Small Mutation, Big Impact: How a Single Change Influences Electrostatic Interactions and Performance of MAO-A Enzyme Linked to Brunner Syndrome

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Enzymes are finely tuned molecular machines, and even one single-point mutation can dramatically affect their function. This is especially critical when such mutations involve charged residues, which play a fundamental role in stabilizing transition states during catalysis. In this study, we focus on clinically observed mutations in monoamine oxidase A (MAO-A)—a mitochondrial enzyme essential for the breakdown of neurotransmitters such as serotonin. Disruption of its function has been linked to Brunner syndrome, a rare neurodevelopmental disorder characterized by impulsivity, aggression, and intellectual disability [1,2].

Using a multiscale simulation approach, we investigated how specific MAO-A mutations affect the catalytic mechanism of serotonin degradation [3]. Our methods combined classical molecular dynamics (MD) with the empirical valence bond (EVB) technique to quantify changes in activation free energy and electrostatic contributions. The studied variants, including C266F, V244I, and E446K, were found to increase the activation barrier by several kcal/mol, resulting in reaction rate reductions of up to ~18,000-fold. These effects are functionally equivalent to a complete loss of enzymatic activity. Electrostatic analysis revealed that the mutations compromise transition state stabilization by disrupting the preorganized charge distribution in the active site. Additionally, subtle structural shifts propagate throughout the protein, affecting folding and active-site accessibility. Together, these findings illustrate how a seemingly minor genetic change can lead to severe functional consequences and provide a clear molecular link between genotype and phenotype in MAO-A–related disorders.

This work underscores the broader significance of atomic-level interactions in enzyme catalysis and illustrates how computational modeling can reveal the molecular origins of disease. Our approach provides a powerful framework for assessing the functional consequences of genetic mutations and supports the application of structure-based simulations in the context of precision medicine.

References:

[1] H. G. Brunner, M. Nelen, X. O. Breakefield, H. H. Ropers, B. A. van Oost, *Science* **262** (1993) 578-580.

[2] E. E. Palmer, M. Leffler, C. Rogers, M. Shaw, R. Carroll, J. Earl, N. W. Cheung, B. Champion, H. Hu, S. A. Haas, V. M. Kalscheuer, J. Gecz, M. Field, *Clin. Genet.* **89** (2016) 120-127.

[3] M. Rajić, J. Stare, *J. Chem. Inf. Model.* **65** (2025) 3439-3450.