Mechanisms of Ageing and Development 129 (2008) 449–459

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Review

# HGPS and related premature aging disorders: From genomic identification to the first therapeutic approaches

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ARTICLE INFO

*Article history:*
Available online 12 April 2008

*Keywords:*
Progeria
Restrictive Dermopathy
Laminopathies
Premature ageing
Lamins

ABSTRACT

Progeroid syndromes are heritable human disorders displaying features that recall premature ageing. In these syndromes, premature aging is defined as "segmental" since only some of its features are accelerated. A number of cellular biological pathways have been linked to aging, including regulation of the insulin/growth hormone axis, pathways involving ROS metabolism, caloric restriction, and DNA repair. The number of identified genes associated with progeroid syndromes has increased in recent years, possibly shedding light as well on mechanisms underlying ageing in general. Among these, premature aging syndromes related to alterations of the LMNA gene have recently been identified. This review focuses on Hutchinson–Gilford Progeria syndrome and Restrictive Dermopathy, two well-characterized Lamin-associated premature aging syndromes, pointing out the current knowledge concerning their pathophysiology and the development of possible therapeutic approaches.


## 1. Progeroid syndromes and Lamin A-related progeroid syndromes

Progeroid syndromes are heritable human disorders displaying features that recall premature ageing. In these syndromes, premature aging is defined as "segmental" since only some of its features are accelerated. A number of cellular biological pathways have been linked to aging, including regulation of the insulin/growth hormone axis, pathways involving ROS metabolism, caloric restriction, and DNA repair. Different animal models, ranging from yeast, to nematodes, to mice, have been instrumental in obtaining evidence for these connections (Hasty et al., 2003).

Several heritable premature aging syndromes have for a long time been linked to defects in genome maintenance, due to altered DNA repair mechanisms. These mainly include the following autosomal recessive syndromes: (i) Werner syndrome, due to mutations in RecQL2 DNA helicase; (ii) Cockayne syndrome (CS) type A and B, due to mutations in the genes encoding the group 8 or 6 excision-repair cross-complementing proteins (ERCC8 and ERCC6), respectively; (iii) Rothmund–Thomson syndrome (RTS), due to RecQL4 mutations; (iv) trichothiodystrophy (TTD), due to mutations in the genes ERCC2/XPD and ERCC3/XPB, encoding the two helicase subunits of the transcription/repair factor TFIIH, as well as in TFB5, encoding the tenth subunit of TFIIH (Giglia-Mari et al., 2004); (v) ataxia-telangiectasia, due to mutations in the ataxia-telangiectasia mutated gene (ATM); (vi) xeroderma pigmentosum (XP), a genetically heterogeneous autosomal recessive disorder in which can be distinguished at least seven complementation groups, due to mutations of different DNA excision-repair proteins (Hasty et al., 2003; Kipling et al., 2004). All these progeroid diseases, involving heritable defects in DNA repair, suggest a central role of genome integrity maintenance in the aging process.

The number of identified genes associated with progeroid syndromes has increased in recent years, possibly shedding light as well on mechanisms underlying ageing in general.

Among these, premature aging syndromes related to alterations of the *LMNA* gene have recently been identified. *LMNA* encodes Lamins A/C, ubiquitous nuclear proteins belonging to the intermediate filament superfamily. These premature aging disorders have thus been classified as "Laminopathies", the large group of diseases associated to Lamin A/C defects. This group of heterogeneous disorders includes three main subgroups: (1) neuromuscular disorders (Emery–Dreifuss muscular dystrophy, limb-girdle

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doi:10.1016/j.mad.2008.04.003

muscular dystrophy type 1B, dilated cardiomyopathy type 1A, Charcot-Marie-Tooth peripheral polyneuropathy type 2B1 as well as a phenotype mimicking autosomal dominant proximal spinal muscular atrophy) (Rudnik-Schöneborn et al., 2007), (2) adipose tissue diseases (Dunnigan familial partial lipodystrophy, LDHCP), and (3) systemic diseases presenting with more or less pronounced premature aging features (mandibuloacral dysplasia type A and B (MAD-A/B), Hutchinson–Gilford Progeria Syndrome (HGPS), Restrictive Dermopathy (RD), atypical Werner syndrome) (for review, see Broers et al., 2006; Navarro et al., 2006; Mattout et al., 2006; Rankin and Ellard, 2006; Worman and Bonne, 2007; Foisner et al., 2007; Vlcek and Foisner, 2007a).

In recent years, the secondary involvement of Lamin A/C in the pathogenesis of several other neuromuscular diseases, including primary torsion dystonia (McNaught et al., 2004), Facioscapulohumeral muscular dystrophy (Masny et al., 2004) and fragile X-associated tremor/ataxia syndrome (Greco et al., 2006; Iwahashi et al., 2006) has been observed, further broadening the contribution of these proteins to different diseases.

The involvement of *LMNA* in Hutchinson–Gilford Progeria Syndrome, a very rare and uniformly fatal segmental progeroid syndrome (Hennekam, 2006), was identified in 2003 (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003). Mutations of *ZMPSTE24*, encoding an enzyme specifically involved in Lamin A post-translational processing, have subsequently been linked to Restrictive Dermopathy, a neonatally lethal genodermatosis (Navarro et al., 2004, 2005), and mandibuloacral displasia (MAD) (Agarwal et al., 2003; Shackleton et al., 2005).

Since these discoveries, a lot of research has been done at clinical and basic research levels, identifying other premature aging syndromes linked to primary or secondary Lamin A/C alteration and beginning to delineate the underlying molecular pathophysiological mechanisms.

Patients affected with rather severe Werner syndromes, but without a history of tumor development, carrying wild-type *RecQL2* sequences, were found to carry dominant *LMNA* mutations most often affecting both Lamin A and C isoforms (Chen et al., 2003; for review, see Kudlow et al., 2007), inscribing "atypical"

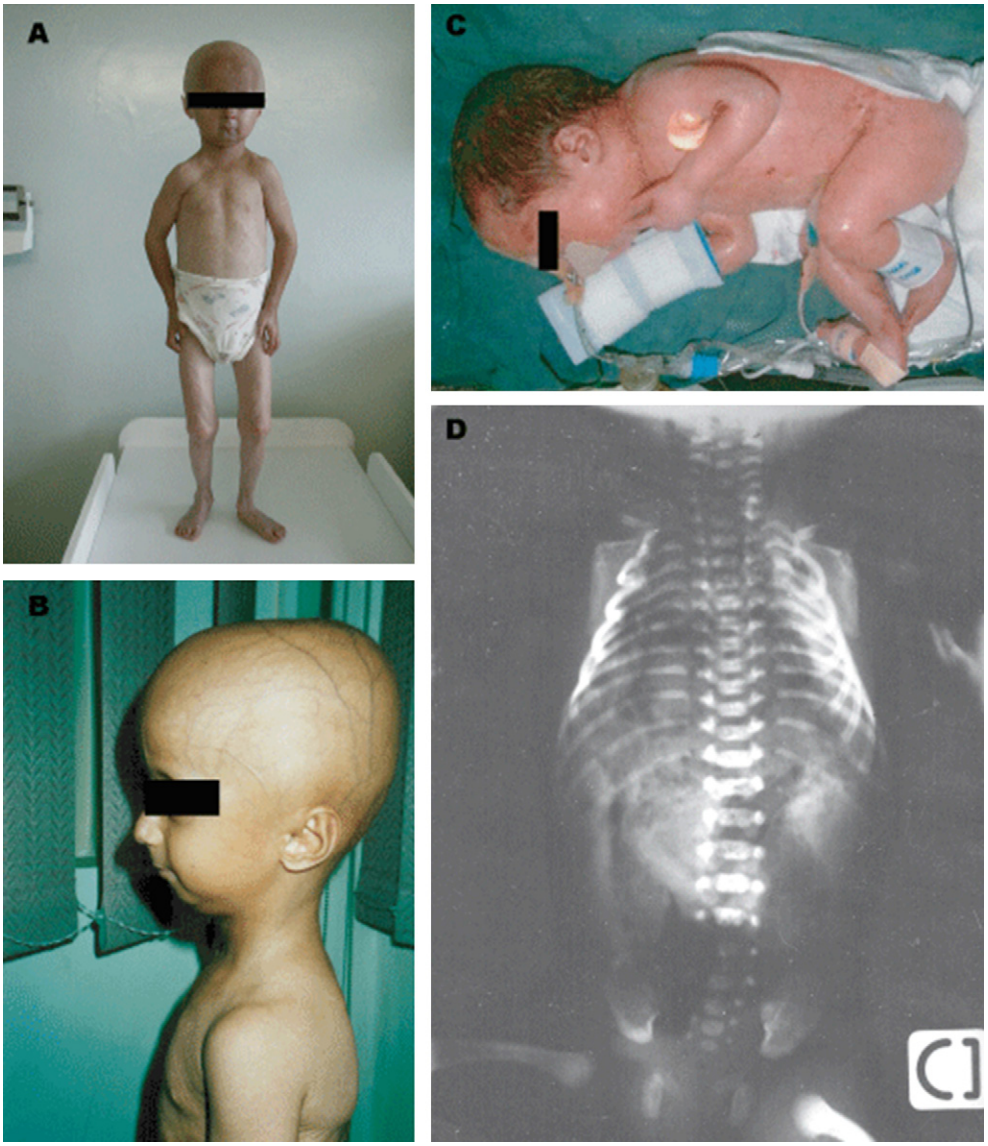


**Fig. 1.** Clinical and radiological findings in two patients affected with HGPS and one patient affected with RD. (A and B) Typical generalized lipodystrophy, alopecia, joint contractures (A), aged-looking and transparent skin with prominent superficial vessels (B), micrognathia (A, B) in two patients affected with HGPS. (C and D) Multiple joint ankylosis, skin erosion at flexure sites (C), generalized osteopenia and clavicular hypoplasia (D) in two patients affected with RD.