caused by variants in the *KCNJ6* gene [74], which encodes G protein-activated inward rectifier potassium channel 2, closed by an increase in intracellular ATP levels. This function links cellular metabolism to electrical excitability of the plasma membrane. This potassium channel is predominantly expressed in central nervous system neurons and generates slow inhibitory post-synaptic potentials, playing an important role in the control of resting membrane potential and regulation of cellular excitability. It may be involved in the regulation of insulin secretion by glucose and/or neurotransmitters acting through G-protein-coupled receptors [75].

Although the neurological disorders are similar to those observed in other types of potassium channelopathies [76], the developmental alteration and the involvement of adipose tissue and bone are poorly understood. Some studies have shown that voltage-gated K^+ channels are involved in the control of some cellular processes, including the adipogenic and osteogenic differentiation of human MSC [77]. Membrane depolarization by high concentrations of extracellular K^+ has also been shown to suppress the adipogenic markers PPARgamma, LPL, and integrin-binding sialoprotein during osteogenic differentiation. Finally, depolarization exerts its effect in the early differentiation process [77].

To date, four cases of KLS have been reported [74, 78]. The clinical picture begins at birth presenting a severe developmental delay. With the exception of one case [78], the other three patients presented different degrees of lipodystrophy, which was generalized in one case. They also present intellectual disability, hypertonia, hyperreflexia, microcephaly, micrognathia, prominent eyes, narrow nasal bridge, tented upper lip, high palate, open mouth, and extremely adherent and wrinkled skin. They also have flexion contractures, severe scoliosis and seizures. Laboratory tests are otherwise normal [74].

4.4. Warburg-Cinotti syndrome

Warburg-Cinotti syndrome (WRCN) (MIM#618175) is an autosomal dominant condition caused by variants in the *DDR2* gene [79], which encodes discoidin domain-containing receptor 2, a tyrosine kinase that is stimulated by collagen in the extracellular matrix. This enzyme regulates cell proliferation, differentiation, migration, and survival and controls extracellular matrix homeostasis and remodeling [79]. It is predominantly expressed in fibroblasts, chondrocytes, osteoblasts, and other connective-tissue cells of mesenchymal origin.

Regarding the pathogenetic mechanisms responsible for the phenotype of WRCN patients, studies in fibroblasts from these patients suggest that the variants present in this gene cause ligand-independent kinase activation [79]. According to the latter studies, the results suggest that the consequence of DDR2 activation in WRCN is targeted to a group of proteins with little signal-transduction crosstalk and well-known growth-stimulatory pathways, such as the RAS/ERK and PI3K/AKT pathways [79].

Six cases have been described to date [79-81]. The phenotype begins in childhood, although they were normal at birth. Some of the patients have already exceeded 50 years of age. The most prominent features of the phenotype are corneal vascularization and subsequent pannus, thin nose and small alae nasi, subcutaneous lipoatrophy in the face, hands and feet, generalized joint enlargements of the fingers, joint swelling, and contractures. Narrow palpebral fissures, reduced vision, long face, posteriorly rotated ears, abnormal teeth, keloid-like plaques, follicular hyperkeratosis, acroosteolysis, palmar fibrotic bands/cutaneous fusions, and loss of toenails/toes

may also be present. Height is normal and a higher prevalence of diabetes, dyslipidemia or hepatic steatosis has not been documented. All individuals have apparently normal intelligence [79].

4.5. Marfanoid-progeroid-lipodystrophy syndrome

Marfanoid-progeroid-lipodystrophy syndrome (MFLS) (MIM#616914) is an autosomal dominant condition caused by variants in the *FBN1* gene [82], which encodes fibrillin-1. Fibrillins are important components of the extracellular matrix. In addition, fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors. It also regulates osteoblast maturation by controlling the bioavailability of TGF-beta [83]. Regarding adipose tissue, asprosin, C-terminal cleavage product of profibrillin and its relationship with TGF-beta participate in the development of fat [84].

MFLS is a consequence of variants between exons 64 and 65 of the *FBN1* gene, located in 3' gene regions encoding the extreme C- terminal domains of fibrillin-1. These variants give rise to premature stop codons that escape nonsense mediated decay and lead to a truncated fibrillin-1, with a dominant negative effect [85]. An aberrant activation of the TGF-β pathway has been observed in Marfan syndrome, which could explain some musculoskeletal abnormalities [86], while Mao Lin et al. [85] have shown upregulation of this pathway in MFLS. On the other hand, other authors have shown that *FBN1* variants that cause MFLS have a dominant negative effect on asprosin secretion [87], which could explain the alterations in adipose tissue observed in this syndrome [84].

To date, eight cases of MFLS have been reported [85]. The onset of the phenotype occurs at birth. Life expectancy is unknown, although patients may reach adulthood. All patients presented with generalized lipodystrophy at birth, prematurity, accelerated growth with poor weight gain and progeroid facial features such as deep-set eyes with proptosis, downward-slanting palpebral fissures, and retrognathia. Other features that overlap with Marfan syndrome are arachnodactyly, digital hyperextensibility, myopia, ectopia lentis, and dural ectasia. Other signs that may be present are pinched nose, high and narrow palate, pectus excavatum, scoliosis/kyphosis, wrist sign, thumb sign, easy bruisability, diminished muscle bulk, lentigines spots on the trunk and back, aortic root dilatation, mitral valve prolapse, and prominent subcutaneous blood vessels. Psychomotor, pubertal

and breast development are normal. No premature graying, atherosclerosis, metabolic disturbances, or cardiovascular complications have been reported [82].

5. Conclusions

Progeroid syndromes constitute a heterogeneous group of disorders in which lipodystrophy is frequently present. Despite this, fewer than half of them present insulin resistance, dyslipidemia, or hepatic steatosis, all of which are comorbidities frequently associated with lipodystrophy syndromes as a consequence of ectopic lipid deposition [6]. I It is hence striking that entities in which lipodystrophy is severe, as it is the case of HGPS, metabolic and hepatic comorbidities are mild, unlike in the classic subtypes of generalized lipodystrophy [6].

Taking into account that metabolic comorbidities are usually present in progeroid syndromes with a longer life expectancy, even if the lipoatrophy is only partial (e.g., Werner syndrome), it could be speculated that insulin resistance, dyslipidemia, and/or hepatic steatosis would eventually develop over time. On the other hand, in some syndromes, such as cutis laxa, lipodystrophy is present only in some patients, while in others, such as those with Bloom's syndrome, the absence of adipose tissue is evident only in the early years or it is an inconspicuous sign, as is the case with Warburg-Cinotti syndrome.

Although the definition of progeroid syndromes as such should be based on evidence that demonstrates an alteration of the molecular mechanisms responsible for physiological aging, their clinical characterization is based on a sum total of signs that mimic old age. As is the case in the elderly, many of these signs are due to alterations of the mesenchymal tissues, which is still striking. In the case of physiological aging, it could be argued that these signs are a consequence of the physical stress that the tissues undergo over time since, ultimately, they are the tissues that maintain the structure of the body. The same could, to a certain extent, be stated with regard to skin signs. However, in progeroid syndromes, by definition, though the passage of time is not the problem, mesenchymal tissues are the most severely affected.

On the other hand, the physiological aging process does not evolve at the same speed in all organs and tissues, with the liver, for example, being a paradigmatic case of resistance to the passage of time [88]. Similarly, in many progeroid syndromes, organs such as the brain remain preserved, as is the case with HGPS and Werner syndrome. Along these lines, there is currently evidence that, at least in certain progeroid syndromes, there is a deterioration in the function of MSCs [89,90] and that, specifically in the case of Werner syndrome, there is a selective reduction in telomerase activity in cells of mesenchymal lineage in relation to those of neural lineage [91] and that progerin interferes with MSC function in HGPS [89], suggesting that the involvement of MSCs and their differentiation could contribute to the reduced potential for cellular homeostasis which is commonly associated with the aging process. Therefore, it could be speculated, as has been suggested by other authors [92], that the deterioration (a consequence of the different molecular processes defined in the hallmarks of aging) of these tissues and of the MSCs present in all of the tissues would play a primordial role not only in the external phenotype of the elderly, but also in the progressive loss of function of the rest of the organs and tissues of our body economy.

A relevant fact in the definition of progeroid syndromes is that they should be associated with a reduction in life expectancy and present molecular mechanisms similar to those that characterize physiological aging. Of the lipodystrophy-associated progeroid syndromes, a reduction in life expectancy has been confirmed in only 45% of them. It is possible that this could be due to the fact that some of these conditions, affecting young individuals, have only recently been described, and this in small numbers and without long-term follow-up. On the other hand, although some conditions clearly meet the nine hallmarks of aging, as is the case with HGPS and Werner syndrome, in some of them it has been possible to identify only some of these hallmarks, or else the information comes from studies which did not include analysis of these patients' cells [5].

Thus, for example, progeroid syndromes associated with nuclear envelope alterations fulfill all or most of the nine hallmarks of aging, although a reduction in life expectancy is well documented only in HGPS.

In conditions related to DNA damage or DNA repair defects, although some meet most of the hallmarks of aging and are characterized by reduced life expectancy (Werner, Bloom, and Cockayne), this is not the case for others such as MDPL syndrome, of which, although presenting a clearly progeroid clinical picture, the life expectancy is unknown, while it does not meet many of the hallmarks. The same is to a degree true of Wiedemann-Rautenstrauch syndrome, although, in general these patients die at an early age.

Among those syndromes related to mitochondrial dysfunction, with the exception of Fontaine progeroid syndrome, patients' life expectancy is unknown and there is no evidence of alterations in the primary hallmarks.

Finally, within the group of syndromes related to alterations in intracellular signaling pathways and in the extracellular matrix, some, such as Penttinen's syndrome, are characterized by reduced life expectancy, and, although no evidence of the presence of the primary hallmarks have been reported, there is evidence regarding the response to damage and to the so-called culprits of the phenotype, while others, such as SHORT syndrome, probably do not present a reduction in life expectancy. However, although the number of hallmarks of aging involved in the pathogenesis of this condition is important, much of this evidence does not come from SHORT patients [93-95].

Regarding the other syndromes of this group, such as Keppen-Lubinsky syndrome and Warburg-Cinotti syndrome, very few cases have been reported and little has been revealed of their pathogenetic mechanisms. Finally, although the MFLS syndrome phenotype is clearly suggestive of a progeroid condition with severe lipodystrophy with many of the hallmarks of aging present, it does not appear to present a reduction in life expectancy.

This said, it would be worth considering whether some of these syndromes actually mimic premature aging or if they are simply Mendelian disorders with a singular gestalt phenotype, such as SHORT syndrome or Warburg-Cinotti syndrome**.**

Although there is currently no cure for these disorders, at least one drug has been specifically authorized for one of them, namely, lonafarnib, a farnesyltransferase inhibitor, approved by the FDA

and EMA for the treatment of HGPS, which prolongs survival by approximately 2.5 years [96]. Other drugs in clinical trials include everolimus, a rapamycin analog, in association with lonafarnib for HGPS (ClinicalTrials.gov Identifier: NCT02579044), progerinin, a drug that reduces progerin expression, for HGPS and Werner syndrome (ClinicalTrials.gov Identifier: NCT04512963) and a recombinant human insulin-like growth factor 1 for patients with Werner syndrome and osteoporosis (ClinicalTrials.gov Identifier: NCT00004815). Recombinant human leptin has been successfully used in some isolated cases of atypical progeroid syndrome for the treatment of associated comorbidities [97].

Thus, there is clearly a need for the scientific community to reach a consensus on what should really be considered premature or accelerated aging as independent nosological entities, with a clear phenotypic definition and a minimum of molecular alterations typical of physiological aging.

6. References

1. Hennekam RCM (2020) The external phenotype of aging. Eur J Med Genet 63:103995. https://doi:10.1016/j.ejmg.2020.103995.
2. Chen H, Liu O, Chen S, Zhou Y (2022) Aging and Mesenchymal Stem Cells: Therapeutic Opportunities and Challenges in the Older Group. Gerontology 68:339-352. doi: 10.1159/000516668.
3. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194-217. https://doi:10.1016/j.cell.2013.05.039.
4. Martin GM (2005). Genetic modulation of senescent phenotypes in Homo sapiens. Cell 120:523-32. https://doi:10.1016/j.cell.2005.01.031.
5. Hennekam RCM (2020) Pathophysiology of premature aging characteristics in Mendelian progeroid disorders. Eur J Med Genet. 63:104028. https://doi:10.1016/j.ejmg.2020.104028.
6. Araujo-Vilar D, Santini F (2019) Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest 42:61-73. https://doi:10.1007/s40618-018-0887-z.
7. Guillín-Amarelle C, Fernández-Pombo A, Sánchez-Iglesias S, Araújo-Vilar D (2018) Lipodystrophic laminopathies: Diagnostic clues. Nucleus 9:249-260. https://doi:10.1080/19491034.2018.1454167.
8. Broers JL, Ramaekers FC, Bonne G, Yaou RB, Hutchison CJ (2006) Nuclear lamins: laminopathies and their role in premature ageing. Physiol Rev 86:967-1008. https://doi:10.1152/physrev.00047.2005.
9. Ashapkin VV, Kutueva LI, Kurchashova SY, Kireev II (2019) Are there common mechanisms between the Hutchinson-Gilford progeria syndrome and natural aging? Front Genet 10:455. https://doi:10.3389/fgene.2019.00455.
10. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Lévy N (2003) Lamin a truncation in Hutchinson-Gilford progeria. Science 300:2055. https://doi:10.1126/science.1084125.
11. Eriksson M, Brown WT, Gordon LB et al. (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 423: 293-298. https://doi:10.1038/nature01629.
12. Schnabel F, Kornak U, Wollnik B (2021) Premature aging disorders: A clinical and genetic compendium. Clin Genet 99:3-28. https://doi:10.1111/cge.13837.

13. Merideth MA, Gordon LB, Clauss S et al (2008) Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med 358:592-604. https://doi:10.1056/NEJMoa0706898.
14. Gordon LB, Brown WT, Collins FS (2019) Hutchinson-Gilford Progeria Syndrome. In: Adam MP, Ardinger HH Pagon SE, Wallace, L. J. H. Bean, K. Stephens, A. Amemiya (Eds.). GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1121/
15. Novelli G, Muchir A, Sangiuolo F (2002) Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am J Hum Genet 71:426-31.https://doi:10.1086/341908.
16. Camozzi D, D'Apice MR, Schena E, Cenni V, Columbaro M, Capanni C, Maraldi NM, Squarzoni E, Ortolani M, Novelli G, Lattanzi G (2012) Altered chromatin organization and SUN2 localization in mandibuloacral dysplasia are rescued by drug treatment. Histochem Cell Biol 138:643-51. https://doi:10.1007/s00418-012-0977-5.
17. Cenni V, D'Apice MR, Garagnani P, Columbaro M, Novelli G, Franceschi C, Lattanzi G (2018) Mandibuloacral dysplasia: A premature ageing disease with aspects of physiological ageing. Ageing Research Reviews 42:1–13. https://doi:10.1016/j.arr.2017.12.001.
18. Chiarini F, Evangelisti C, Cenni V, Fazio A, Paganelli F, Martelli AM, Lattanzi G (2019) The cutting edge: The role of mTOR signaling in laminopathies. Int J Mol Sci 20:847. https://doi:10.3390/ijms20040847.
19. Jéru I, Nabil A, El-Makkawy G, Lascols O, Vigouroux C, Abdalla E (2021) Two decades after mandibuloacral dysplasia discovery: Additional cases and comprehensive view of disease characteristics. Genes (Basel) 12:1508. https://doi:10.3390/genes12101508.
20. Sakka R, Marmouch H, Trabelsi M, Achour A, Golli M, Hannachi I, Kerkeni E, Monastiri K, Maazoul F, M'rad R (2021) Mandibuloacral dysplasia type A in five tunisian patients. Eur J Med Genet 64:104138. https://doi:10.1016/j.ejmg.2021.104138.
21. Hussain I, Patni N, Ueda M et al (2018) A novel generalized lipodystrophy-associated progeroid syndrome due to recurrent heterozygous LMNA p.T10I mutation. J Clin Endocrinol Metab 103:1005–1014. https://doi:10.1210/jc.2017-02078.
22. Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B, D'Apice MR, Novelli G, Crow Y (2009) Atypical progeroid syndrome due to heterozygous missense LMNA mutations. J Clin Endocrinol Metab 94: 4971–4983. https://doi:10.1210/jc.2009-0472.
23. Doubaj Y, De Sandre-Giovannoli A, Esteves-Vieira V, Navarro CL, Elalaoui SC, Tajir M, Lévy N, Sefiani A (2012) An inherited LMNA gene mutation in atypical progeria syndrome. Am J Med Genet A 158A:2881-7. https://doi:10.1002/ajmg.a.35557.
24. Hussain I, Jin RR , Baum HBA et al (2020) Multisystem progeroid syndrome with lipodystrophy, cardiomyopathy, and nephropathy Due to an LMNA p.R349W Variant. J Endocr Soc 4:bvaa104. https://doi:10.1210/jendso/bvaa104.
25. Magno S, Ceccarini G, Pelosini C et al (2020) Atypical progeroid syndrome and partial lipodystrophy due to LMNA gene p.R349W mutation. J Endocr Soc 4:bvaa108. https://doi:10.1210/jendso/bvaa108.
26. Agarwal AK, Fryns JP, Auchus RJ, Garg A (2003). Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. Hum Mol Genet 12:1995-2001. https://doi:10.1093/hmg/ddg213.
27. Hitzert MM, van der Crabben SN, Baldewsingh G, Ploos van Amstel HK, van den Wijngaard A, van Ravenswaaij-Arts CMA, Zijlmans CWR (2019) Mandibuloacral dysplasia type B (MADB): a cohort of eight patients from Suriname with a homozygous founder mutation in ZMPSTE24 (FACE1), clinical diagnostic criteria and management guidelines Orphanet Journal of Rare Diseases (2019) 14:294 https://doi.org/10.1186/s13023-019-1269-0.
28. Agarwal AK, Zhou XJ, Hall RK, Nicholls K, Bankier A, Van Esch H, Fryns JP, Garg A (2006) Focal segmental glomerulosclerosis in patients with mandibuloacral dysplasia owing to ZMPSTE24 deficiency. J Investig Med 54:208-13. https://doi:10.2310/6650.2006.05068.
29. Puente XS, Quesada V, Osorio FG et al (2011) Exome sequencing and functional analysis identifies BANF1 mutation as the cause of a hereditary progeroid syndrome Am J Hum Genet 88:650-6. https://doi.org/10.1016/j.ajhg.2011.04.010
30. Rose M, Bai B, Tang M, Cheong CM, Beard S, Burgess JT, Adams MN, O'Byrne KJ, Richard DJ, Gandhi NS, Bolderson E (2021) The impact of rare human variants on Barrier-To-Auto-Integration Factor 1 (Banf1) structure and function. Front Cell Dev Biol 9:775441. https://doi.org/10.3389/fcell.2021.775441.

31. Cabanillas R, Cadiñanos J, Villameytide JAF, Pérez M, Longo J, Richard JM, Alvarez R, Durán NS, Illán R, González DJ, López-Otín C (2011) Néstor-Guillermo progeria syndrome: A novel premature aging condition with early onset and chronic development caused by BANF1 mutations. Am J Med Genet Part A 155: 2617–2625. https://doi:10.1002/ajmg.a.34249.
32. Fisher HG, Patni N, Scheuerle AE (2020) An additional case of Néstor-Guillermo progeria syndrome diagnosed in early childhood. Am J Med Genet A 182:2399-2402. https://doi.org/10.1002/ajmg.a.61777.
33. Lord CJ, Ashworth A (2012) The DNA damage response and cancer therapy. Nature 481:287-94. https://doi.org/10.1038/nature10760.
34. Lu H, Davis AJ (2021) Human RecQ Helicases in DNA Double-Strand Break Repair. Front Cell Dev Biol 9:640755. https://doi.org/10.3389/fcell.2021.640755.
35. Gudmundsrud R, Skjånes TH, Gilmour BC, Caponio D, Lautrup S, Fang EF (2021) Crosstalk among DNA damage, mitochondrial dysfunction, impaired mitophagy, stem cell attrition, and senescence in the accelerated ageing disorder Werner syndrome. Cytogenet Genome Res 161:297-304. https://doi:10.1159/000516386.
36. Zhang W, Li J, Suzuki K et al. (2015) Aging stem cells. A Werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. Science 348:1160-3. doi: 10.1126/science.aaa1356.
37. Ishikawa N, Nakamura K, Izumiyama-Shimomura N et al. (2011). Accelerated in vivo epidermal telomere loss in Werner syndrome. Aging (Albany NY) 3:417-29. doi: 10.18632/aging.100315.
38. Lauper JM, Krause A, Vaughan TL, Monnat Jr RJ (2013) Spectrum and risk of neoplasia in Werner syndrome: a systematic review. PLoS One 8:e59709. https://doi.org/10.1371/journal.pone.0059709.
39. Goh KJ, Chen JH, Rocha N, Robert K Semple RK (2020) Human pluripotent stem cell-based models suggest preadipocyte senescence as a possible cause of metabolic complications of Werner and Bloom Syndromes. Sci Rep 10:7490. https://doi:10.1038/s41598-020-64136-8.
40. Maciejczyk M, Mikoluc B, Pietrucha B, Heropolitanska-Pliszka E, Pac M, Motkowski R, Car H (2017) Oxidative stress, mitochondrial abnormalities and antioxidant defense in Ataxia-telangiectasia, Bloom syndrome and Nijmegen breakage syndrome. Redox Biol 11:375-383. https://doi:10.1016/j.redox.2016.12.030.
41. Cunniff C, Bassetti JA, Ellis NA (2017) Bloom's syndrome: clinical spectrum, molecular pathogenesis, and cancer predisposition. Mol Syndromol 8:4-23. https://doi:10.1159/000452082.
42. Tiwari V, Wilson 3rd DM (2019) DNA damage and associated DNA repair defects in disease and premature aging. Am J Hum Genet 105:237-257. https://doi:10.1016/j.ajhg.2019.06.005.
43. Pascucci B, Fragale A, Marabitti V, Leuzzi G, Calcagnile AS, Parlanti E, Franchitto A, Dogliotti E, D'Errico M (2018). CSA and CSB play a role in the response to DNA breaks. Oncotarget 9:11581-11591. https://doi:10.18632/oncotarget.24342.
44. Batenburg NL, Walker JR, Noordermeer SM, Moatti N, Durocher D, Zhu XD (2017) ATM and CDK2 control chromatin remodeler CSB to inhibit RIF1 in DSB repair pathway choice. Nat Commun 8:1921-1921. https://doi:10.1038/s41467-017-02114-x.
45. Tiwari V, Baptiste BA, Okur MN, Bohr VA (2021) Current and emerging roles of Cockayne syndrome group B (CSB) protein. Nucleic Acids Res 49:2418-2434. https://doi:10.1093/nar/gkab085
46. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA (2017) Cockayne syndrome: Clinical features, model systems and pathways. Ageing Res Rev 33:3-17. https://doi:10.1016/j.arr.2016.08.002.
47. Lessel D, Vaz B, Halder S et al (2014) Mutations in SPRTN cause early onset hepatocellular carcinoma, genomic instability and progeroid features. Nat Genet 46:1239-44. https://doi:10.1038/ng.3103.
48. Ruggiano A, Ramadan K (2021) The trinity of SPRTN protease regulation. Trends Biochem Sci 46:2-4. https://doi:10.1016/j.tibs.2020.10.007.
49. Ruijs MWG, van Andel RNJ, Oshima J, Madan K, Nieuwint AWM, Aalfs CM. Atypical progeroid syndrome: an unknown helicase gene defect? Am J Med Genet A 116A:295-9. https://doi:10.1002/ajmg.a.10730.
50. Murdocca M, Spitalieri P, De Masi C et al (2021) Functional analysis of POLD1 p.ser605del variant: the aging phenotype of MDPL syndrome is associated with an impaired DNA repair capacity. Aging (Albany NY) 13:4926-4945. https://doi:10.18632/aging.202680.

51. Weedon MN, Ellard S, Brindle MJ et al (2013) An in-frame deletion at the polymerase active site of POLD1 causes a multisystem disorder with lipodystrophy. Nat Genet 45:947-50. https://doi:10.1038/ng.2670.
52. Murdocca M, Spitalieri P, Cappello A, Colasuonno F, Moreno S, Candi E, D'Apice MR, Novelli G, Sangiuolo F (2022) Mitochondrial dysfunction in mandibular hypoplasia, deafness and progeroid features with concomitant lipodystrophy (MDPL) patients. Aging (Albany NY). 14:1651-1664. https://doi:10.18632/aging.203910.
53. Jay AM, Conway RL, Thiffault I, Saunders C, Farrow E, Adams J, Toriello HV (2016) Neonatal progeriod syndrome associated with biallelic truncating variants in POLR3A. Am J Med Genet A 170:3343-3346. https://doi:10.1002/ajmg.a.37960.
54. Tiku V, Antebi A (2018) Nucleolar Function in Lifespan Regulation. Trends Cell Biol 2018 28:662-672. https://doi:10.1016/j.tcb.2018.03.007.
55. Paolacci S, Bertola D, Franco J, Mohammed S, Tartaglia M, Wollnik B, Hennekam RC (2017) Wiedemann-Rautenstrauch syndrome: A phenotype analysis. Am J Med Genet A 173:1763-1772. https://doi:10.1002/ajmg.a.38246.
56. Báez-Becerra C, Valencia-Rincón E, Velásquez-Méndez K, Ramírez-Suárez NJ, Guevara C, Sandoval-Hernandez A, Arboleda-Bustos CE, Olivos-Cisneros L, Gutiérrez-Ospina G, Arboleda H, Arboleda G (2020) Nucleolar disruption, activation of P53 and premature senescence in POLR3A-mutated Wiedemann-Rautenstrauch syndrome fibroblasts. Mech Ageing Dev 192:111360. https://doi:10.1016/j.mad.2020.111360.
57. Traba J, Del Arco A, Duchen MR, Szabadkai G, Satrústegui J (2012) SCaMC-1 promotes cancer cell survival by desensitizing mitochondrial permeability transition via ATP/ADP-mediated matrix Ca(2+) buffering. Cell Death Differ 19:650-60. https://doi:10.1038/cdd.2011.139.
58. Ehmke N, Graul-Neumann L, Smorag L et al (2017) De novo mutations in SLC25A24 cause a craniosynostosis syndrome with hypertrichosis, progeroid appearance, and mitochondrial Dysfunction. Am J Hum Genet 101:833-843. https://doi:10.1016/j.ajhg.2017.09.016.
59. Writzl K, Maver A, Lidija Kovačič L et al (2017) De novo mutations in SLC25A24 cause a disorder characterized by early aging, bone dysplasia, characteristic face, and early demise. Am J Hum Genet 101:844-855. https://doi:10.1016/j.ajhg.2017.09.017.
60. Armstrong LC, Saenz AJ, Bornstein P (1999) Metaxin 1 interacts with metaxin 2, a novel related protein associated with the mammalian mitochondrial outer membrane. J Cell Biochem 74:11-22.
61. Elouej S, Harhouri K, Mao ML et al (2020) Loss of MTX2 causes mandibuloacral dysplasia and links mitochondrial dysfunction to altered nuclear morphology. Nat Commun 11:4589. https://doi:10.1038/s41467-020-18146-9.
62. Fischer-Zirnsak B, Escande-Beillard N, Ganesh J et al (2015) Recurrent de Novo mutations affecting residue Arg138 of pyrroline-5-carboxylate synthase cause a progeroid form of autosomal-Dominant cutis laxa. Am J Hum Genet 97:483-92. https://doi:10.1016/j.ajhg.2015.08.001.
63. Reversade B, Escande-Beillard N, Dimopoulos A et al (2009) Mutations in PYCR1 cause cutis laxa with progeroid features. Nat Genet 2009 Sep;41(9):1016-21. https://doi:10.1038/ng.413.
64. Coutelier M, Goizet C, Durr A et al. (2015) Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain 138:2191-205. https://doi:10.1093/brain/awv143.
65. Thauvin-Robinet C, Auclair M, Diploma L et al (2013) PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy. Am J Hum Genet 93:141-9. https://doi:10.1016/j.ajhg.2013.05.019.
66. Engelman JA, Luo J, Cantley LC (2006) The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet 7:606-19. https://doi:10.1038/nrg1879.
67. Mukherjee A, Rotwein P (2012) Selective signaling by Akt1 controls osteoblast differentiation and osteoblast-mediated osteoclast development. Mol Cell Biol 32:490-500. https://doi:10.1128/MCB.06361-11.
68. Donlon TA, Chen R, Masaki KH, Willcox BJ, Morris BJ (2022) Association with longevity of phosphatidylinositol 3-kinase regulatory subunit 1 gene variants stems from protection against mortality risk in men with cardiovascular disease. Gerontology 68:162-170. https://doi:10.1159/000515390.

69. Chudasama KK, Winnay J, Johansson S et al (2013) SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. Am J Hum Genet 93:150-7. https://doi:10.1016/j.ajhg.2013.05.023.
70. Bredrup C, Stokowy T, McGaughran J et al (2019) A tyrosine kinase-activating variant Asn666Ser in PDGFRB causes a progeria-like condition in the severe end of Penttinen syndrome. Eur J Hum Genet 27:574-581. https://doi:10.1038/s41431-018-0323-z.
71. Lemmon MA, Schlessinger J (2010) Cell signaling by receptor tyrosine kinases. Cell 141:1117-34. https://doi:10.1016/j.cell.2010.06.011.
72. Andrae J, Gallini R, Betsholtz C (2008) Role of platelet-derived growth factors in physiology and medicine. Genes Dev 22:1276-312. https://doi:10.1101/gad.1653708.
73. Aggarwal B, Correa ARE, Gupta N, Jana M, Kabra M (2022) First case report of Penttinen syndrome from India. Am J Med Genet A 188:683-687. https://doi:10.1002/ajmg.a.62558.
74. Masotti A, Uva P, Davis-Keppel L et al (2015) Keppen-Lubinsky syndrome is caused by mutations in the inwardly rectifying K+ channel encoded by KCNJ6. Am J Hum Genet 96:295-300. https://doi:10.1016/j.ajhg.2014.12.011.
75. Cooper A, Grigoryan G, Guy-David L, Tsoory MM, Chen A, Reuveny E (2012) Trisomy of the G protein-coupled K+ channel gene, Kcnj6, affects reward mechanisms, cognitive functions, and synaptic plasticity in mice. Proc Natl Acad Sci 109: 2642–2647. https://doi:10.1073/pnas.1109099109.
76. Kessi M, Chen B, Peng J, Tang Y, Olatoutou E, He F, Yang L , Yin F (2020) Intellectual disability and potassium channelopathies: a systematic review. Front Genet 11:614. https://doi:10.3389/fgene.2020.00614.
77. Sundelacruz S, Levin M, Kaplan DL (2008). Membrane potential controls adipogenic and osteogenic differentiation of mesenchymal stem cells. PLoS One 3:e3737. https://doi:10.1371/journal.pone.0003737.
78. Horvath GA, Zhao Y, Tarailo-Graovac M et al (2018) Gain-of-function KCNJ6 mutation in a severe hyperkinetic movement disorder phenotype. Neuroscience 384:152-164. https://doi:10.1016/j.neuroscience.2018.05.031.
79. Xu L, Jensen H, Johnston JJ et al (2018) Recurrent, activating variants in the receptor tyrosine kinase DDR2 cause Warburg-Cinotti syndrome. Am J Hum Genet 103:976-983. https://doi:10.1016/j.ajhg.2018.10.013.
80. Warburg M, Ullman S, Jensen H, Pedersen H, Kobayashi T, Russell B, Tranebjaerg L, Richard G, Brøndum-Nielsen K (2006) Blepharophimosis, corneal vascularization, deafness, and acroosteolysis: a "new" syndrome? Am J Med Genet A 140:2709-13. https://doi:10.1002/ajmg.a.31543.
81. Cinotti E, Ferrero G, Paparo F, Papadia M, Faravelli F, Rongioletti F, Traverso C, Di Maria E. Arthropathy, osteolysis, keloids, relapsing conjunctival pannus and gingival overgrowth: a variant of polyfibromatosis? Am J Med Genet A 161A:1214-20. https://doi:10.1002/ajmg.a.35908.
82. Graul-Neumann LM, Kienitz T, Robinson PN, Baasanjav S, Karow B, Gillessen-Kaesbach G, Fahsold R, Schmidt H, Hoffmann K, Passarge E (2010) Marfan syndrome with neonatal progeroid syndrome-like lipodystrophy associated with a novel frameshift mutation at the 3' terminus of the FBN1-gene. Am J Med Genet A 152A:2749-55. https://doi:10.1002/ajmg.a.33690.
83. Jensen SA, Handford PA (2016) New insights into the structure, assembly and biological roles of 10-12 nm connective tissue microfibrils from fibrillin-1 studies. Biochem J 473:827-38. https://doi:10.1042/BJ20151108.
84. Muthu ML, Reinhardt DP (2020) Fibrillin-1 and fibrillin-1-derived asprosin in adipose tissue function and metabolic disorders. J Cell Commun Signal 14:159-173. https://doi:10.1007/s12079-020-00566-3.
85. Lin M, Liu Z, Liu G et al (2020) Genetic and molecular mechanism for distinct clinical phenotypes conveyed by allelic truncating mutations implicated in FBN1. Mol Genet Genomic Med 8:e1023. https://doi:10.1002/mgg3.1023.
86. Buchan JG, Alvarado DM, Haller GE et al (2014) Rare variants in FBN1 and FBN2 are associated with severe adolescent idiopathic scoliosis. Hum Mol Genet 23:5271-82. https://doi:10.1093/hmg/ddu224.
87. Romere C, Duerrschmid C, Bournat J et al (2016) Asprosin, a fasting-induced glucogenic protein hormone. Cell 165:566-79. https://doi:10.1016/j.cell.2016.02.063.

88. Verzaro R, Minervini M, Gridelli B (2008) Toward "no age limit" for liver transplant donors. Transplantation.85:1869-70. https://doi:10.1097/TP.0b013e31817b00c2.
89. Scaffidi P, Misteli T (2008) Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. Nat. Cell Biol. 10:452–459. https://doi:10.1038/ncb1708.
90. Tu J, Wan C, Zhang F, Cao L, Law PWN, Tian Y, Lu G, Rennert OM, Chan WY, Cheung HH (2020) Genetic correction of Werner syndrome gene reveals impaired pro-angiogenic function and HGF insufficiency in mesenchymal stem cells. Aging Cell 19:e13116. https://doi:10.1111/acel.13116.
91. Cheung HH, Liu X, Canterel-Thouennon L, Li L, Edmonson C, Rennert OM (2014) Telomerase protects werner syndrome lineage-specific stem cells from premature aging. Stem Cell Reports. 2:534-46. https://doi:10.1016/j.stemcr.2014.02.006.
92. Infante A, Rodríguez CI (2021) Cell and cell-free therapies to counteract human premature and physiological aging: MSCs come to light. J Pers Med 11:1043. https://doi:10.3390/jpm11101043.
93. Guo Z, He Y, Wang S, Zhang A, Zhao P, Gao C, Cao B (2011) Various effects of hepatoma-derived growth factor on cell growth, migration and invasion of breast cancer and prostate cancer cells. Oncol Rep 2011 Aug;26(2):511-7. https://doi:10.3892/or.2011.1295.
94. You L, Wang Z, Li H, Shou J, Jing Z, Xie J, Sui X, Pan H, Han W (2015) The role of STAT3 in autophagy. Autophagy. 11:729-39. https://doi:10.1080/15548627.2015.1017192.
95. Cohen PR, Tomson BN, Elkin SK, Marchlik E, Carter JL, Razelle Kurzrock (2016) Genomic portfolio of Merkel cell carcinoma as determined by comprehensive genomic profiling: implications for targeted therapeutics. Oncotarget 7:23454-67. https://doi:10.18632/oncotarget.8032.
96. Gordon LB, Shappell H, Massaro J, D'Agostino RB Sr, Brazier J, Campbell SE, Kleinman ME, Kieran MW (2018) Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford Progeria Syndrome. JAMA 319:1687-1695. https://doi:10.1001/jama.2018.3264.
97. Araujo-Vilar D, Sánchez-Iglesias S, Guillín-Amarelle C et al. (2015) Recombinant human leptin treatment in genetic lipodystrophic syndromes: the long-term Spanish experience. Endocrine 49:139-47. https://doi:10.1007/s12020-014-0450-4.

Table 1. Phenotypic characteristics of aging

Early graying of hair	Loss of hair	Fine hair
Straight lower part forehead	Cataract	Deeply set eyes
Hearing loss	Flat malae	Loss of nasal cartilage
Depressed nasal tip	Prominent nasolabial folds	Sagging cheeks
Loss of permanent teeth	Downturned corners mouth	Small mandible
Retrognathia	Lipodystrophy	Decreased joint mobility
Sarcopenia	Increased skin wrinkling	Fragile skin
Loss of skin elasticity	Skin hyperpigmentations	Generalized decr pigmentation
Decrease of height	Osteoporosis	Arteriosclerosis

Cancer	Hypogonadism/fertility loss	Premature menopause
Diabetes mellitus type 2	Vulnerability to infections	Tremor
Loss of cognitive abilities		

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Table 2. Lipodystrophy-associated progeroid syndromes

Syndrome	Gene	No. patients/Prevalence	Age range	Inheritance	MIM
Hutchinson-Gilford progeria syndrome	*LMNA*	1:20000000	2-20	AD (*de novo*)	#176670
Mandibulo-acral dysplasia (A and B)	*LMNA/ZMPSTE24*	~65	6-48	AR	#248370 /#608612
Nestor-Guilermo progeria syndrome	*BANF1*	3	1-35	AR	#614008
Werner syndrome	*RECQL2*	1:10000000	20-55	AR	#277700
Cockayne syndrome (A and B)	*ERCC8/ERCC6*	1:200000	0-30	AR	#216400/#133540
Cutis laxa, autosomal dominant 3	*ALDH18A1*	10	1-13	AD	#616603
Penttinen syndrome	*PDGFRB*	8	7-41	AD	#601812
MDPL syndrome	*POLD1*	26	8-62	AD (de novo)	# 615381
Fontaine progeroid syndrome	*SLC25A24*	11	0.5-15	AD (de novo)	#612289
SHORT syndrome	*PIK3R1*	42	0-79	AD	#269880
Wiedemann-Rautenstrauch syndrome	*POLR3A*	20	0-21	AR	# 264090
Mulvihill-Smith syndrome†	?	~7	1-30	AR	%176690
MFLS	*FBN1*	8	3-27	AD	#616914
Warburg-Cinotti syndrome	*DDR2*	6	3-58	AD	#618175
Bloom syndrome	*RECQL3*	~300	0.5-30	AR	#210900

Syndrome	Gene	No. patients/Prevalence	Age range	Inheritance	MIM
LMNA-associated atypical progeroid syndromes*	*LMNA*	~20	8-55	AD	Not in OMIM
Cutis laxa, autosomal recessive, type IIB*	*PYCR1*	43	0-9	AR	#612940
Ruijs-Aalfs syndrome*	*SPRTN*	3	4-18	AR	#616200
Mandibuloacral dysplasia progeroid syndrome*	*MTX2*	7	0-17	AR	#619127
Keppen-Lubinsky syndrome*	*KCNJ6*	4	0-12	AD	#614098

*: Additional lipodystrophy-associated progeroid syndromes; ✝: Not included in this review because the causal gene is not known; MDPL: Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome; MFLS: marfanoid-progeroid-lipodystrophy syndrome; AR: autosomal dominant; AR:autosomal recessive

Figure legends

Fig. 1. Heatmap of main signs of lipodystrophy-associated progeroid syndromes. Dark-red color denotes high severity or frequency, yellow denotes low severity or frequency. Blue color denotes information not available. Atypical PS: LMNA-associated atypical progeroid syndrome; HGPS: Hutchinson-Gilford Progeria Syndrome; Fontaine P. S.: Fointaine Progeroid syndrome; NGPS: Nestor-Guillermo Progeria Syndrome; MAD: Mandibuloacral dysplasia; W-R S.: Wiedemann-Rautenstrauch syndrome; MDPS: Mandibuloacral dysplasia progeroid syndrome; MDPL S.: Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome; MFLS: Marfanoid-progeroid-lipodystrophy syndrome.

Fig. 2. Heatmap of signs related to mesenchymal tissues present in lipodystrophy-associated progeroid syndromes. Dark-red color denotes high severity or frequency, yellow denotes low severity or frequency. HGPS: Hutchinson-Gilford Progeria Syndrome; NGPS: Nestor-Guillermo Progeria Syndrome; MAD: Mandibuloacral dysplasia; MDPS: Mandibuloacral dysplasia progeroid syndrome; W-R S.: Wiedemann-Rautenstrauch syndrome; MFLS: Marfanoid-progeroid-lipodystrophy syndrome.

Fig. 3: A-D: 7 year-old boy with Hutchinson-Gilford Progeria syndrome. A: Note generalized lipodystrophy, leucomelanodermic maculae, generalized absence of hair (including eyebrows and eyelashes), sarcopenia, dental crowding, and joint contractures; B, C: Beaked nose, facial wrinkles, prominent vein tree in the skull, absence of the earlobe and micrognathia/retrognathia; D: nail dystrophy and joint contractures. E: 20-year-old man with *LMNA*-associated atypical progeroid syndrome (generalized lipodystrophy-associated progeroid syndrome, *de novo* p.(Thr10Ile) variant). Note generalized lipodystrophy, sarcopenia, sparse scalp hair, and hand and foot contractures. This patient suffered from dilated cardiomyopathy and underwent a heart transplant. F: 40–year-old man with Werner syndrome. Note partial lipodystrophy affecting limbs, sarcopenia, and sparse, and gray hair.

Figure 1

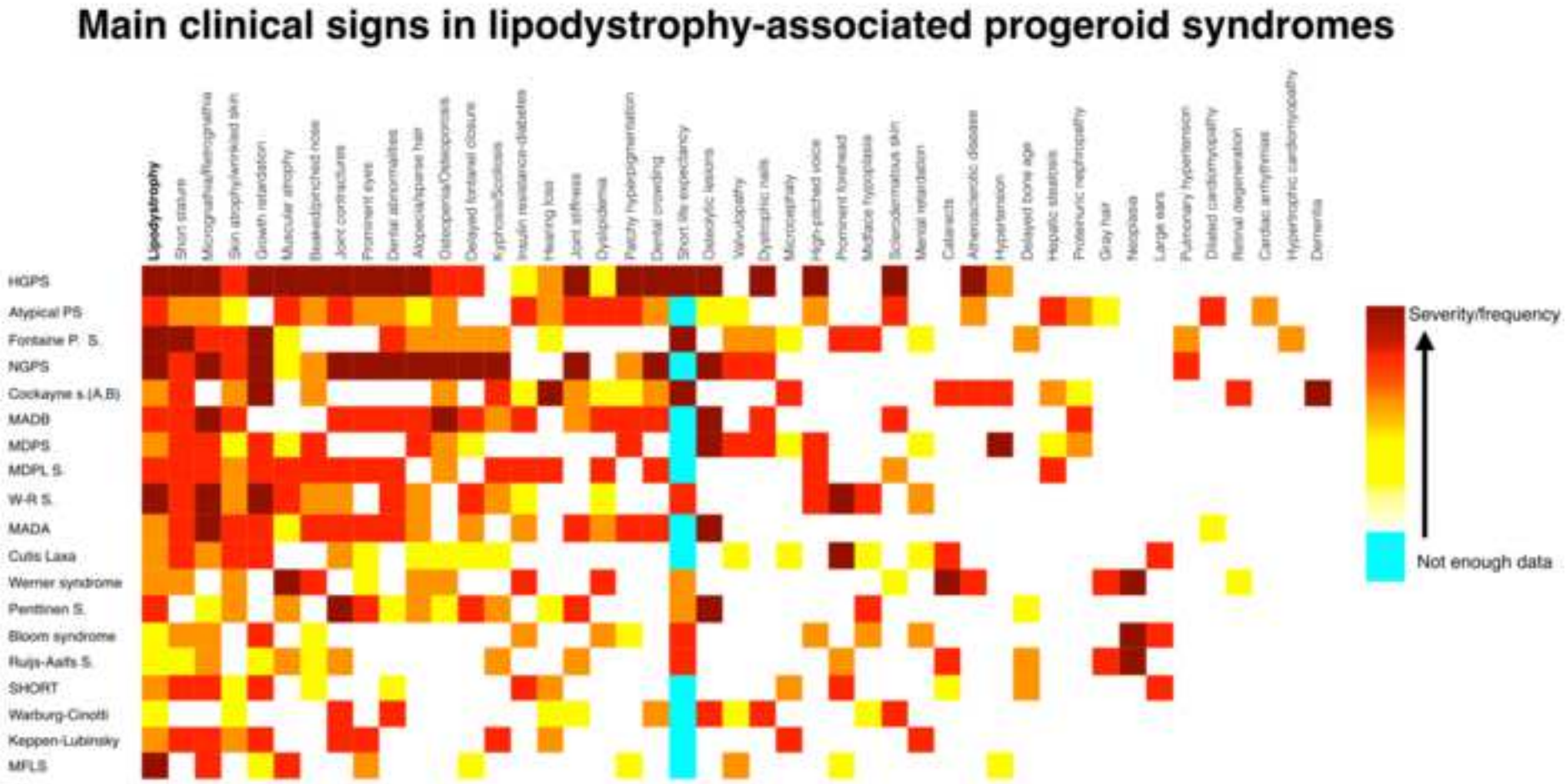

Figure 2

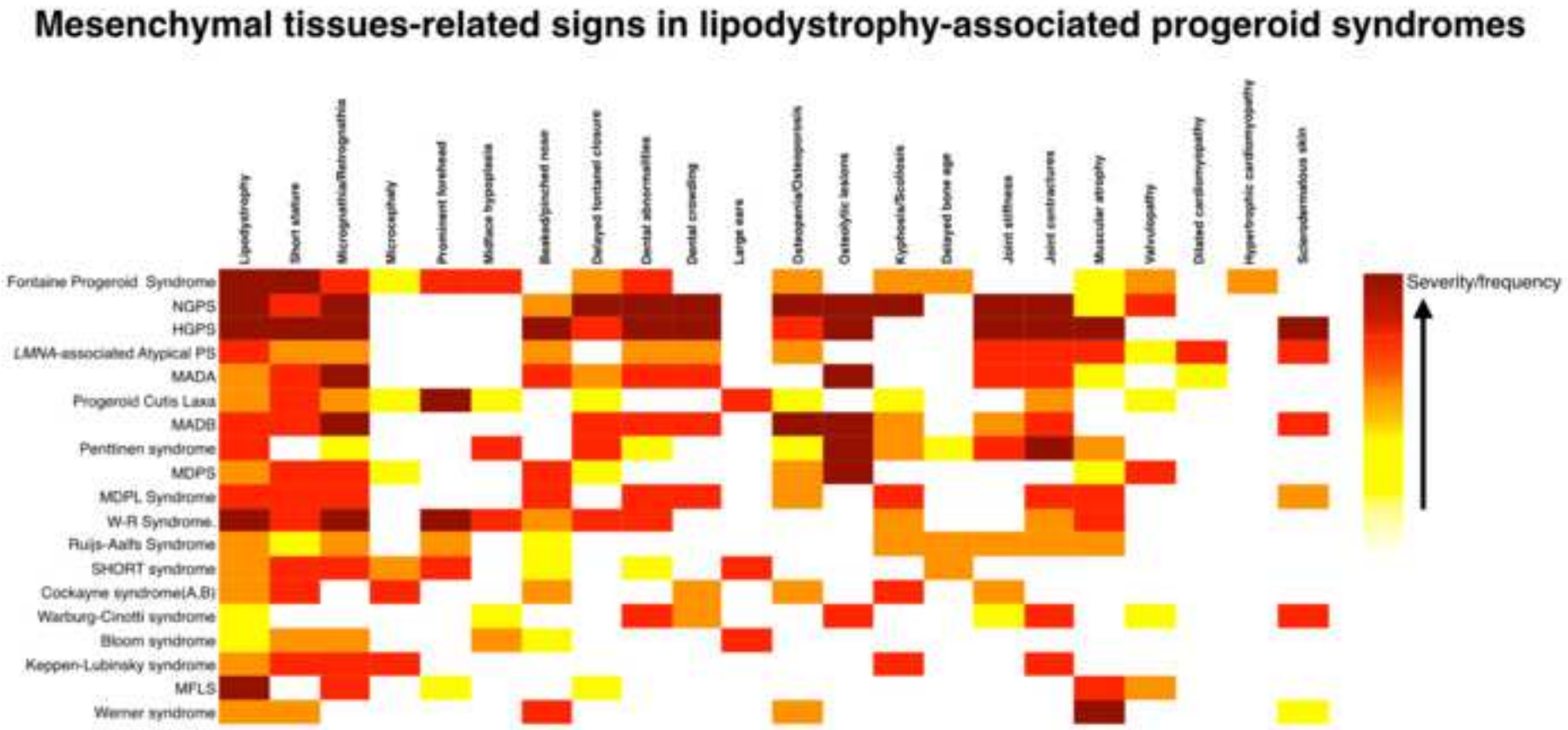

Figure 3

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