Internal Medicine Grand Rounds
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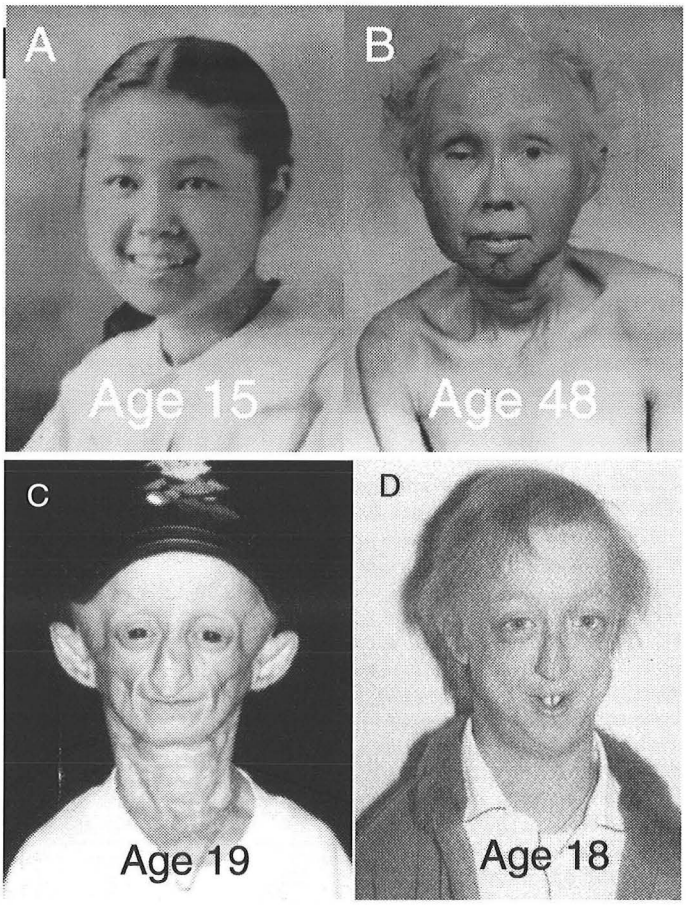
GENETIC BASIS OF PROGEROID SYNDROMES



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Special Interests:
Lipodystrophies and other disorders of adipose tissue
Progeroid syndromes
Lipoprotein disorders in diabetes
Nutrition in patients with diabetes
Regional obesity, insulin resistance and syndrome 'x'

Cover illustration:

A Japanese woman with Werner's syndrome at the age of 15 years (A) and at the age of 48 years (B) (Photo from the University of Washington Werner syndrome Home Page) Originally published by Epstein et al. (37). The disorder is due to mutations in *WRN* gene. A 19-year-old boy with Hutchinson-Gilford Progeria Syndrome (Photo provided by The Progeria Research Foundation) due to *LMNA* mutation. An 18-year-old girl with mandibuloacral dysplasia due to zinc metalloproteinase mutations (Photo courtesy of Dr. Jean-Pierre Fryns, Belgium).

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Historical Background

Approximately, 2500 years ago, Siddhartha, a young Indian prince, who later became known as Buddha, was kept isolated from the world by his father because the astrologers had predicted that there was a possibility that he may become a saint. As a young adult, he went outside the palace for the first time in a chariot and was struck by three sightings: 1. an old man with bent back walking with the help of a cane, 2. a man crying in pain and suffering from disease and 3. A dead man being carried on the shoulders of his relatives for cremation. He asked his minister whether he was going to grow old, suffer from ailments, and then eventually die. He further enquired why humans have to undergo suffering from diseases and aging. Since the minister was unable to answer Siddhartha's queries satisfactorily, he decided to find the answers himself. He left his young son and wife to find the underlying reason for the diseases of mankind but most importantly to solve the puzzle of mystery of natural process of aging and death. He achieved renunciation and got enlightenment under the Banyan tree, and spread the words of wisdom throughout the entire continent. I guess, Buddha was not the first to be intrigued by the process of aging and death and many a civilizations had searched for potions or remedies to attain immortality without success. Certainly, Buddha's understanding of the processes of aging and death were not scientific.

Even today, many of us, scientists and physicians, are still searching for the mechanisms involved in the aging processes, which largely remain mysterious. While basic scientists have elucidated some pathways involved in the process of aging from studies in experimental animals such as *C. elegans, D. melanogaster* and mice, however whether they play a role in aging in humans remains unclear. As far as human aging is concerned, two models have been explored at this time: 1. to study genetic basis of longevity and 2. To study genetic basis of premature aging syndromes. In this grand round, I will review evidence from human progeroid syndromes as in the last decade, substantial progress has been made in understanding these rare monogenic disorders. Understanding the genetic basis of progeroid syndromes may have some bearing on the normal processes involved in aging.

Normal Aging Process

Before in depth review of such progeroid syndromes, a general description of what constitutes normal aging is in order. When does the normal process of aging start? Aging can be defined as a time-dependent loss of organ or tissue function after attaining full reproductive potential. Ancient Indian texts, Vedas, assumed the normal life span of humans to be 100 years and divided the life into four stages, each lasting 25 years; Brahmacharya (Student), Grihastha (Household or Married), Vanaprastha (Retired) and Sanyasa (Renounced). The clinical features of aging mostly manifest during the last two stages.

Among the many clinical features of aging, the one, which comes to the mind first, and is most evident, is graying of the hair on the scalp, face and body. Graying is also accompanied by the loss of hair. On the other hand, increase in hair growth at aberrant places such as the pinnae, ear lobes, inside the nasal cavity and eyebrows. Another striking clinical feature is wrinkling of the skin, which is likely due to atrophy of the epidermis and dermis as well as loss of underlying subcutaneous adipose tissue and elastic tissue.

Ophthalmologic manifestations of aging include arcus senilis, presbyopia (reduced accommodative power due to stiffening of the lens and ciliary body dysfunction), cataracts

(nuclear sclerosis) and macular degeneration (white deposits on retina called drusens). Aging also results in the loss of skeletal muscle mass, increased deposition of truncal and intra-abdominal adipose tissue and osteoporosis. Osteoporosis may manifest with loss of height and development of thoracic kyphosis. Many subjects also develop osteoarthritis. Loss of teeth occurs after the sixties.

Endocrinologic manifestations include menopause in females and benign prostatic hypertrophy in males. Both the genders develop progressive abnormal glucose tolerance, hyperuricemia and hyperlipidemia. Organ specific manifestations of aging include senile dementia, sick sinus syndrome and arrhythmias, gradually declining renal functions. Aging is also associated with atherosclerotic vascular disease and arteriosclerosis including calcification of the arterial wall. Another clinical feature associated with aging is increase incidence of cancers, especially skin cancers.

The critical question still remains how many of these manifestations are purely due to normal aging processes and how many are due to an ongoing interaction between the human beings and environment. The monogenic progeroid syndromes do not manifest all the features of normal aging, however, each one presents with some clinical features and thus some have termed these disorders of "segmental" disorders of accelerated or premature aging.

The progeroid disorders can be classified as autosomal dominant or recessive disorders according to the mode of inheritance. A classification is presented in Table 1.

Table 1. Classification of Monogenic Progeroid Syndromes

A. Autosomal Dominant Syndromes:

1. Hutchinson-Gilford Progeria Syndrome (*LMNA* mutations)
2. Atypical Progeroid Syndrome (*LMNA* mutations)
3. Miscellaneous

B. Autosomal Recessive Syndromes:
1. Werner's syndrome (*WRN/RECQ3* mutations)
2. Mandibuloacral dysplasia associated progeroid syndrome
   a. *LMNA* mutations
   b. *ZMPSTE24* mutations
   c. Other varieties
3. Idiopathic arthropathy associated progeroid syndrome (*LMNA* mutation)
4. Neonatal progeroid syndrome
5. Metageria/Acrogeria syndromes
6. Others
   a. Bloom syndrome (*BLM/RECQ2* mutations)
   b. Rothmund-Thomson syndrome (*RECQ4* mutations)
   c. Cockayne syndrome
   d. Miscellaneous

A. Autosomal Dominant Syndrome:

1. Hutchinson-Gilford Progeria Syndrome (HGPS)

HGPS (OMIM 176670) is a rare and fatal premature aging syndrome first described by Hutchinson (1) and later referred to as progeria by Gilford (2). HGPS occurs in about 1 in 4-8 million births. Approximately 100 patients have been reported with HGPS so far (3-5). These patients appear normal at birth but soon thereafter develop features of early aging even as neonates. Profound delay in growth can be seen as early as six months of age. Loss of scalp hair, eyebrows and eyelashes results in total alopecia. Patients also have extensive loss of sc fat with generalized lipodystrophy; however, systematic evaluation of pattern of body fat distribution has not been done. The veins over the scalp become prominent. Other features include graying of hair, micrognathia, prominent eyes, beaked nose, shrill voice, and extensive wrinkling of the skin due to loss of underlying adipose tissue, poor sexual development, joint contractures and severe atherosclerosis (5). The skin appears old and pigmented age spots appear. Death usually occurs between the ages of 7 to 28 years, with a median age of 13.4 years (3). Other features associated with aging such as cataracts, diabetes, hyperlipidemia and malignancies are not usually present (5).

The patients usually weigh only 12-15 kg even as teenagers and average 40 inches in height. They show some features overlapping with mandibuloacral dysplasia with small jaw, resorption of clavicles and terminal bones of the fingers (acro-osteolysis) (5). The joint contractures usually develop around the elbow and knee and some develop aseptic necrosis of the head of the femur and hip dislocation. Interestingly, the patients have normal or above normal intelligence. Most of the deaths are due to myocardial infarctions and congestive heart failure. Postmortem studies reveal widespread atherosclerosis of the aorta and coronary arteries with interstitial fibrosis of the heart (6, 7). Plaques are markedly calcified and choelsteryl ester crystals are evident. Stehbens et al.(7) have reported marked depletion of smooth muscle cells from the blood vessels and unusual shape of intimal smooth muscle cells with increased cytoplasmic density, ballooning of mitochondria and a few large lysosomal lipid vacuoles.

Development of extensive atherosclerosis in HGPS patients without evidence of risk factors such as diabetes, hypertension, hyperlipidemia and smoking is intriguing. Total cholesterol levels in a total of 20 children have been reported to be either normal or moderately elevated (8). Recently Gordon et al. (9) studied 19 HGPS children with a mean age of 8 years. They reported mean total cholesterol levels of 163 mg/dL, LDL cholesterol levels of 93 mg/dL and HDL cholesterol levels of 39 mg/dL. Plasma CRP levels were not different from controls but adiponectin levels were markedly lower 1.1 mg/mL compared to 8.4 mg/mL in controls ($p<0.001$) (9). Serum leptin levels were not reported.

Genetic Basis: It was difficult to understand the pattern of inheritance. Brown (4, 10) suggested a sporadic autosomal dominant mutation in these patients because of lack of consanguinity among parents, lack of affected siblings, and association with increased paternal age. He further reported two identical twins with HGPS who died at the age of 8 years (4). Cytogenetic studies revealed an inverted insertion of chromosome 1 (46 XY, inv ins {1:1} q32; q44q23) (4). This raised the possibility that the HGPS locus could be located on chromosome 1q.

Eriksson and colleagues (11) failed to find evidence for homozygosity in 12 patients with HGPS on genome wide scan. They however noted uniparental isodisomy of chromosome 1q in two patients. Considering the earlier report of Brown (4) of balanced inverted insertion in twins and the known linkage of lamin A/C (*LMNA*) with many other disorders, they considered it as a candidate gene in that region. Indeed, Eriksson et al. (11) were the first to report *LMNA* mutations in HGPS. Among the 23 classical cases of HGPS patients studied, they found three different heterozygous mutations, G608S and E145K, in exon 11 and 2, respectively, and a G608G (GGC>GGT), a synonymous substitution in exon 11. There were three other cases of HGPS; two were twins with uniparental isodisomy of chromosome 1q, and another patient with 6-Mb paternal deletion involving 1q21.3-1q23.1. Most of the patients were reported to have synonymous heterozygous mutation G608G of *LMNA* gene (11). This mutation occurred *de novo* in all patients and was demonstrated to be of paternal origin in some of the patients (11). Only one patient had a missense G608S mutation of the same residue. Patients with G608G or G608S mutations were found to have typical features of HGPS. Subsequently, two other groups reported *LMNA* mutations in patients with HGPS (12, 13).

Interestingly, G608G as well as G608S mutations activate a cryptic splice site. These mutations result in accumulation of a truncated prelamin A with an internal deletion of 50 amino acids near the C-termimus end of lamin A (delta 50, 608-658, with preservation of CAAX motif) (11). A specific prelamin A endoprotease (zinc metalloproteinase STE24; ZMPSTE24) cleaves carboxy terminus 18 amino acids from prelamin A to from mature lamin A in a two-step process first cleaving the three C-terminal residues and then fifteen more (14). Prelamin A has a CAAX box at the carboxy terminus, which undergoes isoprenylation, specifically farnesylation before undergoing proteolytic cleavage. In patients with HGPS, the first cleavage can proceed normally but the aberrant prelamin A may contain prenylated cysteine. Whether the toxicity is due to prelamin A accumulation per se or due to accumulation of prenylated form, remains unclear.

Eriksson et al.(11) performed Immunofluorescence studies on primary fibroblasts from five patients with classical HGPS and G608G mutation. Irregular shape of nuclear envelope was reported in nearly 48% of the fibroblast cells (11). De Sandre-Giovannoli and colleagues.(13) also reported large cytoplasmic vacuoles and abnormal mitotic figures in lymphocytes from HGPS patients with G608G mutation. Again the nuclear size and shapes were altered. Furthermore, these lymphocytes were found to express only 25% of normal lamin A levels.

LMNA gene: The *LMNA* gene, located on chromosome 1q21-22 region, encodes lamins A and C, which are components of the nuclear lamina; a polymeric structure intercalated between chromatin and the inner membrane of the nuclear envelope. The nuclear lamina, which was once thought to be a silent structural component of the nucleus, is now found to have an important role in keeping membrane integrity and in controlling gene expression. The coding region spans ~ 24 kilobases and contains 12 exons (Fig. 1). Alternative splicing within exon 10 gives rise mainly to two different mRNAs that code for prelamin A and lamin C (15). Other minor products of alternative splicing include, the lamin AΔ10 and lamin C2. Human lamins A and C are identical for the first 566 amino acids (16). Lamin C has 6 unique carboxy-terminal amino acids and has a total of 572 AA. Prelamin A has 98 unique carboxy-terminal amino acids, thus contains 664 amino acids. A specific prelamin A endoprotease (zinc metalloproteinase STE24; ZMPSTE24) cleaves carboxy terminus 18 amino acids from prelamin A to from mature lamin A, thus mature lamin A has

646 amino acids (14). Prelamin A has a CAAX box at the carboxy terminus, which undergoes isoprenylation, specifically farnesylation before undergoing proteolytic cleavage. In contrast, lamin C does not undergo isoprenylation.

Usually, alternative splicing produces approximately equal amounts of the two respective mRNAs within the same cell. However, different splice variants of lamin A may be expressed at different levels depending on the cell types (17).

Fig. 1 Lamin A/C (*LMNA*) gene structure. Numbers under the boxes denote the exons and the arrow indicates the site at which alternate splicing occurs to form Lamin A or C.

LMNA is a member of the intermediate filament multigene family and lamins A and C have primary and secondary structures similar to cytoplasmic intermediate filament proteins. Two other lamins, B1 and B2 are products of two different genes, *LMNB1* and *LMNB2,* respectively. These proteins have a central α-helical rod, an amino-terminal head, and carboxy terminal tail domains (16). They dimerize through their rod domain to form 10-nm diameter filaments and bind and assemble on the surface of mitotic chromosomes at specific sites on the rod (16, 18). Both homodimers and heterodimers can form between various lamins i.e. A, B1, B2 and C (19). Lamins B1 and B2 are expressed widely in tissues whereas lamins A and C are expressed mainly in differentiated non-proliferating cells. Lamins A and C bind to DNA, histones and retinoblastoma gene product (which controls cell cycle and gene expression) and thus play a role in organization of DNA transcription in cells. Lamins B bind to nuclear membrane and are associated with replicating chromatin in mammalian cells. Lamins provide structural integrity to nuclear envelope and also associate with integral nuclear envelope proteins such as emerin, nesprin-1α, lamin associated polypeptides, and lamin B receptor (20).

Disease mechanisms: Nuclear lamins have been found to play an important role in keeping the nuclear morphology intact, in correctly spacing the nuclear pore complexes and in assembling and disassembling the nuclear envelope during mitosis. Fibroblast cells from patients with HGPS as well as those with atypical progeroid syndromes due to *LMNA* mutations show reduced cellular replicative capacity in vitro and increased rates of apoptosis (personal observation). HGPS fibroblasts show progressive deterioration in nuclear shape with increased replicative age. In order to explain how *LMNA* mutations cause various different phenotypes such as progeroid syndromes, lipodystrophies, cardiomyopathies, muscular dystrophies and neuropathies, two models; a. structural model and b. gene expression model, have been proposed (21). Structural model suggests that the loss of lamin A/C function causes nuclear and/or cellular fragility which may lead to cell death in the presence of mechanical or environmental stress. Certainly, cells from many patients with *LMNA* mutations reveal abnormal nuclear shape, envelope ruffling, blebbing and even leakage of DNA into the cytoplasm. The gene expression model suggests that interaction of lamins A and C with DNA, histones and other transcriptional regulators may be of importance in causing the abnormal phenotypes when mutations are present. Different phenotypes associated with various *LMNA* mutations may be due to interaction of specific parts of lamins a and c with various interacting proteins such as emerin, retinoblastoma tumor suppressor protein (pRB), nesprin 1-α, lamin associated protein-1c and 2α, sterol regulatory element

binding protein 1c (SREBP1c)/adipocyte determination and differentiation factor 1 (ADD1) and others. For example, disruption of interaction of lamins A and C with SREBP1c may potentially result in loss of fat (22).

Recent studies reveal that the abnormal phenotype of the fibroblast cells from patients with HGPS was not reversible on introduction of wild type lamin A (23). However, correction of the abnormal splicing event using a modified oligonucleotide targeted to the activated cryptic splice site eliminates the mutant *LMNA* mRNA and lamin A protein (23). This also results in normal nuclear morphology and rescues abnormal nuclear distribution and cellular levels of lamina-associated proteins (23). Similar findings have been reported by Oshima et al (24). These findings provide a rationale for potential gene therapy.

Evidence from mouse models of LMNA gene disruption: *Lmna* null mice have no embryonic abnormalities but have retarded growth and survive for only 6-8 weeks (25). They show marked muscle dystrophy and cardiomyopathy. Interestingly, they lack subcutaneous fat tissue but do not have other metabolic manifestations, such as diabetes or hyperlipidemia. Embryonic fibroblasts from these mice showed elongated or irregular nuclei which exhibited mislocalization of lamin associated protein 2 and nuclear pore complex protein Nup153 (25).

Mounkes et al., (26) created a knock-in mouse model with *Lmna* L530P mutation, associated with Emery-Dreifuss muscular dystrophy in the hope to replicate the features of muscular dystrophy. However, the heterozygous mice did not show any features of muscular dystrophy. Surprisingly, the homozygous mice had growth retardation and died within 4-5 weeks after birth (27). Interestingly, these mice were also noted to have micrognathia and abnormal dentitions, decreased hair follicle density, increased collagen deposition in the skin, features reminiscent of HGPS. Nuclear envelope abnormalities were seen in about 58% of the primary fibroblasts from mice carrying homozygous mutation (26).

2. Atypical Progeroid Syndrome

The University of Washington International Registry of Werner's syndrome has been collecting patients with presumed diagnosis of Werner's syndrome for several years. Of the 129 such patients, 26 were found to have no mutations in the coding region and the splice sites of the *WRN* gene (28). Four of these 26 patients were recently discovered to harbor missense mutations in the *LMNA* gene, A57P, R133L and L140R, which were distinct from those reported in patients with typical HGPS (Table 2). These patients were referred to as having "atypical Werner's syndrome". However, considering that they had heterozygous *LMNA* mutations like the patients with HGPS and some showed autosomal dominant mode of transmission (instead of autosomal recessive mode in patients with Werner's syndrome), we wish to refer these patients as "atypical progeroid syndrome".

Another 27-year-old French male with insulin resistance diabetes, generalized lipodystrophy, disseminated leukomelanodermic papules, liver steatosis and cardiomyopathy was also reported to have a R133L heterozygous mutation in the *LMNA* gene (29). In addition, Csoka et al.(30) using the Coriell's repository, identified heterozygous T10I, E578V and R644C mutations in three patients with progeroid features, such as short stature, high pitched voice, beaked nose and lipodystrophy. In addition, we have identified three novel heterozygous mutations in *LMNA* gene in three patients with atypical progeroid syndrome (unpublished observations).

Interestingly, in the original paper by Eriksson et al.(11) an atypical patient with HGPS was found to have a E146K mutation. Recently, another patient with S143F mutation has been reported to have progeroid features with myopathy (31). Most interesting is a Japanese patient who was previously reported to have HGPS but died at a late age of 45 years due to myocardial infarction (32). This patient was recently found to have a mutation T623S in *LMNA* gene (33). Interestingly, like the HGPS mutations, G608G and G608S, this mutation

Table 2. Characteristics of Patients with Atypical Progeroid syndrome with *LMNA* mutations (28)

Registry #	PORTU8010	ATLAN1010	NORWAY1010	IRAN1010
LMNA mutation	R133L	R133L	L140R	A57P
Ethnicity	Caucasian	African American	Caucasian	Middle Eastern
Gender	F	F	M	F
Age (yrs) of initial symptoms	9	17	14	Early teens
Initial presenting symptoms	Short stature	Fatigue	"Physically inferior"	Short stature
Age (yrs) of Patient	18	18	34	23
Referring Diagnosis	WS	WS	WS	Progeroid syndrome
WS cardinal signs*				
Cataracts	No	No	Yes	No
Scleroderma-like skin	Yes	Yes	Yes	Yes
Short Stature	Yes	Yes	No	Yes
Graying/thinning of hair	Yes	Yes	Yes	No
↑Urinary hyaluronic acid	n/a	n/a	n/a	Yes
Other WS signs*				
Diabetes mellitus, type II	Yes at age 23	Yes at age 18	No	No
Hypogonadism	Yes	No	Yes	Yes
Osteoporosis	Yes	n/a	Yes	Yes
Osteosclerosis of digits	n/a	n/a	n/a	Yes
Soft tissue calcification	No	n/a	Yes	No
Premature atherosclerosis	No	n/a	Yes	No
Mesenchymal neoplasms	No	n/a	No	No
Voice changes	Yes	n/a	Yes	No
Other manifestations		Paternal inheritance	Aortic stenosis/ insufficiency Died at age 36	Dilated cardiomyopathy Sloping shoulders
WS diagnosis *	Possible	Possible	Probable	Possible

also introduces an abnormal splicing site and is predicted to result in a truncated prelamin A protein with 25 amino acids deleted from the C-terminal region (33). Why this mutation resulted in milder phenotype than the classical HGPS patients remains unclear.

B. Autosomal Recessive Syndromes

1. Werner's Syndrome:

Werner's syndrome (WS: OMIM # 27770) is a rare, autosomal recessive disorder, first described in 1904 by Otto Werner, a medical student at the Royal Albrecht University of Kiel. In his thesis, "Uber Katarakt in Verbindung mit Sklerodermie" (34, 35) Werner reported a family with two brothers and two sisters, aged 31 to 40 years, who presented with cataracts, premature graying and loss of hair, as well as skin changes he referred to as scleroderma. Thirty years later, in 1934, Oppenheimer and Kugel from USA described a similar case of what they termed "Werner's syndrome"(36).

The syndrome is characterized by short stature, bird-like appearance of the face and early onset of aging processes such as graying of hair beginning at about age 20, and osteoporosis and formation of cataracts during the third decade of life (37). To date, more than 1200 patients with WS have been reported in the literature, and about two thirds are from Japan (38, 39). About 70% of these patients were from consanguineous pedigrees (39) indicating an autosomal recessive mode of transmission due to a single gene mutation (40).

Natural History: The natural history of WS has been well documented by Goto from Tokyo, Japan (38). These patients appear normal during childhood and the first signs of WS appear around puberty with failure of growth spurt. This is followed by graying of hair and alopecia which occur at the mean age of 20 years, skin sclerosis at the age of 26, followed by skin ulcers at the 35 years of age. Endocrine complications include early menopause which occurs at the age of 36 years followed by osteoporosis. Malignancies and atherosclerotic disorders result in majority of deaths seen in patients with WS in late 40's (38). However, unlike tumors seen in natural aging with predominantly carcinomas, in WS most cancers are of mesoderm and epithelial cell origin (41). These include bone and soft tissue sarcomas, myeloid disorders, and benign meningiomas (42). The frequency of malignant cases range from 5.6% to 25% with the first manifestation among Japanese subjects at 41.4 years (43). Thyroid cancers are one of the most frequent tumors, with an increase in rate of occurrence of thyroid follicular and anaplastic carcinomas among Japanese patients with WS when compared to normal control (42, 44). Furthermore, among Japanese patients, the average age at the diagnosis of thyroid carcinoma is about 10 years younger in patients with WS when compared to normal controls (39 years for those with WS vs. 49 years for the controls) (42, 44).

Insulin resistance and diabetes: Nearly 70% of the patients with WS develop diabetes mellitus with an average age of onset of about 32 years (38). A longitudinal study done by Abe et al. (45) on one patient with WS found decrease insulin secretion over a 16 years period resulting in development of diabetes. Mori and colleagues (46) noted the average 2 hour plasma glucose value after an oral glucose tolerance test was 204 mg/dL with an insulin response of over 200 mU/ml consistent with an insulin resistant state in four patients with known *WRN* mutation. Using glucose clamp technique, Okamoto et al. (47) reported increased fasting insulin level, and a decreased in metabolic clearance rate (MCR) of glucose in patients with WS.

Even though the form of diabetes seen in patients with WS closely resembles that seen in patients with type 2 diabetes mellitus, i.e. with increase fasting insulin levels and

increase in visceral adiposity (46), patients with WS do not develop acanthosis nigricans. Furthermore, limited postmortem studies done on patients with WS has not shown any islet cell amyloidosis (48). Conventionally, patients with WS have been treated with insulin, but also respond to thiazolidinediones (49, 50).

Premature osteoporosis: Early osteoporosis is one of the hallmarks of WS (37). Average age at which osteoporosis is manifested is about 40 years (39). Earlier observations were mainly based on radiological X-ray findings reported in the literature WS (37). The prevalence of osteoporosis in reported case series ranges from 73-100% (51). Patients often have brittle bones with "moth-eaten" appearance (52). Soft tissue calcification has been noted in about one third of the reported cases (37, 52). Postmortem analysis of patients with WS has shown osteoporosis affecting the distal extremities more than the axial bones, a pattern consistent with a hyperparathyroid state even though the parathyroid, calcium, and phosphorus levels have been consistently within normal range (48, 53-55).

Premature osteoporosis in these patients predisposes them to early fractures over both axial and appendicular bones. Healing is often poor and can lead to non-union fractures (55, 56). A trans-cortical iliac crest bone biopsy done by Rubin et al of a 43-year-old white female with osteoporosis showed low osteoid volume and lack of normal bone resorption rates. They also found that serum parameters for bone turnover and resorption were normal (55) however, markers of bone formation were low-normal or reduced. Of note, the patient had menopause at age 31 years and was on hormonal replacement therapy. They concluded that osteoporotic process in WS is due to decreased bone formation and involves both cortical and trabecular bone similar to that described in age-related osteoporosis. There have been limited studies done using dual-energy X-ray absorptiometry in these patients. A report of bone mineral density measurement with dual-energy X-ray absorptiometry in a single patient with WS with non-healing fractures values at the lower end of normal range (57).

Genetics Basis: In 1992, Goto and colleagues using linkage studies demonstrated close linkage of *WRN* to a group of markers on chromosome 8 (58). In 1996, using positional cloning, Yu et al. (59) were able to successfully clone the gene (*WRN*) responsible for WS. *WRN* gene belongs to the RECQ family of DNA helicases, which play an active role in DNA replication, repair, recombination and transcription (39). *In vitro* studies using cells from patients with WS show premature replicative senescence and delayed S phase progression with defective repair and replication mechanism. Thus it was no surprise to find that Werner protein (WRNp) had helicase, exonuclease and ATPase activities (60). Furthermore, WRNp was shown to unwind short and long DNA duplexes. There are 23 different mutations reported in patients with WS (http://www.pathology.washington.edu/research/werner/ws_wrn.html). All of these mutations cause truncation of WRNp and result in complete loss of WRN helicase function (61). Of note, two of these mutations, 1336C>T and IVS25-G>C account for almost 70% of mutations reported in Japanese patients (61).

WRN gene: The DNA helicase named RecQ belong to the family of highly conserved DNA helicases, which are involved in DNA replication, repair and recombination (62, 63). DNA helicases are enzymes that track along single-stranded DNA and unwind duplex DNA, deriving their energy from ATP hydrolysis. The RecQ family of helicases are highly conserved enzymes from bacteria to higher eukaryotes . Humans have five helicases which despite being highly conserved and are non-complimentary to each other. The RecQ-like helicases play critical role in maintaining genomic stability.

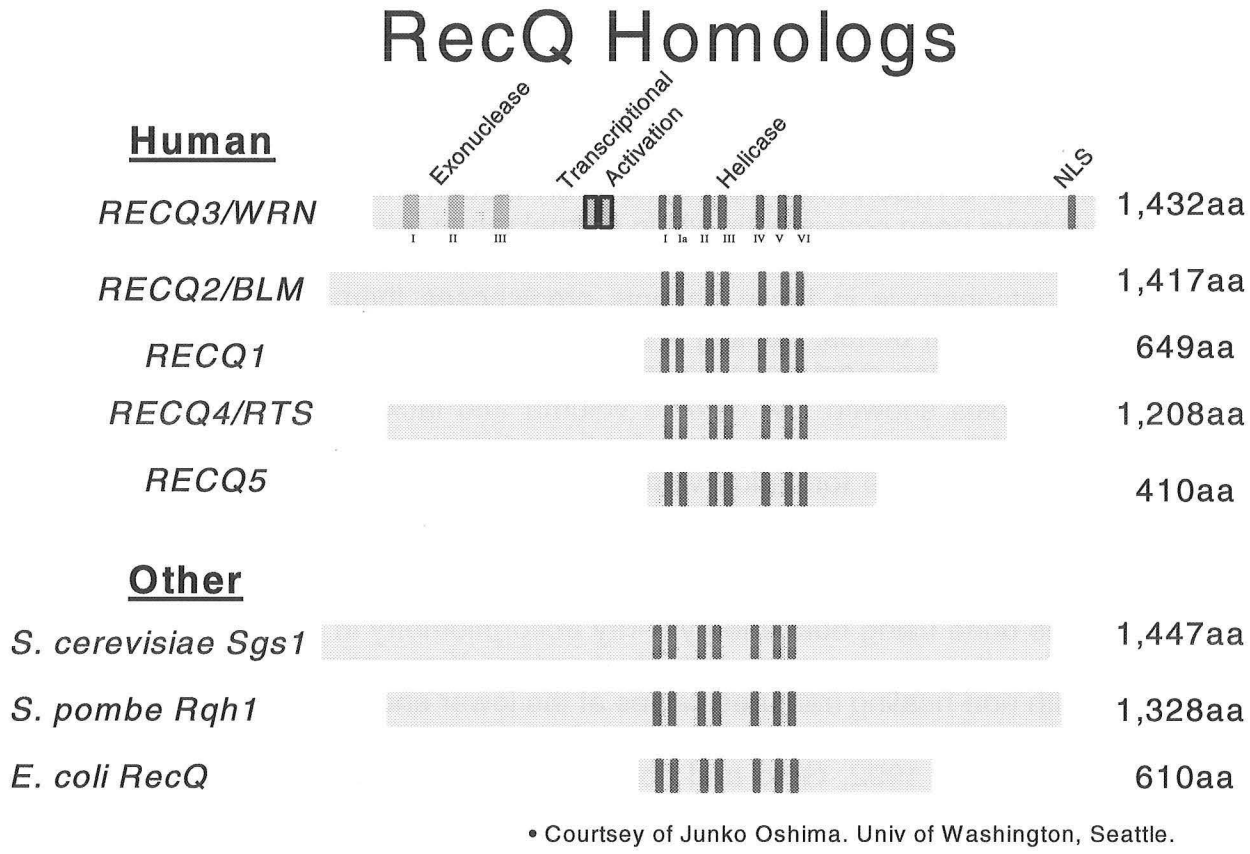

Fig. 2 RecQ homologs in human and other species.

The WRN gene contains 34 exons which are translated into a 1432 amino acid protein WRNp. Besides helicase activity, the WRNp has several proposed functions, such as the exonuclease, DNA replication, homologous recombination, nonhomologous end joining, base excision repair and transcription (64, 65). The unique feature of WRNp is the presence of 3'-5' exonuclease activity not found in any other helicases (66-70). WRN helicase unwinds the duplex DNA, hydrolyzing ATP and proceeds along the 3'-5' direction. It has been suggested that the 3'-5' exonuclease acts on the 3' recessed end of the duplex and repairs the double strand breaks.

Most WRN mutations found in patients with Werner's syndrome are null mutations which delete the nuclear localization signal (71). Thus, the mutated WRNp will be unable to translocate to the nucleus, greatly compromising DNA replication and stability, one of the key mechanisms underlying Werner's syndrome. Interestingly, the Wrn-deficient mice show no features of accelerated aging (72). Only when the mice are deficient in Wrn and telomerase activity ($Wrn^{-/-}$,$Terc^{-/-}$), they show features of premature aging such as premature death, gray

hair, alopecia, osteoporosis, type 2 diabetes and cataracts (73). This mouse model suggests that delayed clinical features of WS may be related to telomere shortening (74).

2. Mandibuloacral Dysplasia (MAD) associated progeroid syndrome

MAD has been considered a rare progeroid syndrome. Approximately forty patients with mandibuloacral dysplasia (OMIM # 248370) have been reported in the literature (75, 76). It is an autosomal recessive disorder characterized by hypoplasia of the mandible and clavicles, and acro-osteolysis (resorption of the terminal phalanges). Other features include delayed closure of cranial sutures, joint contractures, mottled cutaneous pigmentation and short stature. Some patients show progeroid features such as bird like facies, high-pitched voice and ectodermal defects, such as skin atrophy, alopecia, and nail dysplasia. Hypogonadism and sensorineural deafness have also been observed infrequently. Patients with MAD have been classified into type A and B according to the patterns of lipodystrophy: type A pattern with partial loss of subcutaneous fat from the extremities but normal or excess fat in the face, neck and truncal regions similar to that seen in patients with familial partial lipodystrophy of the Dunnigan variety; and type B pattern with more generalized loss of subcutaneous fat involving the face, trunk and extremities (75). Some patients have been reported to have hyperinsulinemia, insulin resistance, impaired glucose tolerance, diabetes mellitus and hyperlipidemia (75).

A. MAD type A due to *LMNA* mutations

Careful characterization of the pattern of lipodystrophy in patients with MAD type A and its similarity to the pattern of lipodystrophy observed in patients with familial partial lipodystrophy of the Dunnigan variety (75) (which was already linked to *LMNA* locus) led Novelli et al. (76) to consider *LMNA* as a candidate gene. They reported linkage to chromosome 1q21 In five consanguineous pedigrees from Italy using homozygosity mapping and upon sequencing the *LMNA* gene found a homozygous Arg527His mutation in all affected subjects (76).The subjects heterozygous for the Arg527His mutation had no skeletal abnormalities or lipodystrophy. We also found the same homozygous Arg527His mutation in two pedigrees, one of Hispanic origin and the other of Italian origin (77). However, the haplotypes associated with the mutation in these pedigrees were different suggesting that the mutations may have arisen independently.

Since then, we found a novel homozygous Ala529Val *LMNA* mutation in a male and a female MAD patient of Turkish origin belonging to two separate pedigrees (78). The phenotype of these Turkish patients was quite similar to those reported previously in MAD patients with homozygous Arg527His *LMNA* mutation (76, 77, 79). The onset of acro-osteolysis occurred in both types of patients at about 4 years of age. Joint contractures around elbow and wrists have been reported in both types of patients. All the patients had mandibular hypoplasia and clavicular resorption by 12-14 years of age. The female patient with Ala529Val mutation had lack of breast development, which has not been reported in other female subjects with Arg527His *LMNA* mutation (75, 77).

Table 3. Clinical features of patients with Mandibuloacral dysplasia associated progeroid syndrome due to *LMNA* mutations (78)

Clinical Features	*LMNA* Mutants			
	R527H/R527H	A529V/A529V	K542N/K542N*	R527C/R471C**
N (M/F)	13 (7/6)	2 (1/1)	5 (2/3)	1 (0/1)
Reported age (y)	1-36[#]	18, 21	4-17	28
Age of onset of acro-osteolysis (y)	4-5	4-5	1-2	2
Age at death (y)	NA	NA	10, 16	NA
Alopecia	Subtotal in males	No	Yes in both genders	Yes
Premature graying of hair	No	No	No	NA
Loss of Eyebrows/ Eyelashes	No	No	Yes	NA
Lipodystrophy	Partial	Partial	Generalized	NA
Open fontanelle	Yes	Yes	Yes (16)	NA
Sexual maturation	Normal	Normal	Delayed	Normal
Mottled Pigmentation	Yes	Yes	Yes	NA
Joint stiffness contractures	Yes, Elbows, shoulder, hips	Yes	Yes	NA
Other features		Absent breast development in female	Premature loss of teeth	Severe osteoporosis and multiple fractures

All patients have mandibular and clavicular hypoplasia, and acro-osteolysis. NA, information not available. * Described by authors as Hutchinson-Gilford Progeria Syndrome. ** Described initially as Hutchinson-Gilford Progeria Syndrome but later the personal physician agreed with the diagnosis of mandibuloacral dysplasia. [†] Paper in press. [#]Personal communication by P. Sbraccia, Rome, Italy.

Recently, a consanguineous pedigree from India was reported with 5 affected subjects with Hutchinson-Gilford Progeria syndrome who carried a homozygous Lys542Asn mutation of *LMNA* (80). All affected subjects from this pedigree had severe mandibuloacral dysplasia with clavicular hypoplasia and onset of acro-osteolysis occurring at 1-2 years of age (Table 3)(80). Both the male and female children showed progeroid features such as alopecia, loss of eyebrows and eyelashes, delayed sexual maturation and early death. The patients were reported to have generalized lipodystrophy. Interestingly, Novelli and co-workers (personal observation) have also observed extensive baldness and graying of hair in a 36-year-old male patient with MAD. Other patients aged 36-46 years, also develop osteoporosis, dermal sclerosis and skin atrophy and loss of muscle mass. Another 28-year-old female with MAD has been described to have compound heterozygous mutations, Arg527Cys and Arg471Cys, in *LMNA* with alopecia, severe osteoporosis and multiple fractures (12).

Novelli and colleagues examined the nuclei of the fibroblast cells from a patient with MAD and homozygous R527H *LMNA* mutation and from the patient's mother who was carrying a heterozygous copy of the same mutation (81). Immunofluorescence analysis of these cultured skin fibroblasts revealed nearly 10% abnormal nuclear morphology in cells harboring the heterozygous mutation. The nuclei from homozygous R527H mutation showed lobular formations at the edge of the membrane in addition to areas of honeycombing. How these *LMNA* mutations cause a predominantly skeletal phenotype in patients with MAD remains unclear.

B. MAD type B due to ZMPSTE24 mutations

Sequencing of the *LMNA* gene in our patients with MAD revealed genotypic and phenotypic heterogeneity (77).Thus, our study suggested additional loci for MAD. Interestingly, some of the phenotypic features of MAD, i.e., partial lipodystrophy and skeletal abnormalities including small mandible, were reported in mice with homozygous deletion of the gene encoding a zinc metalloproteinase, *Zmpste24* (82, 83). Given the role of Zmpste24 in post-translational processing of prelamin A, the abnormal phenotype of *Zmpste24*$^{-/-}$ mice was attributed to defective prelamin A processing (Fig. 2) (82-84). Given the role of ZMPSTE24 in prelamin A processing and the reports of *LMNA* homozygous mutation in MAD subjects, we considered *ZMPSTE24* as a candidate gene and sequenced this locus in the patients who did not harbor any variants in the *LMNA* gene. We discovered compound heterozygous mutations in the zinc metalloproteinase (*ZMPSTE24*) gene in a Belgian woman with severe MAD, progeroid features and generalized lipodystrophy (85). She died prematurely at age 24 years of complications of chronic renal failure due to focal segmental glomerulosclerosis (85).

Since this report, in collaboration with other groups, we have found disease causing ZMPSTE24 mutations in three other patients with MAD, progeroid syndrome and lipodystrophy (86-88). Using a yeast complementation assay, we have found that the mutations found in these patients have either no enzymatic activity or reduced activity (85). Interestingly, besides the clinical features of mandibuloacral dysplasia, i.e., mandibular and clavicular hypoplasia and acro-osteolysis, these patients presented with various progeroid features such as short stature, sclerodermatous skin, alopecia, beaked nose, atherosclerosis, joint contractures, lentigo senilis and lipodystrophy. Three of them have died at the age of 2.75, 24 and 37 years. Two of these died after end-stage renal disease due to focal segmental glomerulosclerosis. Although renal disease in not reported in knock out mouse model of ZMPSTE24 deficiency (82, 83), in humans it seems to be associated with this phenotype.

Table 3. Peculiar Clinical Features of Mandibuloacral Dysplasia type B patients with *ZMPSTE24* mutations.

Clinical Features	*ZMPSTE24* Mutants			
	Belgium	Australia	UK	Germany
M/F	F	M	F	M
Reported age (y)	24*	37*	2.75*	3.5
Age at presentation (y)	2	1.5	0.25	0.25
Short Stature	+	+	+	
Sclerodermatous skin	-	-	+	+
Alopecia	+	-	-	+
Premature graying of hair	No	No	No	NA
Beaked nose	+	+	+	-
Loss of Eyebrows/ Eyelashes		No		No
Lipodystrophy	Generalized	Generalized	Lower limbs	+
Atherosclerosis		CAD, PVD	TIA	
Mottled Pigmentation	Yes	Yes	Yes	NA
Other features	FSGS	FSGS, Skin atrophy		Lentigo senilis

All four patients had mandibuloacral dysplasia with mandibular hypoplasia, clavicular hypoplasia and acro-osteolysis. * Age of death; M, male, F, female; FSGS, focal sclerosing glomerulosclerosis, CAD, coronary artery disease, PVD, peripheral artery disease; TIA, transient ischemic attacks.

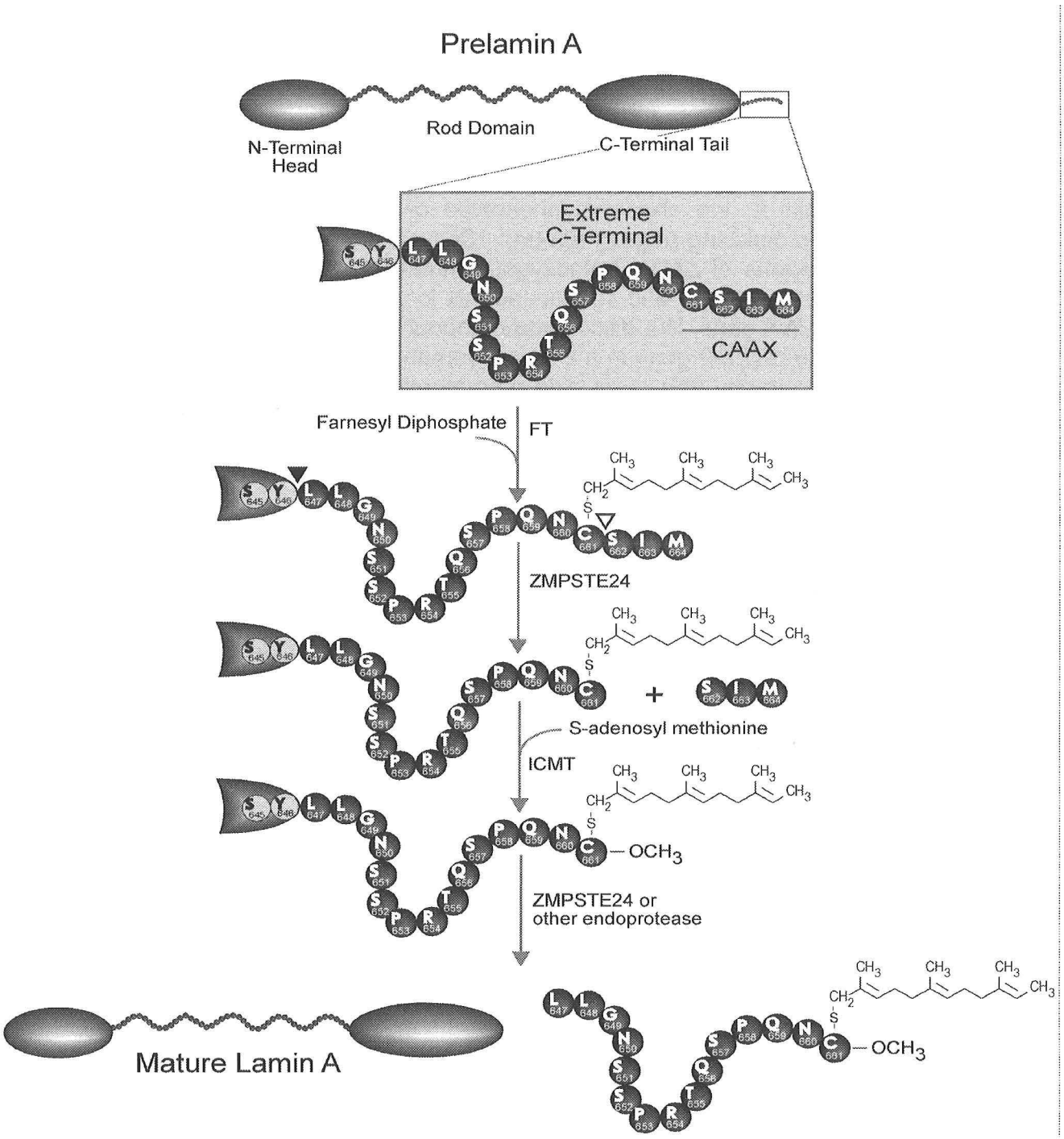

Fig. 3 Schematic of steps involved in prelamin A processing to lamin A. From Agarwal et al. (85).
The posttranslational processing of prelamin A involves the extreme carboxy-terminal residues. In the first step, farnesyl diphosphate is used to farnesylate the cysteine in the conserved CAAX motif (CSIM in prelamin A) at the carboxy-terminal using the enzyme farnesyl transferase (FT). During the second step, the peptide bond between the cysteine and serine residues (indicated by an unfilled triangle) is proteolytically cleaved by ZMPSTE24, resulting in removal of SIM tripeptide. This reaction is followed by methylation of the farnesylated cysteine residue by isoprenylcysteine carboxyl methyl transferase (ICMT) using S-adenosyl methionine as the methyl donor. Finally, a second proteolytic cleavage occurs between the tyrosine and leucine residues (indicated by a filled triangle), which is either catalyzed by ZMPSTE24 or by as yet unidentified endoprotease, and this cleavage removes 15 amino acids from the carboxy-terminal, resulting in formation of mature lamin A.

Besides many similarities in clinical features, there are some differences in the phenotype between the MAD patients due to *LMNA* or *ZMPSTE24* mutations. Compared to MAD patients with *LMNA* mutation (76, 77), those with *ZMPSTE24* mutations had early onset of skeletal defects including acro-osteolysis, had more progeroid appearance, had subcutaneous calcified nodules on the phalanges and developed progressive glomerulopathy (85-88). Longitudinal follow up information, as more affected subjects are identified, is needed to further understand the phenotypic differences between the two genetic varieties of MAD.

C. Other types of MAD

Some patients with MAD reveal no variants in either *LMNA* or *ZMPSTE24* genes, suggesting additional as yet unmapped loci (85). Interestingly, the remaining patients, who do not harbor *LMNA* or *ZMPSTE24* variants, do not seem to develop clavicular resorption or acro-osteolysis.

3. Idiopathic arthropathy associated progeroid syndrome

We recently found a novel autosomal recessive idiopathic arthopathy syndrome affecting predominantly the distal femora and proximal tibia in the knee with subcutaneous calcifications in a 44-year-old man of European descent (89). He also had progeroid features such as pinched nose and micrognathia, cataract, alopecia, generalized lipodystrophy and sclerodermatous skin which led us to consider the lamin A/C (*LMNA*) and zinc metalloproteinase (*ZMPSTE24*) as candidate genes. We found a homozygous substitution of C1718T in exon 11 of *LMNA* gene resulting in substitution of a well conserved residue serine at position 573 with leucine (Ser573Leu). This missense mutation only affects lamin A and not lamin C as the alternative splicing site is located in exon 10. His 15-year-old son who was heterozygous for the mutation was healthy. We conclude that this novel homozygous *LMNA* mutation is associated with a peculiar phenotype of arthropathy with progeroid features distinct from acro-osteolysis previously reported in patients with mandibuloacral dysplasia caused by *LMNA* or *ZMPSTE24* mutations.

4. Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)

This syndrome was first described by Rautenstrauch and co-workers in 1977 (90) in two sisters with congenital malformations reminiscent of progeria. In 1979, Wiedemann defined a new progeroid syndrome based on his two personal observations and the earlier report (91). The syndrome is characterized by a intrauterine growth retardation, progeroid face (triangular, old-looking face with relatively large skull, prominent veins especially of the scalp, sparse scalp hair, large anterior fontanelle) and nearly total absence of sc fat (giving the clinical appearance of prominent veins and muscles). SC fat, however, is evident in the gluteal area. These features are apparent at birth and thus it can be differentiated from HGPS but needs to be differentiated from congenital generalized lipodystrophy. Inheritance is autosomal recessive. To date, only 21 cases have been reported in the literature (92) with 5 pairs of siblings and 5 cases of parental consanguinity. The male-to-female ratio in the reported cases was nearly equal with 11 males and 10 females (92). Most reported cases are of Caucasian ancestry although patients from other ethnic groups including African American, Hispanic and Chinese have also been documented (92-95).

The diagnosis is solely based on clinical findings as the genetic basis remains unknown (96). Patients with WRS often have characteristic progeroid appearance, with macrocephaly, hypotrichosis, prominent scalp veins, large hands and feet with long fingers and toes. Distinctive pattern of tooth eruption in utero (97) often helps distinguish this syndrome from HGPS where dentition is delayed. The pattern of lipoatrophy spares the medical gluteal region, with reduced fat in the lateral gluteal areas. Prenatal ultrasound findings in two cases have shown reduced biparietal diameter (5^{th} percetile), the abdominal diameter at the 25^{th} percentile and the femoral length at the 50^{th} percentile with mild oligohydroamnios (97).

Early in life, these patients often present with failure to thrive and difficulty in gaining weight often requiring tube feeds (96). The delay in mental and motor development can vary from mild to moderate (96). Laboratory evaluation in these patients frequently is normal although in more recent reports hyperinsulinemia, elevated cholesterol and triglyceride levels have been observed (92). Death often is due to respiratory failure at a young age. Pivnick et al (92) reported a median life expectancy of 71 months for male subjects and 2 months for female subjects.

The pathogenesis of Wiedemann-Rautenstrauch syndrome is unclear (98, 99). Telomeres, which are the terminal portions of the chromosome, cooperate in aging and immortalization of cells. Telomere length has been implicated in molecular measure of the proliferating potential of human cells (94). Korniszewski et al.(94) examined the terminal restriction fragment length of fibroblast cells from a single patient with Wiedemann-Rautenstrauch syndrome and found "normal" telomeric DNA, thus it is unlikely to explain the pathogenesis of this disorder. Beavan et al. (100) found reduced expression of Decorin, an extracellular matrix proteoglycan, in fibroblasts from patient with Wiedemann-Rautenstrauch syndrome, however, the level normalized in a fibroblast obtained at a later date suggesting that the initial reduction observed was probably a secondary phenomenon. *LMNA* mutations were excluded in two patients with Wiedemann-Rautenstrauch syndrome (12).

5. Metageria/Acrogeria

Gottron (101) described two sibs with skin changes of aging involving the hands and feet and termed it acrogeria. Since then more than 40 such patients have been described. Its main characteristic is atrophy of the skin of the hands and feet resulting in an aged appearance. In a recent consanguineous family from Iran, acro-osteolysis, mandibular hypoplasia, wide cranial sutures and avascular necrosis of femoral heads was described. Some of these features overlap with those of HGPS and MAD. A subgroup of patients may have mutations in type III collagen (*COL3A1*) gene and may have Ehlers-Danlos syndrome. The genetic basis of other patients have not been determined. Gilkes et al. (102) were the first to describe a progeroid syndrome called metageria. However, subsequent authors questioned the wisdom of classifying these disorders separately (103).

6. Bloom Syndrome

Mutations in another helicase, *BLM or RECQ2,* result in Bloom syndrome. Bloom syndrome patients have short stature, photosensitivity induced hypo and hyperpigmentation and telangiectasia, immunodeficiency, male infertility and predisposition to various malignant neoplasias (104-106).

7. Rothmund-Thomson syndrome

This is a phenotypically and genotypically heterogeneous syndrome. Patients with Rothmund-Thomson syndrome suffer from juvenile cataracts, poikiloderma, early graying of hair and malignancies such as osteogenic sarcomas. Mutations in *RTS or RECQ4* have been identified in less than 10 patients with Rothmund-Thomson syndrome (106-111).

Implications for normal aging

Identification of various loci for the human monogenic progeroid syndromes, such as *WRN. BLM, LMNA* and *ZMPSTE24*, raise questions about their relevance to normal aging. Many single nucleotide polymorphisms, synonymous and non-synonymous, have been identified in the *WRN* gene. The frequencies of these SNPs exceed that of Werner syndrome associated mutations. Some of the mutant proteins associated with non-synonymous SNPs of WRN gene were evaluated for the enzymatic activity and only two T172P and R834C were found to have markedly reduced activity compared to the wild type WRN protein (WRNp) (112). Other mutants such as Q724L, S1079L, F1074L and C11367R did not shown any significant and meaningful reduction in enzymatic activity (112).

Table 4

WRN C1367R Polymorphism and Atherosclerosis

Study	Country	Control (n)	CHD (n)	CVA (n)	RR for CC	P
Ye et al. (1997)	Japan	198	149		2.8	0.009
Morita et al. (1999)	Japan	218	166		2.8	0.005
		218		201	1.0	NS
Castro et al. (2000)	Mexico	37		67		NS
	USA	25	100			NS
Bohr et al. (2004)	USA	86	52		0.6	NS

Association of a few of these non-synonymous SNPs, such as Cys1367Arg and Phe1074Leu, with longevity, coronary heart disease, ischemic stroke, diabetes and osteoporosis have been studied. These studies have included only small number of subjects and did not reveal any consistent association with CHD, Stroke, type 2 diabetes and longevity in Japanese, Mexican, Finnish and North American populations (113-115) For example, two studies from Japan revealed increased risk of CHD among subjects with Cys/Cys alleles compared to others (113, 114), however, other studies did not find such as association (115, 116) and in fact one study found a reduced risk among those with Cys/Cys alleles (116). A single study of 377 healthy postmenopausal Japanese women revealed reduced Lumbar 2-4 bone mineral density, as determined by dual-energy X-ray absorptiometry, in subjects carrying C allele (CT and CC genotypes; 1367Cys/Arg and Arg/Arg) compared to those with TT genotype (1367 Cys/Cys) (P=0.037 or 0.015, respectively for bone mineral density and Z score, respectively) (117). Only one subject had a CC genotype and had a Z score of -0.392 in the lumbar spine. Thus, this study provides some evidence that SNPs in WRN gene may play a role in determining bone density in aging

subjects. No association was observed with diabetes mellitus and C1367R polymorphism (113).

Another interesting cohort to study is the heterozygote carriers of the mutations associated with Werner's syndrome by evaluating the family members of the patients. WRN heterozygotes appear to have a frequency of 1:200 to 1:500 in the US and Japan. Goto et al. reported cancer related deaths in 26 of the 616 (4.2%) sibs of patients with Werner's syndrome when the overall incidence of death from cancer in Japan was about 0.11% (118). In support of this observation, heterozygous carriers of *WRN* mutations reveal increased genetic instability (119). The lymphoblastoid cell lines from heterozygous carriers reveal intermediate rates of apoptosis upon incubation with 4-nitroquinoline 1-oxide and by the DNA topoisomerase I inhibitor, camptothecin (119-121). Rigorous studies are needed in future to document unequivocally the increased frequency of cancer among proven heterozygous carriers of WRN mutations. At the same time, data on risk of CHD, osteoporosis, diabetes and premature graying of the hair will be of great interest.

No data are available about the association of *ZMPSTE24* SNPs in diseases or clinical features associated with normal aging. A few groups have studied the relationship of a common SNP in *LMNA* gene, 1908C/T in exon 10 located at the alternative splicing site for lamin C. This SNP is synonymous (H566H) and does not alter the histidine residue at position 566. Initially, Hegele and colleagues (122), reported increased BMI and waist-to-hip circumference ratio and higher leptin levels in aborginial Canadians with T/T genotypes compared to those with CC and C/T genotypes. The same group reported increased BMI and waist-to-hip circumference ratio but not higher leptin levels in Inuits with T/T and C/T genotypes compared to those with CC (123). A study in Pima Indians from Arizona, however, did not find any significant association of that SNP with DM, BMI, serum leptin, lipids and insulin sensitivity (124). However, another report from Pima Indians revealed increase abdominal adipocyte size in those with C/C polymorphism compared to others (125). Recently, Steinle et al. (126) reported higher serum triglyceride and lower HDL cholesterol concentrations in Amish subjects with C/T and T/T genotypes compared to those with C/C genotypes. Similar results were reported by Murase et al.(127) in Japanese subjects. These studies do suggest that this H566H and other SNPs in *LMNA* may contribute to the risk of obesity and its related phenotype of metabolic syndrome. Both the prevalence of obesity and metabolic syndrome or dyslipidemia increases with aging.

Conclusions

Although normal aging process may be affected by various environmental influences as well as by subtle variations in a number of genes, the discoveries of the association of *LMNA*, *ZMPSTE24*, *WRN, BLM and RECQ4* genes with progeroid syndromes, strongly suggest the role of nuclear function and integrity in determining variations in aging phenotypes among humans. The common variants of these genes may have an important role in the process of normal aging which needs to be explored further.

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