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1. Introduction

Systemic Sclerosis (SSc) is an autoimmune disease that is typified by several characteristic hallmarks such as vasculopathy, immune activation and extensive fibrosis of the skin and inner organs (1). Although the disease has an overwhelming effect on morbidity and mortality, a cure or even a well defined pathogenic chain of events remains to be discovered. SSc is quite a rare disease (prevalence between 3 and 24 per 100,000 persons) and as a consequence, it has taken a relatively long time to define well-recognised classification criteria. This initially hindered detailed research into the pathogenesis of this debilitating disease (2-7). However, during the last 20 years research has intensified and several significant leaps forward have been made, assessing susceptibility risk either via epidemiologic/environmental or genetic research. SSc susceptibility disease does not show typical Mendelian heritability, but appears multi-factorial, with an onset later in life. This implies that the effects of many small genetic variations may combine over time to precipitate the disease in a SSc susceptible individual. Recently, this dogma was further underscored by a genome wide association study in SSc, showing that there was not one single genetic factor posing enough risk to be fully accountable for SSc development (8). However, investigations of interaction networks composed of multiple genetic risk variants, which together culminate in a higher disease risk, are just starting in this field (9-10).

Research focusing on environmental factors has initially yielded some interesting results. Environmental risk factors range from exposure to solvents and silicone breast implants, as well as CMV and parvo B19 virus infection (11,12). Although interesting, these results remain not well established, due to the lack of replication or small cohort size (11). Silica exposure is an exception and seems to be a rather reproducible risk factor among multiple small cohorts and case-series. This even led to the incorporation of SSc in insurance fees for silica workers in some countries (11). Next to these associations, a few studies failed to show an association between silica and SSc risk. A recently published and highly anticipated meta-analysis on this matter was severely hampered by heterogeneity in the methods used by the separate studies (13).

When we overview the results from these two fields of interest in SSc research, it becomes clear that the risk for developing SSc is highly unlikely to be fully explained by genetic
factors on the one hand, but that the field of epidemiology failed to identify clear environmental factors on the other hand. Hence, these observations are suggestive for the presence of more subtle processes that may be involved in determining disease on a genetically susceptible background. Since SSc rarely develops at very young age, it is logical to suppose that these processes may take place in the temporal dimension. More specifically, ageing at the level of cells, tissues and organs, i.e. biological as opposed to chronological ageing, might have an impact on development of the disease and has been increasingly implicated in SSc pathogenesis over the last few years. This review aims at critically describing findings coming forth from this area of research and attempts to place them in a hypothetical framework with regard to SSc pathogenesis.

2. What is biological ageing, how is it defined and how is it measured

Biological ageing is ageing at the level of a cell, tissue or organ and by extrapolation the whole organism. It need not necessarily equate with the chronological age of the individual. Indeed, it can be used to explain inter-individual variation in the rate of ageing between individuals of the same chronological age. Extrapolation of cellular ageing to the level of the tissue or organ, or the whole organism, is not straightforward. To do so, one must take account of the number of senescent cells (generated by both replicative senescence and stress or aberrant signaling-induced senescence (STASIS)), their location and similarly the number and location of cells lost through insult, in each respective organ or tissue, to gauge properly the effect on its functional capacity. Typically, functional capacity would be expected to decline with increasing biological age. The rate of biological ageing is influenced by the levels of oxidative insult at a cellular level, by lifestyle, socio-economic factors and environmental factors.

3. Telomeres

Telomeres are specialized nucleoprotein complexes at the end of eukaryotic chromosomes. They comprise tandem TTAGGG repeat arrays bound to a variety of proteins with roles in chromosomal protection, nuclear attachment and replication. Telomeres function to cap the chromosome, preventing chromosomal fusions and the recognition of the chromosome end as a DNA break. Telomeres facilitate chromosomal attachment within the correct subcellular compartment and have a critical role in DNA replication. The proteinaceous component of the telomere helps maintaining its structural integrity and functions in sensing, signalling and repair of DNA damage (14). The length of telomeric DNA repeats shortens during the ageing of cultured somatic cells (e.g. fibroblasts, peripheral blood lymphocytes and colon epithelia), but the rate of shortening is also under both polygenic and environmental influences (15,16). As a consequence, telomere length reflects the “miles on the clock” of a given individual or cell type. The characteristic telomeric repeats typically end in a 3’ single guanine strand overhang (17). This is folded back into a double loop structure, comprising a large telomeric loop (the T loop) with the single stranded repeat invading the adjacent double stranded DNA helix to form a second loop, called the displacement, or D loop. This loop is stabilized by, and dependent on, a cluster of proteins called the shelterin complex, which allows cells to distinguish telomeres from sites of DNA damage. (18).
Of interest in this respect, is another, non shelterin, telomeric protein, the Werner syndrome protein (WRN) protein, which is involved in the maintenance of telomeric stability (19,20). Mutations in the WRN gene cause the progeroid condition Werner syndrome. Notably, this syndrome is macroscopically quite similar to SSc, with features of scleroderma like skin changes, calcinosis cutis and ulcers and therefore is advocated to be entitled a place in the differential diagnosis when considering SSc (21-23). However, the syndrome also has many features, such as hyperglycemia and osteoporosis that are atypical for SSc and Werner’s is virtually never accompanied by Raynaud’s phenomenon or the typical SSc related auto-antibodies (23).

Increased chromosomal damage has been repeatedly reported in SSc lymphocytes as well as fibroblasts, (24-29). Most authors advocate that such damage is due to a higher amount of oxidative damage, caused by the production of reactive oxygen species (ROS) in the SSc inflammatory state (24, 25). In addition, SSc fibroblasts produce more ROS than their healthy counterparts. It is reasonable to expect that in the presence of such elevated levels of ROS, that telomere biology would be implicated in the chromosomal aberrances observed in SSc.

An initial study investigated telomere lengths of peripheral blood leukocytes (PBLs) and fibroblasts from 43 SSc patients, 182 SSc family members and 96 age-matched controls restriction fragment length polymorphism (RFLP) and chemiluminescent labelled probes. They observed an average loss of telomeric DNA in PBLs from SSc patients and their family members of 3 kb compared to the controls. This loss withstood correction for age and disease duration. Of interest, although telomeres in SSc fibroblasts were shorter overall compared to healthy control fibroblasts, this difference was not significant. The investigators did not observe an association with antibody profiles and telomere shortening. Furthermore, family members of SSc patients often had shorter telomeres compared to the patients. Two things can be distilled from this observation. Firstly, it seems unlikely that the telomeres shorten as a consequence of the disease, but that shorter telomeres are a risk factor for SSc themselves, or a secondary effect from another risk factor. Secondly, following from the previous hypothesis, this risk factor might very well be a genetic one, considering the familial occurrence of the shortened telomeres regardless of age (30).

Another study addressing telomere length in SSc focused solely on females with the lcSSc phenotype. Forty-three lcSSc patients with an age ranging from 37 to 80 years were included. Terminal restriction fragment (TRF) analyses were used to determine telomere lengths in this study. Regression analysis showed significantly longer mean TRF lengths in lcSSc patients compared to their age-matched healthy counterparts. Moreover, these telomeres did not show any attrition, usually observed with ageing. When the authors analyzed the results by defined age groups, the difference between the lcSSc and control telomere lengths was only significant beyond the fifth decade. Below 50 years of age, no difference was observed between healthy females and females with lcSSc. Noteworthy, patients using non-steroid anti-inflammatory drugs (n=3) were observed to have longer telomeres, than those not on NSAIDs (n=17) (31). It is noteworthy that using Southern blotting to determine terminal restriction fragment lengths also includes detection of subtelomeric region sequences which are known to show interindividual variation. Consequently, these observations may indicate a subtelomeric component in lcSSc and masking TTAGGG repeat attrition, simply as a matter of methodology.

Until now, literature addressing the role of telomeres in SSc appears conflicting, but this may be due to the different clinical subsets of SSc investigated by these studies and or
methodological differences (see above). In this aspect it is important to note that each single telomeric repeat is a potential topoisomerase cleavage site (32). Since anti-topoisomerase antibody (ATA) positive patients are usually not of the lcSSc subset but from the dcSSc subset, it is tempting to speculate that the presence of these antibodies contributes to the differences between the studies. This is likely considering the first study included 40% patients with dcSSc. Although the study states no differences were observed with the antibody status of these patients, the authors do not provide numbers or data on this matter. When considering the size of both these studies, it is yet unlikely that they harbour enough power to provide a conclusive answer on the involvement of ATA+ in telomere shortening. A second point of consideration is the dissimilar methodology used in both studies. Both studies used different percentage gels affecting resolution; this is partially reflected by the differences in variation of the mean TRF, which was remarkably larger in the initial study. Considering the currently increasing amount of discrepancies coming forth from the use of diverse methodologies in telomere measurements, a study with a sufficient number of fully clinically characterized patients, analyzed by a single method, is essential to define the exact impact of different SSc clinical features on telomere length (33).

4. Telomerase

Telomerase is a holo-enzyme able to synthesize novel telomeric DNA. Typically, in the absence of telomerase activity (or of a second mechanism-alternative lengthening of telomeres-ALT), telomeres in somatic cells will gradually shorten resulting in cell growth arrest and eventual apoptosis. Telomerase activity is able to circumvent these processes by adding new TTAGGG repeats, thus enlarging the cells proliferative lifespan and combating the cellular ageing process (14). Telomerase has been a target of investigation in SSc several times, although each of the respective studies focused on different aspects of telomerase biology. A synopsis of these studies is presented below.

One study investigating the role of telomerase in SSc hypothesized that telomerase activation may participate in activation and proliferation of circulating lymphocytes. This was based on a study in rheumatoid arthritis (RA) and pigmented villonodular synovitis (PVS) showing that telomerase activity is present at a high level in synovial infiltrating lymphocytes obtained from patients with RA, indicating that telomerase activation may be involved in lymphocyte activation and proliferation in RA (34). To address the role of telomerase activity, peripheral blood mononuclear cells from 9 female SSc patients and 10 healthy age-matched females were obtained and subjected to the telomeric repeat amplification protocol. Next to this, PBLs from SLE, Sjogren syndrome (SS) and mixed connective tissue disease (MCTD) were included. Telomerase activity was detected in 64.7% of SLE patients, 63.6% of MCTD, 54.5% of SS, and 44.4% of SSc. Telomerase activity in SSc was not significantly different from the activity observed in the controls, although it has to be noted that high telomerase activity was detected in some patients with this disease. However, a significant difference was observed in PBLs from patients with SLE, MCTD, and SS. Although of interest, this study is not conclusive considering the very small number of SSc patients included (35).

In SSc, the observation was made that SSc fibroblasts had a longer longevity and were less likely to go into apoptosis than fibroblasts from healthy controls (36). From this perspective, the hypothesis was put forward that SSc fibroblasts have higher telomerase activity compared to fibroblasts from their healthy counterparts. To address this issue indirectly, a
study investigated the presence of a polymorphism at position 514 in the telomerase gene in 53 patients with SSc and 98 healthy controls restriction fragment length analysis. The investigators found a significant higher presence of the 514 AA genotype in SSc. Again, these results are interesting, but the very small sample size and the lack of clearness of any functional implication of this polymorphism renders any firm conclusions vain (37). Notably, somatic cells such as fibroblasts express negligible levels of telomerase, so that a hypothesis based on differential telomerase activity between healthy and diseased cells, is highly questionable.

A further cross-sectional study aimed at evaluating telomerase activity in various connective tissue diseases was similarly hampered by lack of power (38). This used 19 patients with SSc, 15 with SLE, 10 with RA and 14 with SS. Twenty-nine healthy subjects were also included. Human telomerase-specific reverse transcriptase (hTERT) was measured in PBLs, using RT-PCR. The highest values were observed subsequently in RA, SLE and SS. Whereas RA was the only disease with significantly higher telomerase expression than controls, SSc PBLs displayed significantly lower expression compared to controls.

To place this observation in the proper perspective, additional features have to be considered. The mean age of the SSc patients was not the highest of the tested groups, making an effect of age on telomerase activity unlikely. In their discussion the authors put their findings in the light of the study by Artlett et al. describing significantly shorter telomeres in SSc PBLs (reviewed above). They advocated that the shorter telomeres in SSc might be caused by lower telomerase activity. This is not intuitive from the point of view of telomere biology, where disease stress may simply result in increased telomeric attrition and replicative senescence. None of the studies above have tested for this, even by simply looking at senescence associated cell surface markers on PBLs (39). Another pivotal observation is that nearly half of the SSc patients included in this study received cyclophosphamide treatment, which has been suggested to influence telomerase activity (40). Unfortunately, the authors do not provide a comparison between the SSc patients with and without cyclophosphamide treatment, which would have certainly been helpful to rule out this possible bias.

Also of note, is that the initial hypothesis of higher telomerase activity in SSc fibroblasts recently inspired researchers to isolate high collagen-producing fibroblasts from SSc biopsies and extend their lifespan with hTERT immortalization by lentiviral infection. This was done to the purpose of creating long living SSc fibroblast cell lines to better study and phenotype the characteristics of the SSc fibroblast in a consistent model (41). Such cell lines, while useful research tools, are blunt instruments, and negate primary telomere based damage response mechanisms that may be subverted by the disease, as they artificially immortalise the fibroblasts and bypass damage responses, as a consequence. It will be interesting to evaluate such cell lines for levels of DNA damage and chromosomal abnormalities with increasing passage in culture, in order to try to disentangle these from disease specific changes. A further criticism of such an approach is that it negates the contribution of any epigenetic driver of the disease state which may affect telomere biology and hence cellular life span.

5. Impaired cytological senescence in SSc

Immune senescence describes the ageing of the immune system and is rather than a chronological ageing process a biological ageing process. The most well defined findings in
this field surround the involution of the thymus. This process starts after puberty, continues during ageing and ultimately results in partial failure of T cell receptor expression and a decrease in production of CD4+ and CD8+ cells. This ultimately results in a larger T memory cell pool. Both CD4+ and CD8+ cells lose CD28 expression. Intriguingly, CD28- T cells are less prone to apoptosis, autoreactive and profoundly interferon gamma (IFNγ) producing. Among others, defective Fas signalling also plays an important role in the maintenance of thymus function. In addition, interleukin 2 (IL-2) production and response of aged people declines. A recent study showed that patients with SSc, during their lifespan, undergo a progressive expansion of the naive CD4+ T cell subset. This could be addressed to an age-inappropriate peripheral distribution of naive CD4+ T cells. It was regarded as age-inappropriate because, in contrast to healthy controls, the distribution of naive cells increased with age in SSc patients. Intriguingly, this is also in sharp contrast to RA, where the high levels of T cell activation and apoptosis ultimately produce a larger memory subset pool in disadvantage of the naive T cell pool (42). As described above, thymus involution seems to play an important role in maintaining the T cell pool. To investigate the role of thymus involution in the observed differences in T cell populations, the proportion of recent thymus emigrants by analysis of CD31 expression has been investigated. This has led to the observation that there was no correlation with decrease of recent thymus emigrants in the peripheral blood in inactive and the lcSSc forms of the disease, but not in patients with the diffuse and active disease. This indicates that in the lcSSc and inactive disease subsets, the physiological ageing related decrease in thymic T cells is evaded. However, there seems to be more at play than just an increase in thymically produced cells, since the observed increase in CD31 cells did not correlate significantly with the total number of CD4+ T cells. Based on this finding, it has been hypothesized that peripheral mechanisms must be involved as well to explain the increased frequencies of naive CD4+ T cells discovered in SSc patients. Several explanations have been proposed for these observations, including persistent in vivo antigenic stimulation and cytokine production. Of interest however is the finding that higher sFAS and Bcl-2 levels were detected in the SSc patients included in this study, possibly contributing to the difference in T cell homeostasis (43). As mentioned above, defective FAS functioning is implicated in conserving thymic function and has been involved on a functional and genetic level in SSc previously, more specifically in lcSSc patients, which fit with the lcSSc specific observations made in this study (44,45).

Following injury, epithelial cells undergo an epithelial–mesenchymal transition (EMT), in which they start migrating over the wound site and begin proliferating to replace lost cells. In this respect, it is important to note that most cells exhibit a finite ability to replicate, termed the Hayflick limit (46). Based on this, it has been proposed that repeated epithelial injury can lead to epithelial cells that enter a state of replicative senescence and can no longer proliferate. At this point a fibroblast response can be initiated as a compensatory mechanism that serves to patch injury site. This, partially hypothetical framework is consistent with an increasing prevalence of SSc in age and with the occurrence of the most aggressive SSc cases being described in late onset disease (47). More importantly, this hypothesis provides a direct connection between the process of ageing and fibrosis. In line with this hypothesis, although targeting endothelial cells, is a recent study addressing the ability of mesenchymal stem cells (MSCs) to differentiate into endothelial cells in SSc. This process is of interest in SSc, since endothelial damage has been strongly implicated in its
characteristic vasculopathy. A recent study investigated the ability of MSCs derived from 7 SSc patients and 15 healthy controls to differentiate into endothelial cells. The cells were cultured in endothelial-specific medium, and subsequently the endothelial-like MSC phenotype was characterized by surface expression of vascular endothelial growth factor receptors. In addition, the authors investigated cellular senescence of these cells by measuring the telomerase activity in MSCs from SSc patients and controls. Intriguingly, telomerase activity in MSCs from SSc patients was significantly reduced as compared with that in MSCs from the controls. This observation is counterintuitive to previous hypotheses relating to higher telomerase activity in disease SSc. MSC’s are a telomerase positive cell type. A lack of or a decrease in telomerase activity in these cells is indicative of a reduced proliferative repair capacity. This significant difference between SSc and control MSCs disappeared after full endothelial differentiation. At this point, both subsets displayed decreased activity, with a stronger decrease in endothelial like MSCs from SSc patients as compared with those from controls. The authors propose that this reflects early senescence and that it is caused by an increased number of pathologic stimuli and events encountered by these cells during their lifespan in the SSc patients (48). It is also consistent with aberrant telomere biology in SSc and a reduced damage repair capacity.

6. The X chromosome and age

Perhaps unexpectedly at a first glance, X chromosomal expression alters with age. This is of particular interest in SSc, since this disease predominantly affects females, with ratio’s reported as high as 14:1 (2-6). Interestingly, skewing of X chromosome inactivation and X chromosome monosomy, both affecting X chromosomal expression, have been implicated in SSc susceptibility or pathogenesis. These two aspects of biological ageing will be discussed in this paragraph in the context of SSc.

The X-chromosome accommodates 1098 genes (49). Most X-linked genes are present with one copy in males (XY) and two copies in females (XX). To level differences between males and females in X chromosomal gene expression, several species including mammals, evolved dosage compensation mechanisms (50). One of these mechanisms balances expression of the X-linked genes, present as a single copy in males (XY) and as two copies in females (XX), by inactivation of one of the two X-chromosomes in females (50). The human X chromosome goes through several phases of inactivation and reactivation during germ cell development and in the first part of the embryogenesis. In female embryos, imprinted inactivation of the paternal X chromosome is effectuated at the two- to four-cell phase, pursued by random X-inactivation at the blastocyst stage. As a consequence of this, females are functional mosaics for inactivation of the paternal or maternal X-chromosome (51). About 15% from the X chromosomal genes escapes inactivation; this inactivation pattern shows some heterogeneity between females (52). Although inactivation of the X-chromosome is apparent to be permanent for all descendants of a cell, the XCI pattern alters with age. The frequency of skewed XCI in peripheral blood cells increases in elderly compared to younger healthy females. This is thought to be caused by the exhaustion of progenitor cell populations in the bone marrow with ageing, leaving only a few progenitor cells left to produce cells that will reflect the skewed XCI patterns of their progenitors in the periphery (53).
Intriguingly, women with SSc comprise a significantly higher frequency of peripheral blood cells with a skewed XCI pattern compared to healthy women. The same observation has been made in females with auto-immune thyroid disease and juvenile arthritis, but was not observed in systemic lupus erythematosous and primary biliary cirrhosis (54). Two overlapping Turkish studies postulated that in 195 female SSc patients and 160 female controls skewed XCI patterns were significantly more present; 44.9% of 149 informative patients and in 8% of 124 healthy controls. (55,56). Interestingly, there seemed to be no age related increase in skewed XCI patterns. A recent study replicated the significantly higher percentage of XCI skewing in a cohort of 217 women with SSc and 107 healthy women. More depth was added to this observation by showing that there was no significant difference between skewing patterns of peripheral blood mononuclear cells, plasmacytoid dendritic cells, T cells, B cells, myeloid dendritic cells and monocytes. At sharp contrast with the healthy control population, skewing percentages of X chromosomal inactivation were independent of age in patients with SSc. Furthermore; this study investigated the effect of the skewed XCI on Foxp3 gene expression. Foxp3 plays an important role in T regulatory cell development. Intriguingly, Foxp3 expression was diminished in the patients with SSc exhibiting the most markedly increased skewing, which in turn was associated with less efficient suppressive activity (57).

Females suffering from Turner’s syndrome, and are hence harbouring only one X chromosome, are at increased risk for developing autoimmune disease. Based on this observation an effort was undertaken to investigate the presence of X monosomy in peripheral blood leukocytes from 44 females with SSc and 73 age-matched healthy women. Interestingly, monosomy rates in SSc, regardless of its clinical subtype, were significantly higher compared to healthy women. Furthermore, X monosomy rates increased with age and were higher in T and B cells compared to monocytes/macrophages, polymorphonuclear, and natural killer cells. Noteworthy, male cell microchimerism, also advocated to play a role in SSc, was ruled out by excluding the presence of an Y chromosome in these cells (58). These observations together imply that age related X chromosomal changes might play a role in the higher SSc prevalence in females at increasing age.

7. Conclusions

This review aimed to summarize findings related to biological ageing that are involved in SSc susceptibility and pathogenesis. When we overlook the publications in this field it becomes obvious that most of the investigations can be traced back to chromosomal changes, whether it concerns telomere and telomerase associated damage control, or senescence as well as alteration of X chromosomal expression.

The pivotal question in addressing the relevance of the described findings is whether the observed changes in cell senescence, XCI and telomeres/telomerase are caused by a higher turnover of cells, forced by the ongoing inflammatory processes in SSc, or that some of these results are truly involved in initiating or perpetuating SSc. When considering the results describing telomere shortening, increased XCI, X monosomy and early MSC senescence, these results might all flow logically from a higher demand of immune progenitor cells and epithelial/endothelial cells in SSc. This cannot be said about the finding of decreased
telomere attrition in lcSSc PBLs and the decreased rate of physiologic thymus function reduction, which seems counterintuitive considering healthy ageing processes and which is different to other autoimmune diseases. These findings are potentially very relevant in pointing towards processes sustaining or initiating the inflammatory status. More specifically, the factors sustaining thymic cell production and telomeric repeat length could be involved in the decreased capability to drive out immune cells based on cell damage or senescence, more prone to be autoreactive. It has to be noted here, that both processes take place predominantly in the lcSSc subset of patients, advocating for full clinical data to be included in future studies. The sustenance of telomeric length in PBLs from lcSSc patients is, based on the published literature, unlikely to come from an increase in telomerase activity, which was found steeply decreased in SSc patients. In this light it is of interest to compare telomere shortening in SSc with other ageing markers, such as CDKN2A, to see whether the shortening is an isolated process, or follows a general, systemic state of increased biologic ageing (33). Notably, although telomeric shortening seems to be influenced by socio-economic factors and events, no ubiquitous socio-economic correlations have been made with SSc so far (2-6, 15, 59).

The involvement of the X chromosome in SSc is also interesting, considering the increased prevalence of SSc in females. In this light it has to be noted that genetic data on X chromosomal genes in SSc are a scarce commodity and were not included in a recent GWAS publication (8). Genetic analysis of the X chromosome might identify genes involved in SSc directly or either indirectly in prompting XCI and X monosomy at an earlier onset than expected by physiological ageing alone. Finally, when over-viewing the literature in this field it becomes apparent that although very interesting observations have been made, the results described are hampered by small numbers of SSc patients and therefore have to be regarded cautiously. Nevertheless, these observations warrant more research since a strong point can be made for the involvement of age related phenomena in SSc. Therefore, a large study with well characterized SSc patients addressing current controversies in telomere and telomerase functioning, as well as further corroboration of EMT response aberrances is currently highly anticipated.

8. References


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Biologic Ageing Research in Systemic Sclerosis: Time to Grow Up?


Systemic sclerosis (SSc), or often referred to as Scleroderma (tight skin), is characterized by an exaggerated formation of collagen fibers in the skin, which leads to fibrosis. Accumulating evidence now points toward three pathological hallmarks that are implicated in Ssc, the order of which has yet to be determined: endothelial dysfunction, autoantibody formation, and activation of fibroblasts. This current book provides up-to-date information on the pathogenesis and clinical features of this severe syndrome. It is our hope that this book will aid both clinicians and researchers in dealing with patients with this clinical syndrome. In addition, we hope to shed more light on this rare and severely disabling syndrome, ultimately leading to better research and successful therapeutic targeting.

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