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Novel Systematic Prioritization Method and Sensitive Monitoring of Critical Phosphorylation Sites in Huntington's Disease

Huntington's Disease (HD) is a neurodegenerative disease caused by a polyglutamine tract expansion in the huntingtin gene resulting in a mutated huntingtin protein (htt). Phosphorylation is the most widespread reversible post-translational modification (PTM) in a cell and can be readily manipulated to regulate protein behavior using conventional drugs. Therefore, identifying phosphorylation sites in htt critical to HD pathogenesis is crucial in developing potential clinical treatments that restore normal htt function. Here, we used biological filters to develop an efficient novel method of prioritizing critical phosphorylation sites in htt. This method was empirically validated by measuring phosphorylation levels between mutant and normal htt and revealed three sites critical to HD pathogenesis: S2076, S1181, and S2342. Two of these sites, S1181 and S2342, were successfully optimized using parallel reaction monitoring (PRM), a highly-sensitive mass spectrometry technique useful in clinical studies. Our novel prioritization method and PRM analysis laid the groundwork for future HD clinical studies. Furthermore, our novel method which uses biological filters to prioritize phosphorylation sites is applicable to other disease proteins.