ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

LETTER

Autosomal dominant segregation of *CAPN3* c.598_612del15 associated with a mild form of calpainopathy

Mathieu Cerino[1,2,3], Marc Bartoli[1], Florence Riccardi[1,2], Brigitte Le Goanvic[2], Véronique Blanck[2], Alexandra Salvi[1], Nicolas Lévy[1,2,4], Martin Krahn[1,2] & Ariane Choumert[5]

[1]Aix-Marseille Université, Inserm, U1251-MMG, Marseille Medical Genetics, Marseille, France
[2]Département de Génétique Médicale, APHM, Hôpital Timone Enfants, Marseille, France
[3]APHM, Hôpital de la Conception, Laboratoire de Biochimie, Marseille, France
[4]GIPTIS (Genetics Institute for Patients, Therapies Innovation and Science), Marseille, France
[5]Centre de Référence des Maladies Neuromusculaires PACA-Réunion-Rhônes-Alpes, CHU La Réunion, France

Correspondence
Mathieu Cerino, Aix Marseille Univ, Inserm, U1251-MMG, Marseille Medical Genetics, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille, France. Tel: 04 91 32 49 06; Fax: 04 91 80 43 19; E-mail: mathieu.cerino@univ-amu.fr

Funding Information
This study was supported by Assistance Publique – Hôpitaux de Marseille (APHM), AFM-Telethon (under grant agreement #19272) and GIPTIS (Genetics Institute for Patients, Therapies Innovation & Science).

Received: 28 August 2012; Accepted: 15 February 2013

Annals of Clinical and Translational Neurology **2020; 7(12): 2538–2540**

doi: 10.1002/acn3.51193

Martin Krahn and Ariane Choumert authors are equal contribution.

Dear Editor,

We read with interest the article published by Nallamilli and colleagues describing a large limb–girdle muscular dystrophy (LGMD) cohort of patients.[1] In particular, the chapter describing the association of the *CAPN3* variant, c.598_612del15 [p.(Phe200_Leu204del)], with an autosomal dominant form of calpainopathy. Indeed, this novel transmission mode for calpainopathies was initially suggested by Vissing and colleagues in 2016[2] and led to the revision of the LGMD classification, introducing the *CAPN3* associated limb–girdle muscular dystrophy dominant type 4 (LGMDD4),[3] whereas calpainopathies had until then been considered as restrictively autosomal recessive. Up to the present time, only eight variants are associated with LGMDD4, the initial c.643_663del21 [p.(Ser215_Gly221del)] inframe deletion,[2,4] the c.598_612del15 [p.(Phe200_Leu204del)] inframe deletion reported by Nallamilli and colleagues[1] and more recently six additional missenses, c.700G>A [p.(Gly234Arg)],[5] c.1327T>C [p.(Ser443Pro)],[5] c.1333G>A [p.(Gly445Arg)],[5,6] c.1661A>C [p.(Tyr554Ser)],[5] c.1706T>C [p.(Phe569Ser)][5] and c.1715G>C [p.(Arg572Pro)].[7] While autosomal dominant segregation was confirmed through family analyses for most of these variants, this has not to date been the case for the variant c.598_612del15, identified at a simple heterozygous state in 16 sporadic cases among a large LGMD cohort of more than 4500 patients.[1]

We recently identified a family harboring this same c.598_612del15 *CAPN3* variant for which familial segregation analysis (Fig. 1A) and phenotypical exploration was performed including creatine kinase (CK) levels measurements.

The proband (patient II.2 in Fig. 1A) presented with muscle fatigue of arms associated with weakness and atrophy of the brachioradial muscle. The CK level was about 2000 UI/L.

Western blot also revealed calpain 3 deficiency for the proband.

Moreover, the muscular MRI performed for the proband revealed a mild muscular impairment pattern of the lower limbs (including fatty transformation of the rear thigh, the soleus and medial gastrocnemius muscles) suggestive of autosomal dominant calpainopathy (Fig. 1B) as previously described in the literature.[6]

Finally, familial segregation analysis was performed for the mother and the sister of the proband who harbor this same heterozygous *CAPN3* variant (Fig.1A), presenting meanwhile with isolated moderate hyperCKaemia

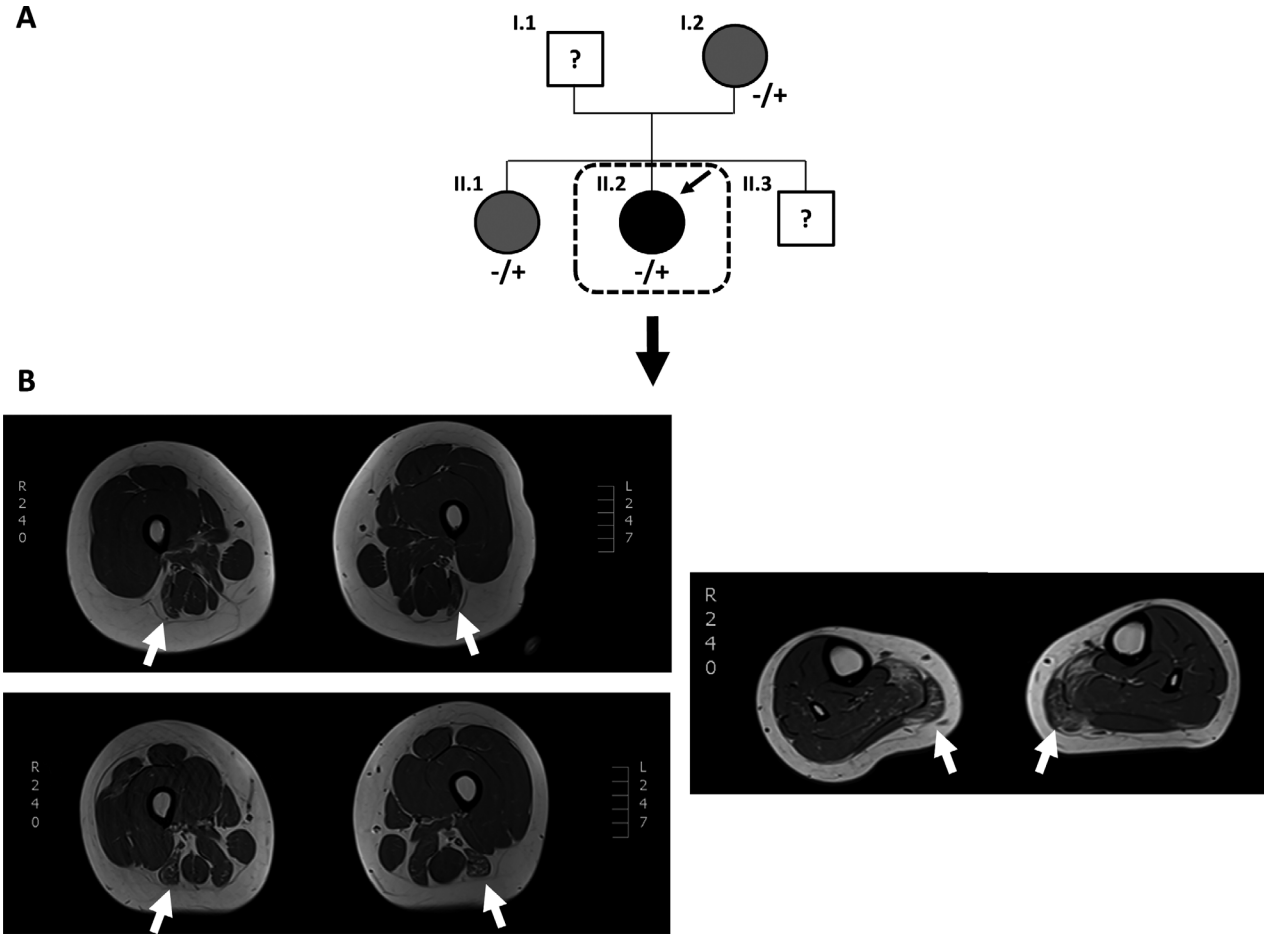

Figure 1. (A) Pedigree and familial segregation analysis of the c.598_612del15 [p.(Phe200_Leu204del)] *CAPN3* variant. (+) indicates nonmutated allele and (-) indicates mutated allele for the c.598_612del15 *CAPN3* variant; (?) denotes individuals with unknown clinical status and/or ongoing clinical exploration; Black color indicates clinically symptomatic patients; Gray color indicates subjects with isolated hyperCKaemia. (B) Muscle imaging findings for the index case (patient II.2) harboring the c.598_612del15 [p.(Phe200_Leu204del)] *CAPN3* variant. MRI shows fatty replacement and atrophy of the posterior thigh compartment of the soleus and medial gastrocnemius muscles (white arrows).

(respectively 285 UI/L and 148 UI/L CK levels). This subclinical presentation is consistent with previous descriptions of autosomal dominant calpainopathies associated with the c.643_663del21 and the c.1333G>A *CAPN3* variants.[2,6]

Thus, by describing this additional family harboring the c.598_612del15 *CAPN3* variant, we confirm the association of this eighth variant with autosomal dominant calpainopathies (or LGMDD4).

Acknowledgments

We sincerely thank Karine Bertaux, Cécile Mouradian, Pierre Cacciagli, Annachiara De Sandre-Giovannoli, Jean-Pierre Desvignes, David Salgado and Christophe Béroud for their contribution to this work. We also wish to thank the patients, and health professionals whose participation made possible this research.

Author Contributions

MC, MK, and AC initiated and directed the study. MC, MB, AS, FR, VB, BLG and MK contributed to data acquisition and analysis. AC conducted clinical phenotyping. MC, AC, AS, FR, MB, MK, and NL contributed to drafting the manuscript.

Conflict of Interest

The authors have no conflict of interest to disclose.

References

1. Nallamilli BRR, Chakravorty S, Kesari A, et al. Genetic landscape and novel disease mechanisms from a large LGMD cohort of 4656 patients. Ann Clin Transl Neurol 2018;5:1574–1587.
2. Vissing J, Barresi R, Witting N, et al. A heterozygous 21-bp deletion in CAPN3 causes dominantly inherited limb girdle muscular dystrophy. Brain 2016;139(Pt 8):2154–2163.
3. Straub V, Murphy A, Udd B, LGMD workshop study group. 229th ENMC international workshop: limb girdle muscular dystrophies - Nomenclature and reformed classification Naarden, the Netherlands, 17–19 March 2017. Neuromuscul Disord 2018;28(8):702–710.
4. Martinez-Thompson JM, Niu Z, Tracy JA, et al. Autosomal dominant calpainopathy due to heterozygous CAPN3 C.643_663del21. Muscle Nerve 2018;57:679–683.
5. Gonzalez-Mera L, Ravenscroft G, Cabrera-Serrano M, et al. Heterozygous CAPN3 missense variants causing autosomal-dominant calpainopathy in seven unrelated families. Neuropathol Appl Neurobiol 2020; https://doi.org/10.1111/nan.12663
6. Cerino M, Campana-Salort E, Salvi A, et al. Novel CAPN3 variant associated with an autosomal dominant calpainopathy. Neuropathol Appl Neurobiol 2020; https://doi.org/10.1111/nan.12624
7. Vissing J, Dahlqvist JR, Roudaut C, et al. A single c.1715G>C calpain 3 gene variant causes dominant calpainopathy with loss of calpain 3 expression and activity. Hum Mutat 2020; https://doi.org/10.1002/humu.24066

