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History of international connections of myology in Europe

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Abstract

Over the past centuries, myology as a basic and clinical science has passed through three major stages of development: the classical period, the modern nosographic stage, and the molecular era. The classical period spans the sixteenth century up to the earlier parts of the twentieth century. During this time, several major muscle diseases were clinically and pathologically characterized, including Duchenne muscular dystrophy (DMD), myotonic dystrophy, and facio-scapulo-humeral dystrophy, by master clinicians such as Duchenne, Erb, Becker, Steinert, Landouzy, Dejerine, Meryon, and others. These accomplishments laid solid foundations for the following modern era with nosographic classification and the following molecular era. European clinicians and scientists were major contributors to the modern era in the second half of the twentieth century, which is characterized by three major discoveries. First, it was observed that substantial elevation of the serum activity of creatine kinase indicates muscle damage or destruction. Then, the adaptation of modern histo-and cytochemical techniques to the study of muscle biopsies markedly improved the diagnostic accuracy and made possible the identification of new changes and structures. Thirdly, the advent of modern biochemical techniques permitted the identification of various enzyme defects/storage diseases such as Pompe disease, McArdle's disease, and carnitine deficiency states. The molecular era was made possible by the strikingly fast development of molecular biology and its application to muscle diseases. This permitted the identification of gene defects in many inherited diseases, leading to an accurate and specific diagnosis. The growth of international collaboration in Europe was achieved through the exchange of international scientists and collaborative networks.

Key Words: muscle dystrophy; mitochondrial disorders; limb-girdle dystrophy; facio-scapulo-humeral dystrophy; metabolic myopathies.

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Over the past centuries, myology as a basic and clinical science has passed through three major stages of development: the classical period, the modern nosographic stage and the molecular era.[1]

Classical Period

The history of Myology begins in the 16th century with muscle anatomy pictures by Vesalius and Canani. The historical development of inherited muscle disorders dates back to the 16th century after the anatomical descriptions of Andreas Vesalius (1514–1564), who taught anatomy at the University of Padua. His most famous work, *De Humani Corporis Fabrica*, published in 1543, was based on human dissections and included beautiful woodblock plates prepared by Titian's pupil Jan von Calcar illustrating whole human bodies with all the muscles displayed ("muscle men") as well as studies of individual muscle groups (Figure 1). Although Vesalius accurately illustrated most of the major muscle groups of the human body he did not specifically discuss diseases of muscle tissue. The oldest printed text devoted exclusively to myology was written by G. B. Canani (1515–1579) in 1541 and entitled *Musculorum Humani Corporis Picturata Dissectio*. Unfortunately, only a few copies have survived including one originally in the library of the pathologist Giovanni Battista Morgagni (1682–1771). Morgagni in *De Sedibus et Causis Morborum per Anatomen Indagatis*, issued in 1761, showed several heart and brain disorders, but no specific muscle diseases, although in an *epistola* he observed muscles of a "yellow" color. Another prominent 18th-century scientist, Luigi Galvani (1737–1798), published *De Viribus Electricitatis in Motu Musculari* in 1792 and was the first to demonstrate the excitability of muscle and to illustrate the electrical neuromuscular junction. In the 19th century, the Neapolitan physician Gaetano Conte described what was then called Duchenne muscular dystrophy on a clinical basis as "*scrophola muscolorum*".

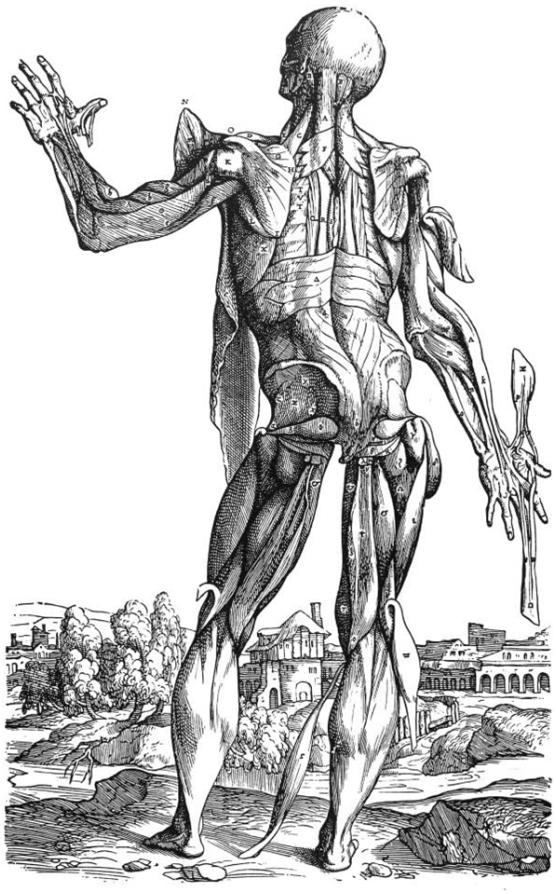

Fig 1. De Humani Corporis Fabrica *by Andreas Vesalius: whole human body with all the muscles displayed ("muscle men") as well as studies of individual muscle groups.*

It was then followed by the clinicopathological description of Duchenne in France,[2] which named the disease, and by the pathological description of Meryon in the UK.

The contributions to X-linked muscular dystrophy were further extended in 1955 by Peter Becker (1908–1989) who first clearly identified an allelic benign form of X-linked muscular dystrophy. Prof. Peter E. Becker trained at the Universities of Marburg and Berlin and was a professor of Human Genetics in Gottingen. Alan Emery was able to describe a family with a different type of benign muscular dystrophy with heart block and prominent contractures in heel cords, elbows, and muscles in the back of the neck during his visit in the mid-1960 by Fritz Dreifuss in Charlottesville in the USA and recognized an X-linked autosomal dominant form named "Emery-Dreifuss" syndrome, although a great genetic heterogeneity was found.

Limb-girdle muscular dystrophies (LGMD) were first recognized chiefly by a group of German physicians working in Heidelberg, i.e., Wilhelm Erb (1840–1921), Nicolaus Friedreich (1825–1885) and Johann Hoffman (1855–1919). The "Heidelberg myological trio" was founded by Friedreich. He was born in Würzburg, Westphalia, and became acting chairman of Pathology and Internal Medicine, in Heidelberg. In 1863 Friedreich discovered spinocerebellar ataxia and in 1872 he taught Erb, who attended medical school at the early age of 17 and received his *Abilitatur* at age 25. Erb was the first to develop the concept of progressive muscular dystrophy and also provided classic descriptions of the juvenile form of myopathy. He proposed the term dystrophy, and the name "*dystrophia muscularis progressiva*" was invented. Erb syndrome was recognized as a limb-girdle muscular dystrophy whose gene was mapped to chromosome 15q and described also myasthenia gravis. He was also interested in electrophysiology and described the Erb phenomenon, i.e., increased electrical irritability of motor nerves in tetany. Landouzy and Dejerine are widely recognized to have distinguished facio-scapulo-humeral dystrophy (FSHD) as a nosographic form in 1884–1885 and to have proved its myopathic nature. They were the first ones to characterize the main clinical features of the disease and to consider it as a new entity.[3] Their report contained the key elements, including early involvement of facial muscles, progressive weakness and atrophy of scapular and humeral muscles, and clinical variability among affected members of the same family.

The Modern Era

This stage was characterized by three main discoveries: first, it was observed that substantial elevation of the serum activity of creatine kinase indicates muscle damage or destruction in both patients and vitamin E-deficient rabbits.[4] Then, the adaptation of modern histo- and cytochemical techniques to the study of muscle biopsies markedly improved the diagnostic accuracy and made possible the identification of new changes and structures. Examples of this are the demonstration of nemaline rods in nemaline myopathy,[5] and ragged red/blue muscle fibers in mitochondrial diseases.[6] Thirdly, the advent of modern biochemical techniques permitted the identification of various enzyme defects/storage diseases such as Pompe disease, McArdle's disease,[7] and carnitine deficiency.[8]

Myology in Italy reached a major development in the second part of the 20th century with the establishment of the CNR Center for Muscle Pathology and Physiopathology in Padova (Professor Massimiliano Aloisi), a cardiological and genetic center in Naples (Professor Giovanni Nigro) and a neurological center in Milan (Professor Guglielmo Scarlato). The first congress in Neuromuscular Diseases took place in Milan in 1969 by the organization of Professors Scarlato, Aloisi, and Canal and was attended by several outstanding international muscle researchers such as A. G. Engel, W. K. Engel, L. P. Rowland, M. Fardeau and I. Hausmanowa-Petrusewicz. A series of meetings in many countries followed, up to the last International Congress on Neuromuscular Diseases held in Bruxelles in 2022.[9]

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Table 1. The main international connections of European Myologists.

USA - Mayo Clinic (Engel AG)	Angelini, Mora, Milone, Fumagalli, Zierz, De Bleeker.	Glycogenosis type 2, carnitine deficiency, myasthenia gravis, congenital myasthenia
USA - Children Hospital (Hoffmann):	Pegoraro, Gorni, Bello.	Duchenne dystrophy, carriers
USA - USC Los Angeles (Engel WK, Askanas)	Martinuzzi, Vita, Broccolini, Mirabella, Vattemi, van Den Bergh.	McArdle disease, Inclusion body Myopathy, Dysimmune Neuropathies
USA - Columbia University (Rowland, Di Mauro-Hirano)	Trevisan, Bresolin, Bruno, Mancuso, Zeviani, Servidei, Ricci, Minetti, Moggio, Musumeci, Sacconi Salviati, Lamberti, Lombes.	Mitochondria, CPT, Coenzyme Q deficiency.
Canada - Montreal (Karpati):	Armani, Molnar.	DMD
UK - London (Dubowitz, Muntoni)	Muntoni, Mercuri, Sorarù, Ferlini, Sarkozy.	Spinal muscular atrophy, congenital dystrophy
UK - London (Morgan-Hughes):	Harding, Toscano.	Mitochondria
UK - Oxford (Vincent)	Evoli, Cao.	Myasthenia gravis
UK - Liverpool (Edwards)	Siciliano	Muscle fatigue
UK - Newcastle (Walton, Bushby, Straub):	Vita, Guglieri, Diaz-Manera	LGMD, DMD
Germany – Munich (Schoser):	Montagnese	Myotonic dystrophy
France - Paris (Fardeau, Tomè):	Villanova, Laforet, Urtizberea, Berardinelli, Malfatti, Navarro.	Congenital myopathies
France - Nice (Desnuelle):	Sacconi	FSHD
Italy - Padova (Angelini):	Desnuelle, Ringel, Siciliano, Rodriguez	DMD, metabolic myopathies, LGMD

Several laboratories arose in Europe, especially in Neurological Institutes, or institutions founded by AFM (Institut de Myologie, Genethon in France) or founded by Telethon, Italy (TIGEM, NEMO); several European researchers emigrated permanently or went for a stage to improve their myological skills, especially in the USA, UK, Canada, and France both in basic and/or pathological, clinical research (Table 1).

The laboratory of Columbia University in New York, led by Professor Salvatore Di Mauro was a commonplace of training, especially in the field of mitochondrial myopathies. Here both the study of ragged red/blue muscle fibers in mitochondrial diseases, of cybrids, and the identification of various mitochondrial syndromes were accomplished, such as Kearns-Sayre syndrome (KSS), MELAS, and MERRF.

It is of relevance that many European scientists contributed, also by traveling to other laboratories such as Attardi's laboratory to learn the cybrid techniques and eventually returned to Europe to establish national and international networks in mitochondrial disorders. Two great discoveries were made in '90 by two famous researchers, Anita Harding at the Department of Clinical Neurology, Institute of Neurology, Queens Square, London, UK, the second was the creation of the so-called "cybrid" (cytoplasmic hybrid) immortal fibroblast cell lines in Attardi's laboratory at Caltech, California, USA. It consists in transferring into rho-zero cells (deprived of their mtDNA) heteroplasmic mitochondria from cultured skin fibroblasts of patients carrying mtDNA mutations. These heteroplasmic or homoplasmic cybrids provided hallmark models to evaluate biochemical consequences and functional threshold effects in MELAS, MERRF, and KSS.

The advent of modern biochemical techniques permitted the identification of various enzyme defects and metabolic myopathies such as late-onset Pompe disease, McArdle's disease, and carnitine deficiency states.

In all developed countries of Europe, the basis of neuromuscular research and diagnosis was expanded by the new immunohistochemical, biochemical and molecular techniques, including the Netherlands, Sweden and France. In Italy during the last part of the 20th and the beginning of the 21st century, Enzo Ferrari – a race car factory engineer – was a generous supporter to research in muscular dystrophy in Milan, Padova, and Modena, Italy. Telethon, Italy has contributed to supporting research in this area since the '90.

The Molecular Era

The molecular era was made possible by the strikingly fast development of molecular biology and its application to muscle diseases. This permitted the identification of gene defects in many inherited diseases, leading to an accurate and specific diagnosis. The best example of this is DMD and the discovery in the late 1980s of the gene at a locus on Xp21 whose mutation causes the deficiency of an essential protein, dystrophin, in muscle fibers, identified by Eric Hoffmann.[10] This was followed by an avalanche of discoveries revealing the molecular basis of dozens of hitherto unrecognized muscle diseases. Parallel with the spectacular development of genomics

Fig 2. June 6th, 1993. 23rd ENMC Workshop on "Rare Neuromuscular Diseases, from left, first raw: C. Angelini, C. H. Vermullen, C. Wallgreen-Peterson, F. Muntoni, A. E. H. Emery, second raw: L. Middleton, H. Hoser, K. Zorres, T. Grimm, M. Rutgers.

concerning muscle disease, histochemistry, and immunoblotting also produced remarkable discoveries.
The term 'limb-girdle muscular dystrophy' (LGMD) was first used in the seminal paper by Walton and Nattrass in 1954, where they identified LGMD as a separate clinical entity.[11] In LGMD description they pointed out that the category of LGMD most likely comprises a heterogeneous group of disorders. After that the clinical entity was discussed but the LGMD nosography reached a permanent classification during two ENMC workshops held in 1995 and 2017, in the last one an operating definition of LGMD was agreed upon. Several sarcolemmal proteins were identified whose deficiency causes different forms of limb-girdle dystrophy, including calpain,[12] sarcoglycans,[13] dysferlin,[14,15] and caveolin among others.[16] Dramatic advances also occurred in immunopathology that had remarkable effects on the molecular diagnosis and treatment of nongenetic dysimmune muscle diseases and other neuromuscular disorders.[17] Myology with the enlargement of its scientific basis in the molecular era began to split into subspecialties i.e. genetics, physiopathology, etc. and a spectrum of knowledge was accumulated both for diagnostic and therapeutic purposes. In the field of metabolic diseases and limb-girdle myopathies, several laboratories described new entities.
In 1991 the first locus to be mapped in a recessive LGMD was chromosome 15q15 (LGMD2A/R1)(11), probably due to the easy availability of large families, and a pioneer study on a French population, leading to an observation that indirectly implies a high population frequency of the disease. Erb's type limb-girdle muscular dystrophy (LGMD) was identified and clinically studied in detail in a small community living on Reunion Island. It was linked to chromosome 15q and related to six different mutations A series of cases were afterward clinically and genetically identified in the French metropolitan community.
In the following years, many additional loci in inbred recessive LGMD families have been mapped to chromosome region 13q12 (LGMD2C/R5), to 17q21 (LGMD2D/R3) to 4q12 (LGMD2E/R4), to 5q33 (LGMD2F/R6), to 2p (LGMD2B/R2).[15-17]

European Collaborative Networks

In the translation area, many laboratories and European groups continue with new researchers and they have contributed to meetings of the European Neuromuscular Center (ENMC) and the Foundation and organization of the World Muscle Society with meetings in Europe, and the Treat – NMD and Eurobiobank networks. The ENMC that was created in the '90 allowed by the close collaboration of European scientists or individuate molecular defects in the realm of congenital muscular dystrophies, i.e., laminin alpha2 or merosin, and other rare diseases such as nemaline myopathies or congenital myasthenia (Figure 2).
Due to the genetic characterization of several LGMDs in the late 20th century, in 1995 the first consortium meeting, under the auspices of the European

Fig 3. (left panel) and Fig 4 (right panel). 229th ENMC Workshop: Limb-girdle muscular dystrophies – Nomenclature reformed classification Naarden, The Netherlands, 17-19 March 2017.

Fig 5. *229th ENMC Workshop: Limb-girdle muscular dystrophies - Nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. From left: Carsten Bönneman (Bethesda, USA), Bjarne Udd (Tampere, Finland), Maggie Walter (Munich, Germany), Volker Straub (Newcastle, UK), Pascal Laforêt (Paris, France), Marianne de Visser (Amsterdam, Netherlands), Ada Hamosh (Baltimore, USA), Yvan Torrente (Milan, Italy), Corrado Angelini (Padua, Italy), Nina Khizanishvili (Tblisi, Georgia), John Vissing (Copenhagen, Denmark), Vincenzo Nigro (Naples, Italy), Madelon Kroneman (Spierziekten, Netherlands), Alex Murphy (Newcastle, UK), Laura Rufibach (Seattle, USA), Anna Sarkozy (London, UK), Andoni Urtizberea (Hendaye, France).*

Neuromuscular Center (ENMC), reached a consensus on a classification of LGMD subtypes based on molecular and genetic criteria, the autosomal dominant loci were designated as LGMD type 1, and the autosomal recessive loci were designated as LGMD type 2. However, the continuous growth and scientific discoveries in the field required soon to revise such as classification and in 2017 they were renamed LGMD D and LGMD R.[18] Also, the genetic diagnosis of LGMD using linkage analysis was too cumbersome and has been substituted by NGS. At the 229th ENMC, it was discussed the phenotypic presentation of both dominant and recessive LGMD, grouping the subtypes into proximal, distal, and pseudo-metabolic phenotypes (Figures 3, 4, and 5). The importance of incorporating pathophysiology into the classification was discussed, as this is likely to be the most important factor in future clinical trials.[18,19] Potential common features that could be used include elements of pathophysiology, i.e. sarcolemmal disorders (sarcoglycans and dysferlin) or enzymatic defects (calpainopathy, enzymes involved i.e., α-dystroglycan glycosylation). Several LGMD subtypes were identified that showed both recessive and dominant modes of inheritance and had other classifications,[18] which are more commonly used (i.e. desminopathies).

FSHD syndrome appeared one of the most complicated issues and requested the cooperation of several European groups to solve it. Thanks to genetic findings, it is now known that in most FSHD patients (FSHD1 group) a deletion of a subset of D4Z4 microsatellite repeats on chromosome 4q35, that result in an array of fewer than 11 units, is responsible for the de-repression of the transcription factor DUX-4 in muscle, and a trial with anti-DUX-4 agents is on the way.

Research Related to Therapeutics

The continuous challenge of the treatment of primary muscular dystrophy remains for the future since so far there are only emerging molecular therapies: antisense oligonucleotides in DMD, adenoviral therapy in sarcoglycanopathies, and cell therapy might contribute to answering a promise since the use of conventional treatment modalities is still rather limited. Even the use of corticosteroids in DMD only offers a reduction of the pace of the downhill course and only in some patients and has been the subject of several ENMC meetings, and is

still defined as the "gold standard" there can no longer be any doubt that use of steroids in ambulant children with DMD alters the natural history of the condition. Children treated with daily steroids are likely to walk for longer, have improved respiratory function, may avoid the need for spinal surgery, and might have better heart function than untreated children. Benefits of starting steroids in children who have already lost ambulation needed to be established, since the two main types of steroids used (prednisone/ prednisolone and deflazacort) appear to be equally effective. Side effects seen with the long-term use of steroids in DMD use include weight gain, (which may be less prominent using deflazacort) loss of height, asymptomatic cataracts (with deflazacort predominantly), and thinning and possibly fractures of the bones. At an ENMC meeting in 2004 a clinical trial acronym "FOR DMD "with various steroid dosage regimes in DMD was planned by clinicians in the field as well as patient organizations, reflecting a high level of dissatisfaction with the inconsistency of use of corticosteroids and the profusion of different steroid regimes in use in clinics across the world. The trial results were finalized, and recently published,[20] concluding that both daily prednisone and daily deflazacort were more effective than intermittent prednisone for the primary outcome ($p < 0.001$) for daily prednisone vs intermittent prednisone.

The first ENMC workshop on Pompe disease also referred to as glycogen storage disease type II, was held in Hoofddorp from the 22nd to the 24th of April 2005. Twenty participants from The Netherlands, France, Germany, Italy, Austria, Denmark, the United Kingdom, and the United States attended this meeting. Workshop participants covered areas of basic research, diagnostics, clinical care, and therapies in Pompe disease. Another area that was discussed was nomenclature. Allan Lund (Denmark), Dr. Anna Pichiecchio (Italy), Prof. Arnold Reuser (The Netherlands), Dr. Bruno Bembi (Italy), Dr. Benedikt Schoser (Germany), Dr. Christian Schwake (Germany), Prof. Corrado Angelini (Italy), Dr. David Hilton-Jones (UK), Prof. Francesco Muntoni (UK), Dr. Irene Maire (France), Prof. Luciano Merlini (Italy), Prof. Marc Nicolino (France), Dr. Marloes Hagemans (The Netherlands), Prof. Olaf Bodamer (Austria), Dr. Otto van Diggelen (Netherlands), Dr. Pascal Laforet (France), Dr. Priya Kishnani (USA), Ria Broekgaarden (Representative from IPA, The Netherlands).

Pompe disease is an autosomal recessive condition caused by mutations in the gene for acid a-glucosidase, an enzyme responsible for the breakdown of lysosomal glycogen. The reduction or complete loss of a-glucosidase activity leads to lysosomal glycogen storage and finally to impaired cellular function. The effect of glycogen accumulation on cell function becomes notably effective in muscle cells, in which it compromises contractile activity. As a consequence muscle weakness is one of the predominant clinical features in patients with Pompe disease. A major focus of the workshop was dedicated to the clinical spectrum and natural course of the condition, including unusual clinical presentations and diagnostic pitfalls.

The results of Enzyme Replacement Treatment (ERT) and the guidelines for ERT were covered at the 177th ENMC workshop, where lectures on the therapeutic outcome, good and bad responders were delivered by C. Angelini for adult cases and E. Mengel for infants.

In October 2014 at the 208th ENMC workshop, there was the formation of an European network to develop an European data-sharing model and treatment guidelines for Pompe disease. An European network was formed. The network was initially composed of the participants of the meeting, but over time was expanded to involve more European countries, and later possibly also experts from countries outside Europe. Areas the network intends to work on include data sharing, developing recommendations on starting and stopping ERT, standards of care, harmonization of outcome measures, and responses to questions from health authorities. An agreement was reached on a minimal dataset to be collected for adult patients. For infants and children, a workgroup was set up. A consensus was reached about recommendations for start and stop criteria for adult patients.[21] The group reached also a permanent network that was called the EPOC network and a subsequent meeting in Hamburg has been reported.[22]

A great deal of expectation developed from cell and gene therapy, which has been outlined in the previous section. At present, most of the described methods are still in the preclinical stage. A limited phase I project in a few DMD/BMD patients using a plasmid-mediated dystrophin gene transfer into a single arm muscle has been initiated by the Association Francaise contre les Myopathies and Transgene Corp. Other groups have undertaken limited short-term trials with gentamycin or Ataluren (PTC) in DMD patients with a stop codon mutation.[23] These trials yielded variable results in terms of dystrophin production in muscle. It appears that the nature of the stop codon and the flanking nucleotide sequence have a significant effect on the "readthrough" efficiency.

International cooperation in myology is therefore an obligatory avenue for further progress in the field of neuromuscular diseases.

List of acronyms

AFM - Institut de Myologie, Genethon in France
BMD – Becker muscular dystrophy
CNR – Italian *Consiglio Nazionale delle Ricerche*
cybrid - cytoplasmic hybrid
DMD - Duchenne muscular dystrophy
DMD/BMD - Duchenne muscular dystrophy/Becker muscular dystrophy
ENMC - European Neuromuscular Center
ERT - Enzyme Replacement Treatment
FSHD - facio-scapulo-humeral dystrophy
IPA - International Patient Association

KSS - Kearns-Sayre syndrome
LGMD - Limb-girdle muscular dystrophies
MELAS - Mitochondrial Encephalopathy Lactic Acidosis Stroke
MERRF - Mitochondrial Epilepsy Ragged Red Fibers
mtDNA - mitochondrial DNA
NEMO - Neuromuscular Omni Center
NMD - Neuromuscular Diseases
PTC - Post transcriptional Control
TIGEM - Telethon Institute Genetic Medicine
UK – United Kingdom
USA – United States of America

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