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In silico characterization of the novel SDR42E1 as a potential vitamin D modulator

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ABSTRACT

The short-chain dehydrogenase/reductase (SDR) superfamily encompasses enzymes that play essential roles in the metabolism of steroid hormones and lipids. Despite an enigmatic function, recent genetic studies have linked the novel SDR 42 extended-1 (*SDR42E1*) gene to 25-hydroxyvitamin D levels. This study investigated the potential SDR42E1 functions and interactions with vitamin D using bioinformatics and molecular docking studies. Phylogenetic analysis unveiled that the nucleotide sequences of human SDR42E1 exhibit high evolutionary conservation across nematodes and fruit flies. Molecular docking analysis identified strong binding affinities between SDR42E1 and its orthologs with vitamin D_3 and essential precursors, 8-dehydrocholesterol, followed by 7-dehydrocholesterol and 25-hydroxyvitamin D. The hydrophobic interactions observed between the protein residues and vitamin D compounds supported the predicted transmembrane localization of SDR42E1. Our investigation provides valuable insights into the potential role of SDR42E1 in skin vitamin D biosynthesis throughout species. This provides the foundation for future research and development of targeted therapies for vitamin D deficiency and related health conditions.

1. Introduction

The short-chain dehydrogenase/reductase (SDR) superfamily comprises diverse enzymes highly conserved across various organisms [1]. These enzymes rely on nicotinamide adenine dinucleotide phosphate ($NADP^+$) as a cofactor for their oxidation-reduction reactions and substrate binding stability [2]. The SDR family consists of classic globular forms involved in signal transduction and extended forms that catalyze crucial biological processes, ranging from gene regulation to whole-body homeostasis [1,3]. Of particular significance are the extended SDRs, which play a vital role in singling and metabolizing diverse biochemicals, including steroid hormones and lipids [3,4].

Genetic investigations have revealed numerous SDR gene mutations that significantly impact the enzyme structure and function, leading to severe conditions, including cancers [5,6] and metabolic disorders [7,8]. One notable variant identified in a novel gene called short-chain dehydrogenase/reductase 42 extended-1 (*SDR42E1*) has recently emerged through genome-wide association studies (GWAS) associated explicitly with 25-hydroxyvitamin D (25(OH)D) [9,10], which has received relatively little attention. This nonsense mutation involves a premature stop codon that substitutes amino acids, specifically Glutamine to Termination, at position 30 of the protein (p.Q30 * GLN>*TER), potentially leading to a nonfunctional SDR42E1 enzyme.

A family-based study has identified a missense variant of *SDR42E1* linked to steroid hormone synthesis that manifests as oculocutaneous genital syndrome [11]. While its precise function remains unclear, SDR42E1, in conjunction with $NADP^+$, is believed to regulate cellular processes and steroid biosynthesis through its proposed functions as an oxidoreductase and steroid delta-isomerase [12]. Further exploration is necessary to fully elucidate the specific mechanisms and biological significance of SDR42E1 in vitamin D biosynthesis and metabolism. To effectively investigate the SDR42E1-Vitamin D interactions,

Abbreviations: SDR, short-chain dehydrogenase/reductase; $NADP^+$, nicotinamide adenine dinucleotide phosphate; SDR42E1,, short-chain dehydrogenase/reductase 42 extended-1; SDR9C7, short-chain dehydrogenase/reductase 9C7; HSD3B7, 3β-hydroxysteroid oxidoreductase 7; GWAS, genome-wide association studies; 25OHD, 25-hydroxyvitamin D; 8-DHC, 8-dehydrocholesterol; 7-DHC, 7-dehydrocholesterol; 1, $25(OH)_2D$, 1,25-dihydroxyvitamin D; *C. elegans*, hsd-2 hsd-3, *Caenorhabditis elegans*β-hydroxysteroid dehydrogenases-2 and − 3; *D. melanogaster*, *Drosophila melanogaster*; LSS, lanosterol synthase; SQLE, CYB5B, squalene monooxygenasecytochrome b5 type B; FAXDC2, fatty acid hydroxylase domain-containing protein 2.

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