

NCBRS Family Conference Murcia Spain, Nov. 2025

NCBRS Clinical Overview

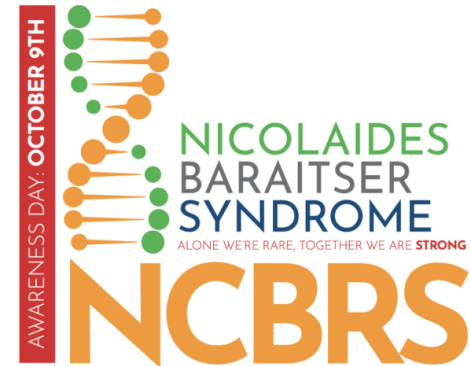
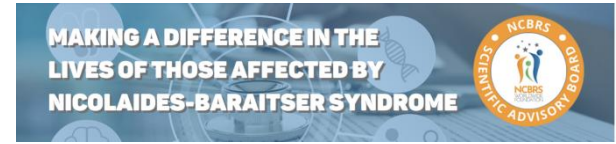
Paola Nicolaidis,
Consultant Paediatric Neurologist,
Clinical Professor, University of Nicosia Medical School

Co-chair of the Scientific Advisory Board
NCBRS Worldwide Foundation
www.ncbrs.com
Registered Charity: 1190194



Outline of today's talk:

- Introduction of the NCBRS Worldwide Foundation
- History of the NCBRS
- Clinical features
- Broader medical issues
- Therapies, interventions & multidisciplinary care
- Response to clinical questions
- The NCBRS Registry and CORDs



Introducing the NCBRS Worldwide Foundation

NCBRS WWF founded in 2016 USA Non-Profit Organisation

Mission: The NCBRS Worldwide Foundation is a nonprofit organisation that aims to support and educate families, carers and professionals who work with them.

Together we will work to promote awareness and understanding of the syndrome. We will advocate for scientific research that increases the medical knowledge of Nicolaides-Baraitser Syndrome and best treatments.



NCBRS WORLDWIDE FOUNDATION

WWW.NCBRS.COM | #NCBRS | #NCBRSRARE



NCBRS WORLDWIDE FOUNDATION
NICOLAIDES-BARAITSER SYNDROME

ALONE WE'RE RARE, TOGETHER WE ARE **STRONG**

Big Thanks to all the children and their families !!



Vision

To create a global community where families, healthcare professionals and researchers work together to ensure that every person diagnosed with Nicolaides-Baraitser Syndrome has every opportunity to reach their full potential.



What are the goals of the Foundation?

- To build on the existing NCBRS community
 - [Bring together all stakeholders involved with NCBRS](#)
 - [Families, Medical Professionals, Researchers and collaborators](#)
- Family support
 - [Allow families to meet/develop long-term relationships with others in same situation](#)
 - [To meet one to one with consultants and geneticists](#)
 - [To discuss main areas of concern/unmet needs and coping strategies](#)
- Awareness
 - [Help researchers and Medical professionals better understand the syndrome by meeting the families/children/adults with NCBRS](#)
- Drive Research
 - [Updates from Scientific advisory board](#)
 - [Talk about latest research ideas and research tools available](#)



Trustees of the NCBRS Worldwide Foundation!



Nuala Ryan

Chair of Trustees &
SAB Member



Lee Reavey

Co-Founder, CEO
& Trustee



Dr. Chui Fung Chong

Trustee &
SAB Member



Christine Mutena

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Scientific Advisory Board Members!



Dr. Paola Nicolaidis

Co-chair



Dr. Carine De Marcos

Co-chair



Dr. Stephanie Efthymiou

SAB Member



Dr. Jackelyn Orabone

SAB Member



Phyllis Reed

SAB Patient Advocate Member



Maria Chatztheodorou

SAB Patient Advocate Member



Connect with the NCBRS Worldwide Foundation!

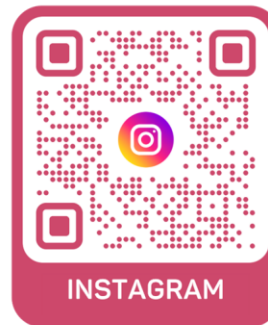
Email us at: contactus@ncbrs.com

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and important information.



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WEBSITE

Michael Baraitser

- Born in Cape Town, South Africa in 1937
- Studied Medicine and Agriculture at the University of Stellenbosch
- Emigrated to the UK 1970's as a Neurologist
- Studied Genetics in UK
- Appointed Consultant at the, Great Ormond St. Hospital for Children

Michael Baraitser



Michael Baraitser (right), with colleague Robin Winter (1950-2004)
Photo courtesy of London Medical Databases

- Wrote over 200 clinical papers, and several books with Robin Winter
- Founded London Dymorphology Club, the London Database series
- He was married for 50 years to Marion, playwright and publisher, has 4 children and 9 grandchildren



First patient described with NCBRS: 1993 (met at the age of 16 yrs)

June's story

- Born 9th October 1975, premature BW 1.8 kg, 7/52 in SCBU normal early development
- Speech delay (15 words) able to communicate her needs, sparse hair, erratic sleep, sensitive skin, myopia, scoliosis ongoing mobility problems
- Age 3 years developed seizures (focal onset, generalised, episodes of status epilepticus)
- Referred to Michael Baraitser Geneticist at GOSH for further investigations
- Mum described her life as a funfair, rollercoaster, “June was a very strong person in character and in spirit, enjoyed bowling country dancing, musicals, bird sanctuary, going to the pub and living and enjoying life to the fullest of her abilities.” June passed at the age of 34 years.



NCBRS

June's legacy...



A huge inspiration to all those who were fortunate to have known her



June would be saying to her NCBRS siblings

"Sure I had many of the symptoms, mostly at the severe end, but you know what? I have certainly enjoyed my time at the funfair of life!"



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What is NCBRS ?

Morin et al 2003 proposed the name **Nicolaides-Baraitser syndrome** after the authors of the 1993 article who **described** the earliest known person with NCBRS -

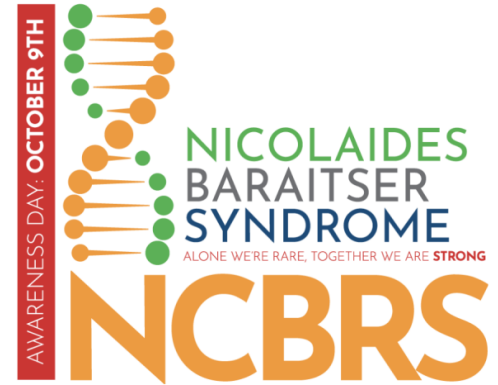
Ultra-rare genetic disorder /syndrome encompassing:

~300 cases worldwide

- developmental delay (inc. language disorder)
- intellectual Impairment
- sparse hair
- seizures (epilepsy)
- short stature, prominent interphalangeal joints
- characteristic facial features

Present at birth, affects males and females Usually recognised in childhood
Approximately 80 patients reported in the literature to date, around 300 worldwide

The physical features and medical problems associated with NCBRS may vary widely from individual to individual

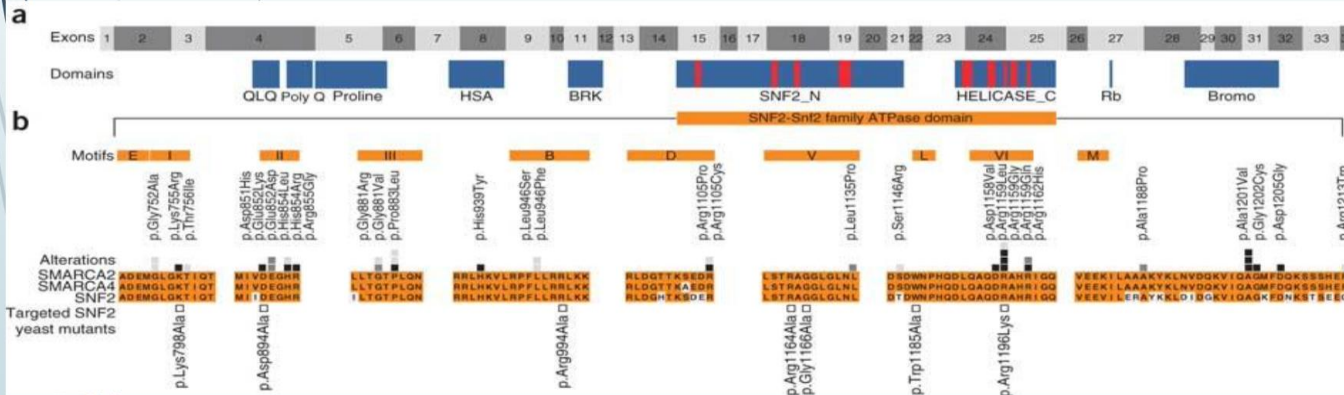
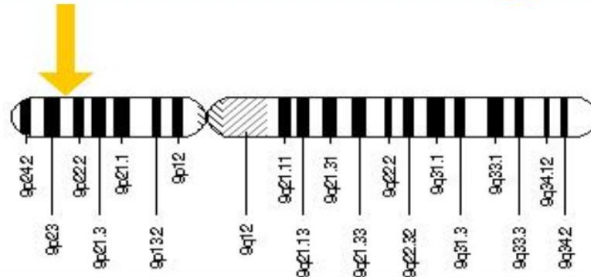


Why does it happen?

- Mutations /variants in the SMARCA2 gene, part of BAF chromatin remodelling complex
- involved in chromosome remodelling to allow gene expression
- helps activate genes that may otherwise be turned off
- plays an important role in neural development
- located on chromosome 9p24.3
- Chromosome analysis -normal karyotype in all patients



The SMARCA2 gene



<http://ghr.nlm.nih.gov/gene/SMARCA2>

Van Houdt JKJ et al. 2012. Heterozygous missense mutations in SMARCA2 cause Nicolaides-Baraitser syndrome. Nat Genet



How in NCBRS inherited?

- Autosomal dominant manner
- De novo SMARCA2 pathogenic variant
- No affected siblings have been reported (risk for siblings presumed higher than the general population due to possibility of germline mosaicism in a parent)
- Prenatal testing is possible if variant identified in an affected family member
- No familial cases are known except the molecularly proven monozygotic twins
- Parental consanguinity has not been reported



Diagnosis

- Blood test to sequence the SMARCA2 gene
- If new variant/ mutation is found, can check to see if parents carry the same one
- Sometimes, can incidentally diagnose NCBRS by checking all of the genes in the genome through exome test

Previously would rule out similar conditions, such as Coffin-Siris syndrome (has fifth finger underdevelopment)



Clinical features I

Face – Usually triangular in shape, dense eyelashes, prominent nose with thick nostrils, thin upper lip, full lower lip wide mouth

- facial characteristics become more pronounced with age,
- subcutaneous fat in cheeks decreases, making the skin sag and wrinkle



<http://www.ncbrs.com/our-stories/callum>



Clinical features II

Teeth - are widely spaced

- Delayed eruption of the baby and adult teeth

Hair - sparse scalp hair key sign of NCBRS

- all diagnosed cases
- The growth and texture is normal
- Over time the sparseness of the hair increases, while in others it decreases with time
- Facial hair is limited in adult male

Skin - Eczema and skin sensitivity 1/3



Clinical features III

Hands - as the child ages, the finger tips become broad and the joints become more prominent

Feet - sandal gaps

- Progressive thickening of the distal toe tissues especially at the 5th toe

Hearing loss uncommon (conductive type)

Vision: Myopia 16% and astigmatism 6.5%



American Journal of Medical Genetics Part C: Seminars in Medical Genetics
Volume 166, Issue 3, pages 302-314, 28 AUG 2014 DOI: 10.1002/ajmg.c.31409
<http://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31409/full#ajmgc31409-fig-0005>



Clinical features IV

Growth

45% have low birth weight

56% develop short stature

100% growth less than the 50th no evident disproportion



Microcephaly of variable degree

- 35% at birth and 82% later

Skeletal

Broadening of the distal phalanges develops over years

-Interphalangeal joints become more prominent

-Fingers may be shorter than average

-Arthritis is not present at a young age

-Scoliosis (curvature of back) was seen in 17/60 patients

-Hip dislocation is less common – 4/45 patients



Clinical features V

Hernias - groin and umbilical hernias are more common in individuals with NCBRS than the general population

Undescended testes - about 60% of boys, often requiring surgery

Scoliosis - < 1/3 of children ranging from mild to severe

Cardiac problems - (double aortic arch; mitral valve regurgitation; thick ventricular septum)

Vesico-ureteric reflux, mild dyslipidaemia,



Epilepsy

> 2/3 of patients

- Start on average around 1.6 years
- Range birth to 14 years, regression may be seen
- Generalised variable semiology (tonic- clonic, tonic, clonic, atonic, myoclonic, impaired awareness/complex partial
- Increasing seizures frequency in some patients despite multiple anti-seizure medications / intractable difficult to control seizures in some cases
- Seizures may become more refractory with age or disappear
- A co-occurrence of decreasing intellectual abilities with the onset of seizures has been noticed



Investigations

EEG

- Generalized spike wave discharge (41%)
- Slow background (41%)
- Focal slowing
- EEGs may not be significantly abnormal

Neuroimaging

- Most are normal
- Alteration of white matter
- Asymmetric ventricles
- Hippocampal sclerosis





Treatment

Pharmacological

- Valproic acid, levetiracetam, topiramate, oxcarbazepine,
- Not as common: clobazam, felbamate, lacosamide, phenytoin, zonisamide

Non pharmacological treatment

- Ketogenic Diet
- Vagal Nerve Stimulator
- Focal resection is seizure focus identified
- Corpus callosotomy

Epilepsy: Status Epilepticus (SE)

- A seizure that lasts longer than 30 minutes
- SE can occur with any type of seizure
- SE is very metabolically demanding on the body and the brain and can result in permanent brain damage and even death
- Must be treated emergently
- Diazepam, lorazepam, IV pheytoin, Levetiracetam, valproate



Development / Intellectual abilities

Development is an important concern for families and often acts as the first trigger for a medical assessment

- Degree of intellectual disability varies, reported numbers are mild (18%), moderate (36.1%), and severe (45.9%)
- Currently we are trying to see if gene variant /mutation can predict expected delay
- Speech can also range from absent (30%), limited, to conversational
- Speech decline may be related to seizure onset in some cases



How NBCRS may affect intellectual abilities....

One of the main Features

Deficits in IQ and adaptive functioning

- IQ less than 70
- Effective coping with common life demands
- Ability to meet standards of independence
- Difficulties adapting to new environments
- Difficulties with safety awareness, self-care and communication skills

Wide range:

- 45.9% severe (IQ 20 to 34)
- 36.1% moderate (IQ 35 to 49)
- 18% mild (IQ 50 to 70)



Behaviour

- Commonly individuals with NCBRS have behaviour difficulties including temper tantrums, episodes of aggression ? Language Level
- Autistic behaviours/ features
 - Short attention Span (inattention) ADHD
 - Sensitive to loud noises
 - High threshold for pain
- Oral Sensitivity (like Salty and Spicy foods)
 - Eating difficulties, much less common
 - Sleeping and night-waking difficulties



Autism Spectrum Disorders (ASD) and NCBRS

- Some reported children presented with autistic features although the diagnosis of ASD may not be formally made
- Mutations in BAF subunit genes have so far been linked to Coffin-Siris syndrome (CSS), Nicolaides-Baraitser syndrome (NBS), schizophrenia, and Autism Spectrum Disorder (ASD)
- Gana S. 2011 described two unrelated children with clinical features suggestive of NCBRS & ASD



Summary

NCBRS features	Reported patients
Small for gestational age	33.3%
Pre & post-natal microcephaly	23% pre, 65% post
Short stature	53.5%
Sparse hair	96.7%
Seizures	63.9%
Intellectual disability	Mild 18%, moderate 36%, severe 46 %
Interphalangeal joint prominence	84.7%
Speech delay	31.7% absent speech, 21.4% with speech decline
Behavioural changes	19 patients, hyperactivity, aggression
Hypospadias	2.8%, 1 patient
Cryptorchidism	58.8%
Scoliosis	28.3%

Variability in clinical manifestations in NCBRS. Reported patients from Sousa et al., 2014.



Management

Multidisciplinary approach to ensure all medical needs are addressed:

- Early interventional support to promote development
- Speech and Language Therapy
- Occupational /Physical Therapy
- School (additional educational needs)
- Parent Education: *help them become effective advocates “Expert” on their child*
- Seizure control -Paediatric Neurologist
- Strategies for behavioural modifications -Developmental Paediatrics
- Weight monitoring and optimise nutrition -Dietician



Language development in NCBRS

- Particularly limited
- At least 30% never develop speech
- Speech Delay first Words ~ 18 months
- Mostly use single words
- Lots of repetition and word approximation
- 15% initial words lost or significantly reduced later in life

-

In some patients the loss of speech coincided with 1st seizure

- Regression due to Autism spectrum disorders (ASD)



Speech and Language therapy

What are important skills to teach young children with ID and language delay?

- Communication skills
 - Allow the child to get their needs met
 - Replace maladaptive behaviours & engage in social interactions
- Non-verbal communication
 - Teaches that people's faces/bodies carry important information
- Interactive Play Skills
 - Teaches flexibility
 - Improves relationships
 - Replaces self-stimulatory behaviours



Motor Skills in NCBRS

- Majority achieve all the basic skills “ Sitting /Walking”
- Same sequence as in typical children but may be later
- Improve with practice
- Considerable individual variation in rates of progress
- Recreational skills vary
- Balance seems to be a particular difficulty relative to progress in general coordination and muscle strength
- In older individuals slowing down of movement has been reported



Physiotherapy

- May well not make children walk earlier
 - Assist in avoiding negative compensatory postures:
 - Turned out legs
 - Lordotic gait
 - Sitting with rounded back
 - Work on Balance and Coordination
- Consider Groups as they get older !




Occupational Therapy

Promote Independence

- Self care skills (feeding, dressing, etc.)
- Skills related to school performance
- Play and leisure skills

OT's work in conjunction with speech therapists and physiotherapists as there is overlap in their fields





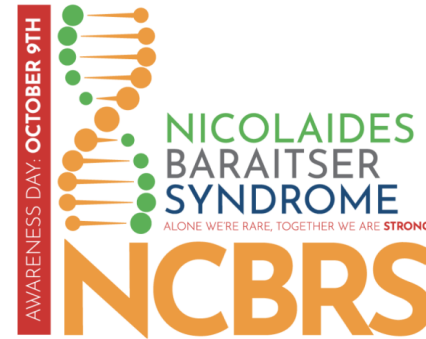
Use Whatever Works to Teach the Most Important Skills to each Individual child at the Given Time....

Social, Communication Skills and civil behaviour are the foundation to future social, emotional, cognitive, and. academic success



Looking Ahead: Research and Clinical Priorities

- Relationship of mutation type to predicted presentation of NCBRS
- Relationship to seizure onset or persistence to speech development
- Better understanding of SMARCA2 function to look towards developing targeted therapies



Questions from the audience

Together we create moments **NCBRS**

4th FAMILY MEETING
Nicolaides Baraitser Association
November 22-23, 2025
Fotana, Murcia

Text
Text
Text

www.nicolaidesbaraitser.es
Follow us on social media

WE LOOK FORWARD TO SEEING YOU!!

NCBRS

This year we celebrate the 10th anniversary of our association, born from the effort and unity of families. Although diagnosed cases are very few – only 25 confirmed cases in our country – we are a small but strong family, united by the desire to stay connected and to support each other for the benefit of all.

The **NCBRS syndrome** is a rare genetic disorder caused by a mutation in the **SMARCA4** gene. Understanding and studying it are key to improving diagnosis, care, and hope for those affected.

This family meeting allows us to get to know each other better, share experiences, and continue improving the quality of life of our children. It also promotes research and understanding of this still little-known syndrome.

THANK YOU FOR BEING PART OF OUR GREAT NCBRS FAMILY!

Collaborate **TOGETHER WE ARE STRONGER!**
Join us and help improve the future of people living with Nicolaides Baraitser Syndrome.

Saturday, November 22

10:30 - 11:00 Reception of families and registration
Welcome from the President of the Spanish Federation for Rare Diseases (FERER)
Online connection with families who cannot attend in person.

11:00 - 11:30 Opening of the event
Speech by **Helena Cruz**, President of the NCBRS Spanish Association.
Acknowledgements and presentation of the program.

11:30 - 12:30 Speakers:
• Dr. Paula Nicolaides, pediatric neurologist. She first described, together with Michael Baraitser, the syndrome that today bears their names (NCBRS).
• Dr. Stephanie Elftomina, biologist and neurogeneticist. She promotes research and support for families living with NCBRS
Q&A session

12:30 - 1:30 Speaker:
Dr. Juan Cuatrecasas, President of FERER
His dedication and work have been key to strengthening the network of associations within FERER of which we are members.
Q&A session

1:30 - 1:40 Closing of the parents' session.

11:00 - 1:40 Children's activities
Our little ones will enjoy a fun morning with workshops and activities coordinated by specialised instructors.

1:40 - 1:50 Family lunch.

1:50 - 1:70 Charity raffle
Ball of a Babolat tennis racket signed by Carlos Alcaraz.
Talk by José Luis Capitan "In love with Life"
Foreword to the President of FERER.

1:70 - 2:00 Afternoon family gathering and shared time.

2:00 - 2:30 Family dinner.

Sunday, November 23
NATIONAL NCBRS DAY

10:30 - 1:30 Morning family gathering.

1:30 - 1:40 Family lunch, farewell and closing of the event.



1 “Based on studies of older individuals affected by the syndrome, what might the future look like?”

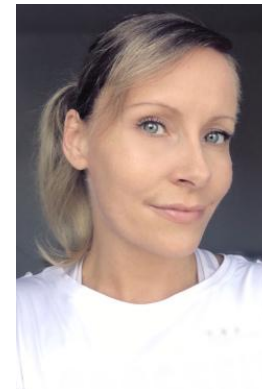
- Adults with NCBRS have been reported into their 20s–40s.
- No current evidence that NCBRS itself shortens life expectancy.
- Development is **stable** over time (non-degenerative).
- Epilepsy may become more stable or easier to manage with age.
- **Behaviour varies**: may settle in some, but can persist or worsen in others.
- Many individuals maintain **strong social interest and engagement**, even with limited speech.
- Lifelong challenges with. intellectual disability, limited expressive speech, fine-motor and coordination difficulties, ongoing support needs for daily living
- Only very severe medical complications (such as uncontrolled epilepsy or complex medical issues unrelated to NCBRS) have been reported to impact health

Call for Patients - Adult Study

Understanding Nicolaides-Baraitser Syndrome Beyond Childhood



Prof. Dr. med. Dagmar Wieczorek
Dagmar.Wieczorek@med.uni-duesseldorf.de



Dr. rer. nat. Svenja Daschkey
Svenja.Daschkey@med.uni-duesseldorf.de

Background: Adult Study on Nicolaides-Baraitser Syndrome

Background

- Advances in genetic sequencing have enabled the identification of many rare diseases.
- However, little is known about the clinical picture of rare genetic syndromes in adulthood.

Aim of the Study

- To systematically document and describe the clinical features of adults with Nicolaides-Baraitser syndrome.
- To improve understanding, medical care, and preventive options for affected individuals.

Study Design

- Conducted by the Institute of Human Genetics, University Hospital Düsseldorf.
- Approved by the local ethics committee.
- Participants and their physicians complete a detailed health questionnaire (~1 hour).
- No blood sampling

Data Protection

- Participation is voluntary.
- All data are pseudonymized and anonymized before publication.

How to Participate

Requirements for Participation

- Completed and signed questionnaire (to be filled in together with the supervising physician).
- Signed consent form from the patient or legal guardian.
- Separate consent regarding the use and publication of photographs (participation possible with or without this consent).

- **The results of the Adult Study are expected to be published next year.**
- **So far, 13 families agreed to participate.**

The group will be very happy to hear from interested participants.

Contact

Prof. Dr. med. Dagmar Wieczorek
Dagmar.Wieczorek@med.uni-duesseldorf.de

Dr. rer. nat. Svenja Daschkey
Svenja.Daschkey@med.uni-duesseldorf.de

2 “At what stage of cell function does SMARCA2 act? Does epilepsy cause brain damage? Is cancer a risk?”

- **SMARCA2** is part of the **SWI/SNF chromatin-remodelling complex**, which regulates how DNA is read and how genes turn on/off.
It is crucial during **early brain development** and continues to play a role throughout life.
- **Epileptic seizures in NCBRS:**
- Most seizures are **brief, self-limiting, and do not cause brain damage.**
- What causes harm is **very prolonged or uncontrolled seizures**, which is why management is important.
- **Cancer risk:**
- There is **no evidence** that SMARCA2 variants in NCBRS increase cancer risk.
- No cancer-related trend has been observed in the adult cohort.



3“Are there advanced clinical studies on glaucoma, scoliosis, epilepsy or behaviour?”

At present:

- **No disease-specific clinical trials** exist for NCBRS.
- Research is largely observational: registries, genetic studies, natural-history studies.

However:

- Children and adults with NCBRS benefit from **standard best-practice management** for glaucoma, scoliosis, epilepsy, and behavioural needs.
- Many centres share data internationally, which gradually strengthens understanding of patterns and risks.

4“Can seizures return later in life? What happened in June’s case?”

- In most individuals, **epilepsy improves with age**. Many become seizure-free.

However:

- Seizures **can** return under certain circumstances (illness, fever, puberty, medication changes, sleep deprivation).
- The case of June is **not typical**.

Sudden unexpected death in epilepsy (SUDEP) is extremely rare and most commonly associated with **uncontrolled epilepsy, night-time seizures, or very specific high-risk seizure types**.

- Families should be reassured that **the vast majority of individuals with NCBRS do not experience such outcomes**.

5 “Is there any reliable study on Coenzyme Q10 for NCBRS?”

No. There are:

- **No clinical trials**
- **No controlled studies**
- **No evidence** that CoQ10 improves development or behaviour in NCBRS.
- It is generally safe, but **there is no proven benefit**, and it should never replace evidence-based therapy.



Summary for families

- We currently don't have enough data on long-term life expectancy.
- Adults studied so far appear stable, with some improvement in behaviour or epilepsy.
- No evidence of increased cancer risk.
- Research is expanding, but gene therapy is not yet applicable.
- Best outcomes come from early intervention and ongoing support.
- Each person is unique, more adult data is needed to understand lifelong outcomes.

Patient Registry and Demographics

Speakers:

Nuala Ryan

Chair of Board Trustees/Scientific Advisory Board member
NCBRS Worldwide Foundation/Parent of a child with NCBRS
www.ncbrs.com

Dr. Jackelyn Orabone

Scientific Advisory Board member
NCBRS Worldwide Foundation/Parent of a child with NCBRS

Registered Charity: 1190194



The NCBRS Registry

Reasons for set up of the NCBRS Registry

- Understand Incidence/Severity
- Drive Connections between individuals
- Drive Research
- Drive Awareness
- Map out the Condition



Steps taken to set up the NCBRS Registry

Started simply!

- Excel tracker (family list) started by an NCBRS Family Volunteer in 2015
 - Documented name, locations, age, gender, guardian name.
 - Managed as members joined the Facebook private group through messenger.
 - Agreement to track/store/share on private FB page.
 - Process formalised through group registration form to collect data in 2022, including email contact and contact preferences.
- Process formalised through group registration form to collect data in 2022,
 - including email contact and contact preferences, genetic information.



Development of more detailed Registry

Why?

- Get more detailed information on clinical features
- Get more detailed information on genetic mutations/deletions
- Understand conditions that may arise as children get older to help drive care plans

Solution: CORDS – Why?

- Free of charge
- Patients own the data and ultimately control its use
- Ability to design our own questionnaire (track both genetic information and symptoms)
- Ability to update on yearly (or more) basis to keep information current



CORDS Rare Disease Registry via Sanford Research

- [Rare Disease Registry | Sanford Research](#)

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Coordination of Rare Diseases at
Sanford (CoRDS)



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Researcher Access
Form

Coordination of Rare Diseases at
Sanford (CoRDS)

Please log in

Enroll



nualaryan@outlook.ie



.....

CoR

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Frequently Asked
Questions

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Why Enroll in CORDS?



Broadens the scope of NCBRS data available to researchers



Anonymized data is available to all researchers, even if they aren't aware of the NCBRS Foundation/research

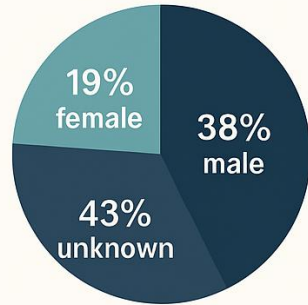


Remember, CORDS is a separate registry from **the NCBRS Foundation Patient Registry!**

CORDS Registry Data – Demographics Summary

TOTAL INDIVIDUALS ENROLLED (AS OF NOV 2024)

N = 126*



*As of 8 Oct, 151 carers/patients have completed the registry
20 enrolled in registry since 2024

 69% REPORT SEIZURES

 77% HAVE COMMUNICATION CHALLENGES

 70% HAVE FEEDING DIFFICULTIES

 34% REPORT SCOLIOSIS

BEHAVIORALLY, OVER 50% OF RESPONDENTS REPORTED INDIVIDUALS TO BE OVERLY FRIENDLY, ALWAYS SMILING, NOT AFRAID OF STRANGERS OR DANGER

