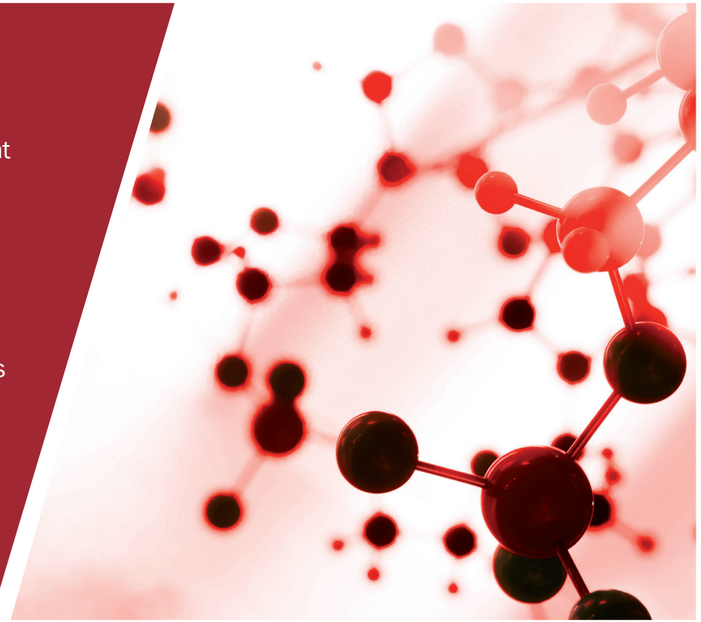
NIMNet® Epilepsy

A comprehensive genetic approach for the study of epilepsy

NIMGenetics
New Integrated Medical Genetics

Epilepsy and genetics

- Epilepsy is a disorder characterized by the presence of recurrent epileptic seizures. In recent years, causal genetic alterations have been identified in a significant and growing number of cases.
- Because epilepsy can occur as a result of a combination of multiple genetic factors that increase the risk of developing the disorder, or as a consequence of mutations in a single gene, its genetic diagnosis is complex.



NIMNet® Epilepsy

When is the genetic study of epilepsy indicated?

- Molecular confirmation of clinical diagnosis
- Optimization of the treatment and clinical management of the epileptic patient
- Identification of families that carry causal mutations

Is the patient´s epilepsy associated with a neurodevelopmental disorder or a polymalformative syndrome?

NO

YES

KaryoNIM® Array CGH

Unidentified causal variant

NIMNet® Epilepsy
A global approach based on NGS

NIMNet® Epilepsy
A comprehensive solution to the genetic study of epilepsy

From the sequencing of the complete exome, NIMGenetics offers an approach to diagnosis that adapts to clinical needs through directed and / or broad spectrum analysis.

ExoNIM® Targeted

Analysis targeted to defined epileptic syndromes

- CEE* of Early Onset and / or Infantile Spasms
- Nocturnal frontal lobe epilepsy
- Juvenile Myoclonic Epilepsy
- Progressive Myoclonic Epilepsy
- Generalized Epilepsy with Febrile Seizures Plus
- Focal Epilepsy
- Benign Familial Neonatal-Infantile Seizures
- Epilepsy associated with neurometabolic disorders

(*) Childhood Epileptic Encephalopathy.

ExoNIM® Plus Epilepsy

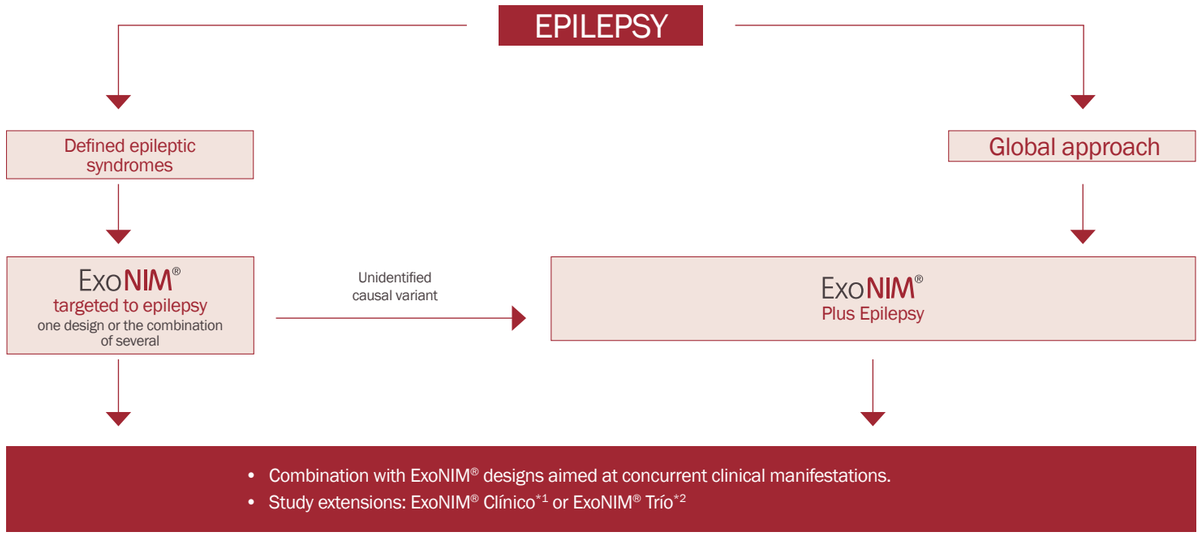
A broad spectrum approach

1. 223 genes previously associated with the development of this pathology.

2. It encompasses, in addition to the genes included in the ExoNIM® Targeted designs, the study of syndromic epilepsy and that associated with mitochondrial, lysosomal or neurometabolic disorders.

Selection of genes whose association with epilepsy is registered in the databases and / or in the current scientific literature.

NIMNet® Epilepsy
A global approach



From the most directed to the most extensive study, in stages or in a single step.
NIMGenetics offers you all the possibilities and advice you need.

(*1) An approach that studies more than 5,700 OMIM genes.
(*2) An approach based on the sequencing of probands and progenitors for the identification of the inheritance pattern of the variants identified in the patient.

NON-SYNDROMIC EPILEPSY	
Benign Familial Neonatal-Infantile Seizures	*KCNQ2, KCNQ3, PRRT2, SCN2A, SCN8A*
Childhood Epileptic Encephalopathy of Early Onset and / or Infantile Spasms	*AARS, ALDH7A1, ALG13, ARHGEF15, ARHGEF9*, ARX*, ATP6AP2*, CACNA1A, CACNA2D2*, CASK*, CASR, CBL, CDKL5, CHD2, CSNK1G1, DNM1, DOCK7, EEF1A2, FASN, GABBR2*, GABRA1, GABRB1, GABRB3*, GNAO1, GRIN1, GRIN2A, GRIN2B, HCN1, HDAC4, HNRNPH1, HNRNPU, IQSEC2*, KCNA2, KCNB1, KCNQ2, KCNT1, MAGI2*, MAPK10, MEF2C, MTOR, NEDD4L, NECAP1, OTC, PCDH19, PIGA*, PIGQ, PIGV, PLCB1, PNKP, PNPO, POLG, QARS, RYR3, SCN1A, SCN1B, SCN2A, SCN8A, SIK1, SLC12A5, SLC13A5, SLC25A12, SLC25A22, SLC2A1, SLC35A2*, SPTAN1, ST3GAL3, STXBP1, SYNGAP1*, SZT2, TBC1D24, TSC1, TSC2, WWOX, YWHAG*
Generalized Epilepsy with Febrile Seizures Plus	*SCN9A, ADGRV1 (GPR98), CHD2, CPA6, GABRA1, GABRB3, GABRD*, GABRG2*, HCN1, PCDH19, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, STX1B, STXBP1*
Myoclonic Epilepsy	**Infantile:** *BRAT1, TBC1D24* **Juvenile:** *CACNB4, CLCN2, EFHC1, GABRA1, GABRD* **Progressive:** *ASAH1, CERS1**, CSTB, EPM2A, GOSR2, KCNC1, LMNB2*, NHLRC1, PRDM8*, PRICKLE1, PRICKLE2, SCARB2, TBC1D24*
Focal Epilepsy (Autosomal Dominant)	**E. Focal and associate:** *GRIN2A, PRRT2, SCN1A, SCN1B, SCN3A* **E. Familial temoporal lobe:** *LGI1* **E. Nocturnal frontal lobe:** *CHRNB2, CHRNA4, CHRNA2, CRH, KCNT1* **E. Familial with variable foci:** *DEPDC5*

SYNDROMES ASSOCIATED WITH EPILEPSY	
Rett or Rett-like syndrome	*CDKL5, FOXG1**, MBD5, MECP2, MEF2C*
Angelman, Angelman-like and Pitt-Hopkins syndromes	*UBE3A, SLC9A6, MBD5, ATRX*, EHMT1, TCF4, NRXN1, CNTNAP2*
Mowat-Wilson syndrome	*ZEB2*

ExoNIM® Plus Epilepsy

SYNDROMES ASSOCIATED WITH EPILEPSY	
Neuronal ceroid lipofuscinoses	*PPT1, TPP1, CLN3, CLN5, CLN6*, MFSD8, CLN8, CTSD, DNAJC5, CTSF*, ATP13A2, GRN, KCTD7*
Alternating hemiplegia of childhood	*ATP1A2, ATP1A3*
EAST/SeSAME syndrome	*KCNJ10*
Epilepsy associated with mental retardation	*ATP6AP2, CASK, CLCN4, CNKSR2*, DYRK1A, EEF1A2, GABRB2, GALC, GATM, GRIN2A, GRIN2B, KANSL1, KCNJ11, MEF2C, OPHN1, PNKP, PPT1, RBFOX1, RBFOX3, SLC6A8, SNIP1, SPATA5, SRPX2, SYN1**
Epilepsy associated with cerebral malformations (lissencephaly, microcephaly, porencephaly, and/or cerebellar hypoplasia)	*ADGRG1 (GPR56), ARHGAP31, ARX, ASPM, CASK, CENPJ, COL4A1,COL4A2, DCX, DOCK6, EMX2, EOGT, FLNA, MCPH1, MTOR, NDE1, NOTCH1, OPHN1*, PAFAH1B1, QARS, RBPJ, RELN, SLC25A19, STIL, TSEN54*, TUBA1A, WDR62, ZEB2*
Channelopathies associated with neurological diseases	*KCNA1, KCNMA1, KCND2, KCNH5*

NEUROMETABOLIC / MITOCHONDRIAL / LYSOSOMAL EPILEPSIES	
Epilepsy associated with mitochondrial encephalomyopathy	*NDUFA1, NUBPL*, POLG2, POLG, POLG2, SURF1**
Epilepsy associated with lysosomal pathology	**Ceroid lipofuscinosis:** *ATP13A2, CLN3, CLN5, CLN6, CLN8, CTSD, CTSF, DNAJC5, GRN, KCTD7, MFSD8, PPT1, TPP1* **Gaucher syndrome:** *GBA, PSAP* **Sialidosis:** *NEU1*
Epilepsy associated with neurometabolic disorders	*ADSL, ABAT, AGA, ALDH5A1*, ALDH7A1*, ALG13*, AMT, ARG1, BCKDK, BTD, DPYD, FH*, FOLR1, GAMT, GCH1, GCSH*, GLDC*, GNE, L2HGDH, LIAS, MMACHC, MOCS1*, MTHFR, PDHA1*, PDHB*, PEX1, PGK1*, PHF6, PNPO, PRODH**, PTS , QDPR, SLC19A3, SLC25A15, SLC2A1, SLC46A1 , SLC6A8, ST3GAL5*, SUOX*

All the genes included in this approach have a 20× coverage greater than 99%, with the exception of 36 genes that have coverage of 90 – 99% * and 3 genes that have a coverage of 80 – 90% **

NIMNet® Epilepsy

Orientated to the diagnosis of epilepsy

SOLICITING ExoNIM® Targeted and ExoNIM® Plus Epilepsy

NECESSARY DOCUMENTATION:

1. Request form*
2. Informed consent*
3. Medical report

CONDITIONS OF SAMPLE SHIPPING:

Peripheral blood: 3–5 ml in EDTA

For other samples, please consult with our technical management.

NIMGenetics has extraction centers in all the countries where it operates.

Consult with the delegate or the central office.

* Available on our website or upon request to our delegates.

BIBLIOGRAPHY

Scheffer I.E., Berkovic S., Capovilla G., Connolly M.B., French J., Guilhoto L., Hirsch E., Jain S., Mathern G.W., Moshé S.L. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–521.

McTague A et al. Lancet Neurol. 2016 Mar;15(3):304-16.

Advantages of NIMNet® Epilepsy

1 **An integral solution** that allows two approaches:

- **A broad spectrum approach**, using ExoNIM® Plus Epilepsy.
- **The study of defined epileptic syndromes**, using ExoNIM® Targeted designs (combinable with each other).

2 **Great flexibility** based on the sequencing of the complete exome:

- **Addresses complex pathologies through combined analysis** of designs directed to the different signs and symptoms of the patient, together with designs associated with epilepsy.
- **Studies can be expanded,** by:
  - Inclusion of genes described after the initial analysis.
  - Conducting broad spectrum studies (ExoNIM® Plus Epilepsy, ExoNIM® Clinical o ExoNIM® Trio).

3 **Selection of genes with clinical relevance** that allows for genetic diagnosis and/or making decisions in a clinical context.

4 **Reports are interpreted in a clinical context.** This includes clinical recommendations in relation to the management of the patient, complementary confirmatory tests and studies of familial segregation.

NIMGenetics
New Integrated Medical Genetics

SPAIN

Parque Científico de Madrid
Faraday, 7 (Campus de Cantoblanco)
28049 Madrid
Ph. +34 91 037 83 54
M. +34 672 060 393

BRASIL

Rua Elvira Ferraz, nº 250, Cj. 211
Itaim - Sao Pauolo, SP.
CEP: 04552-040
Ph. +55 11 3044 1813

MÉXICO

World Trade Center
Montecito, 38 - Piso 35 - Oficina 10
Col. Nápoles - 03810 Ciudad de México
Ph. +52 55 68232076

PORTUGAL

Complexo Interdisciplinar da Universidade de Lisboa
Salas 2.12 e 2.14
Avenida Prof. Gama Pinto nº 2,
1649-003 Lisboa
Ph. +351 932 34 80 32

www.nimgenetics.com

La Suma de Todos

Comunidad de Madrid

NIMGenetics is a Genetic Diagnosis centre authorised by the Department of Health and Consumption of the Community of Madrid, registered in the corresponding Register under number CS 10673

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