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MEGDEL syndrome is phenotypically heterogeneous

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In a recent paper Rhada Rama Devi et al. presented 2 pediatric Indian patients, both of them had consanguineous parents, with 3-methyl-glutaconic academia, deafness, encephalopathy, and Leigh-like (MEGDEL) syndrome due to mutations in the SERAC1 gene [1]. In the majority of the cases, parents of patients with MEGDEL syndrome are consanguineous. The SERAC1 gene encodes for a phosphatidyl-glycerol remodeler, essential for mitochondrial functions and intracellular cholesterol trafficking [2]. Cardinal features of MEGDEL syndrome not only include 3-methyl-glutaconic aciduria, hypoacusis, encephalopathy, and Leigh-like features on MRI but also other cerebral and extra-cerebral phenotypic features. We have the following comments and concerns.

We do not agree that only 22 patients with MEGDEL syndrome have been reported as mentioned in table 1 of Devis' paper. Altogether at least 54 patients with MEGDEL syndrome have been reported so far (table 1) [1-14]. In 45 of these patients a SERAC1 gene mutation had been detected and 9 patients were diagnosed without confirmation of a genetic cause [5,13,14]. A detailed description of these patients is available in 53 cases. In a single case, descriptions are available only as an abstract since the reporting language is Chinese (n=1) [3]. Furthermore, the 30 patients reported by Wortmann et al. in 2015 are hardly clinically characterized [2]. It is also unclear if the four patients reported by Wortmann et al. in 2006 were included in the evaluation of the 30 patients reported in 2015. Furthermore, Blommaert et al. in 2016 reported that 60 patients were in their database, but they do not mention how many of these had been published so far.

We also do not agree with the phenotypic characteristics as provided in table 1 of Devi's paper [1]. The phenotypic spectrum of MEGDEL syndrome is much broader than so far reported and includes the eyes, the endocrine organs, the heart and the skeletal muscle in addition to the brain, ears, and gastro-intestinal tract. Phenotypic features of cerebral involvement not only include dystonia, psychomotor delay, optic atrophy, microcephaly, and drooling, but also epilepsy, spasticity, ataxia, hypotonia at birth, dysphagia, dysarthria, aphonia, failure to thrive, and temper tantrum. A further disadvantage of several reports is that the clinical manifestations were not specified in detail (e.g. "extrapyramidal symptoms" without details) and that the description of phenotypic features overlap.

Overall, this interesting case study could be more meaningful if more clinical data of the index cases, the parents, and the other first-degree relatives would have been provided. The phenotypic spectrum of MEGDEL syndrome is broader than so far anticipated. Also, the eyes, endocrine organs, the heart, and the skeletal muscle may be affected.

Key Words: Key words: mitochondrial, spasticity, Leigh syndrome, ribosomal, hypotonia, MEGDEL, glutaconic acid

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Table 1. Articles describing patients with MEGDEL syndrome diagnosed either genetically or clinically

Reference	NOP	ALF	Sex	SERAC1 mutation	Only clinically diagnosed
Devi et al. 2017	2	7, 12	f, f	yes	no
Sequeira et al. 2017	1	8	f	yes	no
Chen et al. 2017	1	na	na	yes	no
Harbulot et al. 2016	1	7	f	yes	no
Blommaert et al. 2016	4	19, 15, 2, 6	4f	no	yes
Rodriguez-Garcia et al. 2016	1	6	m	yes	no
Ünal et al. 2015	2	15,13	2f	yes	no
Wortmann et al. 2015	30	na	na	yes	no
Dweikat et al. 2015	1	2	m	yes	no
Lumish et al. 2014	1	5	m	yes	no
Sarig et al. 2013	4	9, 4, 5, 3	4m	yes	no
Tort et al. 2013	1	19	f	yes	no
Karkucinska et al. 2011	1	4.5	f	no	yes
Wortman et al. 2006	4	na	na	no	yes
NOP: number of patients, ALF: age at last follow-up, M: male, F: female, na: not available					