Research is like a detective, uncovering new possibilities in rare disease treatments

A research team at the Francis Crick Institute and Great Ormond Street Hospital (GOSH)/UCL Great Ormond Street Institute of Child Health have identified new potential treatments for children with rare genetic conditions of blood vessels, which cause severe, lifelong, and disabling symptoms like seizures and impaired development. Below are the findings. Read the entire research paper here: https://tinyurl.com/sws-research

We're pleased to share some essential discoveries from our research into Sturge-Weber syndrome (SWS), thanks partly to early The SWF grant funds and the highly related disease, Phakomatosis Pigmentovascularis with Dermal Melanocytosis (PPV-DM). PPV-DM, for those who don't know, is the same as SWS but has pigmentary problems, which can affect the skin, eyes, and/or brain. We and other dedicated research teams had previously spotted that these diseases are caused by 'mosaic mutations' - genetic changes that appear in some cells in the body but not all – in two genes, GNAQ or GNA11. To identify new potential treatments, particularly for children who experience early-onset neurological symptoms such as seizures and developmental delay, which worsen over time, we delved deeper into an intriguing clue in brain images known as "tramlining." This distinctive calcium deposition pattern, seen in parallel lines within blood vessels, led us to hypothesize that calcium levels might be an essential part of the diseases.

We examined 42 children thoroughly by analyzing the calcium profiles in their blood. Our results revealed that approximately 41% had slightly reduced calcium levels, and intriguingly, lower calcium levels (even within the normal range) were linked to seizures and some specific anti-epileptic medications, even in the presence of regular vitamin D levels. We don't know if this association is because one thing is causing another; at the moment, this is simply an observation. As we carried out repeated measurements, we uncovered a notable trend of fluctuating calcium levels in patients, so different measurements on different days produced different results. Still, across the cohort, a substantial proportion was always abnormal. The calcium level was not so low as to be concerning for health, and bone density scans in patients with low calcium levels were normal. However, when we closely examined brain tissue from patients who had undergone epilepsy surgery, we identified calcium deposits within blood

vessels, around small vessels, and inside brain cells. This neurovascular calcification was progressive over time when brain scans were reviewed. This has expanded our understanding of the disease as it challenges the earlier belief that calcium deposits were simply a non-specific sign of brain damage. Instead, they might play a central role in the neurological progression of this condition.

In parallel, we tested what was happening in the cells with these gene mutations in the lab. We discovered a continuous release of excessive calcium within these cells, much like an "always-on" calcium switch. This overacting calcium signalling was so strong that it led the cells to pull in even more calcium from outside through transporters on the cell membrane called CRAC channels. We do not yet know if this calcium signalling problem is directly related to the findings in the blood of the patients or not. It is possible that. We aimed to find a way to "turn off" this overactive signalling; to achieve this; we explored different therapeutic approaches in the lab. First, we developed specialized molecules, known as siRNAs, designed to silence these genes' "overactive" regions. Second, we used a drug that blocks the entry of calcium into cells through the specific CRAC channels. Both treatments improved the excessive calcium signalling calcium problems, but genetic therapy was the most effective.

In conclusion, our research has pinpointed overactive calcium signalling as the primary problem in Sturge-Weber syndrome/PPV-DM. This breakthrough paves the way for new potential future treatments, either through genetic approaches or targeted calcium drugs. These drugs are not yet available for these conditions, but we will continue working on this.