Response to Briuglia et al.

It is with great pleasure that we received the letter by Briuglia et al., who provide a detailed phenotypic description of an individual carrying a novel de novo pathogenic variant of the *USP7* gene.[1] In addition to features that are part of the established phenotypic spectrum of the *USP7*-associated disorder, which was recently named Hao–Fountain syndrome (HAFOUS; OMIM 616863), the patient reported by Briuglia et al. also shows abnormal heart morphology, and cystic hygroma was noted during pregnancy. Both findings have not been previously associated with HAFOUS. The reported variant type (frameshifting deletion of 4 bp in exon 21 of 31 [NM_003470.2]) fits well with the notion that loss-of-function is the common disease mechanism, which is based on the presence of nonsense or frameshift single-nucleotide variants, and genomic deletions of *USP7*, in the cohort reported by Fountain et al. in 2019.[2] While the novel *USP7* variant may result in nonsense-mediated decay of mutant RNA, residual expression of a truncated USP7 protein cannot be excluded without further functional investigation.

The patient reported by Briuglia et al. is, to our knowledge, the 24th individual with HAFOUS described in the literature. Given the rarity of individuals with pathogenic *USP7* variants (there are a total of 65 individuals diagnosed with HAFOUS currently in touch with our group), the full phenotypic spectrum of the disorder is still emerging. It is therefore conceivable that the patient's pathogenic *USP7* variant is causative for the congenital heart malformations and prenatal ultrasound anomalies, especially since *USP7* has been implicated in embryonic development in different species: Sun et al. found that homozygous loss of *Drosophila Usp7* was lethal before the emergence of first instar larvae.[3] *Usp7*, previously also known as *Hausp*, was found to be ubiquitously expressed in mouse embryos between embryonic day (E) 7.5 to 10.5, and homozygous knockout of *Hausp* was embryonically lethal also in mice, resulting in severe growth retardation and lack of recognizable structures in embryos at E7.5.[4] However, if congenital heart malformations and abnormal nuchal translucency are indeed part of the phenotypic spectrum of HAFOUS, these are probably among the less common features of this disorder.

As more phenotypic details of HAFOUS emerge, similarities to the *MAGEL2*-associated Schaaf–Yang syndrome (SYS) become more apparent. Both disorders are functionally related on the molecular level, primarily by the presence of USP7 and MAGEL2 within the MUST (MAGEL2-USP7-TRIM27) complex, which regulates endosomal protein recycling through ubiquitination of target proteins.[5] This shared molecular mechanism seems to be reflected by the respective phenotypes, which both include features such as muscular hypotonia, contractures, feeding difficulties in infancy, hypogonadism, gastroesophageal reflux, constipation, and excessive weight gain in some individuals, in addition to more unspecific features typical of neurodevelopmental disorders (e.g., developmental delay, intellectual disability). Both disorders, together with the more frequent Prader–Willi syndrome (PWS), represent a small "syndrome family," consisting of conditions related to one another both by molecular mechanisms and clinical phenotypic overlap, according to the definition proposed by Brunner and van Driel.[6] While the phenotypic characterization of more individuals may reveal additional shared features of SYS and HAFOUS, it is important to note that both disorders remain distinct with regard to the frequencies of their main symptoms in affected individuals. For example, neonatal hypotonia, which is present in almost all individuals with SYS, was only observed in about 45% (9/20) of individuals with HAFOUS, and contractures, which are present in >85% of individuals with SYS, were only found in about one quarter (4/17) of the HAFOUS cohort reported by Fountain et al.[2,7] A wide range of neuroradiologic anomalies, such as enlarged ventricles, is observed in the majority of individuals with HAFOUS including the individual reported by Briuglia et al., while structural anomalies of the brain are uncommon in patients with SYS. As both disorders continue to be investigated, a more detailed picture of this small syndrome family will surely emerge.

We thank Dr. Briuglia and colleagues for their contribution to the characterization of HAFOUS, and the editors of *Genetics in Medicine* for giving us the opportunity to comment on this subject.

DISCLOSURE

The authors declare no conflicts of interest.

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