Arginine- but not alanine-rich carboxy-termini trigger nuclear translocation of mutant keratin 10 in ichthyosis with confetti

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4596923
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Year 2019
Title Arginine- but not alanine-rich carboxy-termini trigger nuclear translocation of mutant keratin 10 in ichthyosis with confetti
Journal Journal of cellular and molecular medicine
Volume 23
Number 12
Pages / **Article-Number** 8442-8452
Keywords KRT10; alanine-rich C-terminus; arginine-rich C-terminus; carboxy terminus; ichthyosis with confetti; keratin 10; nuclear localization
Ichthyosis with confetti (IWC) is a genodermatosis associated with dominant-negative variants in keratin 10 (KRT10) or keratin 1 (KRT1). These frameshift variants result in extended aberrant proteins, localized to the nucleus rather than the cytoplasm. This mislocalization is thought to occur as a result of the altered carboxy (C)-terminus, from poly-glycine to either a poly-arginine or -alanine tail. Previous studies on the type of C-terminus and subcellular localization of the respective mutant protein are divergent. In order to fully elucidate the pathomechanism of IWC, a greater understanding is critical. This study aimed to establish the consequences for localization and intermediate filament formation of altered keratin 10 (K10) C-termini. To achieve this, plasmids expressing distinct KRT10 variants were generated. Sequences encoded all possible reading frames of the K10 C-terminus as well as a nonsense variant. A keratinocyte line was transfected with these plasmids. Additionally, gene editing was utilized to introduce frameshift variants in exon 6 and exon 7 at the endogenous KRT10 locus. Cellular localization of aberrant K10 was observed via immunofluorescence using various antibodies. In each setting, immunofluorescence analysis demonstrated aberrant nuclear localization of K10 featuring an arginine-rich C-terminus. However, this was not observed with K10 featuring an alanine-rich C-terminus. Instead, the protein displayed cytoplasmic localization, consistent with wild-type and truncated forms of K10. This study demonstrates that, of the various 3' frameshift variants of KRT10, exclusively arginine-rich C-termini lead to nuclear localization of K10.
Publisher John Wiley & Sons
ISSN/ISBN 1582-4934 ; 1582-1838
URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6850952/
edoc-URL https://edoc.unibas.ch/78587/
Full Text on edoc Available;
Digital Object Identifier DOI 10.1111/jcmm.14727
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/31638346
ISI-Number WOS:000491843000001
Document type (ISI) Journal Article