

Protein Modeling Seeks to Isolate the Culprit in the “Breast Cancer Gene”

Challenge

Every human carries the genes labeled BRCA1 and BRCA2 — the so-called breast cancer and ovarian cancer genes — but only certain structural variations in these proteins mark who is more at risk to develop disease. Variations or defects in a protein can damage health through

1. A total loss of function, caused by blocked synthesis or inability to fold properly;
2. A partial loss of function, caused by impaired properties; or
3. The introduction of new properties, such as cancer.

Determining the structure and function of the genes known to influence the development of breast and ovarian cancer may, in the future, allow intervention at the molecular level.

Argonne’s Role

Genes are proteins made up of hundreds — even thousands — of amino acids arranged in specific, and sometimes repeating, sequences. If only a small piece of a gene signals trouble for human health, the first goal is to find that piece. At Argonne, the modeling of protein structures is closing the gap in the search. Protein modeling reveals far more similarity between proteins than could be inferred from previously available statistical methods; small variations account for changes in function and illustrate common evolution.

Data comparison reveals “missing links” between proteins once regarded as dissimilar or as having evolved to a similar point from divergent paths. These associations, or “homologs,” assist researchers in discovering what variations cause functions to be diminished or perverted. Some variations are

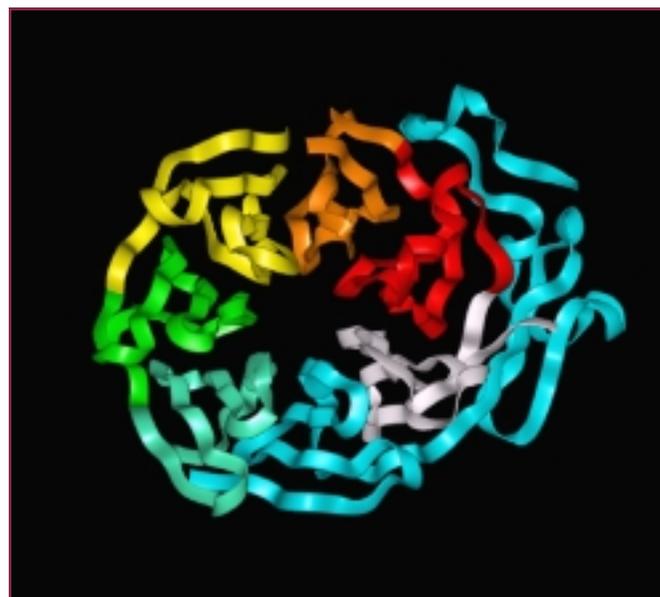


Figure 1. Up to one-half of the human BRCA2 gene may consist of structural elements similar to this betapropeller protein.

innocuous, while others are potentially life-threatening. There is hope that the variations in BRCA1 and BRCA2 may yield to scrutiny (Figure 1).

Scientific Approach

Researchers in the genomic, molecular, and structural sciences are working to understand variations in the amino acid sequences of normal human proteins and to determine how molecular changes affect functions and properties. Argonne scientists work together across disciplines, using the concepts and methods of

- **Bioinformatics** to analyze amino acid sequence data
- **Molecular biology** to create variant proteins with single amino acid changes
- **Computational biology** to model protein structures and interactions



Figure 2. Robotic workstations perform multiple modeling experiments in weeks instead of years.

- **Biophysics** to make experimental measurements of protein stability and interactions (Figure 2)
- **Protein crystallography** to determine structures of conceptually significant variants (Figure 3)

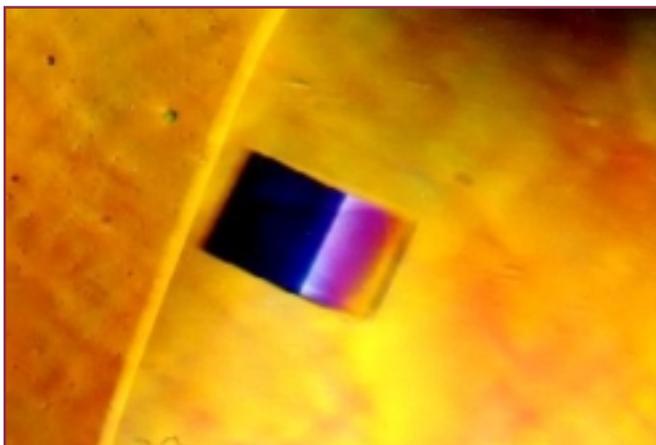


Figure 3. Protein crystals are needed before a structure can be determined by x-ray diffraction methods.

Applications

Understanding proteins will provide a window into understanding their metabolic pathways. Ultimately, it may be possible to compensate for a pathway that is lost, or to turn off a pathway that is being inappropriately turned on, thereby changing the course of development of disease or possibly averting it altogether.

Collaborator

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Sponsor

National Institutes of Health

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