PURA Syndrome Epilepsy Research Project

In 2014, the first PURA patients were described in medical literature. Symptoms including severe neurodevelopmental delay, hypotonia, respiratory problems, feeding difficulties, hypothermia and seizures were reported in patients with PURA mutations. Epilepsy in particular is a concern in the development and treatment of patients, with events reported in over 50% of diagnosed individuals.

Epilepsy usually starts with myoclonic jerks progressing to other seizure types including generalized tonic-clonic seizures, tonic seizures, and epileptic spasms. In some instances, the seizure disorder progresses to the Lennox-Gastaut syndrome. The seizures are often drug resistant. Non-epileptic movements that may be seen include dystonia, dyskinesia, and dysconjugate eye movements.

While general clinical research has led to a greater understanding about the characteristics of PURA syndrome, there are still a lot of unanswered questions about how and why seizures and epilepsy develop, how they can best be treated and prevented. We hope that in gaining a clearer understanding of the epilepsy issues being faced by PURA patients, we can develop better care and treatment options long term for PURA syndrome children and adults.

Supporting Institutions/Groups:

- Filadelfia Epilepsy Research Hospital, Denmark
- Maastricht University Medical Centre, The Netherlands
- University of Southampton, UK
- Helmholtz Zentrum Munchen, Germany
- Temple University Philadelphia, USA
- DZNE (German Center for Neurodegenerative Diseases) Munich, Germany.
- PURA Syndrome Foundation
- PURA syndrome families

Epilepsy research goals for PURA syndrome.

1. To understand the pathophysiology of PURA syndrome epilepsy.
2. To establish the epilepsy phenotype of PURA syndrome and assess genotype-phenotype correlations.
3. To evaluate possible treatment options for PURA syndrome epilepsy and enable a treatment guide for patients.

Goal 1 : To understand the pathophysiology of PURA syndrome epilepsy.

Pathophysiology explains the processes within the body that result in the signs and symptoms of a disease. In PURA syndrome, epilepsy pathophysiology refers to the underlying cause of the epilepsy. What is causing the seizures? Is it a structural issue? Is it a chemical imbalance?

This research involves:

- Studying how seizures start, spread, and stop in both human cells and animal models.
- Use of existing patient samples provided by patients for the PURA Syndrome Global Biobank.
- Creation of induced pluripotent stem cells (iPSCs) from the skin cells of PURA patients, to develop and study neurons (brain cells).
- Potential development of Mini Brains (organoids - miniature organs resembling the brain) from induced pluripotent stem cells (iPSC) of PURA patients. The electrical activity (neurophysiology) of these Mini Brains could be studied.
- Studies of brain development and epilepsy in PURA animal models (Zebrafish, Mice).

Goal 2: To establish the epilepsy phenotype of PURA syndrome and assess genotype-phenotype correlations.

Epilepsy phenotype refers to the characteristics of PURA syndrome epilepsy.
Genotype refers to your complete set of genes. In this case, researchers are focussed on the PURA gene in particular.
Phenotype refers to your characteristics – from how you look, to how you behave.

With PURA syndrome, researchers want to understand what specific characteristics are being seen in the patients who have the condition. With regard to PURA epilepsy, researchers want to know what commonly occurs with both the PURA syndrome patients who have seizure activity and those who do not. What types of seizures do patients have? What common issues are happening as a result of the epilepsy?

This research involves:

- Neurology studies of patients with PURA syndrome, known as clinical research.
- Long term collection of epilepsy information about PURA patients (PURA Syndrome Global Patient Registry – Natural Histories Study)
- Collection of EEG (electroencephalography) reports and EEG "raw data" from all PURA patients (irrespective of seizures), for on-going analysis and comparison.
- Brain imaging for viewing the structure and functioning of the brain (neuroimaging), such as magnetic resonance imaging (MRI) and positron emission tomography (PET).

Goal 3: To evaluate possible treatment options for PURA syndrome epilepsy and enable a treatment guide for patients.

Evaluating possible treatments for PURA epilepsy involves collating data regarding which epilepsy medications have and haven't shown positive results with PURA patients. It also requires an understanding of the chemical changes that occur in the cells of PURA syndrome patients because of the condition.

Once these areas are better understood, researchers can commence the process of testing existing epilepsy treatments and potential new medicines that could possibly be repurposed for PURA syndrome. This testing is completed via the use of both human cells and animal models.

This research involves:

- Long term collection of information about epilepsy medications trialled by PURA patients (PURA Syndrome Global Patient Registry – Natural Histories Study)
- Use of relocated existing patient bio-samples, provided for the PURA Syndrome Global Biobank.
- Use of PURA animal models (Zebrafish, Mice) to screen potential new treatments for PURA syndrome epilepsy.
- Use of induced pluripotent stem cells (iPSCs) created from the skin cells of PURA patients, to study existing and potential epilepsy medications.
- Development of an epilepsy treatment guide supporting both PURA syndrome families and their clinicians.