2. The Genes Responsible for Human Progeroid Syndromes

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Key words: age-related genes, positional cloning, human genome projects, Cockayne syndrome, Bloom syndrome, Xeroderma pigmentosum, helicase, ataxia telangiectasia

In 1978, Martin screened genetic diseases described in "Mendelian Inheritance In Man" which was edited by McKusick, in order to find genetic syndromes with potential relevance to the pathobiology of aging. He selected 162 progeroid syndromes out of 2,336 genetic diseases according to the phenotypic criteria shown in Table 1 (1). Table 2 shows the upper twelve progeroid syndromes. Down syndrome is the top progeroid syndrome having 15 phenotypes. Down syndrome, Klinefelter syndrome and Turner syndrome are from chromosomal aneuploidies, and thus it is hard to find a single gene responsible for each syndrome. The responsible genes of six diseases have been isolated recently. Surprisingly, the genes for the Werner's syndrome (WS), the Cockayne syndrome (CS), the Bloom syndrome (BS) and the Xeroderma pigmentosum (XP) have a helicase domain. The ataxia telangiectasia (AT) gene has a phosphatidylinositol 3'-kinase domain which is involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Myotonic dystrophy is one of the triplet repeat diseases.

WS satisfied 12 phenotypes. There were some discordances between the phenotype in WS and in normal aging. For example, dementia or degenerative neuropathology, autoimmunity and hypertension are not characteristic phenotypes in WS. There was no obvious deposition of amyloid or lipofuscin. WS is an autosomal recessive genetic condition characterized by the premature occurrence of many age-related features. The symptoms include diffuse arteriosclerosis, glucose intolerance with hyperinsulinemia, high incidence of neoplasms, hypogonadism, osteoporosis, bilateral cataracts, loss or graying of hair, atrophy of skin and muscle, skin ulcers, and sclerosis. Laboratory findings include an excessive excretion of hyaluronic acid in the urine. The modal age at death is about 50 years, and death usually is caused by complications of arteriosclerosis and malignant neoplasm. Fibroblast from WS patients have a reduced life span *in vitro*, and increased mutation rate, but no apparent abnormalities in DNA repair. About 800 cases with WS have been reported in Japan. The incidence of WS in the Japanese population is higher than that in other ethnic groups.

WS provides a unique aging model, because the premature occurrence of many age-related features in WS is thought to

Table 1. The Phenotypes of Progeroid Syndromes (Martin GM, 1978)

	WS	BS	CS	XP	AT
1) Intrinsic mutagenesis	0	0	0	0	0
2) Chromosomal aberrations	0	0		0	0
3) Neoplasms	0	0		0	0
4) Stem-cell function	0				
5) Graying or loss of hair	0				0
6) Dementia or neuropathology			0	0	0
7) Slow virus infection					
8) Amyloid deposition					
9) Lipofuscin pigments			0		
10) Diabetes mellitus	0		0		0
11) Disorder of lipid metabolism			0		
12) Hypogonadism	0	0	0		0
13) Autoimmunity					
14) Hypertension			0		
15) Degenerative vascular disease	0		0		
16) Osteoporosis	0		0		
17) Cataracts	0		0		
18) Abnormalities of mitochondria					
19) Regional fibrosis	0	0	0	0	0
20) Variations in adipose tissues	0		0		
21) Other disorders					

WS: Werner syndrome, BS: Bloom syndrome, CS: Cockayne syndrome, XP: Xeroderma Pigmentosum, AT: Ataxia Telangiectasia.

Table 2. Segmental Progeroid Syndromes

	Score	Helicase domains
• Down syndrome	(15)	Trisomy 21
• Werner syndrome	(12)	(+)
• Cockayne syndrome	(12)	(+)
• Hutchinson-Gilford syndrome	(12)	
• Ataxia telangiectasia	(8)	PI-3 kinase
• Seip syndrome	(8)	
• Familial cervical lipodysplasia	(8)	
• Klinefelter syndrome	(8)	47, XXY
• Turner syndrome	(8)	45, XO
• Myotonic dystrophy	(6)	Triplet repeat disease
• Bloom syndrome	(5)	(+)
• Xeroderma pigmentosum	(5)	(+)

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Table 3. Helicases and Diseases

Code	Disease	Size		Helicase activity	Homology			
		A. A.	KDa		Hamster	yeast	E. coli	others
WRN	WS	1,432	162			SGS1	recQ	Q1 (human)
BLM	BS	1,417	159			SGS1	recQ	Q1 (human)
XPB	XP	782	89	3'-5'	ERCC3	RAD25		XPB (mouse)
XPD	XP	760	87	5'-3'	ERCC2	RAD3		
CSB	CS	1,493	168		ERCC6	RAD26		HBRM (human)

WS: Werner Syndrome, BS: Bloom Syndrome, XP: Xeroderma Pigmentosum, CS: Cockayne Syndrome.

be caused by defects of only one protein. However, despite many cytogenetic and biological studies, the primary defect in WS has remained elusive. In 1989, we therefore started a research project to isolate the gene responsible for WS (WRN). We have constructed a genetic, physical and expression map in the short arm of chromosome 8 and narrowed the position of the WRN locus on the basis of a homozygosity analysis, an extended homozygosity analysis, a linkage disequilibrium study and a haplotype study. As a result of our endeavor, in 1996, we identified the WRN gene (2).

The WRN gene is a 5.2 kb full-length cDNA clone which encodes a predicted protein of 1,432 amino acids. Comparison of the WRN sequences to known protein shows a striking homology to genes in the superfamily of DNA and RNA helicases. These genes include RECQ1 (man), F18C5C (*Caenorhabditis elegans*), Sgs1 (*Saccharomyces cerevisiae*) and RecQ (*Escherichia coli*). The region of shared homology is in the center of the protein (WRN-H), spanning from amino acid 540 to 963, the helicase domain. Other than the helicase domain, the WRN amino acid sequence does not show any significant homology

to known genes. Thus, WS joins a list of inherited disorders caused by mutations in helicase genes. These disorders are xeroderma pigmentosum, complication group B and D (helicase ERCC2 and ERCC3, respectively), trichothiodystrophy (ERCC2), Cockayne syndrome (helicase ERCC6), BS and X chromosome-linked α -thalassemia mental retardation syndrome (Table 3). These five helicases are divided to two groups. One group, XPB, XPD and CSB, bind other proteins and consist of protein complex, transcription factor II H. In the case of another group, WRN and BLM, their binding proteins were not detected. WS and BS shared the same homologous yeast Sgs1 gene, however there are slight differences in phenotype between the two syndromes. To clarify these differences, further study is needed.

References

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3. Neuronal Death in Alzheimer's Disease

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Key words: amyloid β -protein, neuronal death, seed, cholesterol, detergent-insoluble glycosphingolipid domain (DIG), tau, FTDP-17

Production and aggregation of amyloid β -protein

Line of evidence indicates that deposition of aggregated amyloid β -protein ($A\beta$), β -amyloid fibril, play a pivotal role in the induction of neuronal death in Alzheimer's disease (1-7). Thus, it is of fundamental importance to elucidate the mechanism of $A\beta$ aggregation leading to the generation of β -amyloid fibril.

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