UNIVERSITÀ DI TRENTO
Dipartimento di Fisica

Prof. Francesco Musiani

Department of Pharmacy and Biotechnology – University of Bologna

2024, September 16 - 10:30 a.m.
Room A203

Studies of the effect of pathogenic variants causing Leber hereditary optic neuropathy on respiratory complex I function and inhibition

Abstract

Variants found in the respiratory complex I (CI) subunit genes encoded by mitochondrial DNA can cause severe genetic diseases. However, it is difficult to establish a priori whether a single or a combination of CI variants may impact oxidative phosphorylation. On the other hand, the high-resolution CI structures released starting from 2020 opened a new era in the determination of the structure/function relationship of the enzyme. For example, the study of the structures allows a new explanation to be proposed for a long-standing debate on the rotenone resistance of one of the most common mitochondrial DNA mutations, m.11778G>A/MT-ND4, associated with Leber's Hereditary Optic Neuropathy (LHON). Moreover, docking calculations provide new hints regarding the poor idebenone therapy response in patients carrying another common LHON mutation (m.3460G>A/MT-ND1). Finally, with the aim of investigating CI variants, a computational approach based on coarse-grained molecular dynamics simulations was developed. The third common CI variant associated with LHON (m.14484T>C/MT-ND6) was used as a test case and was investigated alone or in combination with two additional rare CI variants whose role remains uncertain. We found that the m.14484T>C/MT-ND6 variant positioned in the E-channel region, which is fundamental for CI function, stiffens the enzyme dynamics. Moreover, a new mechanism for the transition between π- and α-conformation in the helix carrying the primary variant is proposed. Furthermore, our findings show that one of the rare variants, located next to the primary one, further worsens the stiffening, while the other rare variant does not affect CI function. This approach may be extended to other variants candidate to exert a pathogenic impact on CI dynamics, or to investigate the interaction of multiple variants.

Contacts:

Department of Physics Secratariat

0461 28-1504-1575-2042-1545

df.supportstaff@unitn.it

Scientific Coordinator

Prof. Gianluca Lattanzi

gianluca.lattanzi@unitn.it