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EDITORIAL

Apparently rare cases are worth studying because….

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As suggested by Dr. Robert B. Mellins in 2007, ''apparently rare cases are worth studying, not because they are rare, but because they provide an opportunity to unravel an important homeostatic mechanism of disease present in all of us but not so apparent except in those missing some important protective mechanism'' [1]. This special issue of *Clinical Autonomic Research* focuses on five rare to ultra-rare respiratory and autonomic disorders of infancy, childhood, and adulthood (RADICA), including Congenital Central Hypoventilation Syndrome (CCHS) [2], Familial Dysautonomia (FD) [3], Prader Willi Syndrome (PWS) [4], Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) [5], and Rett Syndrome (RS) [6], and introduces a comprehensive data dictionary [7] with focus on autonomic signs and symptoms. This special issue additionally introduces the success of applying big data methodology [6] and objective neurocognitive biomarkers [8] to advance Dr. Mellins' wisdom and the emerging discipline of Pediatric Autonomic Medicine. This full circle is particularly noteworthy since Dr. Mellins described the first patient with CCHS in 1970 [9], before going on to advance the then emerging discipline of Pediatric Pulmonary Medicine.

Among the five described pediatric conditions there is significant overlap in presentation. However, each has a distinct unfolding of and constellation of symptoms. Further, each has a distinct etiology. Four of the five have an identified genetic basis, each with clinically available genetic testing. ROHHAD alone remains a condition without an identified cause or diagnostic test. The authors of the individual articles covering each of these conditions provide the readers with much to consider. There is discussion of a neurocristopathy basis (CCHS and ROHHAD), obesity-related conditions (PWS and ROHHAD), DNA methylation and parental expression of critically imprinted genes (RS and PWS), highly conserved genes that are transcription factors or have a key role in transcription (CCHS and RS), evolving phenotype with advancing age (ROHHAD) vs. fairly stable phenotypes, and more. These rare conditions have their own registries that provide longitudinal data to better characterize the phenotypes. And after decades of research, two of these rare conditions have recently gained approval for medications that effectively modify the clinical phenotype to decrease disease burden (FD and RS).

Each individual article included in this special edition of *Clinical Autonomic Research* is especially inspiring because of its application to and implications for children and young adults with these conditions. And hidden between the lines of these publications is recognition of the tireless and devoted parents and caregivers, who deserve special accolades because of their steadfast dedication to improve the quality of life and safety for their children and maintain advocacy in rare disorders. Hopefully, readers of these articles will be inspired to further advance this emerging discipline of Pediatric Autonomic Medicine, join the quest to better understand the basic underpinnings of each of these rare disorders, and identify biomarkers that will empower future intervention trials when pharmacologic and other interventions become available. Ideally, readers of this special edition will also find the data dictionary pertinent to the care they provide patients with rare disorders of autonomic

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regulation and patients with more common conditions that have related autonomic dysregulation. The tie-in between the data dictionary and the big data article not only highlights autonomic dysregulation in rare conditions, but notably also in very common conditions. Taken together, this special edition of *Clinical Autonomic Research* should inspire deep thoughts into the autonomic nervous system in health and disease, and how each of us might recognize how dysfunction of this system that functions automatically and impacts virtually all organ systems to sustain life and optimize health is itself a biomarker that requires recognition as an integral consideration in the care of all pediatric patients.

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Declarations

Conflict of interest The authors declare no competing interests.

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