

## WORKSHOP REPORT

# Laminopathies: many diseases, one gene. Report of the first Italian Meeting Course on Laminopathies

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The first Italian Meeting Course on Laminopathies entitled “Laminopathies: many diseases, one gene” was held in Bologna on April 8-9, 2011 and it was attended by 100 participants, including neurologists, dermatologists, cardiologists, biologists, geneticists, and physiotherapists besides patients and families Associations. This meeting was organized by the Institute of Molecular Genetics of the National Research Council, the Italian Network for Laminopathies and the AIProSaB, the Italian association for the study of Hutchinson-Gilford progeria.

The main aim of the meeting was to join scientists involved in clinical practise and research on lamin A/C linked diseases (1) and to offer an overview on current clinical protocols and medical research to clinicians, researchers and patients.

The meeting focused on the following main areas: 1) the biology of the nucleus and the nuclear envelope and the biological pathways affected in laminopathies; 2) the epidemiology of muscle laminopathies, lipodystrophies and progeroid syndromes; 3) the Emery-Dreifuss Muscular dystrophy (EDMD) from a clinical point of view; 4) Dilated cardiomyopathy with conduction defects (CMD-CD) from diagnosis to therapy; 5) Familial partial lipodystrophy of the Dunningan type (FPLD): diagnosis and therapy; 6) Progeroid laminopathies, including mandibuloacral displasia (MADA) and Hutchinson-Gilford progeria (HGPS): diagnosis and therapeutic trials.

## Biology of the cell nucleus and pathogenetic pathways in laminopathies

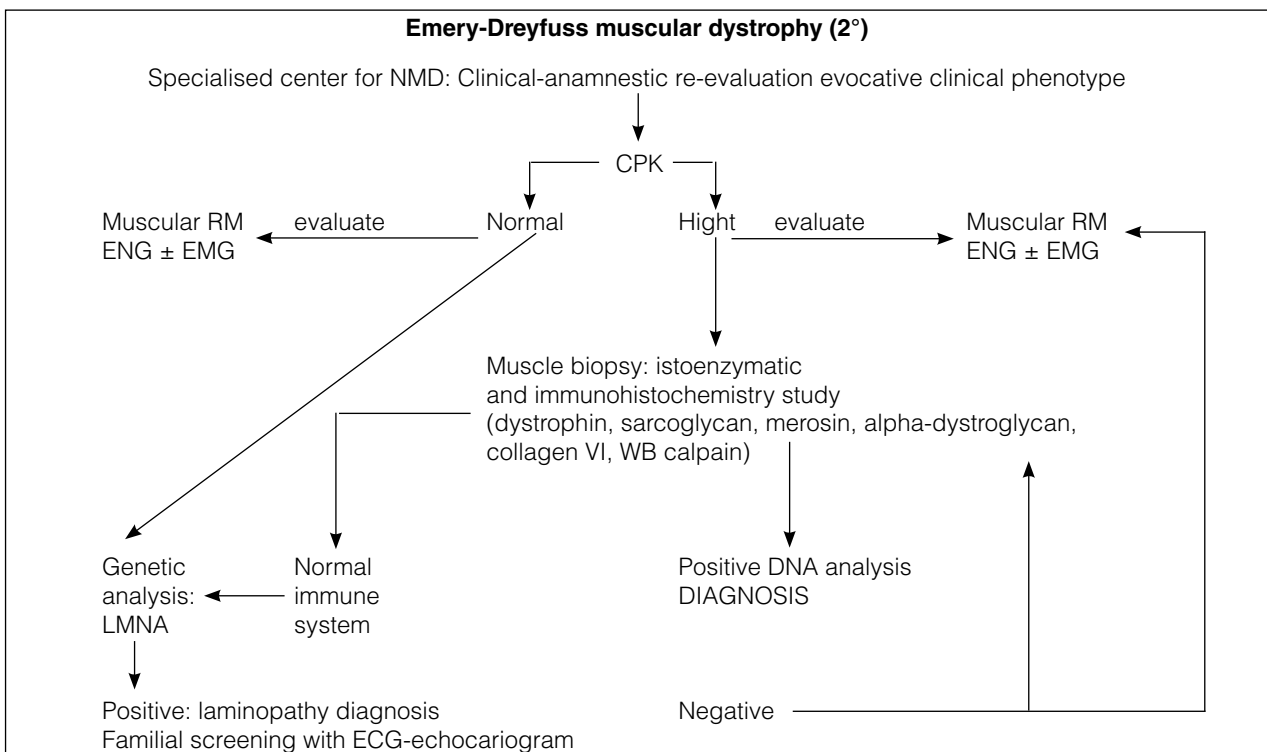
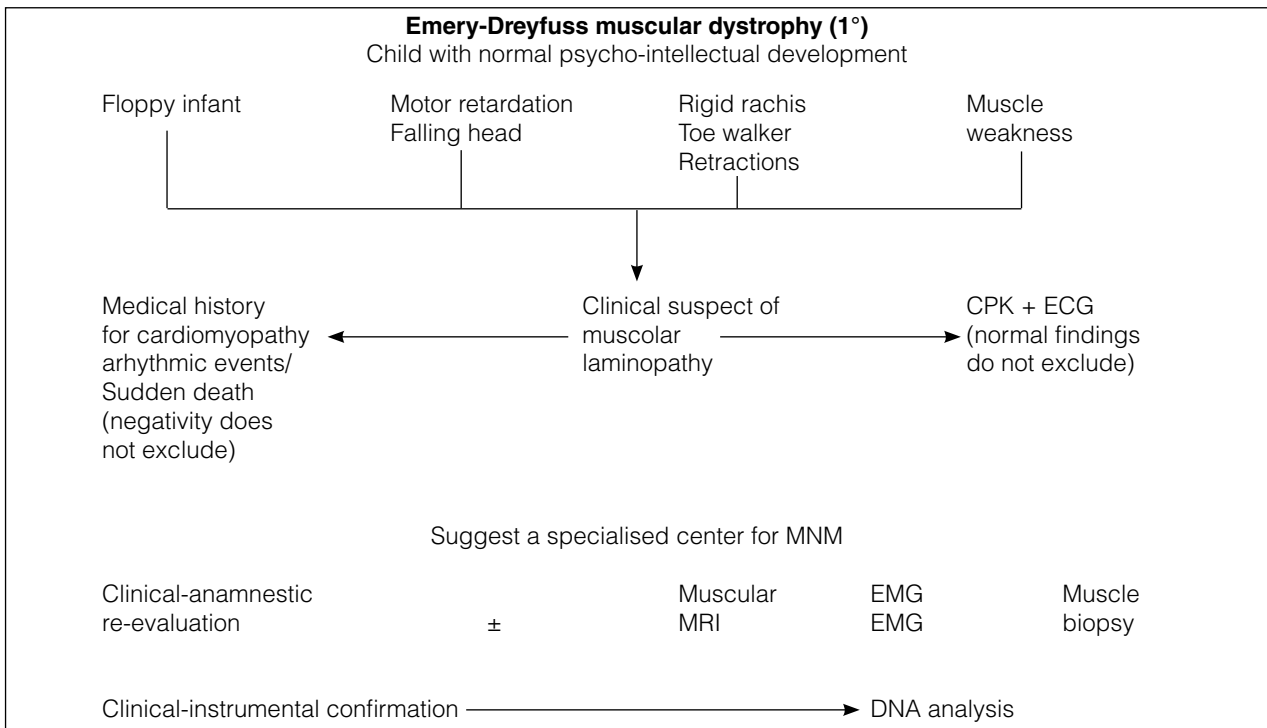
The first day of the meeting was devoted to an introduction to the biology of the cell nucleus (2). New

insights into the understanding of nuclear functionality have been presented. The nucleus is now considered a complex interaction platform, where proteins regulate nucleo-cytoskeleton interplay in view of chromatin organization and transcriptional activity (Nadir M. Maraldi, Bologna).

The main pathogenetic pathways in lamina A/C-linked disorders have been reviewed. Altered mechanosignaling transduction, chromatin modulation and differentiation-related gene transcription (3, 4) have been highlighted as the key events at the basis of laminopathic diseases. Prelamin A accumulation (5) has been reported as the main molecular defect in systemic and adipose tissue laminopathies (Cristina Capanni, Bologna).

## Epidemiology of lamin-linked diseases

Muscle laminopathies, including EDMD, LGMD1B and CMD-DC, are transmitted by dominant inheritance or may occur due to spontaneous mutations. The clinical phenotype (6) is characterized by joint contractures, muscle weakness and wasting and cardiac conduction defects, most of them evolving to pictures of dilated cardiomyopathy. The epidemiology of muscle laminopathies is complex and as yet not well defined. The incidence of autosomal dominant EDMD caused by mutations in lamin A/C gene (Enrico Bertini, Rome) has been reported as extremely variable, ranging from 1 to 3:100.000. Lipodystrophies may be caused by mutations in several genes including PPARGgamma, *LMNA*, *AKT* and seipin gene or also acquired, such as it happens in 40 percent of HIV infected patients undergoing anti-retroviral therapy. An overview of these disorders has been presented, with particular emphasis on *LMNA*-associated familial partial



**Figures 1 and 2.** Flow chart for diagnosis and follow-up of Emery-Dreifuss muscular dystrophy.

lipodystrophy, the most represented form of the disease (Renato Pasquali, Bologna). Progeroid syndromes linked to mutations in several genes including *LMNA* have been reviewed (Claudio Franceschi, Bologna).

### Genotype-phenotype correlation in laminopathies

During the second day, the lecture held by Giuseppe Novelli (Rome) focused on the genotype-phenotype correlation in laminopathies.

Beside mutations in the *LMNA* gene that give rise to eight different laminopathic phenotypes, other diseases are linked to mutations in lamin A-related proteins, namely the ZMPSTE24 endoprotease, which catalyses prelamins A maturation, the nuclear envelope constituents emerin, nesprin 1 and 2 and BAF, the lamina-associated protein LAP2alpha, which interact with lamin A/C, chromatin and cytoskeleton proteins. The clinical phenotype of each laminopathy has been described in relationship with mutations in the lamin A/C gene. The high degree of interfamilial and intrafamilial variability in clinical severity observed among patients (7), possibly due to modifier loci or allelic differences, takes it difficult to correlate the genotype with the phenotype.

### Emery-Dreifuss Muscular Dystrophy

The clinical spectrum of laminopathies was discussed with a special emphasis on the tissue-specificity of the various laminopathies and the overlapping clinical features (8). A detailed analysis of diagnostic protocols for EDMD, Limb-Girdle muscular dystrophy type 1B and congenital *LMNA*-linked muscular dystrophy (9-13) has been presented by Tiziana Mongini, Eugenio Mercuri, Lucia Morandi, Antonella Pini, Stefano Previtali, Nicola Carboni and Adele D'Amico. Mercuri and D'Amico described the *Dropped Head Syndrome* in young patients affected by EDMD, which they suggest to consider it as a clinical sign of laminopathy. Mongini and Carboni reported mild phenotypes of EDMD, even in aged patients with minimal contractures and difficulty in climbing stairs or in patients undergoing muscle biopsy for different causes such as hyperCKemia or myalgias in the course of therapy with statin, a widely used anticholesterol agent. Morandi reported typical aspects of histochemistry and immunohistochemistry in biopsies from EDMD patients, showing different phenotype depending on the affected muscle. Pini presented the flow-chart for diagnosis and follow-up of children with EDMD (Figs. 1, 2).

### Dilated cardiomyopathy with conduction defects

A special emphasis was made on the cardiac diseases (14, 15) with the aim to give recommendations for clinical management of these disorders and the use of implantable devices. Elena Biagini reviewed the cardiac phenotype of laminopathies and highlighted the existence of undiagnosed cases, especially in patients followed in standard cardiological units. Luisa Politano underlined that patients with mutations in *LMNA* gene presented an increased risk of cardiac sudden death and reported the flow-chart for diagnosis and fundamental clinical follow-up of patients with CMD-DC (Fig. 3); Giuseppe Boriani presented the advantages and the risk to benefit ratio of new implantable cardioverter defibrillators in CMD-CD and/or EDMD patients suffering from conduction defects, although yet asymptomatic. Roberta Poletti presented new imaging techniques for the early diagnosis of fibrosis in the heart of laminopathic patients.

### Progeroid laminopathies and familial partial lipodystrophy. Future trial developments

The new perspectives for the treatment of laminopathies affecting adipose tissue and/or causing premature ageing have been presented. Paolo Sbraccia presented the clinical features and the outcome of the first clinical trial performed in MADA (16) by the use of statins and bisphosphonates. Alessandra Gambineri presented the flow-chart for diagnosis and follow-up of familial partial lipodystrophy (Fig. 4) and the efficacy of pioglitazone treatment in patients with metabolic disturbances. Emanuela Scarano presented the flow-chart for diagnosis and follow-up of patients affected by HGPS (Fig. 5) and the clinical outcome in a patient undergoing a clinical trial using statins and bisphosphonates.

Cardiac laminopathy
• Cardiology visit
• Standard ECG (12 derivations)
• 24-hour dynamic ECG according to Holter
• Echocardiogram with echocolor Doppler and acoustics densitometry
• Electrophysiological study (EFS) when indicated
• PMK/ICD implant

**Figure 3.** Flow chart for diagnosis and follow-up of cardiac laminopathy.

<b>Familial partial lipodystrophy (FPLD2)</b>
• Distribution of adipose tissue. SC adipose tissue?
• Muscular hypertrophy?
• Familiarity?
• Strong insulin resistance – if yes: increased probability
• Hepatic steatosis/Dyslipidemia – if yes: increased probability
• Leptin and adiponectin measurement
• Qualifying fat mass (DEXA)

**Figure 4.** Flow chart for diagnosis and follow-up of FPLD2.

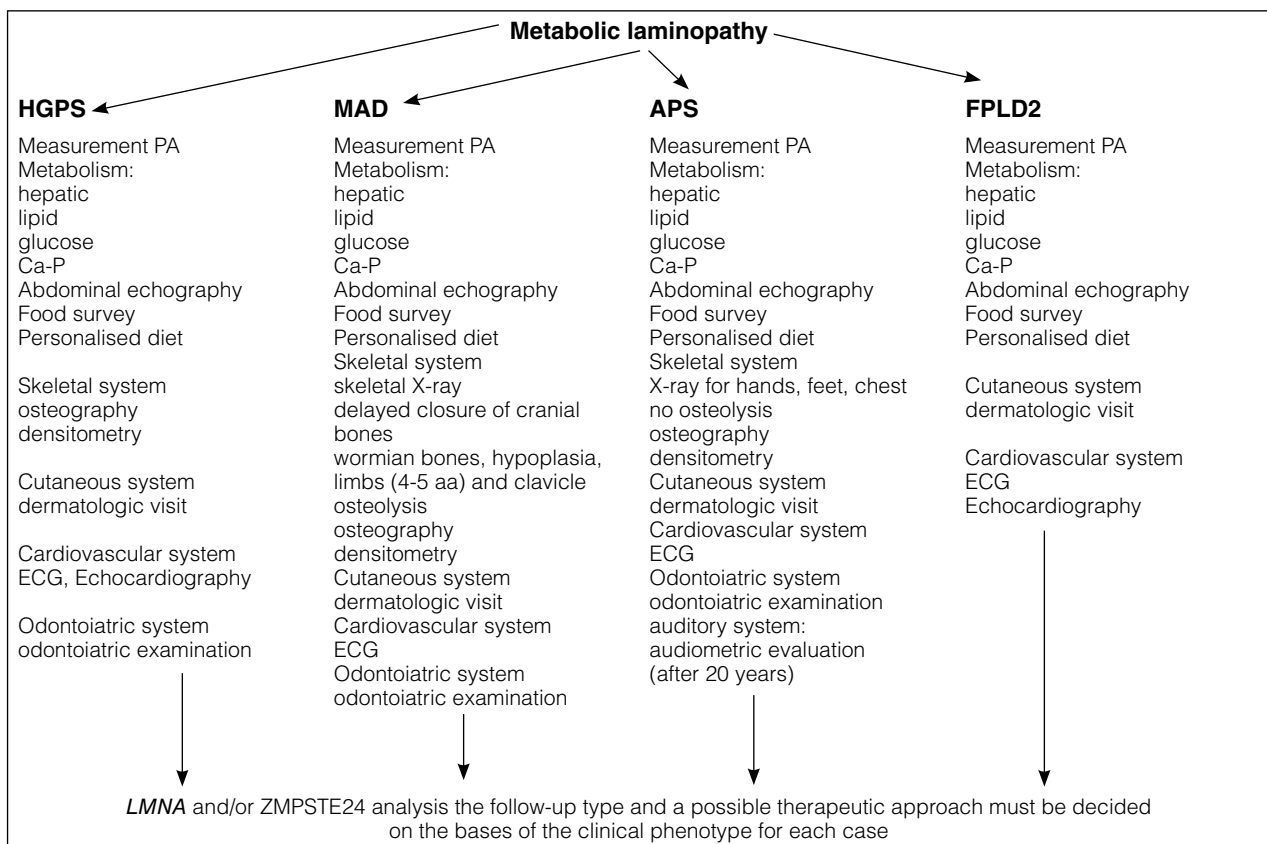
Giovanna Lattanzi presented new experimental therapeutic approaches for laminopathies affecting bone, such as MADA and HGPS, by the use of drugs limiting the levels of cytokines (TGFbeta 2 and osteoprotegerin) (17), and the rationale of therapies based on the use of statins and bisphosphonates. Further, recent data showing decline of IGF1 levels in models of progeroid laminopathies (18) have been reported as a suggestion for new pathogenetic mechanisms and/or new therapeutic perspectives.

## Patients' contribution

Patients, affected by progeria or EDMD2, have presented their experiences and their point of view on diagnosis, follow-up and treatment of diseases. They suggested closer interplay among clinicians, researchers and patients and were in favour of the website as a way of information for family doctors and patients to improve diagnostic approach and follow-up. They also encouraged the research activity.

## Conclusions

Animate discussions during this meeting clarified different points of view, and constructively resulted in a proposal for specific guidelines and flow-charts in laminopathies. The inter-disciplinary approach to laminopathic disorders was highly encouraged. This was an enjoyable and fruitful workshop that will lead to new collaborations into the network (<https://www.igm.cnr.it/index.php?id=383>) and will contribute significantly to the improvement of future therapeutic perspectives in laminopathies.



**Figure 5.** Flow-chart for the follow-up of metabolic laminopathies.

## List of participants

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