Zoghbi has combined cell biology, mouse genetics, and human clinical genetics to reveal fundamental mechanisms underlying a wide range of diseases and disorders. Her forays into basic developmental neurobiology have led to insights in conditions ranging from hearing loss to colon cancer. Her best-known work, however, is in the area of neurology: adult-onset neurodegenerative conditions and post-natal onset neurodevelopmental disorders.

She and her collaborators have made compelling insights into why neurons die in polyglutamine tract disorders, a group of neurodegenerative disorders that includes Huntington disease and the spinocerebellar ataxias. In spinocerebellar ataxia type 1 (SCA1), Zoghbi discovered that the disease-causing protein is more stable and drives disease through enhanced interactions. Zoghbi demonstrated in animal models of SCA1 that reductions of levels of the protein ataxin-1 “cures” features of the disease, making this a promising therapeutic target. Her work has implications for the larger family of neurodegenerative disorders known as “proteinopathies,” diseases caused by malformed proteins of which Alzheimer’s and Parkinson’s disease are the most well known,

Zoghbi has also had a profound influence on the field of neurodevelopment through her work on Rett syndrome, a form of autism. In 1999, Zoghbi discovered that the syndrome is caused by mutations in the X-linked gene *MECP2*, which binds methylated DNA and is involved in the epigenetic regulation of gene expression. This established Rett syndrome as the first autism spectrum disorder that is caused by largely sporadic gene mutations. Zoghbi would go on to demonstrate that the brain is exquisitely sensitive to *MECP2* levels, that doubling *MECP2* levels is responsible for a devastating progressive neurological syndrome, and that small

antisense oligonucleotides can be used to normalize *MECP2* levels and reverse symptoms of the disorder in a mouse model.