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In silico evaluation of human ARID1A protein structural flexibility using molecular dynamics simulations.

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Nearly 3 lakh women are diagnosed with ovarian cancer annually in the U.S. with the majority of patients being menopausal women. About 45% of the ovarian clear cell carcinoma patients have mutations in the ARID1A protein which is a component in the human SWI/SNF chromatin remodeling complex. ARID1A is known to mutate notoriously and is a protein that binds to the "A, T-rich" region of the DNA helping the SWI/SNF complex in remodeling the nucleosomes for transcriptional activation of genes. Many cancers are caused due to loss and/or mutations in ARID1A protein. In this study we evaluated the structural flexibility of wild type and A1089T mutant of ARID1A proteins by subjecting each one of them to 100 ns molecular dynamics (MD) simulations. The 3D models of wild type and mutant ARID1A proteins were built using the AlphaFold server. The post MD trajectories were analyzed to understand the protein backbone flexibility and the sustainability of secondary structural elements over 100 ns. Subtle differences were observed in both proteins suggesting that their DNA binding abilities may not be severely affected.

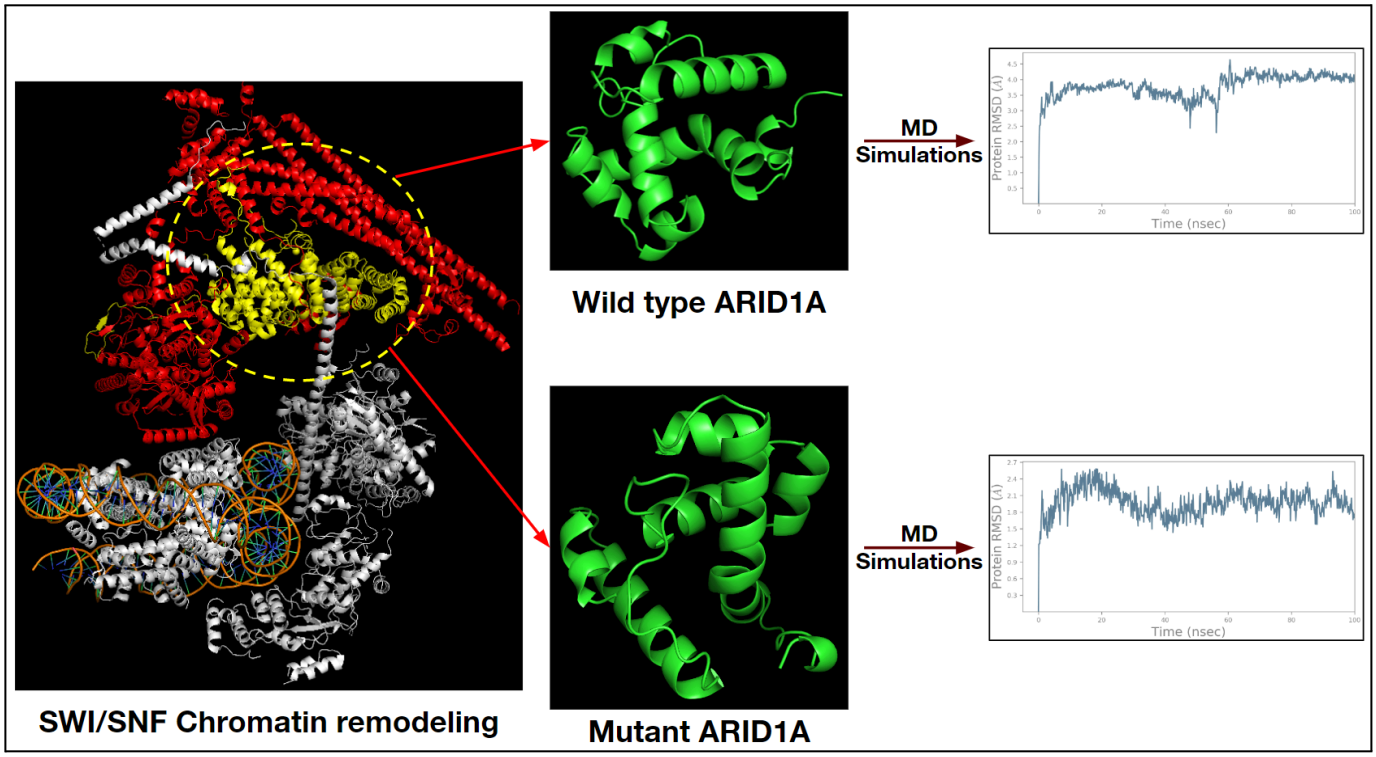

Figure 1. *In silico* analysis of human ARID1A protein (highlighted in yellow color) within the SWI/SNF (red color) complex.

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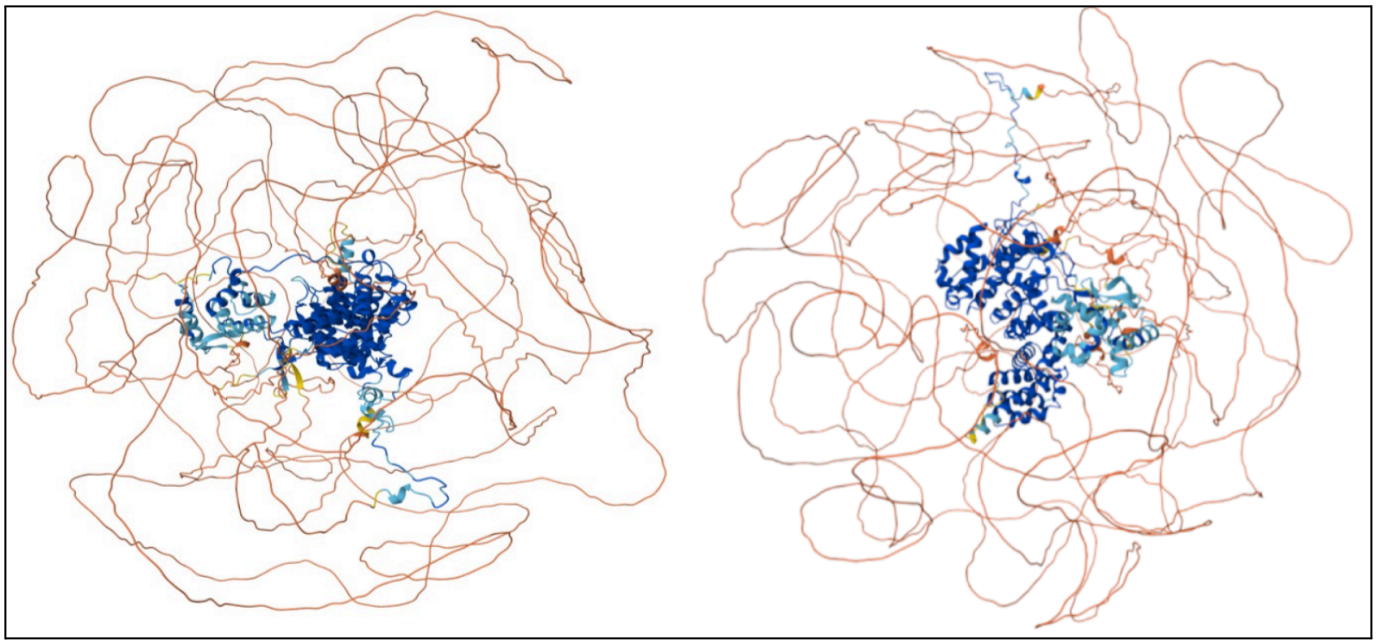

Figure 2. The AlphaFold models of wild type (left panel) and the mutant (right panel) of human ARID1A protein.

Ovarian cancer is one of the most lethal gynaecological malignancies and represents a major challenge in women's health worldwide [1]. It originates in the ovarian tissue and is often diagnosed at advanced stages due to the absence of specific early symptoms [2]. Common symptoms, such as abdominal discomfort, bloating, and pelvic pain, are often vague and easily overlooked, leading to delayed diagnosis [3]. Chromatin remodeling complexes such as the SWI/SNF (SWitch/Sucrose Non-Fermentable) complex play a vital role in switching between tightly packed form (heterochromatin) and loosely packed chromatin (euchromatin) (Figure 1), thereby regulating gene expression [4]. Disruption of chromatin remodeling can lead to abnormal gene expression patterns and genomic instability, which are hallmarks of cancer [5]. Mutations in genes encoding components of chromatin remodeling complexes have been identified in several types of cancers, highlighting their importance in maintaining cellular integrity [6]. In recent years, increasing attention has been given to mutations in SWI/SNF complex components, particularly ARID1A, due to their strong association with cancer development [7].

The ARID1A (AT-Rich Interactive Domain-containing protein 1A) gene encodes a key subunit of the SWI/SNF chromatin remodeling complex and functions as a tumor suppressor [8]. Mutations in the ARID1A gene are frequently observed in various cancers, particularly ovarian clear cell carcinoma and endometrioid carcinoma [9]. These mutations are predominantly loss-of-function mutations, often resulting in truncated or structurally unstable proteins [10]. As a result, the normal function of the SWI/SNF complex is disrupted [11]. From a structural perspective, protein function is closely related to its three-dimensional conformation. Mutations in ARID1A can alter its folding, stability, and interaction with other proteins in the SWI/SNF complex. Therefore, studying the structural differences between wildtype and mutant ARID1A proteins is essential for understanding their functional consequences.

In this study, molecular models of both wild type and mutant human ARID1A proteins were generated using Alpha Fold server [12]. As shown in Figure 2, both models exhibited a major portion of unfolded protein suggesting that ARID1A might be an intrinsically disordered protein. However, the DNA binding domain (DBD) was found to be well folded in both models. The DBDs of both wild type and mutant models were subjected to 100 ns of molecular dynamics (MD) simulations each. MD simulations were performed as described earlier [13]. As shown in Figure 3, >2.0 Å difference is observed in the C-alpha root mean square deviations (RMSD) between the wild type and mutant models while subtle differences in root mean square fluctuations (RMSF) were seen in between the models. Based on the RMSD and RMSF differences it is evident that both wild type and mutant models of human ARID1A exhibit different profiles of their structural flexibility that may affect the affinity of DBD to the nucleosomes resulting in improper regulation of gene expression due to inefficient chromatin remodeling by the SWI/SNF complex. However, this study is focused only on one mutant, several mutants must be tested in future.

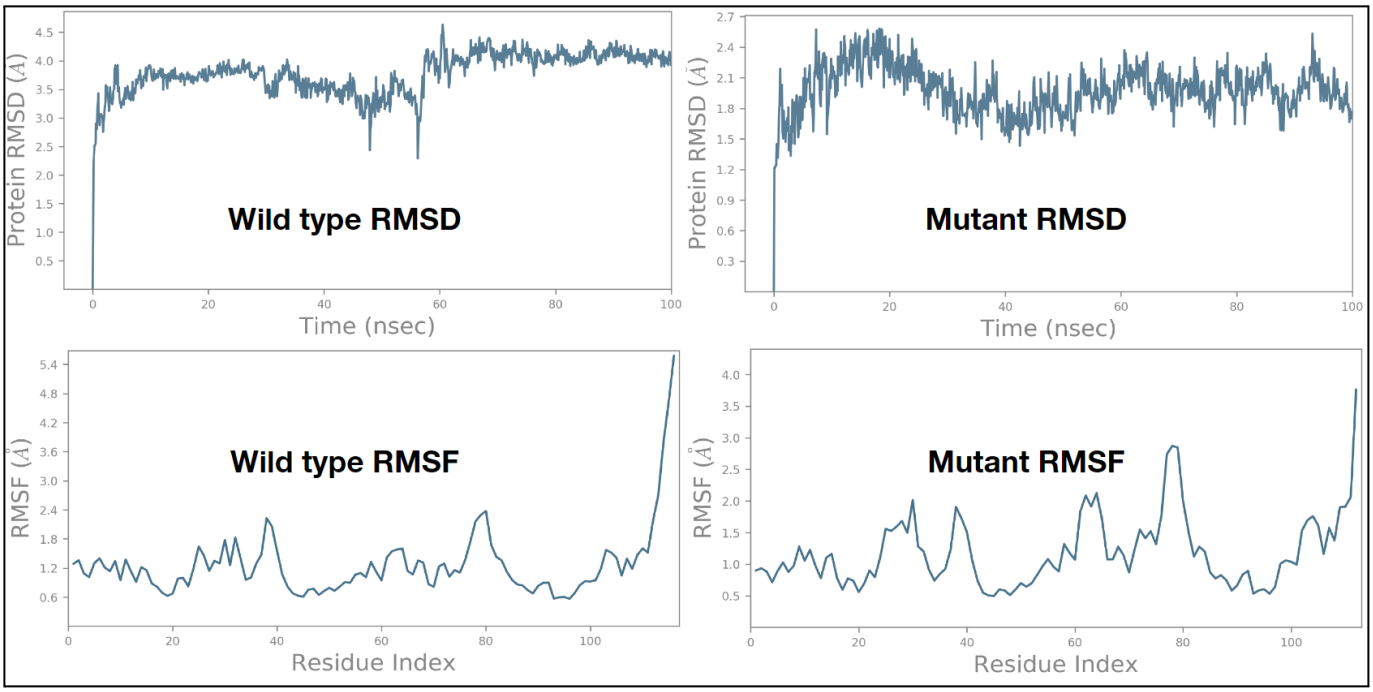

Figure 3. The C-alpha RMSD (top panels) and RMSF (bottom panels) for wild type (left panels) and mutant (right panels) models of human ARID1A protein obtained over a 100 ns molecular dynamics simulation are shown here.

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Author contributions: C.G., G.S.C. and P.T. performed the work under the guidance and supervision of R.S.Y., the principal investigator. R.S.Y. wrote, edited and finalized the manuscript.

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