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RECQ helicase disease and related progeroid syndromes: RECQ2018 meeting

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Abstract

Progeroid syndrome is a group of disorders characterized by the early onset of diseases that are associated with aging. Best known examples are Werner syndrome, which is adult onset and results from disease-causing DNA sequence variants in the RecQ helicase gene *WRN*, and Hutchison-Gilford progeria syndrome, which is childhood-onset and results from unique, recurrent disease-causing DNA sequence variants of the gene *LMNA* that encodes nuclear intermediate filaments. Related single gene RecQ disorders are Bloom syndrome and Rothmund-Thomson syndrome. The RecQ disorders Cockayne syndrome and xeroderma pigmentosum result from disease-causing DNA sequence variants in genes involved in the nucleotide excision repair pathway. RECQ2018: The International Meeting on RECQ Helicases and Related Diseases was held on February 16–18, 2018 in Chiba, Japan. The purpose of the meeting was to facilitate clinical and research collaborations for the goal of developing effective treatments for RECQ disorders and other progeroid syndromes.

Keywords

Werner syndrome; Progeroid syndrome; Genomic instability; Aging; RECQ2018

1. Background and meeting overview

Progeroid syndromes are a group of disorders that exhibit multiple features consistent with accelerated aging. Genetic causes of progeroid syndromes range widely from genomic instability, altered nuclear structure, and abnormal telomere metabolisms to altered carbohydrate and lipid metabolisms and chromosomal abnormalities. Among them, genomic instability is a major pathogenic mechanism that leads to progeroid syndrome. “RecQ diseases” are caused by DNA sequence variants in genes that encode RecQ helicases, which are ATP-dependent 5′–3′ DNA unwinding enzymes. Humans have five RecQ helicases: *RECQL1*, *BLM*, *WRN*, *RECQL4*, and *RECQL5*. Of those, pathogenic variants of *BLM*, *WRN*, and *RECQL4* are linked to human diseases; Bloom syndrome (BS), Werner syndrome (WS) and Rothmund-Thomson syndrome (RTS) respectively. All of these are

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associated with accelerated aging and higher frequencies of cancers (Croteau et al., 2014). Cockayne syndrome (CS) and xeroderma pigmentosum (XP) are caused by pathogenic variants of the genes involved in nucleotide excision repair. Hutchinson-Gilford progeria syndrome (HGPS) is a classic progeria caused by pathogenic variants in the *LMNA* gene that encodes the nuclear structural protein lamin A/C. Unique splice variants of *LMNA* lead to the accumulation of progerin, which is responsible for HGPS.

Japan has a relatively high frequency of WS due to the presence of a founder mutation with an estimated heterozygote frequency of one in 167. In 2015, with the help of the Werner patient advocacy group and the Japanese Werner Consortium (Koutaro Yokote, Chiba University, Japan), WS was added to Japan's list of "Nanbyo" (intractable rare orphan diseases) along with RTS and CS/XP, earning the government's financial support for medical care. This effort also led to the RECQ2018 meeting being supported by the Japan Intractable Disease (Nanbyo) Research Foundation. RECQ2018 was the sequel to RECQ2016, which was held in Seattle, USA, in May 2016. A total of 124 participants gathered for RECQ2018 from Japan, USA, Europe, and Southeast Asia. The meeting also included concurrent family sessions, presentations on age-related common diseases and cellular senescence, and a session on human induced pluripotent stem cell (hiPSC) applications. This review focuses on the updated findings on progeroid syndromes.

2. Werner Syndrome

Werner Syndrome (WS) is caused by biallelic mutations of *WRN*, which encodes a multifunctional nuclear protein with helicase and exonuclease activities. Virtually all pathogenic variants of *WRN* are null variants, with a few exceptions of amino acid substitutions that abolish its helicase activity and those that provoke protein instability, as reviewed by George M. Martin (International Registry of Werner Syndrome, University of Washington, USA) (Yokote et al., 2017). The most common initial symptom, which is often recognized retrospectively, is the lack of a growth spurt during one's teens. WS patients typically have an aged appearance and early onset of age-related disorders starting after adolescence. Their symptoms include the graying and loss of hair, cataracts, skin atrophy, diabetes mellitus, atherosclerosis and malignancies. Median age of diagnosis is around 37 years of age (Oshima et al., 2017). Based on the results of Japanese nationwide survey, Koutaro Yokote (The Japanese Werner Registry, Chiba University, Japan) added soft tissue calcification around the Achilles tendon that leads to refractory skin ulcers into the revised diagnostic criteria as cited previously (Takemoto et al., 2013). By far, the most important quality-of-life issue is indolent skin ulcers around the ankles and elbows, which are associated with excruciating pain as testified by a patient from the Japan Werner Syndrome Patient and Family Group. Median lifespan of WS patients is now reported to be extended to 54 years, likely due to the advancement of medical care and particularly due to better management of diabetes. Yokote observed an increase of myelodysplastic syndrome among older WS patients. The pattern of hierarchical deterioration in WS is distinct from that of normal aging. Alzheimer's disease, Parkinson's disease, and hearing loss, for example, are not typical features of WS. Makoto Goto (Nerima-Hikarigaoka Hospital, Japan) noted a possible correlation between *WRN* expression levels, types of affected organs, and onsets of symptoms. He observed the significantly elevated levels of pro-inflammatory proteins such

as high sensitivity CRP, MMP-9, and various cytokines such as IL-4,6,15, GM-CSF, and TNF- α in WS sera as well as in normal old people, supporting the inflammatory theory of aging (Goto et al., 2012).

Recent studies by Raymond J. Monnat Jr. (University of Washington, USA) support the hypothesis that DNA sequences with a propensity to form G-quadruplex (G4) structures are physiologic substrates for *WRN* to modulate gene expression in human cells (Tang et al., 2016). G4 sequences are also the substrates for BLM helicase, although in this case the modulated genes are different (Nguyen et al., 2014). *WRN* protein is involved in various DNA transactions including double strand break (DSB) repair, replication, base excision repair, transcription, and telomere maintenance. Vilhelm A. Bohr (NIA, USA) discussed how *WRN* plays a role in determining the choice of DSB repair pathways. There is emerging evidence that *WRN* plays a role in mitochondrial health. Bohr also discussed how nuclear DNA damage leads to mitochondrial dysfunction in progeroid syndromes, particularly in people with neurodegeneration. *WRN* may be involved in discarding the damaged mitochondria through the mitophagy process (Shamanna et al., 2017).

Clinical trials of topical drugs are in progress for the treatment of skin ulcers in Japan. Potential systemic treatments of WS are also being investigated. Junko Oshima (University of Washington, USA) observed that long term treatment of an mTOR inhibitor, rapamycin, restores diseased cellular phenotypes of *WRN* deficient cells including those associated with accumulation of DNA damage foci and growth rate (Saha et al., 2014). Another mTOR inhibitor, metformin, is beginning to be used for the treatment of diabetes in WS patients in Yokote's group. This has led to favorable results, possibly because of pleiotropic effects. WS hiPSCs have been established by several investigators which should be useful for future drug screening. RecQ helicases could be a target of cancer therapy in the general population. Yasuhiro Furuichi (GeneCare Research Institute, Japan) presented that gene silencing of *RECQL1* and *WRN* by cognate siRNAs induces a mitotic death in checkpoint-defective cancer cells but not in normal cells. In particular, the preclinical trial studies showed that *RECQL1*-siRNA was effective for drug resistant clear cell ovarian carcinoma lines (Futami and Furuichi, 2014).

3. Rothmund Thomson Syndrome

Rothmund-Thomson Syndrome (RTS) is generally caused by pathogenic variants in the *RECQL4* gene, as are the allelic disorders RAPADILINO syndrome and Baller-Gerold syndrome (BGS). Classical RTS is characterized by poikiloderma, small stature, skeletal and dental abnormalities, juvenile cataracts, and an increased risk for cancer, especially osteosarcoma and skin cancers. Skeletal abnormalities include radial ray defects, ulnar defects, absent or hypoplastic patella, and osteopenia. RAPADILINO, which has been described as occurring in the Finnish population, is characterized by irregular pigmentation with café au lait macules (but no poikiloderma), small stature, skeletal abnormalities, and gastrointestinal abnormalities. Osteosarcomas and lymphomas are reported in RAPADILINO. Baller-Gerold syndrome (BGS) is characterized by craniosynostosis, radial ray defects, skeletal dysplasia, short stature, and poikiloderma. A midline NK/T cell lymphoma has been reported in BGS. Clinical phenotypes and mutation spectrum of

RECQL4 were reviewed by Lisa L. Wang (The Rothmund-Thomson Syndrome Registry, Baylor College of Medicine, USA) (Wang and Plon et al., 2016). Approximately two third of RTS patients carry at least one truncation mutation of *RECQL4* associated with the increased risk of osteosarcoma (Wang et al., 2001), while most common RAPADILINO mutation is the 44 amino acid in-frame deletion which abolishes helicase and ATPase activities (Croteau et al., 2012).

Like other RecQ helicases, *RECQL4* plays major roles in DNA replication and repair. Deborah Croteau (NIA, USA) reported that *RECQL4* protein undergoes cell cycle dependent phosphorylation, which regulates *RECQL4* pathway choice between homologous recombination (HR) and non-homologous end joining (NHEJ) during DSB repair (Lu et al., 2017). Sagar Sengupta (National Institute of Immunology, India) found that *RECQL4* also participates in mitochondrial DNA (mtDNA) replication by acting as an accessory factor to mitochondrial polymerase, Pol γ A/B2. In the tissues of aged mice, RecqL4 undergoes K6-linked ubiquitylation by the mitochondrial E3 ligase Mitol. This ubiquitylation diminishes the entry of RecqL4 into mitochondria. RTS mutant RecqL4 proteins are hyper-ubiquitylated by Mitol, which prevents their entry into mitochondria (De et al., 2012). In wildtype mice, Mitol expression decreases with age. Shigeru Yanagi (Tokyo University of Pharmacy and Life Sciences, Japan) showed that Mitol knockout mice exhibit increased mitochondrial ROS, accumulate β -gal positive senescent cells, and develop signs of accelerated skin aging and cardiac dysfunction. These changes were partially rescued by the inhibitor of a Mitol substrate, Drp1. Drp1 is a dynamin-related GTPase and is ubiquitylated by Mitol to undergo proteasomal degradation. These data indicated that optimal Mitol is required for the maintenance of mitochondrial function (Nagashima et al., 2014).

4. Bloom syndrome

Bloom syndrome (BS) is characterized by pre- and post-natal growth deficiency, skin photosensitivity, and a predisposition to both haematologic and solid malignancies. A hallmark of *BLM* deficient cells is increased sister chromatid exchange (SCE). *BLM* helicase has been shown to function in replication fork stabilization, fork rescue, and HR repair. The *BLM* protein is recruited at DSB sites in bimodal fashion. Sengupta showed that ATM is required for *BLM* recruitment – but not retention – at the DSB sites, while MRE11 is required for both recruitment and retention (Tripathi et al., 2018). *BLM* can also direct the choice of repair pathway between HR and classical NHEJ in a cell cycle dependent manner. Nathan Ellis (University of Arizona, USA) presented a molecular model of the rescue of collapsed replication forks involving *BLM* helicase. *BLM* protein is activated through the sumoylation by a SUMO E3 ligase, NSMCE2. While *BLM* deficient cells expressing SUMO-mutant *BLM* protein increased focal RPA and decreased focal RAD51 (Ouyang et al., 2013), *NSMCE2* deficient cells show an increased focal RAD51 and exhibit a defect in the generation of DSBs following the hydroxyurea-induced replication fork collapse. This raises the possibility that an important source of SCEs in *BLM*-deficient cells may be derived from the repair of DSBs during collapsed-fork rescue.

At the cellular level, the *BLM* helicase localizes to the nucleolus and PML bodies. *BLM* moves in and out of the nucleolus in response to DNA damage and other stresses. Joanna

Groden (University of Ohio, USA) showed that BLM protein interacts with topoisomerase II α to localize to PML bodies and also interacts with topoisomerase I to localize to nucleoli. She generated a mouse model with the DD mutant Blm protein that is excluded from the nucleolus. The DD mutation is located in the interaction domain in BLM with topoisomerase I (Behnfeldt et al., 2018). This model displayed signs of accelerated aging and alterations of rDNA copy number. These data indicate the significance of ribosomal genome instability in the pathogenesis of BS (Tangeman et al., 2016).

5. Hutchinson-Gilford Progeria Syndrome

Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare, uniformly fatal, premature aging disease. Early symptoms include short stature, total alopecia, global joint contractures, and skeletal dysplasia. Children die of the consequences of premature atherosclerosis, leading to heart attacks and strokes at a median age of 14.6 years without treatments. Soft tissue calcification reminiscent of WS is also seen in HGPS. Prevalence of HGPS is 1 in 20 million (incidence is 1 in 8 million live births) and there are expected to be 380 patients worldwide.

Classical HGPS is caused by a recurrent, single base substitution, c.1824C > T in the *LMNA* gene. This alteration creates a cryptic splice site, which causes the in-frame deletion of 50 amino acids that includes a proteolytic site required for the maturation of lamin A (Ullrich and Gordon, 2015). The HGPS mutant lamin A called progerin retains the C-terminal end with a farnesyl moiety that exhibits cellular toxicity. The first clinical trial using a farnesyltransferase inhibitor (FTI), lonafarnib, showed an improvement of cardiovascular phenotypes. Leslie B. Gordon (Progeria Research Foundation, USA) presented the latest results of the FTI trial, which was very encouraging in that mortality was reduced from 29.6% to 3.7% (untreated vs treated) during a 2.2 year follow-up (Gordon et al., 2018). Another trial with FTI and the mTOR inhibitor, everolimus, is ongoing. There remain a number of challenges that HGPS and other rare diseases must address in developing concrete, morbidity-relevant, objectively measurable clinical biomarkers for successful assessments of whether a drug has treated a disease. One such effort is a Japanese nationwide survey of HGPS initiated by Kenji Ihara (Oita University, Japan) (Sato-Kawano et al., 2017).

The Progeria Research Foundation (PRF) was started by Gordon in 1998 with the original purpose of causal gene identification. Following the identification of the recurrent *LMNA* mutation in 2003, the PRF has maintained and expanded the International Progeria Registry, provided HGPS patients' materials and other research resources, and facilitated a series of clinical trials.

6. Cockayne syndrome and xeroderma pigmentosum

Genomic instability syndromes can also be caused by variants at loci involved in nucleotide excision repair (NER). NER has two major pathways; global genome NER (GG-NER) and transcription-coupled NER (TC-NER). These pathways are distinguished by their initial DNA damage recognition events. In general, GG-NER causes XP and TC-NER leads to CS,

but overlap in the syndromes can occur. CS is characterized by microcephaly, growth retardation, progressive neurological abnormalities, and photosensitivity, but no increased risk of cancers. It is also associated with hearing loss, hepatic and renal dysfunctions, and retinopathy and/or cataracts. CS is classified into subtypes based on their onset and clinical severity: type-I (classic form), type-II (severe form, also known as Cerebro-Oculo-Facio-Skeletal (COSF) syndrome), and type-III (milder form). Most CS patients have defects in the *ERCC8* (CSA) or *ERCC6* (CSB) genes and have substantial loss of TC-NER activity. No obvious genotype-phenotype correlations were found for pathogenic variants in either *ERCC8* or *ERCC6*. There has been a report of an *ERCC6* null variant (p.Arg77*) case, who exhibits the mildest phenotype, and UV-sensitivity syndrome (UVSS) and displays only slight photosensitivity with no devastating symptoms. Tomoo Ogi (Nagoya University, Japan) showed that the milder clinical pictures in UVSS cases with the N-terminal truncation mutations can be explained by faster degradation and removal of stalled DNA damage-dependent RNA polymerase II (RNAP II) from DNA damage sites (Nakazawa et al., 2012).

XP is characterized by photosensitivity, pigmentary changes, premature skin aging, and a 10,000-fold increased risk of skin cancer. XP is caused by biallelic pathogenic variants of *DDB2*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *POLH*, *XPA*, or *XPC*. The *XPC* and *ERCC2* pathogenic variants are most common among XP patients in US and Europe, while *XPA* variants are most common among Japanese XP patients due to the presence of a founder mutation, c.390-1G > C. Chikako Nishigori (Kobe University, Japan) conducted a Japanese nation-wide survey of XP and developed a severity scale to classify XP. This scale correlated well with patients' ages and should be useful to follow the progression of the symptoms and to evaluate the effect of treatment drugs (Moriwaki et al., 2017). Defective GG-NER in XP is thought to recognize DNA distortions and bulky lesions, while TC-NER detects smaller lesions. Based on the cell-free NER assays, Kaoru Sugawara (Kobe University, Japan) proposed an updated model of GGNER. In his model, *XPC* first interacts with unpaired normal bases within the 'undamaged' strand and then loads the *XPD* ATPase/helicase in TFIIH onto the 'damaged' strand. The helicase activity and the damage verification function of TFIIH are markedly enhanced by the presence of *XPA* (Sugawara, 2016).

To date, there is no cure for CS or XP. Jan H. J. Hoeijmakers (Erasmus University, the Netherlands) tested dietary restriction (DR) in *Ercc1* deficient mice in four DNA repair pathways: TC-NER, GG-NER, cross-link repair deficient in Fanconi anemia, and single strand annealing of persistent DSBs. The *Ercc1*^{-/-} mice showed extensive premature multi-morbidity in virtually all tissues including brains, limiting their lifespans to 4–6 months. Subjecting these mutant mice to actual (30%) DR tripled their remaining lifespans, and drastically retarded numerous aspects of accelerated aging, with the neuronal system benefitting disproportionately. *Xpg*^{-/-} that showed many premature aging symptoms responded similarly. His findings indicate a counterintuitive DR-like therapy for progeroid syndromes and DR-like interventions for preventing neurodegenerative diseases (Vermeij et al., 2016).

7. Human induced pluripotent cell applications to progeroid syndrome research

HiPSC technology was first reported in 2007 by Drs. Takahashi & Yamanaka and has been broadly applied in medical science, especially for modeling diseases in many different organs. Guang-Hui Liu (Chinese Academy of Sciences, China) generated hiPSCs from the fibroblasts of various patients including those with WS, HGPS, CS, and XP (Kubben et al., 2016). Using targeted gene correction technique, the mutated genes in HGPS-hiPSCs and other diseased hiPSCs were successfully corrected, demonstrating the proof of principle. Future goals include the establishment of safer hiPSCs that are resistant to transformation. Masato Fujioka (Keio University, Japan) established a protocol to induce cochlear cells efficiently from the hiPSCs derived from patients with progressive hearing loss due to *DFNB4* mutations. This *in vitro* model may offer a platform for a fast-track, reliable, and rational approach to the drug's development (Hosoya et al., 2017). Wado Akamatsu (Juntendo University, Japan) developed a protocol to accelerate differentiation and maturation of hiPSC-derived neurons, which otherwise require long-term *in vitro* cultivation to exhibit phenotypes of neurodegenerative disorders (Fujimori et al., 2017). The hiPSC-derived neurons were successfully used for high throughput pharmaceutical drug screening for juvenile Parkinson's disease.

8. Summary

One estimates that there are 5000–7000 distinct rare genetic diseases. Together, 6 – 8% of the population may be affected by one of these orphan diseases. With technological advancements, new progeroid syndrome genes continue to be discovered. They include *POLD1* (DNA polymerase delta), *SPRTN* (recruitment of translational DNA polymerase eta), *MDM2* (an inhibitor of p53), and *SAMHD1* (regulation of dNTP pool). These findings continue to support the concept of genomic instability as a major mechanism of biological aging. The organizer of RECQ2018 hopes that progeroid syndrome research will proceed into the new era, leading to cures for these diseases and contributions to the understanding of human aging.

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Abbreviations:

BS	Bloom syndrome
CS	Cockayne syndrome
DSB	double strand break
HGPS	Hutchinson-Gilford progeria syndrome
hiPSC	human induced pluripotent stem cell

HR	homologous recombination
NHEJ	Non-homologous end joining
RTS	Rothmund-Thomson syndrome
WS	Werner syndrome
XP	xeroderma pigmentosum

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