Research brings hope for early treatment of brain degeneration in children with xeroderma pigmentosum

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Xeroderma pigmentosum (XP) is a rare and devastating genetic disorder characterized by an inability to repair skin damage caused by ultraviolet

(UV) light. As a result, patients with XP develop skin cancers, usually in childhood. Once diagnosed, they can be protected by avoiding sunlight (hence sometimes being called "children of the night"), wearing special clothing and sunglasses, and using sunscreen.

But some will also develop neurodegenerative conditions such as hearing loss, loss of intellectual function, poor co-ordination and seizures. Finding out why this is, and which patients are likely to develop such conditions, is a priority for XP researchers.

Dr. Sophie Momen, a consultant dermatologist at Guy's and St Thomas' NHS Foundation Trust, London, UK and a researcher in Professor Serena Nik-Zainal's lab at the University of Cambridge, will tell the annual conference of the European Society of Human Genetics of her team's work in the development of an early detection algorithm to predict which patients may develop such neurodegeneration.

Until now there has been little research in this area, partly because XP is a rare condition, affecting one person in a million, and because the brain, being an inaccessible organ in live patients, is very difficult to perform research on.

The researchers took blood samples from patients with XP with and without neurodegeneration, and from family members without XP, and turned these samples into pluripotent stem cells (cells that can be groomed into different cell types). The researchers were then able to identify the stem cells that would become brain cells (neurons).

"We carried out various experiments on these neurons using multi-omic technologies to try to understand why some XP patients developed neurodegeneration and some did not. From this we were able to develop our algorithm. This will be useful if we can offer something to patients to try to slow down or halt the onset of neurodegeneration. Our research

has revealed possible drug targets, which may do just that in the future," says Dr. Momen.

The researchers were fortunate, they say, in having access to a large group of patients from the national XP clinic at Guy's and St Thomas, where all British-resident patients with the condition are cared for by the same clinical team. "Having such a clinic means that patients with rare diseases can be followed up long-term in one place, and this facilitates investigations such as ours," Dr. Momen says. "This is the first time that so many patients with XP have been studied and their neurons have been characterized in such depth."

Since the clinic came into being in 2010 , patients in the UK have been well-informed about photoprotection and about early detection of skin cancers, and as a result they are living long lives. "None of our patients has died from skin cancer," says Dr. Momen.

"It is often said that patients with XP die in their 20s and 30s, either due to skin cancers or neurodegeneration, but this is not always the case. It is important to recognize that there are some patients with XP who do not develop neurodegeneration and mainly develop skin cancers, against which they can take protective measures at an early stage."

The results may also be useful in understanding why otherwise healthy people develop neurodegeneration as they age. Over the past few years, the study of patients with XP has helped scientists to understand why some otherwise healthy people develop skin cancers after exposure to UV light. "We can now extrapolate the findings in our study to the understanding of why the faulty DNA repair pathway involved in XP is involved in brain health and this may, in turn, help us understand why some people develop neurodegeneration as they age."

Further validation studies of the early detection algorithm will be

necessary before it can be used as a predictive tool in clinical practice. Clinical trials will also be needed to see which, if any, medications may be useful in halting or delaying neurodegeneration in patients identified as being at risk.

"I did not expect that we would be able to characterize the neurons derived from those patients with and without neurodegeneration so clearly. When we used proteomics, the results allowed us to see clearly whether patients had neurodegeneration or not," says Dr. Momen. "This is very encouraging and, we hope, a further step along the road to effective treatment of this distressing condition."

Professor Alexandre Reymond, chair of the conference, said, "Our ability to personalize treatments will translate into a more effective health system. To reach this goal, we need new approaches to recognize those in the population who are more at risk."

More information: Abstract no. 3869 Functional multi-omic studies unveil ER stress and proteasomal dysfunction in early-onset neurodegeneration in XP, The European Human Genetics Conference, 2023.eshg.org/

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