Response to Hall et al.

To the Editor: We agree with Dr. Hall that loose use of the term *Amyoplasia* could lead to confusion. Indeed, other than capitalizing this term in the title, an AJHG-style standard at the time, we used the term *amyoplasia* with a lowercase "a," rather than use the term *Amyoplasia*, throughout our manuscript to describe the state of having partial or complete absence of skeletal muscles in a body segment.[1,2] Moreover, we agree that Amyoplasia is, in most cases, unlikely to be due to germline mutations. But we do think it reasonable to hypothesize that somatic mosaicism for large-effect alleles underlies the condition in some persons with Amyoplasia. Such an observation would be consistent with the lack of familial cases. As we also noted, reports of "familial amyoplasia" accompanied by identification of the underlying pathogenic variant do exist.[3–5] But the "amyoplasia" in such reports is typically limited to the upper or lower limbs,[6] which is again why we stated that "at least in some families with amyoplasia [lower case], large-effect risk alleles appear to be segregating."

Addressing a couple of additional points more precisely will further clarify the issue for readers. First, we don't know how many affected persons we reported had complete absence of the skeletal muscles of the ankle and foot. The one individual we described with this finding was the only person who underwent sophisticated imaging and pathological exam of the affected limb. Although we don't think the complete absence of skeletal muscles in a limb segment is likely to be a common finding, it was striking enough to draw attention to it, particularly because the zebrafish model we reported points toward a potential mechanism for muscle loss in persons with pathogenic *MYLPF* variants. Moreover, although one or several muscles have been reportedly absent in individuals with various arthrogryposis conditions, we are not aware of other reports of absence of *all* of the muscles of a limb segment. If such persons exist, we would be delighted to study them. Finally, we would like to emphasize that this work was a collaborative effort among multiple groups: the Bamshad group contributed the human clinical genetic analyses, and the Amacher group contributed the zebrafish model and analysis.

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