First Person – Sai Sanwid Pradhan

Huntington disease (HD) is an incurable disease affecting five in 100,000 people in India. It is a familial disease with a 50% chance of the offspring inheriting the disease from their affected parent. HD is caused by cytosine-adenine-guanine (CAG) repeats within the huntingtin gene (HTT), which – when exceeding 36 repeats – result in the manifestation of the disease. The mutation causes misfolding and aggregation of HTT protein, leading to neuronal degeneration. The clinical symptoms of HD include cognitive, behavioural, psychiatric and motor dysfunctions. Since identification of the mutation in HTT in 1993, there has been remarkable progress in the research towards disease pathology and potential cure of the disease. Currently, only treatment for symptomatic forms of HD is available. Although the length of the CAG-repeat inversely correlates with the age of disease onset, considerable variations exist regarding the severity of the disease, which suggests the presence of disease modifiers. In our study, we used a method of analysis that combines patient-derived data (metabolomics profile) and data from a HD yeast model, and showed considerable overlap of pathways involved in amino acid and energy metabolism between the datasets. Furthermore, by using yeast model systems, we demonstrated that the observed deregulated metabolism directly modulates aggregation of mutant HTT. Treatments that modulate deregulated metabolic pathways, and which help to achieve metabolic homeostasis, might help in mitigating HTT aggregation. Previous studies from our lab as well as others have demonstrated that neuronal cell death and, hence, changes in brain volume, glucose utilization and metabolism within the affected brain regions of HD patients, precedes the onset of symptoms. Taken together, these results suggest that maintaining metabolic homeostasis and neuronal protection during the presymptomatic stage delays the onset of symptoms and helps in better management of the disease.

How would you explain the main findings of your paper to non-scientific family and friends?

What are the potential implications of these results for your field of research?

“Steps that help prevent protein aggregation during the presymptomatic stage in genetically susceptible individuals might help neuronal protection and, potentially, delay [Huntington] disease onset.”

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

The multi-omics approach helped us to identify key elements that are translated in each omics study, which narrowed down our research approach regarding the disease. Since protein aggregation precedes actual symptoms of HD, the use of yeast as a model...
It is widely accepted that neurodegenerative diseases are associated with metabolic remodelling. Gene knockout affecting metabolic pathways has been shown to modulate protein aggregation in yeast model systems. Our study showed that the mere addition of the correct metabolite from the deregulated pathway can modulate aggregation of mutant HTT. Our findings, concomitant with previous studies of changes in brain volume, metabolites and glucose utilization in presymptomatic individuals, show that neuronal protection by maintaining metabolic homeostasis might help mitigate disease.

What do you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

One of the major shortcomings is the availability of matched data. HD patients and families are clinically characterized for unified HD score, multimodal MRI and disease complications. We also envisage to get the multi-omics datasets from these families for analysis, together with their follow-up data. By using artificial intelligence and other techniques it should be possible to distinguish between patients according to disease onset and severity, and development of complications, i.e. regarding cognition, behaviour, depression, etc., such that preventive measures can be taken. Steps have been taken to address some of these shortcomings by establishing patient-sample repositories together with lymphoblastoid cells that could be used for iPSC development. In future, the availability of human leukocyte antigen (HLA)-typed stem-cell repositories will help to expand cell-based therapeutics for many neurodegenerative diseases. Currently, the availability of sample repositories based on population is highly skewed and there should be a general representation. In addition, patients should clinically be well-characterized regarding symptoms, diet, etc. The development of ‘higher animal’ models that are more representative to the disease in human will be helpful for a better understanding of the disease.

What changes do you think could improve the professional lives of scientists?

One of the many problems an aspiring PhD student faces are the low number of PhD fellowships, together with small stipends. In addition, grants or funding for open access publication or registration and travel fees for attending conferences, and hands-on training workshops are relatively small, especially for those from developing countries. The HD mouse model is beyond the reach of laboratories in developing countries. The HD mouse model is beyond the reach of laboratories in developing countries. There are very limited postdoctoral positions. Training programs for PhD students would empower researchers to write proposals and get fellowships or to translate their ideas into industrial applications. Article processing charges (APCs), i.e. the fee authors are sometimes charged to make a publication open access, are usually very high. Only selected journals, such as Disease Models and Mechanisms and some of the Springer journals waive this fee entirely for developing nations like India. Funding opportunities and journal collaborations with institutes in India support research being published in reputed journals.

**FIRST PERSON**
What’s next for you?
During my PhD I have had the chance to attend workshops and conferences, involving HD patients and their families, and have encountered problems of both patients and caretakers. Hence, I intend to pursue a career in neurodegenerative diseases and healthcare, where my work might help to mitigate these problems by delaying the onset or by enabling better management of the disease. In particular, I like to focus on the mechanistic aspect of the disease, patient stratification and predictions of complications, potentially implementing stem cell therapy. I plan to continue my research as a postdoctoral fellow in the field of neurodegenerative diseases.

How might the HD community or funding agencies focussing on neurodegenerative diseases help PhD students directly?
One of the ways to be more inclusive is to have training programs or PhD fellowships for students from developing counties. However, travel, accommodation and registration costs are often prohibitive, making it difficult to train a higher number of students. Technologies currently available could be used better by, for example, enabling online training on multi-omics and other techniques, with emphasis on neurodegenerative diseases. Information regarding data repositories, funding and databases of potential collaborators would be helpful.

References