



CRELD1 Research Update

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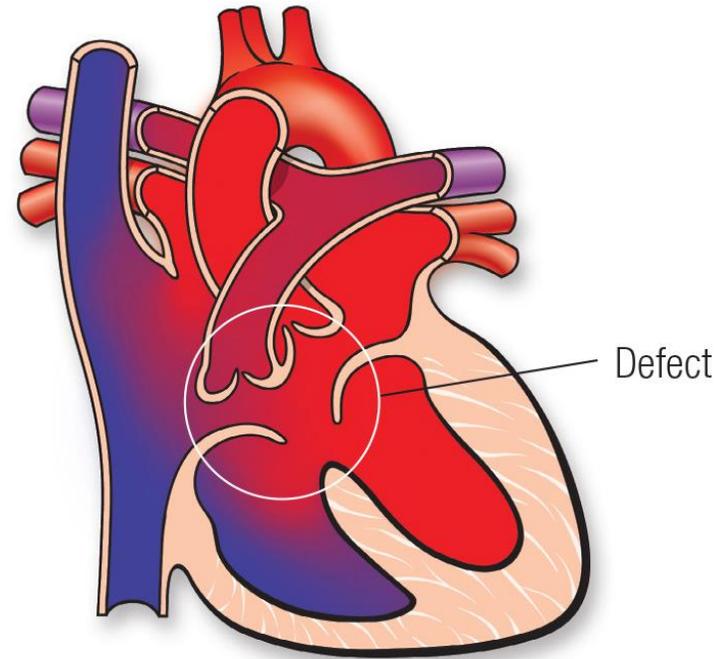
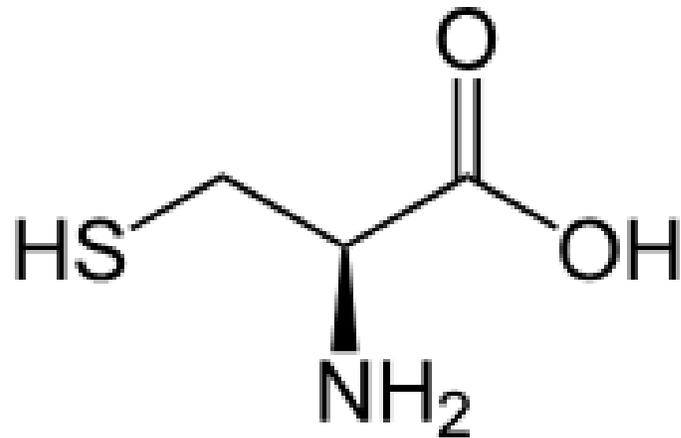
19th October 2023 – UKRET and Genomics England Roundtable



A fated meeting and an inspiring story towards continued research partnership

CRELD1

Cysteine Rich with EGF Like Domain 1



In 2000s, identified as gene associated with atrioventricular septal defect, particularly in Down Syndrome. (*Maslen et al, 2006*)

JELANS – Jeffries Lakhani Syndrome



- 18 children from 14 families
- Developmental delay, early-onset epilepsy, hypotonia
- Some experiencing cardiac arrhythmias and some experiencing recurrent infections
- *Xenopus tropicalis* or tadpoles were generated using CRISPR gene-editing that carry patient mutation – found to have elevated risk of seizure and head malformation



Yale University

Challenge in JELANS

What does CRELD1 do?

What happens when CRELD1 is mutated?

How can we best model JELANS?

Where to start?

Why is the brain affected by CRELD1?



How we address the challenge in our lab?



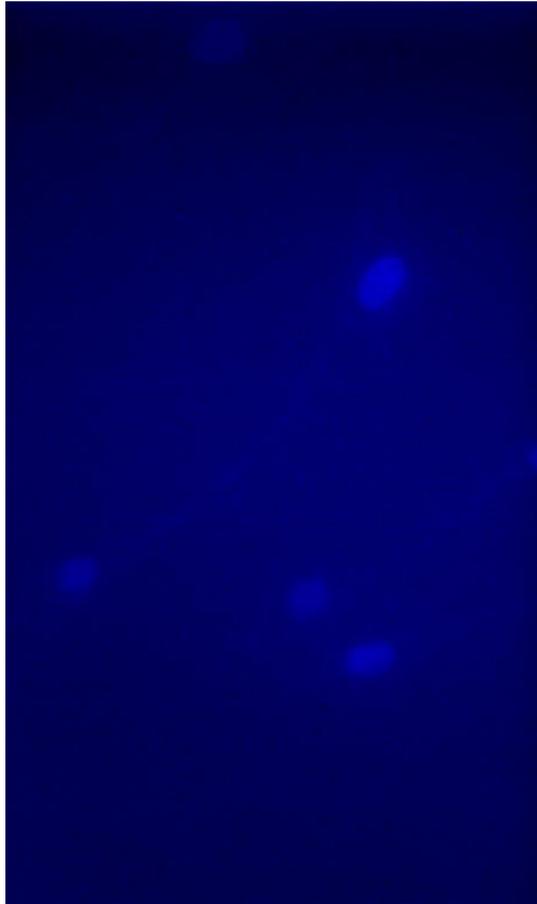
- Skin biopsy to collect skin cells from the CRELD1 or JELANS community worldwide.
- For children, this is done under anesthesia.
- Skin biopsy can be used to generate fibroblasts – a type of skin cells that can replicate well in the lab.
- Having cell models enable us to study the function of CRELD1 in the cells and what happen when CRELD1 is mutated in JELANS.

Skin biopsy collection update

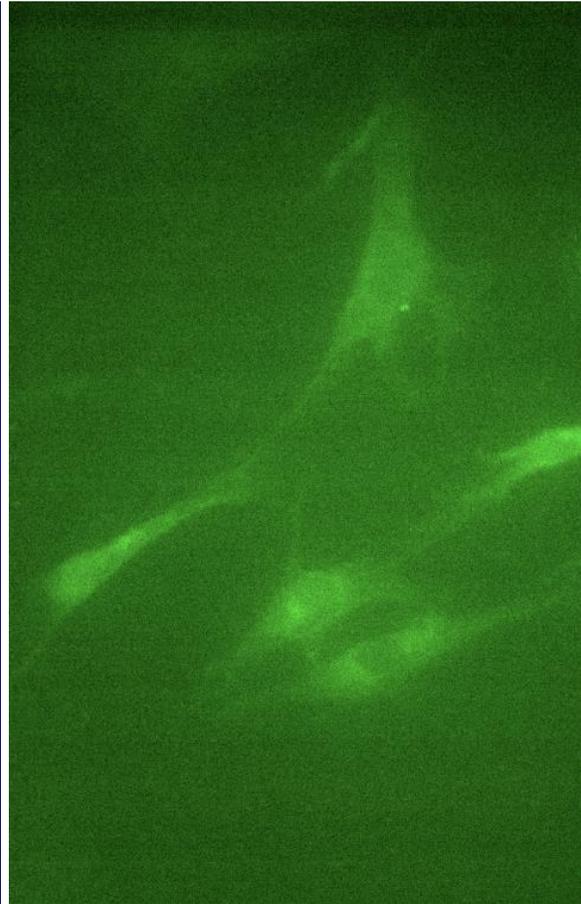
Cell line ID	CRELD1 variants	Sex / age
FC_CRLD1	c.1105A>G p.Met369Val, c.1128_1129del p.Ala377ThrfsTer7	M / 13 years old
FC_CRLD2	c.575G>A p.Cys192Tyr, c.959del p.Gln320ArgfsTer25	M / 4 years old
FC_CRLD3	c.575G>A p.Cys192Tyr (homozygous)	F / 8 years old
FC_CRLD4	c.47G>A p.Gly16Asp, c.959del p.Gln320Argfs Ter25	M / ? years old



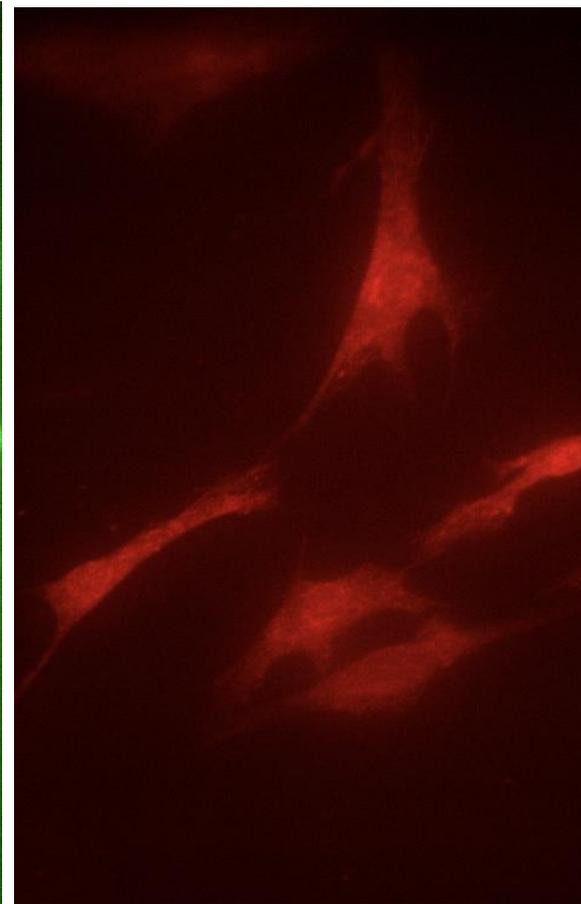
Using skin cells to study CRELD1



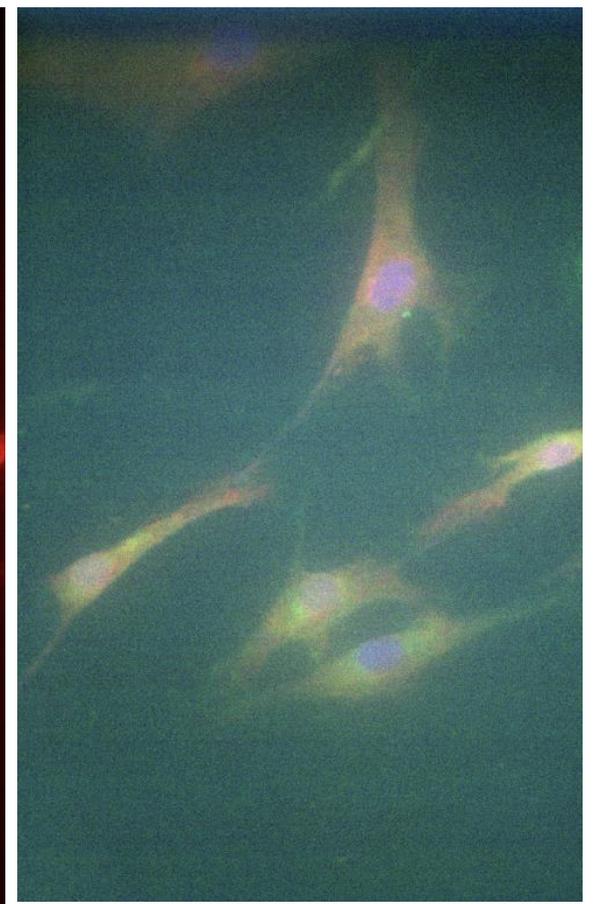
Nucleus



Mitochondria



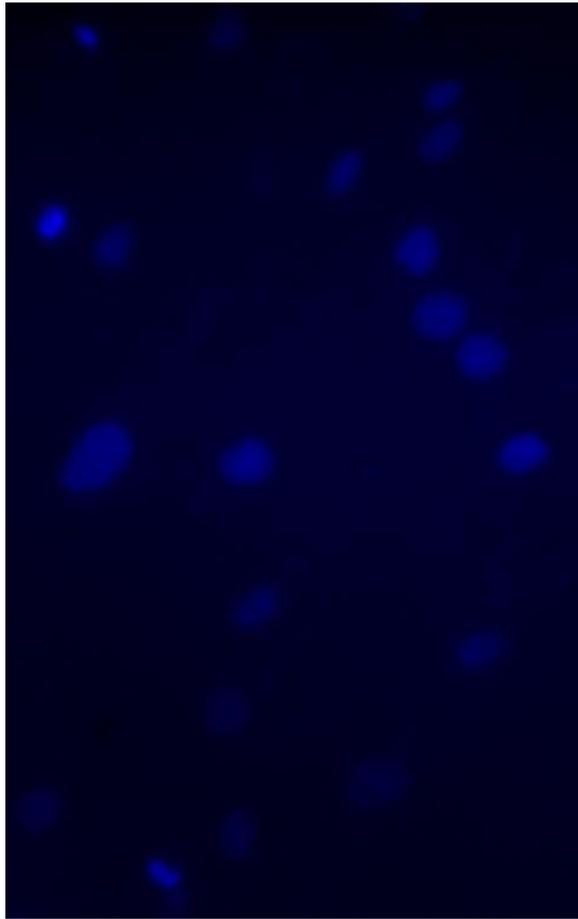
CRELD1



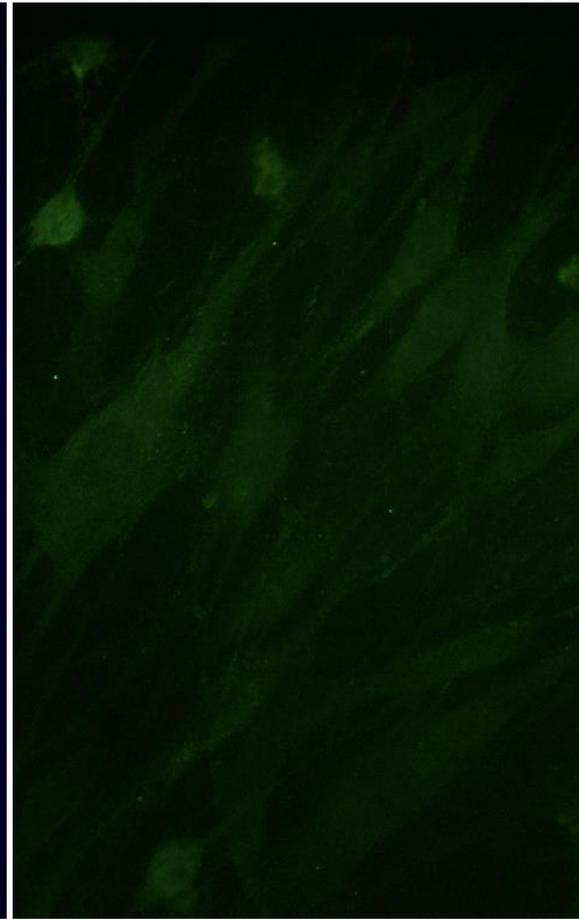
Combined

Healthy donor skin cells

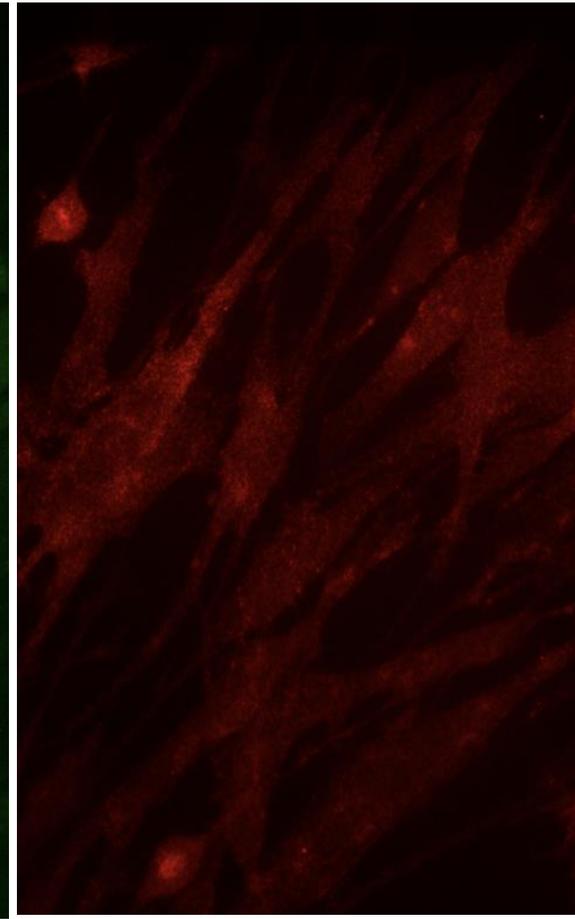
Using skin cells to study CRELD1 (2)



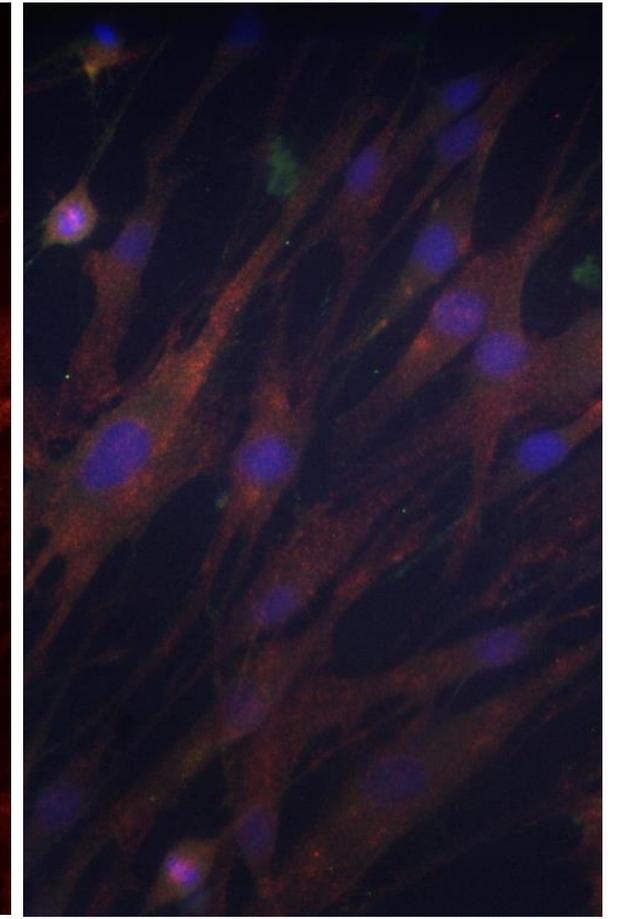
Nucleus



Mitochondria



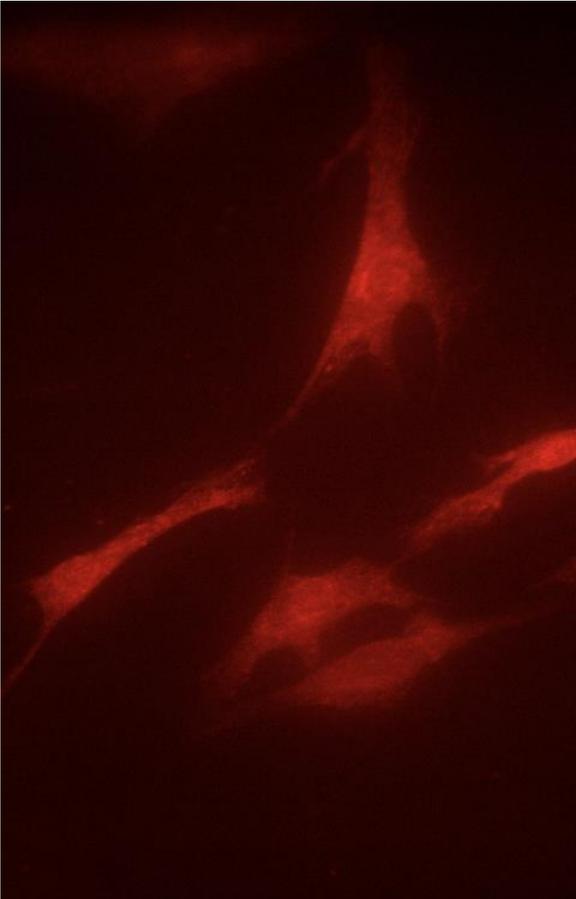
CRELD1



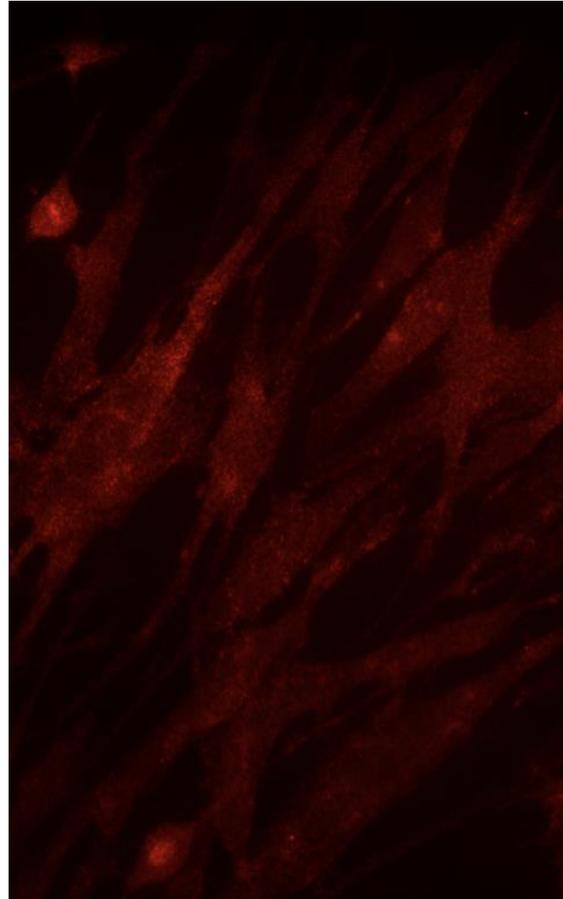
Combined

Skin cells FC_CRLD1

What did we notice? (1)



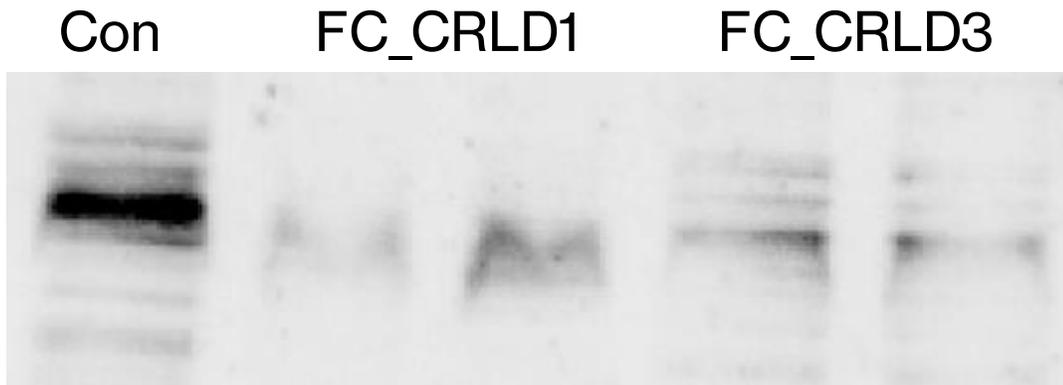
CRELD1 in healthy donor cells



CRELD1 in skin cells from male JELANS patient

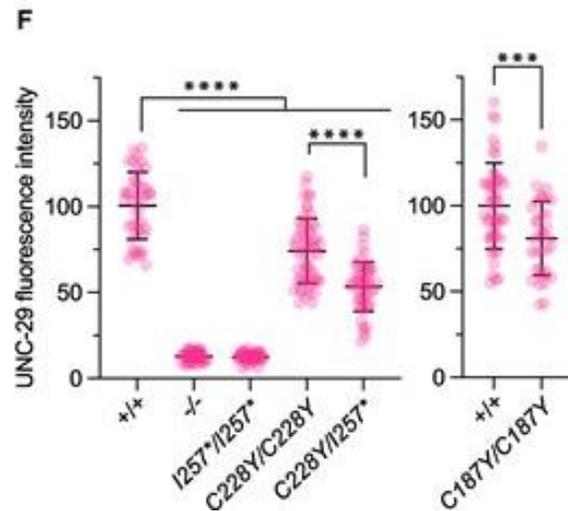
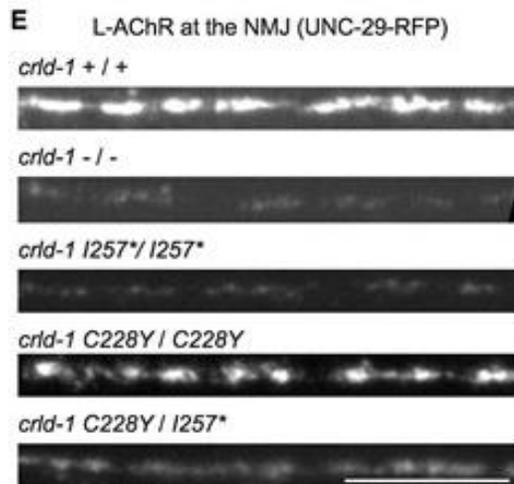
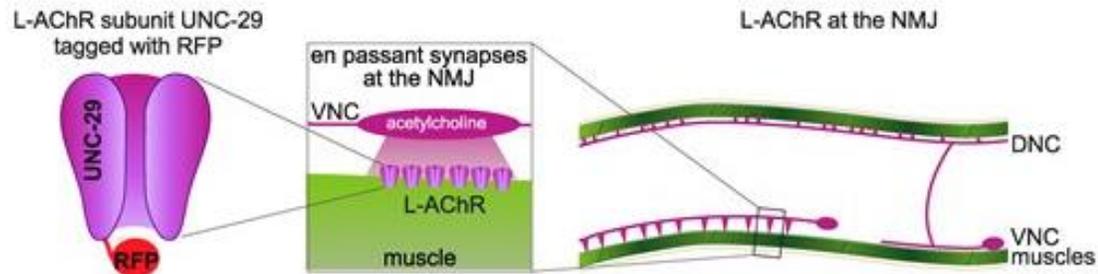
- The more protein you have, the brighter the color will be under the microscope.
- We see massive loss of CRELD1 protein in patients with JELANS.
- This means that CRELD1 mutation likely leads to loss of CRELD1 protein expression or function → 'loss of function' mutation.

What did we notice? (1)



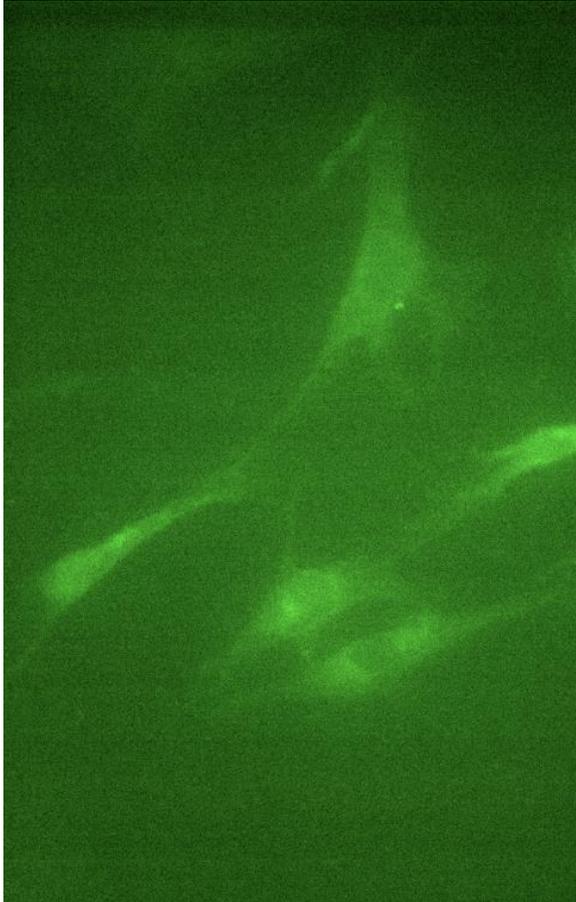
- A different approach to separate protein by weight fragment and labelling it to measure specific protein expression – Western Blot.
- Again, CRELD1 protein expression appears significantly reduced in patient cell extracts compared to healthy donor cell extracts.
- We continue to characterize all the different patient cell lines we have in the laboratory.

Next-steps

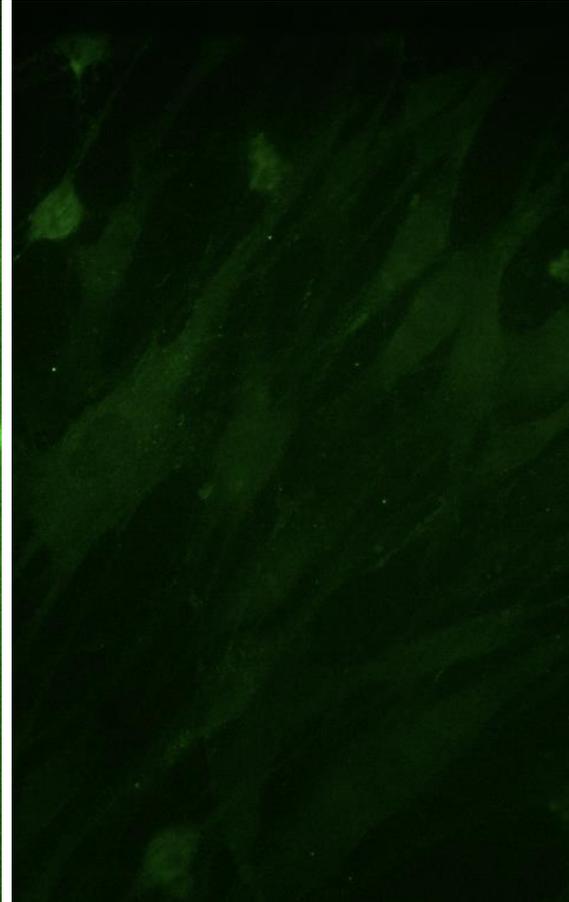


- Look at acetylcholine receptor expression in CRELD1 patient skin cells.
- Study reported reduction in acetylcholine receptor in worm with CRELD1 mutation.
- This contrasts with typical finding of increase in acetylcholine receptor associated with epilepsy in other conditions.
- Is this the mechanism of JELANS?

What did we notice? (2)



Mitochondria in
healthy donor cells

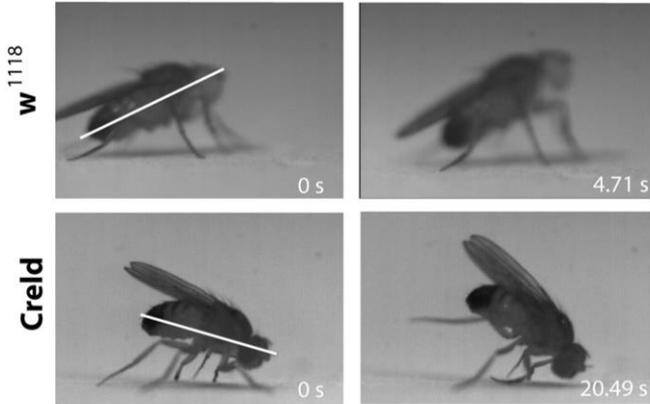


Mitochondria in skin
cells from male
JELANS patient

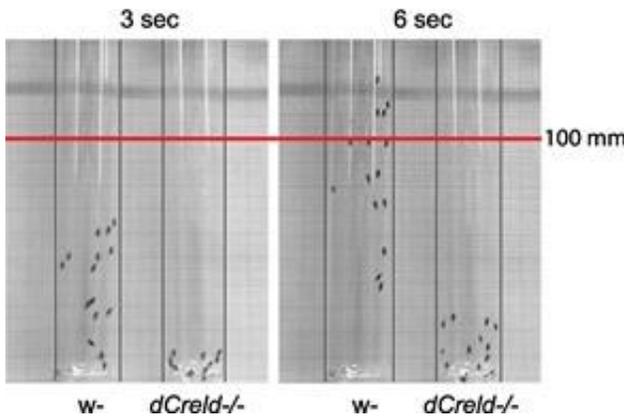
- We see massive loss of mitochondria in CRELD1 patient skin cells.
- Mitochondria is the powerhouse of the cells.
- Loss of mitochondria → loss of energy in the cell – can be associated with seizures.

CRELD1 in fruit fly model

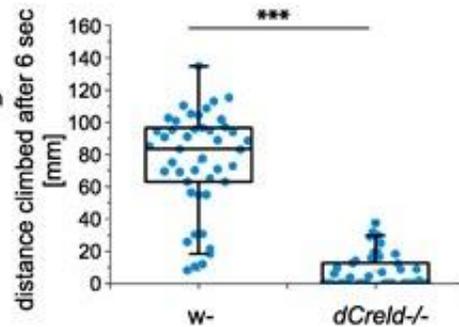
B Adult locomotion



D Adult locomotion in *Drosophila*: negative geotaxis assay

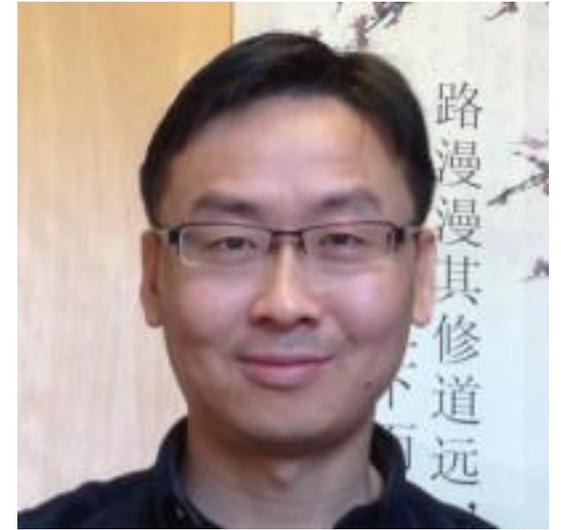


E Adult locomotion



- Flies developed in the context of Parkinson Disease; which often has dysfunction in the mitochondria.
- Published evidence showed ‘loss of energy’ in climbing or locomotion.
- Loss of mitochondrial complex activity in the CRELD fruit fly.

Do the flies have seizure?



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What does this mean for the community?

Cred **1**
Warriors

ALONE WE ARE RARE. TOGETHER WE ARE STRONG



Within one year, we now have cell models from patient with JELANS and we now have animal model with seizure resembling JELANS patient.

We are in a very strong position now to test treatment strategies for JELANS.

Support from all over



ISN
International Society
for Neurochemistry

A \$10,000 USD grant to further develop the cell model for JELANS, including new patient and new genetic variant.

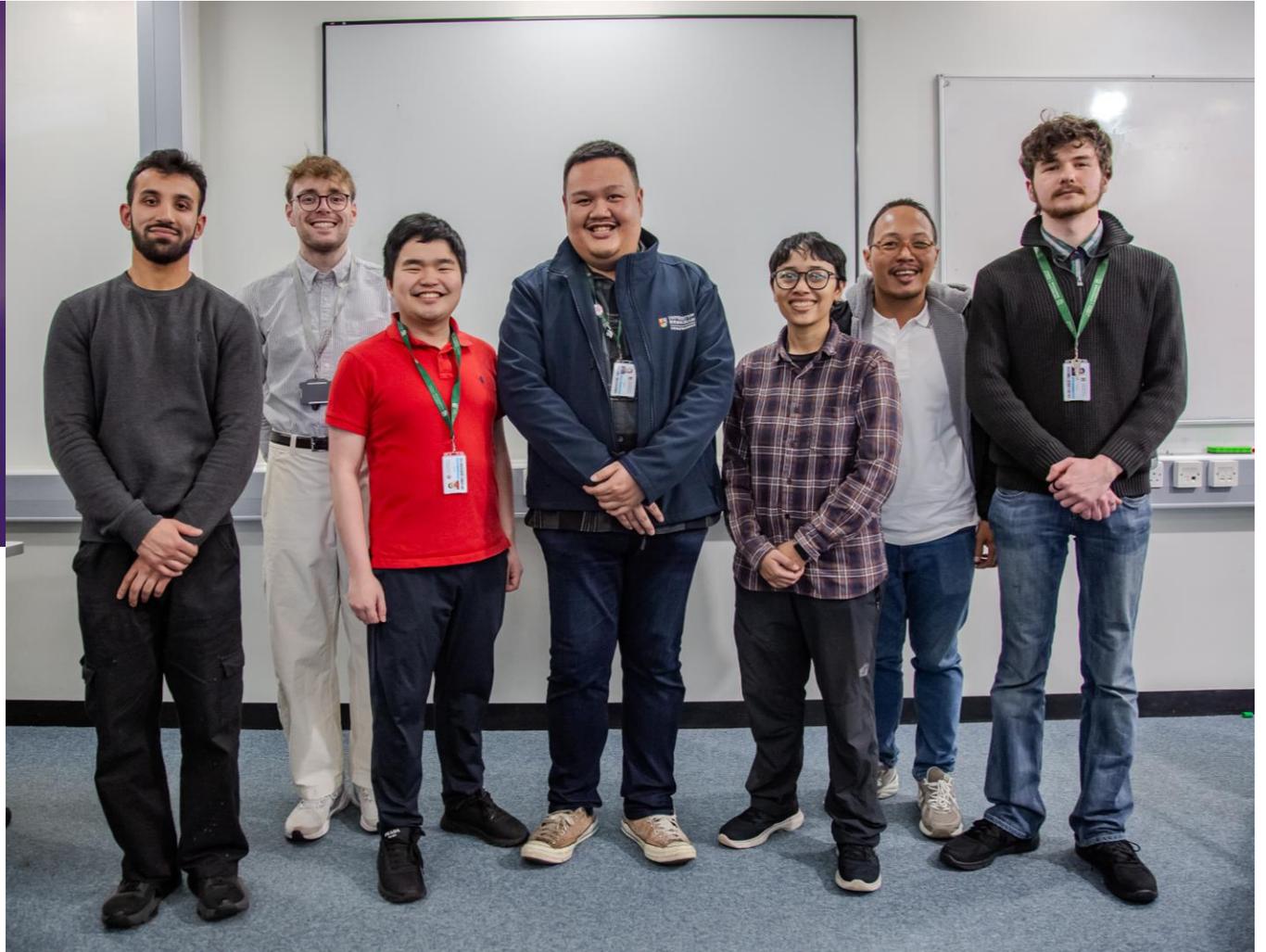


Action Medical Research
UK grant now put in.

Plan to put in more grant from ERC and/or other funders.



Nicolas Banerjee Martin to start in the Chan Lab in the summer 2026 to work on an M.Sc project on CRELD1.



CHANLAB

Our lab studies epilepsy as one of our research focus – see <https://www.chanlab.co.uk/> for more information.
E-mail: f.chan@bham.ac.uk