GENETICS AND GENODERMATOSES

CRYSTAL STRUCTURES OF KERATIN 1/KERATIN 10 TETRAMERIC COMPLEXES DEMONSTRATE THAT THE K1-S233L MUTATION CAUSES EPIDERMOLYTIC PALMOPLANTAR KERATODERMA THROUGH ABERRANT HYDROPHOBIC AGGREGATION OF KERATIN

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Introduction: Epidermolytic palmoplantar keratoderma is primarily mediated by keratin 9 mutations that cause hyperkeratosis of the palms and soles. A subset of EPPK patients, however, have a Ser233Leu mutation in the 1B coiled-coil region of keratin 1. Keratins share a basic structural organization defined by four coiled-coil/helical segments termed 1A, 1B, 2A, 2B. The K1S233L mutation leads to a distinct abnormality visualized by electron microscopy, where normal 10-nm keratin tonofilaments are re-arranged into aberrant 43-nm keratin tonotubules.

Objective: To understand how K1S233L mutation alters the biochemical and structural properties of keratin filaments in order to cause epidermolytic palmoplantar keratoderma.

Materials and Methods: 1B coiled-coil regions of keratin 1 (wild-type and S233L mutation) and keratin 10 were expressed in Escherichia coli, purified, and crystallized using vapor diffusion. X-ray data were collected at Argonne National Laboratory and processed using HKL-2000, Coot, and Phenix software.

Results: Two x-ray crystal structures were determined: first, the heterodimer between the 1B segments of wild-type K1 and K10 at 3.0 Å resolution; second, the keratin 1/10 1B heterodimer harboring the S233L keratin 1 mutation at 2.39 Å resolution. The mutation of serine to leucine creates an exposed hydrophobic patch on the surface of the keratin heterodimer, leading to aberrant aggregation between keratin dimers and tetramers. Three aromatic residues (Tyr230, Phe 234, Phe314) and one hydrophobic residue (Leu233) from neighboring K1 molecules envelope the primary mutant Leu233 site. The wild-type K1/K10-1B structure was a tetramer, whereas the K1S233L mutant structure formed an octamer because the L233 hydrophobic patch drove higher-order assembly of tetramers.

Conclusions: The K1/K10 crystal structures reveal distinct surface characteristics of the 1B heterodimer and 1B heterotetramer and suggest a mechanism of aberrant hydrophobic interactions through which the S233L mutation in K1 can potentiate tonotubular keratin formation.