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LETTER TO THE EDITOR

Lack of resemblance between Myhre syndrome and other "segmental progeroid" syndromes warrants restraint in applying this classification

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As members of the Myhre Syndrome Foundation (MSF) Professional Advisory Board (PAB), we welcome the efforts of these experts in the field of aging to investigate the links between the molecular events and developmental pathways affected in Myhre syndrome and premature aging [1]. The authors were inspired by a 55-

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year-old male identified through the International Registry of Werner Syndrome (IRWS) who was found by exome sequencing to carry one of the few and recurrent pathogenic variants in *SMAD4*, p.Arg496Cys, that cause Myhre syndrome [2]. However, we are concerned about the designation of Myhre syndrome as a "segmental progeroid" syndrome based on research involving a single individual. At least from a clinical perspective, we do not view Myhre syndrome as either a syndrome with premature aging or a condition that fits the pathophysiology of a Mendelian progeroid syndrome [3]. With fewer than 100 patients with Myhre syndrome reported in the literature, we do not find significant phenotypic overlap with individuals affected with Werner syndrome or other progeria syndromes.

Collectively, we represent clinical and basic science researchers with the largest international experience in caring for individuals with Myhre syndrome across the lifespan. Several of the adults we follow have been reported [4–6], but we have not observed signs of accelerated aging. In fact, several adults over the age of 30 years appear younger than their chronological ages and do not manifest the defining phenotypic features of aging [7]. Several of the clinical features in the individual reported by Kandhaya-Pillai and colleagues are typical of adults with Myhre syndrome (tight skin of extremities, short stature, hearing loss). Other features seem either relatively non-specific or unproven to be directly related to Myhre syndrome (diabetes mellitus, osteoporosis, premature thinning of hair, "high-pitched" voice). The authors did not mention whether the following features were absent or not sought: small size at birth, relative macrocephaly, stiff joints (or arthropathy later in life), stiff gait, digital anomalies (camptodactyly, brachydactyly, clinodactyly, syndactyly), hypertrophic scars, firm skin, or the distinctive facial features (small deep-set eyes, relatively prominent nose, relative prognathism, small mouth, small low-set ears), which persist in adults with varying expressivity. Functional problems such as systemic hypertension, chronic constipation, restrictive lung disease, learning and social disabilities were not reported. Moreover, imaging to rule out vasculopathy, valvulopathy, cardiomyopathy, or radiographic features (thick and short vertebral pedicles, thick calvaria) were not included. A worrisome morbidity in Myhre syndrome is the exuberant fibroproliferation leading to scarring, serositis (pleural, pericardial, peritoneal), or progressive large airway stenosis [8]. In some patients, this appears to be stimulated by tissue trauma. Overall, these clinical features are dissimilar from Werner syndrome and other diseases of senescence [9]. Unlike many premature aging syndromes, we can confidently state that lipodystrophy is not present in Myhre syndrome.

We realize that the purpose of the classification proposed by Kandhaya-Pillai and colleagues is to characterize Myhre syndrome at the *cellular level*, and to stimulate discussion about interacting pathways. In the manuscript, the authors provide interesting and intriguing connections between the TGF-β signaling pathway and other signaling pathways that contribute to cell degeneration, tissue fibrosis, inflammation, decreased regeneration capacity, and metabolic malfunction. However, such alterations occurring at the cell and possibly at the tissue level do not result into a progeroid clinical presentation in Myhre syndrome. It is too late to change the nomenclature using the term "segmental" [10] that generally brings to mind the involvement of a discrete part of the body, e.g., segmental neurofibromatosis or Proteus syndrome that are typically due to somatic mutations. When applied to progeria syndromes, "segmental" refers to early senescence of some part but not all the body [10]. However, we think this designation is misleading in the context of Myhre syndrome. We recommend improved clinical phenotyping. The natural history of Myhre syndrome is a timely topic, and we invite the authors to collaborate with us on an extensive review underway of both unreported adult patients and those in the literature.

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Author contribution AEL conceived the paper; all other authors contributed to the writing and review.

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