

NCBRS Worldwide Foundation

Genetics of the Nicolaides-Baraitser Syndrome (NCBRS)



Dr. Stephanie Efthymiou

NCBRS Worldwide Foundation
www.ncbrs.com

Registered Charity: 1190194



Me

Researcher / Geneticist
Molecular Biology
PhD in Neurogenetics

UCL Queen Square Institute of Neurology (since 2015)
<https://www.neurogenetics.co.uk/>



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What is DNA, gene, protein?

DNA is like a book of instructions written with the letters G, C, T and A

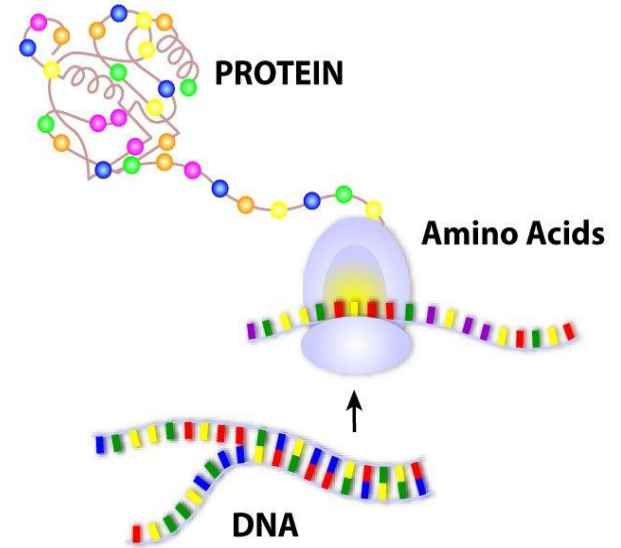
- unique to every individual

GENES are specific sequences of bases

- 20,000 in human

They encode instructions on how to make PROTEINS

- important to the structure, function, regulation of the body

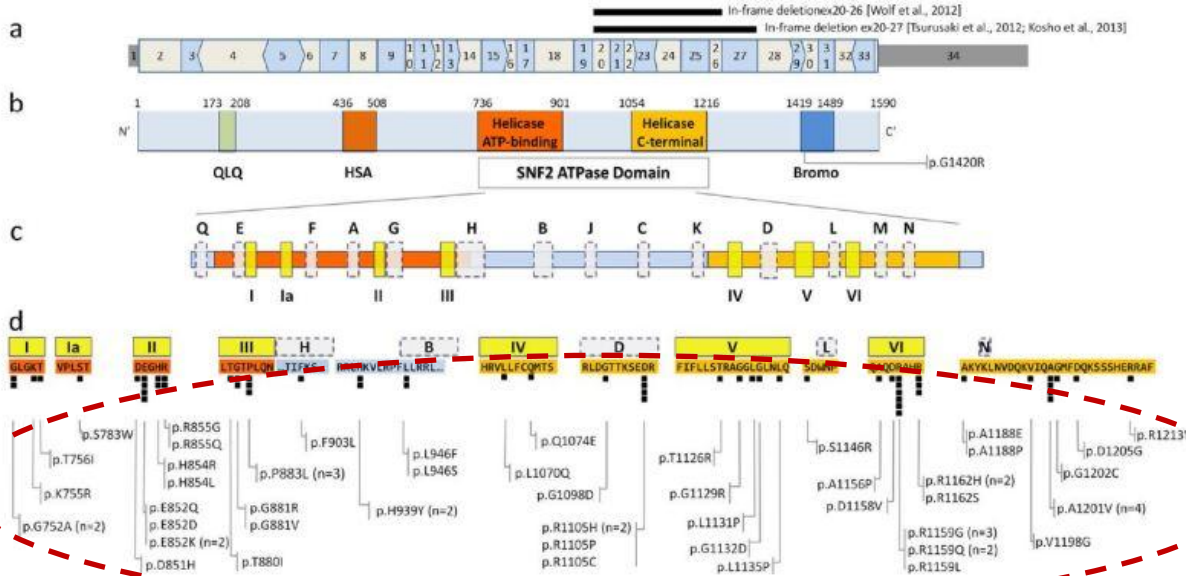


Heterozygous missense mutations in *SMARCA2* cause Nicolaides-Baraitser syndrome

Jeroen K J Van Houdt, Beata Anna Nowakowska, Sérgio B Sousa, Barbera D C van Schaik, Eve Seuntjens, Nelson Avonce, Alejandro Sifrim, Omar A Abdul-Rahman, Marie-José H van den Boogaard, Armand Bottani, Marco Castori, Valérie Cormier-Daire, Matthew A Dearnorff, Isabel Filges, Alan Fryer, Jean-Pierre Fryns, Simone Gana, Livia Garavelli, Gabriele Gillesen-Kaesbach, Bryan D Hall, Denise Horn, Danny Huylebroeck, Jakub Klapceki, Malgorzata Krajewska-Walasek, ... Joris Robert Vermeesch

✉ + Show authors

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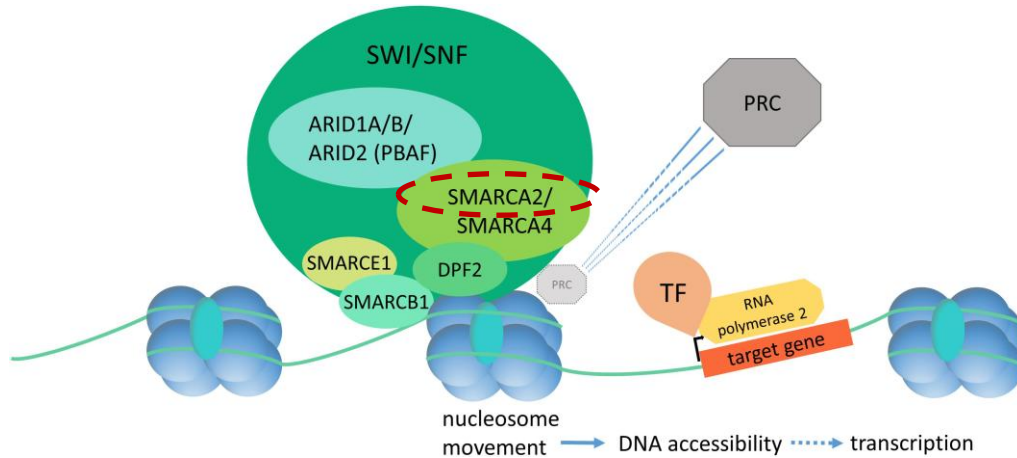
44 individuals

2012 thanks to new sequencing techniques, the gene was identified, **SMARCA2**

- part of the **BAF** or **SWI/SNF** complex
- important for gene transcription



SWI/SNF dependent chromatin remodeling



- Subunit of the complex
- regulates gene expression by chromatin remodeling
- Chromatin = how DNA gets packaged into chromosomes
- provides energy (ATP) for this process

NCBRS:

- altered protein interferes with the normal function of SWI/SNF complex
- complex becomes nonfunctional
- ~~chromatin remodeling~~
- alters the activity of genes → NCBRS symptom



Inheritance of SMARCA2

- autosomal dominant inheritance
(one copy of the altered gene is sufficient to cause the disorder)
- new (de novo) mutations in the
occur during the formation of reproductive cells (eggs or sperm) or in early
embryonic development
- occur in people with no family history of the disorder



Molecular diagnosis

Variant = a change in SMARCA2 gene
identified through a blood test (analysis of many genes simultaneously)

Previously reported pathogenic variants are located **from exon 15 to exon 25** (ATPase domain)
→ variants in *SMARCA2* most likely cause a dominant-negative or gain-of-function effect.

What does gain of function mean?

A gain-of-function mutation is a genetic variation that causes:

- 1) gene to be expressed inappropriately (at abnormally high levels and/or at the wrong time or location), or
- 2) to acquire a new abnormal function through alteration of the gene product itself.



Molecular diagnosis (cont)

- Patients with mutations in other BAF complex genes are diagnosed with Coffin-Siris syndrome (SMARCA4)
- Very rare for another family member to have NCBRS i.e. second affected child is extremely low
(Prenatal diagnosis to check future pregnancies)
- Parent with NCBRS has 50% chance that child will also have NCBRS



Patient registry and mutations

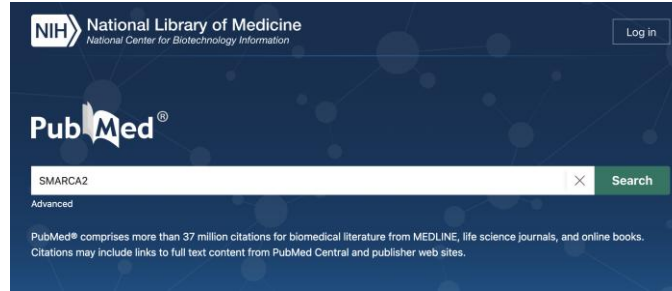
Patient registries can play an important role in:

- Recording the mutational spectrum of affected individuals
- Determining the incidence in defined populations
- Identifying persons for subsequent enrolment in case-control studies
- Studying the natural history of the disease
- Assisting in improving the quality of care and understanding healthcare burden.
- Monitoring the safety of medicines



NCBRS PATIENT REGISTRY

Enrolling in the NCBRS Patient Registry is a vital and effective way to a



Why is it important to record patients and their mutations?

Patient registries are organised systems that use observational methods to collect uniform data on a population defined by a particular disease/ condition over time



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Study outline



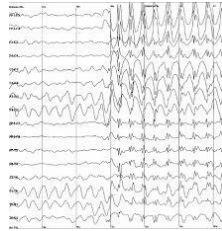
185 cases (81 previously reported, 104 new cases)



Family medical history



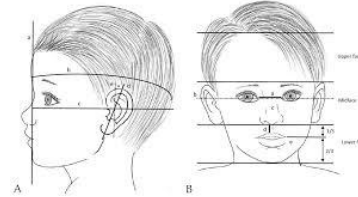
Genetic reports



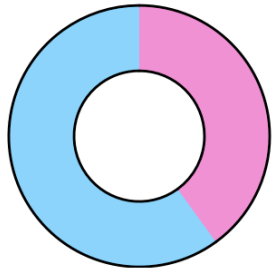
Epilepsy / EEG



Examination



dysmorphology



Gender distribution

40.00% 68 Female
60.00% 102 Male

Key phenotypic features:

- Global developmental delay
- ID severity breakdown
- Speech regression/absent speech
- Seizure occurrence and age of onset
- Craniofacial and skeletal features prevalence



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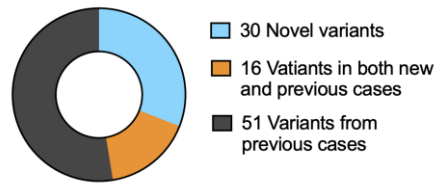
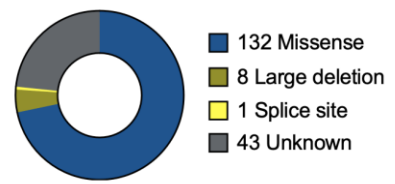
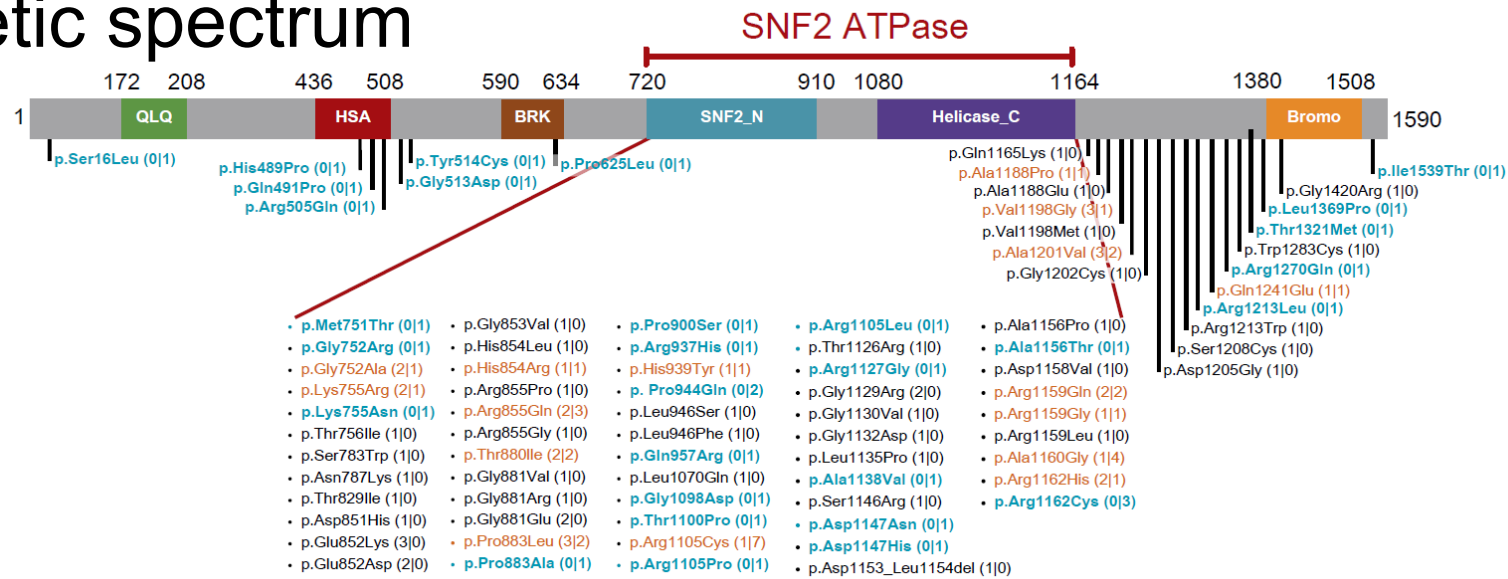
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Genetic spectrum



Total=97



Are Certain Variants More Severe?

ATPase variants vs non-ATPase variants

- Variant-dependent changes in chromatin accessibility
- BAF complex recruitment
- Neuronal outgrowth

Patient recruitment!

Please contact the UCL team (Dr Stephanie Efthymiou s.efthymiou@ucl.ac.uk)

1. Clarify emerging genotype–phenotype subtypes
2. Expand the diversity of molecular models
3. Accelerate the path toward targeted therapeutic testing



Why is it important for our foundation and our aims?

- To record which ones are more common within the SMARCA2 community
- To distinguish common variants (likely not disease-causing) from real pathogenic mutations
- To design research projects around the most detrimental or more common mutations (at first)
- To make correlations between specific variants and disease subtypes



Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been noted yet

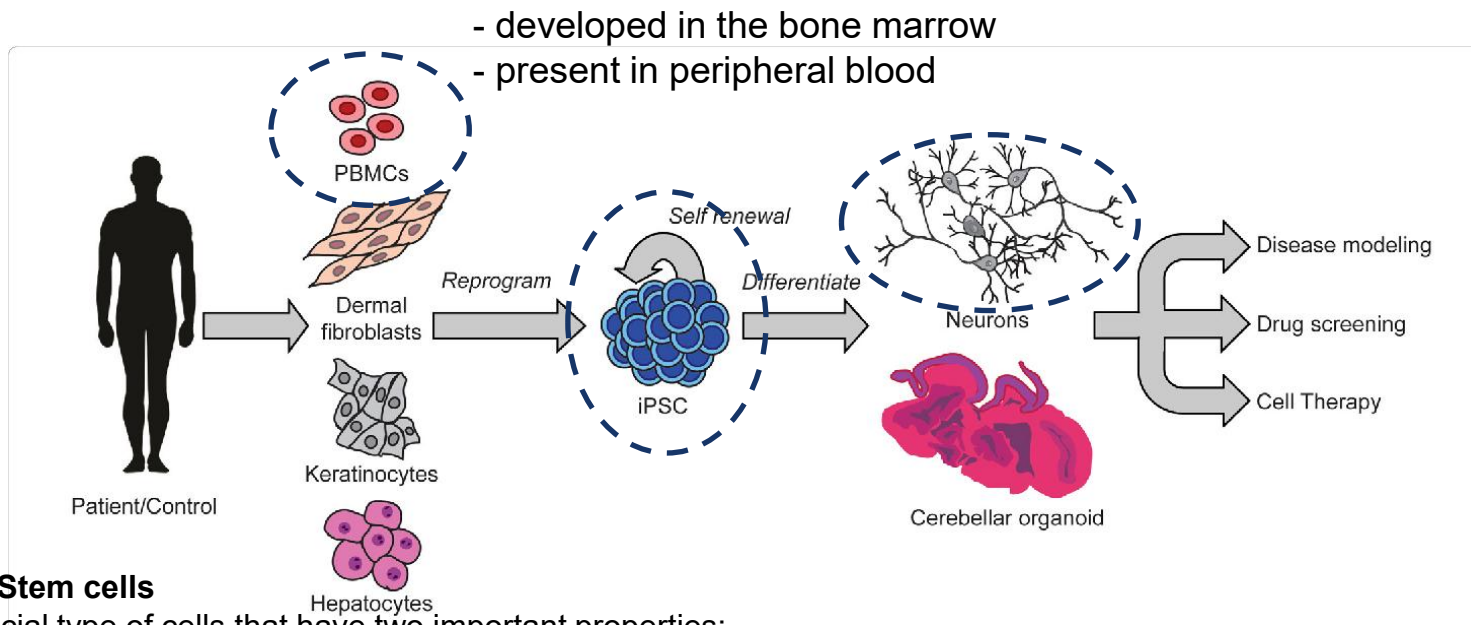
All individuals with a pathogenic variant within the C-terminal helicase region of the ATPase domain have severe intellectual disability and epilepsy – a frequency higher than that in individuals with pathogenic variants in other parts of the gene.



DNA banking is essential



Why we need your blood sample



iPSC / Stem cells

= a special type of cells that have two important properties:

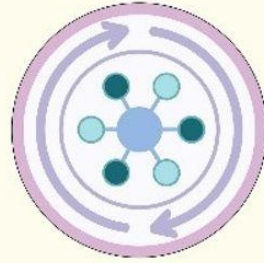
- 1) They are able to make more cells like themselves (self-renew)
- 2) They can become other cells that do different things (differentiation) e.g. neurons





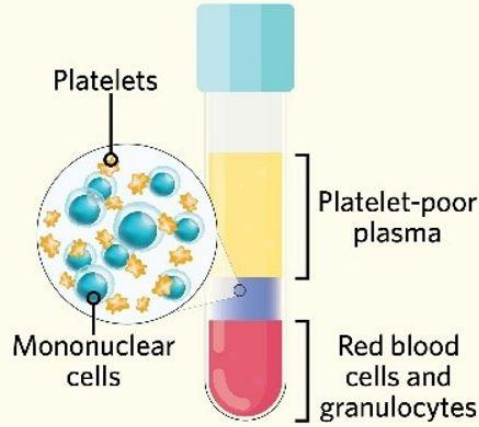
1

Blood collection
(leukapheresis)



2

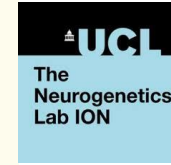
Continuous flow
centrifugation



3

Isolate PBMC
fraction

Lab procedure established and used in our UCL lab and ECACC
Cryostored in 2 locations for future studies



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Future research directions

1. SMARCA2 associated with minimal phenotypes in mice and rats (Reyes et al. 1998, Maher et al. 2023).

We need patient derived iPSC neuron models!

2. SMARCA2 heterozygous mutations act in a genetically dominant fashion, however it is not clear whether the mutations arise from a dominant gain or loss of function

Chromatin remodeling biochemical analysis is needed!

3. PROTAC based methods enable acute inhibition of remodelling enzymes

Test PROTAC-mediated degradation or domain-specific rescue in SMARCA2 models

4. Better facial analysis using AI tool **GestaltMatcher AI**

THANK YOU!

