Computational Study of Collagen Structure in Osteogenesis Imperfecta Genetic Mutations

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ABSTRACT

Collagen is the most abundant protein in the human body. Health formation of collagen is integral for bone structural integrity as well as having many other vital roles in the body, partly due to its significant durability and elasticity. The superior tensile strength in type one collagen is due to its repeating amino acid construction with glycine as every third amino acid in the sequence. When this repeating motif is disrupted, it can cause a bone degradation disease called Osteogenesis Imperfecta (OI). Altogether, the goal of this study is to compare wild type and mutated collagen in molecular dynamics simulations in order to better understand their overall stability and contribution to OI. Through biomolecular computational modeling, collagen structural formation will be simulated and analyzed. All of the mutations will be created by substituting glycine for a different amino acid, and the resulting effects on structure and energetics will be analyzed. This experiment will provide better understanding the structural formation in normal and mutated collagen one molecules.

INTRODUCTION

- OI is a genetic bone disease that affects twenty thousand people in the United States each year. It is also known as “brittle bone disease” because the disease affects bone formation, and can lead to frequent bone fractures, below average height, scoliosis, hearing loss, and breathing problems. [5]
- Severity of OI and genetic mutations vary, with about twenty different types of OI that each have a unique gene mutation. [3]
- Collagen is responsible for strengthening and supporting cartilage, bone, tendon, skin, and sclera, and consists of a helix made up of three strands that are wrapped around each other. This “rope-like” structure is very elastic and hard to break. [1]
- This protein’s healthy formation and application are necessary for bone integrity in the human body as well as many other structural aspects.

METHODS

PDB files for the collagen molecule were used from Research Collaboratory for Structural Bioinformatics’s Protein Data Bank. Using these files molecular dynamic simulations will be run using GROMACS software. Proline-Proline-Gylcine (PPG) and Proline-Hydroxyproline-Glycine (PHG) Collagen motifs will be used for the healthy collagen pdb models. These pdb files will then be simulated for short periods of time to determine energetics as well as radius of gyration (RG), measure of the size of the collagen triple helix, and root-mean-square-deviation (RMSD), the deviation of the molecule from an ideal triple helix. Both of these will be used to measure the overall movements of the molecule. All simulations will be run for approximately 100ns.

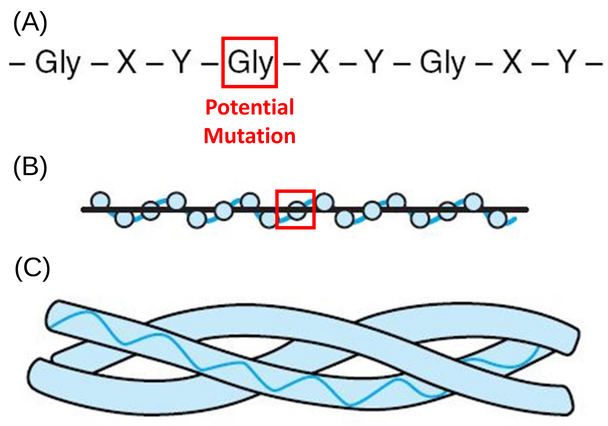
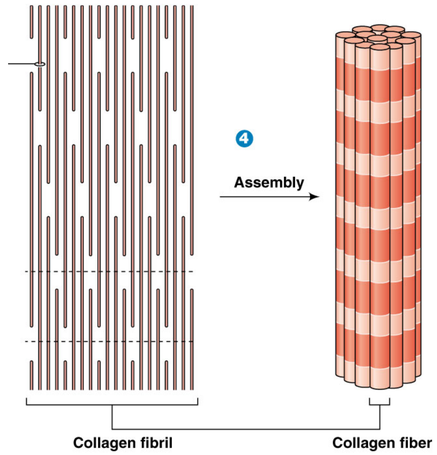
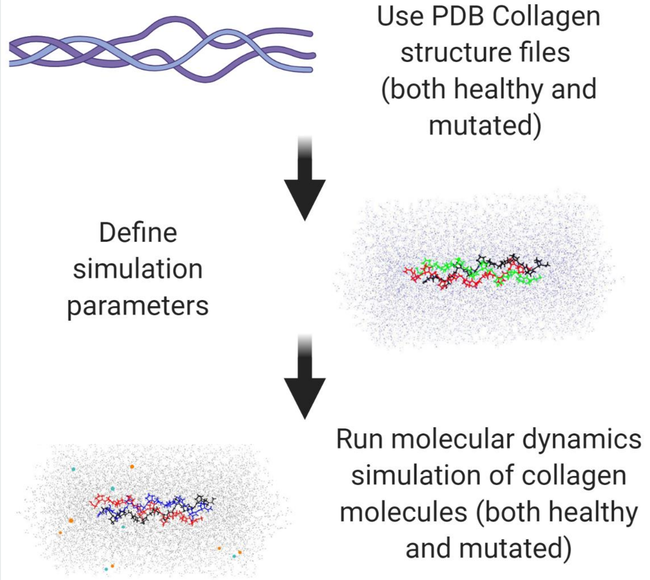


Figure 1.
(A) Shows the amino acid chain for collagen. In wild type collagen glycine is every third residue
(B) Shows glycine’s role in secondary structure formation
(C) Shows three strands forming a rope, increasing strength and elasticity

Figure 2.
Collagen rope structures as shown in Figure 1 (C) come together to form collagen fibrils which together form collagen fibers





CONCLUSION AND FUTURE WORK

From analyzing the differences between healthy and mutated collagen formation, particular RMSD and Rg values, which provide quantitative means to assess the overall stability of the structure, and verify that the simulation is running properly. In the future, computational molecular dynamic simulations have the potential to shed more light on collagen energetics data for various genetic mutations like in OI disease. Moving forward, the computational data obtained from the experiment will be most helpful when compared to and supported by quantitative empirical observations conducted in physical experimental labs.

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