Bridging the gap between clinical neuropsychiatry and chemical physics: rare genetic disorder explained by Empirical Valence Bond simulations

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Brunner syndrome is a rare genetic disorder marked by aggressive behavior, intellectual disability, autism, and other neuropsychiatric symptoms. It is linked to impaired serotonin metabolism due to mutations in the *MAOA* gene, which encodes the monoamine oxidase A (MAO-A) enzyme responsible to oxidative decomposition of serotonin. These point mutations, such as p.C266F, p.V244I, p.E446K, and p.R45W, are suspected to reduce MAO-A's catalytic efficiency, leading to elevated serotonin levels. However, direct evidence quantifying this effect has been lacking.

We addressed this gap using Empirical Valence Bond (EVB) simulations to model the catalytic step of serotonin degradation in both wild-type and mutant MAO-A. EVB, a hybrid QM/MM technique, allowed us to compute free energy profiles and estimate reaction rate constants. Our results show that all studied mutations raise the activation barrier by 3-5 kcal/mol, corresponding to a 500- to 18,000-fold reduction in activity, which is comparable to a gene knockout. Additionally, by breaking down the catalytic effect of MAO-A to the level of individual residues, we found that the mutations induce widespread structural effects beyond the mutation site, underscoring their complex impact. These findings link clinical symptoms to molecular dysfunction and offer mechanistic insights into Brunner syndrome from a fundamental physical perspective.