Physics-based approach to understanding and targeting disease-causing missense mutations

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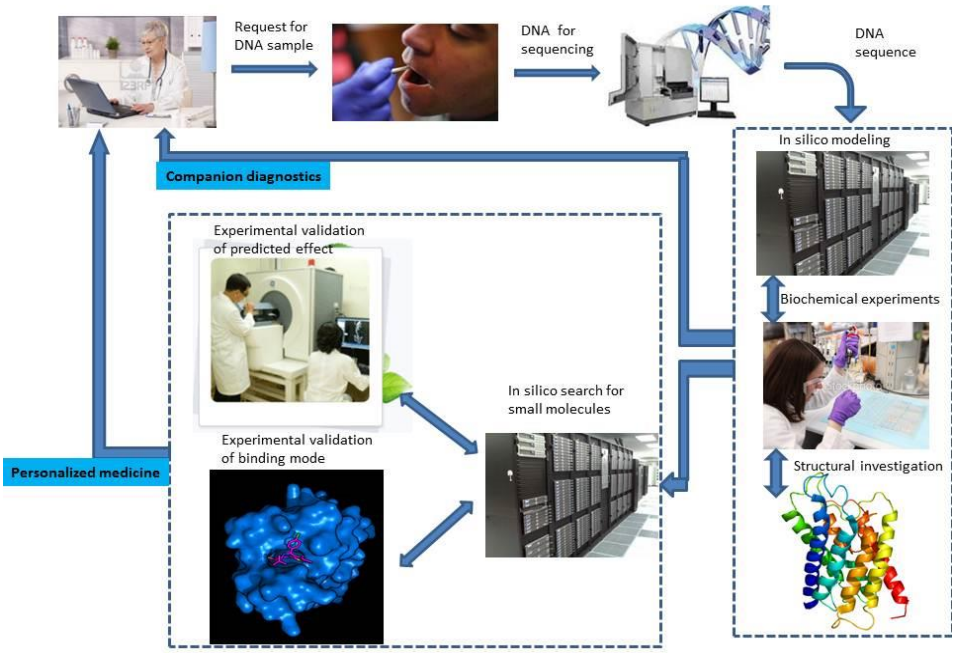
Abstract and background:
This investigation is aimed at revealing the molecular mechanism of selected monogenic diseases and to find small molecules (potential drugs) which bounding to the corresponding malfunctioning protein suppresses these unwanted disease-causing effects. The target genes and the corresponding genetic defects are provided by Greenwood Genetic Center (GGC), institutions collaborating with GGC and NYS Institute for Basic Research in Developmental Disabilities. We choose to investigate cases provided by GGC and NYS Institute because of the existing collaborations. The diseases which will be investigated range from various intellectual disabilities associated with defects in X chromosome (XLID) to Alzheimer disease, and they are all monogenic diseases. The XLID is rare disease and reported families are small, but collectively the impact of XLID is significant because the patients almost always cannot fully participate in society (see attached letter from such a family). On the other end of the spectrum is the Alzheimer's disease. It is estimated that as many as 5.1 million Americans may have Alzheimer's disease. Although Alzheimer's disease is not a normal part of aging, the risk of developing the illness rises with advanced age. Current research from the National Institute on Aging indicates that the prevalence of Alzheimer's disease doubles every five years beyond age 65. Thus, as our population ages, the disease impacts a greater percentage of Americans as indicated below. The number of people age 65 and older is expected to double between 2010 and 2050 to 88.5 million or 20 percent of the population; likewise, those 85 and older will rise three-fold, to 19 million, according to the U.S. Census Bureau. The estimated cost for caring for individuals with Alzheimer's disease is at $100 billion annually. Thus, any treatment is highly desirable.

Here we propose the development and use of methods to reveal the molecular mechanism of selected diseases for cases involving proteins with available 3D structure. The 3D structures will be used to predict the effect of disease-causing missense mutations on the folding free energy, conformational dynamics, hydrogen bond network and, if appropriate, on protein binding free energy. Our primary investigations indicate that for the selected cases the mutations indeed affect the above-mentioned wild type protein biophysical properties. However, so far the vast majority of the mutation sites are found to be outside of the active pocket and are accessible from the water phase which can provide the opportunity for their effect to be altered by binding appropriate small molecules within the vicinity of the mutation site (excluding a minor number of cases of non-sense mutations resulting in truncated protein). The goal is to find small molecules which bind specifically to a disease-causing protein and thus reduce the effects of the missense mutation. This will be done by *in silico* modeling of the stability, dynamics, hydrogen bond, and interactions of the disease-causing protein complexed with the corresponding small molecule and will include a comparison with the properties of the wild type protein. The results of *in silico* predictions will be experimentally validated by *in vitro* protein studies in the presence of, and without, the small molecules. Since the search for small molecule candidates will include already approved FDA cases, any successful case involving a FDA molecule can be directly used to provide treatment to the patients. In addition, although the proposal is aimed at investigating specific diseases, in principle, the very same approach can be used to target any monogenic disease.

Flowchart of the plan:

The proposed hires represent a comprehensive extension of research capacity that begins with a clinical phenotype (GGC) to gene variant mapping & characterization with an ultimate goal of developing tools for potential curative or ameliorative therapies that translate across areas of various specific scientific expertise. In brief, genetics researchers identify disease-associated genes, pathways and genetic variations using various approaches including targeted or whole genome sequencing and data mining through bioinformatics.



Cell biologists, developmental biologists, biophysicists, physiologists, and biochemists epidemiologists then analyze that data in order to determine the impact of the variant or mutation on cellular and organismal function, and what other modifying factors (epigenetics and environment e.g. environmental factors) may play a role in exacerbating or resolving the disease status. This multidisciplinary research approach allows the variant to be identified so that drug development work can begin. The faculty proposing this approach, which indicates strong potential, both scientific and commercial, have already produced some preliminary results.

Current funding: 3 postdoctoral one-year positions supported by Clemson University, The office of the Provost.