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Review

Molecular genetics of the *COL2A1*-related disorders

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ABSTRACT

Type II collagen, comprised of three identical alpha-1(II) chains, is the major collagen synthesized by chondrocytes, and is found in articular cartilage, vitreous humour, inner ear and nucleus pulposus. Mutations in the collagen type II alpha-1 gene (*COL2A1*) have been reported to be responsible for a series of abnormalities, known as type II collagenopathies. To date, 16 definite disorders, inherited in an autosomal dominant or recessive pattern, have been described to be associated with the *COL2A1* mutations, and at least 405 mutations ranging from point mutations to complex rearrangements have been reported, though the underlying pathogenesis remains unclear. Significant clinical heterogeneity has been reported in *COL2A1*-associated type II collagenopathies. In this review, we highlight current knowledge of known mutations in the *COL2A1* gene for these disorders, as well as genetic animal models related to the *COL2A1* gene, which may help us understand the nature of complex phenotypes and underlying pathogenesis of these conditions.

Contents

Abbreviations: COL2A1, the collagen type II alpha-1 gene; OMIM, Online Mendelian Inheritance in Man; ACG2/HCG, achondrogenesis type II/hypochondrogenesis; PLSDT, platyspondylic skeletal dysplasia, Torrance type; SPD, spondyloperipheral dysplasia; SEDC, spondyloepiphyseal dysplasia congenita; SEMDSTWK, spondyloepimetaphyseal dysplasia, Strudwick type; STL1, Stickler syndrome type I; DRRD, dominantly inherited rhegmatogenous retinal detachment; ANFH, avascular necrosis of the femoral head; LCPD, Legg–Calve–Perthes disease; EDMMD, epiphyseal dysplasia, multiple with myopia and deafness; OSMED, otospondylomegaepiphyseal dysplasia; SEDN, spondyloepiphyseal dysplasia, Namaqualand type; VPED, vitreoretinopathy with phalangeal epiphyseal dysplasia; HGMD, human gene mutation database; indel, insertion–deletion; DSC, dysspondyloenchondromatosis; Dmm, disproportionate micromelia; ENU, *N*-ethyl-*N*-nitrosourea.

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1. Introduction

Type II collagen, comprised of three identical alpha-1(II) chains, is the major collagen synthesized by chondrocytes, distributing in articular cartilage, vitreous humour, inner ear and nucleus pulposus [1]. Mutations in the collagen type II alpha-1 gene (*COL2A1*, OMIM 120140) have been described to be responsible for a series of abnormalities, known as type II collagenopathies. Significant progresses in mutation analysis of the *COL2A1* gene and type II collagenopathies have been achieved in the last twenty-six years [2–4]. The *COL2A1* mutations were reported to be responsible for at least 16 definite disorders, including achondrogenesis type II/hypochondrogenesis (ACG2/HCG, OMIM 200610), platyspondylic skeletal dysplasia, Torrance type (PLSDT, OMIM 151210), spondyloperipheral dysplasia (SPD, OMIM 271700), spondyloepiphyseal dysplasia congenita (SEDC, OMIM 183900), spondyloepimetaphyseal dysplasia, Strudwick type (SEMDSTWK, OMIM 184250), Kniest dysplasia (OMIM 156550), Stickler syndrome type I (STL1, OMIM 108300), non-syndromic ocular STL1 (OMIM 609508), osteoarthritis with mild chondrodysplasia (OMIM 604864), avascular necrosis of the femoral head (ANFH, OMIM 608805), Legg–Calve–Perthes disease (LCPD, OMIM 150600), epiphyseal dysplasia, multiple with myopia and deafness (EDMMD, OMIM 132450), otospondylomegaepiphyseal dysplasia (OSMED, OMIM 215150), Czech dysplasia (OMIM 609162), spondyloepiphyseal dysplasia, Namaqualand type (SEDN), and vitreoretinopathy with phalangeal epiphyseal dysplasia (VPED) (Fig. 1). These disorders are clinically characterized by different serious abnormalities in the ocular, skeletal, oro-facial, and audiological systems (Table 1). Clinical variability and phenotypic overlap in *COL2A1*-related disorders were commonly observed in patients, even within the same family [5]. Though the prevalence as a whole is unknown, the worldwide estimated incidence is more than 20.4–35.9/100,000 in different regions and populations [6–10].

For this review, we searched literatures in NCBI PubMed database using the search terms "COL2A1", "collagen type II alpha-1", "epiphyseal dysplasia", "skeletal dysplasia", "spondyloepiphyseal dysplasia", and "multiple epiphyseal dysplasia", in combination with "genetics", "mutation", and "variant" from January 1980 to June 2015, and other related papers were also retrieved from important papers using reference lists. Only those publications in English were included. In this review, we provide an overview of the *COL2A1* gene and its protein, *COL2A1*-related disorders and clinical features, genotype-phenotype associations, and related animal models, which may provide us better understanding of the pathogenesis, and contribute to clinical diagnosis and therapeutic strategies.

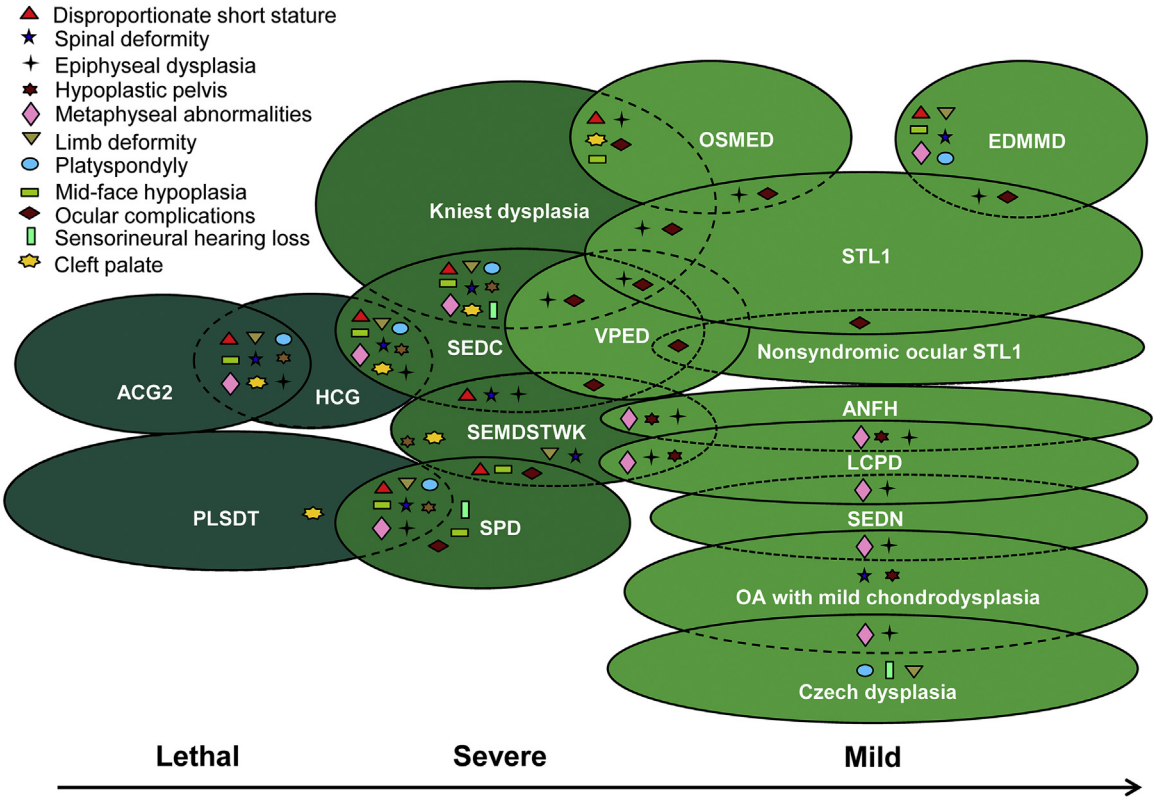

Fig. 1. The phenotypic spectrum of type II collagenopathies. Symbols indicate clinical manifestations, and overlapping portions between disorders indicate shared phenotypes. ACG2, achondrogenesis type II; HCG, hypochondrogenesis; PLSDT, platyspondylic skeletal dysplasia, Torrance type; SPD, spondyloperipheral dysplasia; SEDC, spondyloepiphyseal dysplasia congenita; SEMDSTWK, spondyloepimetaphyseal dysplasia, Strudwick type; STL1, Stickler syndrome type I; OA, osteoarthritis; ANFH, avascular necrosis of the femoral head; LCPD, Legg-Calve-Perthes disease; EDMMD, epiphyseal dysplasia, multiple with myopia and deafness; OSMED, otospondylomegaepiphyseal dysplasia; SEDN, spondyloepiphyseal dysplasia, Namaqualand type; VPED, vitreoretinopathy with phalangeal epiphyseal dysplasia.