COMMENT

A fresh cup of DCAF: DCAF13 implicated in a neuromuscular disorder

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DCAF13 has traditionally been studied in the context of reproduction and development. Its expression peaks in the morula as the pre-implantation zygotic cells undergo compaction to create the blastocyst [1]. *Dcaf13* knock-out leads to embryonic lethality in mouse while RNAi mediated downregulation in *Caenorhabditis elegans* results in stunted growth, developmental delay, and reduced fertility [2]. Within the oocytes, DCAF13 localizes to the nucleolus and is involved in ribosomal RNA processing as well as chromatin compaction [3]. In this issue, Manzoor et al. describe a novel association of *DCAF13* with a neuromuscular disorder (NMD) characterized by waddling gait and muscle weakness [4].

Manzoor et al. discovered this novel biallelic missense variant in *DCAF13* in a consanguineous family from Pakistan. Harnessing the dual power of a family-based study design and exome sequencing, they found this variant rs1209794872 within the region of homozygosity shared among the four affected individuals and it perfectly segregated with the disease in this family. This variant NM_015420.7c.907G>A replaces an aspartic acid residue with an asparagine in the third WD40 domain of DCAF13 protein, retaining the polarity but altering the charge at this position, thus potentially reducing its stability. The variant is extremely rare (allele frequency 0.000007081 and 0.000003983 in gnomAD and ExAC databases, respectively; none found homozygous) and absent in the 600 ethnically matched chromosomes they genotyped as controls. Aspartic acid (Asp) at this position is remarkably well conserved across taxa, although the sequence identity progressively decreases for the whole protein (87.4%, 68.1%, 42.7%, 17.8% and 15.3% for primates, mammals, vertebrates, animals, and eukaryotes, respectively). Such strong selection pressure operative on a particular site points to its likely functional relevance. Interestingly, only three benign and fourteen variants of uncertain significance have thus far been listed in Clinvar, making this the first likely pathogenic *DCAF13* variant to be reported.

DCAF13 is a multifaceted protein with established roles at multiple stages of embryogenesis. It supports oocyte development through meiotic maturation and sustained protein synthesis through PI3K signaling by degrading PTEN, a lipid phosphatase [5]. Maternally inherited DCAF13 regulates zygotic genome activation. In a pre-implantation embryo, it is an early responsive gene and functions as a CRL4 ubiquitin ligase adapter to ubiquitinate SUV39H1 and tag it for proteasomal degradation. The timely removal of SUV39H1 facilitates the activation of zygotic genome, thereby making DCAF13 indispensable for embryogenesis [1]. It also plays an important role in decidualization [6]. At the cellular level, DCAF13 promotes cell proliferation [7]. Consequently, it is found to be overexpressed in multiple cancers and its increased levels are correlated with poor prognosis. Both DCAF13 deletion and knockdown induce cell cycle arrest and promote apoptosis. It would be interesting to see if Asp303Asn variant impairs any of these known functions of DCAF13.

DCAF13 also interacts with both proteins (such as PERP) and RNA to regulate multiple signaling pathways (like Notch) [7, 8]. Its interaction with DDB1 is WD40 domain dependent, so this variant might modulate that interaction, especially because it is located within a beta hairpin turn. DCAF13 also participates in 18S rRNA processing in oocytes, so it remains to be seen if this variant affects ribosomal RNA processing and protein synthesis. Since *Dcaf13* null is not tolerated, this variant is unlikely to be a complete loss of function allele. Rather, it might modulate certain functions of the protein. Future studies should elucidate the functional impact of this variant using knock-in cell lines and mouse model.

The DCAF (DDB1/CUL4 associated factors) family of proteins are E3 ubiquitin substrate receptors. Multiple members of this family have been previously associated with neurological and neuromuscular conditions. Heterozygous variant of *DCAF13* has also been associated with autism spectrum disorder. However, to test the causality in all these cases, the underlying mechanism needs to be investigated. In the absence of functional evidence and a mechanistic understanding, all these associations remain tentative. Although the authors have carried out multiple bioinformatic analyses to test the effect of Asp303Asn on DCAF13 function, these need to be experimentally validated in future studies.

The diagnosis of NMDs is often complicated by underlying genetic heterogeneity and a significant phenotypic overlap with disorders of purely neurological origin. With the integration of genetic testing into healthcare, recessive variants are increasingly being associated with certain forms of NMDs. Although individual NMDs are relatively rare, their cumulative population frequency varies between 1 and 10 for every 100,000 individuals, exerting a significant healthcare burden [9]. This study adds a novel variant to the growing body of literature describing genetic associations in NMD.

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ADDITIONAL INFORMATION

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