Jornadas de Genómica Clínica

Jueves 27/10 y viernes 28/10/2022

Aula 1403, Pabellón Cero+Infinito, Ciudad Universitaria, CABA

Facultad de Ciencias Exactas y Naturales - UBA.

Genómica en la Práctica Neurológica del HEC

CRISTIAN R. CALANDRA
Especialista en Neurología
Hospital El Cruce

- "(…)next generation sequencing (NGS) is transforming the practice of medicine, including neurology".

- "It may seem tempting for the clinician (…) to consider this technology to be the magic bullet, and in many ways it can be. (…) challenges and complexities of interpretation that the **clinician** has to be fully aware of and that require not only genetic but also **clinical expertise**, perhaps more so than ever before".

- Neurol Genet 2015;1:e13; doi: 10.1212/NXG.0000000000000019

- “(…) “pre-test” deep phenotyping, NGS, and “post-test” clinical plausibility checking, the potential outcomes of NGS for the clinician include:
  - (1) genetic diagnosis confirmed, as suspected;
  - (2) genetic diagnosis confirmed, but not as suspected;
  - (3) incomplete genetic diagnosis in a highly suspected gene, such as a missing second pathogenic allele in a recessive disease;
  - (4) genetic variants of unknown significance (VUS) in more than 1 gene, which are possibly causative; and
  -

Neurol Genet 2015;1:e13; doi: 10.1212/NXG.0000000000000019

- “ (…) Familial segregation testing (…) and additional phenotyping may help shed light on the interpretation of these variants.(…) one of the most important steps in clinical validation (…) can only be **pursued by the clinician**, frequently requiring **considerable additional effort”.**

- “Collaborating with **geneticists and translational scientists**

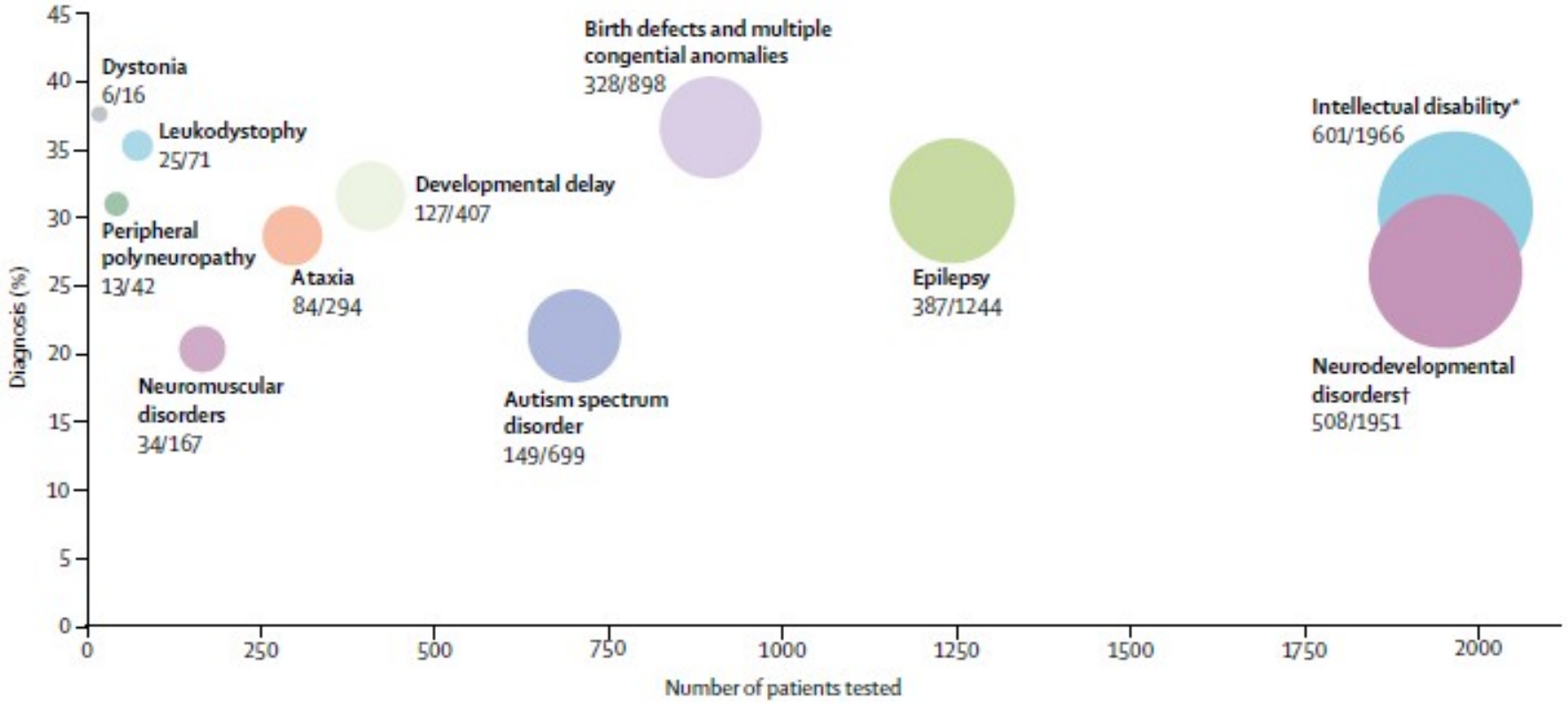
Neurol Genet 2015;1:e13; doi: 10.1212/NXG.0000000000000019

- “It is not the gene alone that makes a diagnosis but the entirety of the clinical phenotype and genotype. If “potentially damaging” variants are found in a gene that does not seem to fit with the patient’s phenotype, then this should not be the unchallenged diagnosis, unless it constitutes a considerable expansion of the phenotypic spectrum associated with the gene, which requires substantial additional proof “.

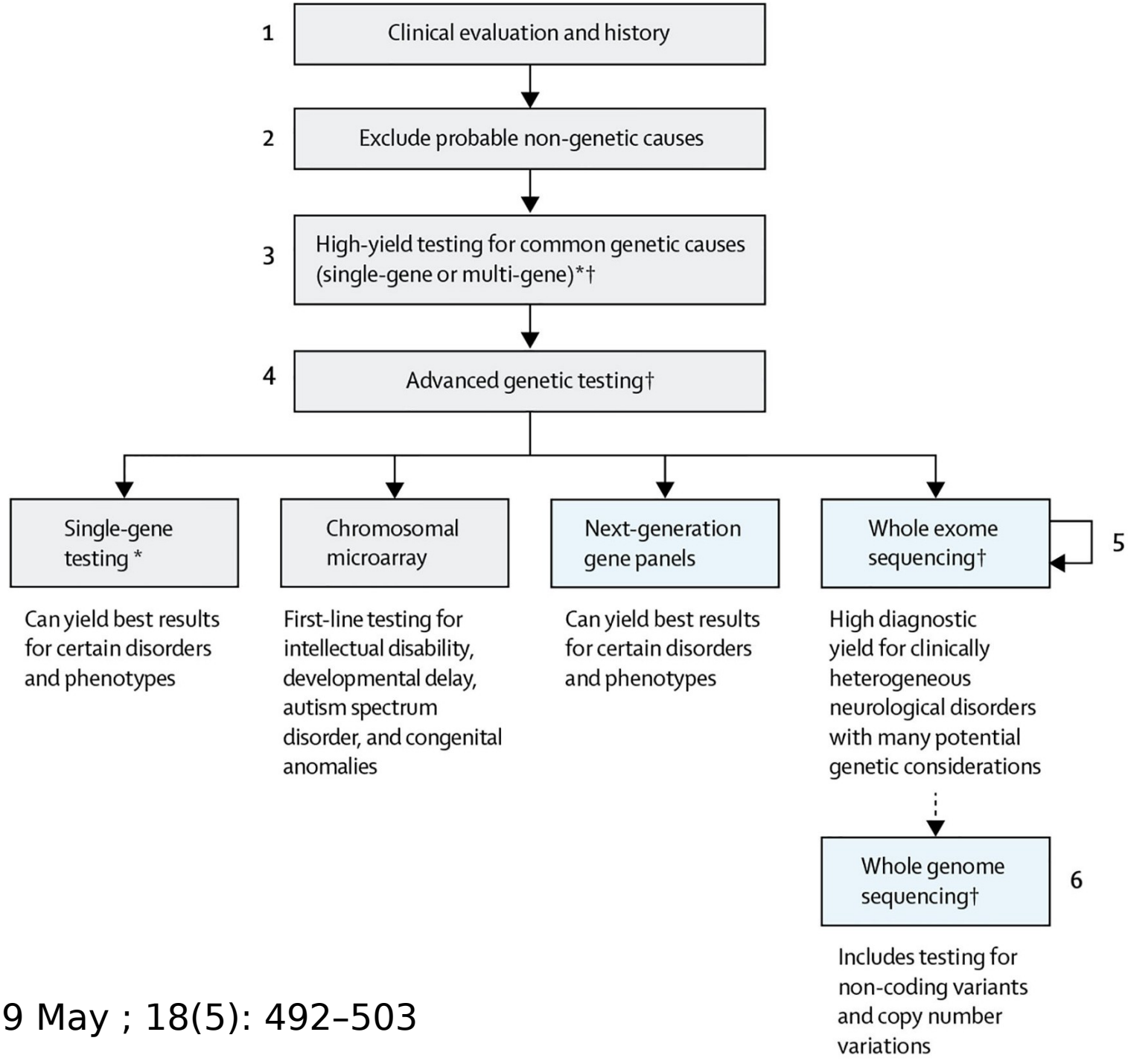
Neurol Genet 2015;1:e13; doi: 10.1212/NXG.0000000000000019

Clinical application of next-generation sequencing to the practice of neurology

Jessica Rexach, Hane Lee, Julian A Martinez-Agosto, Andrea H Németh, Brent L Fogel

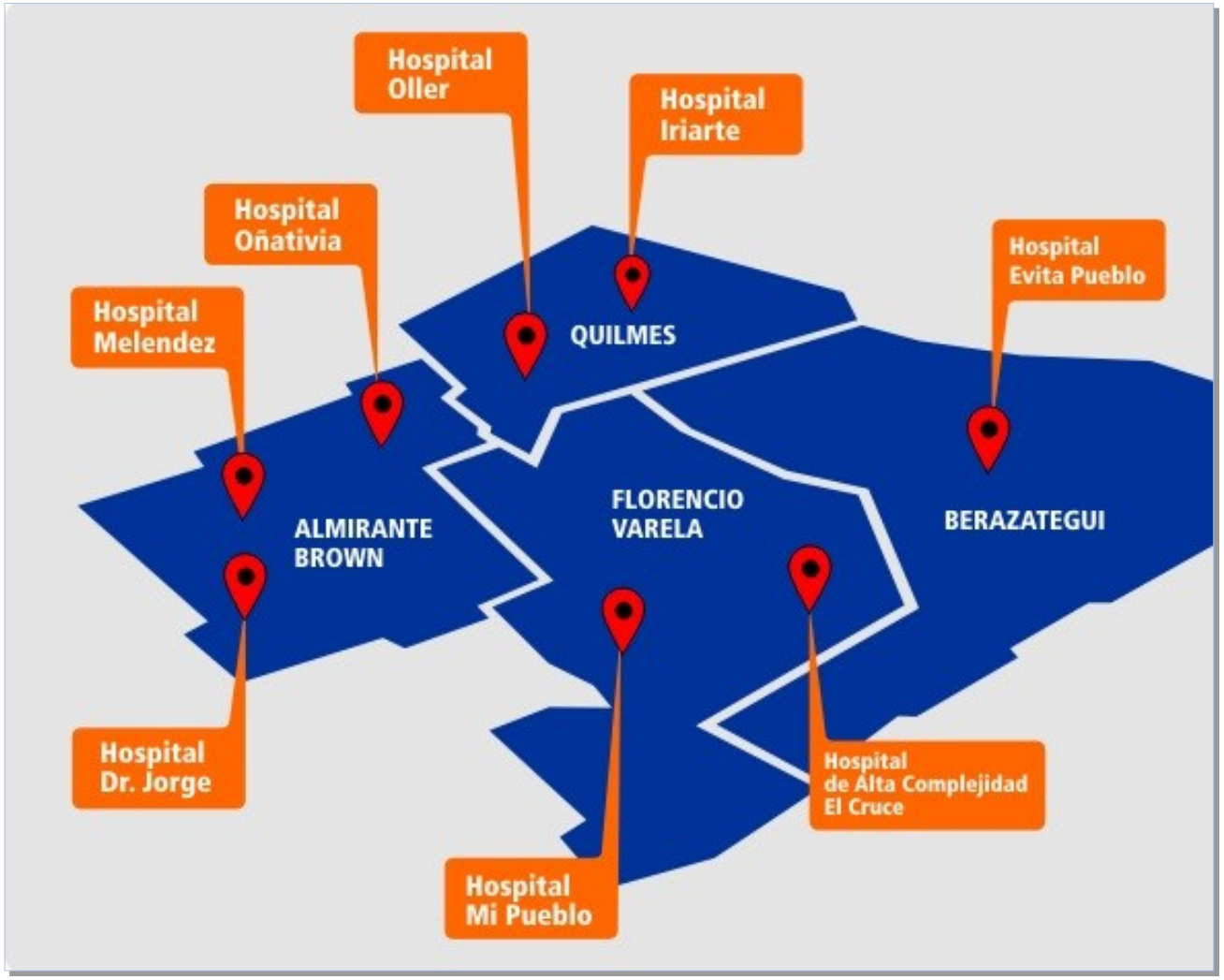


Lancet Neurol. 2019 May ; 18(5): 492–503

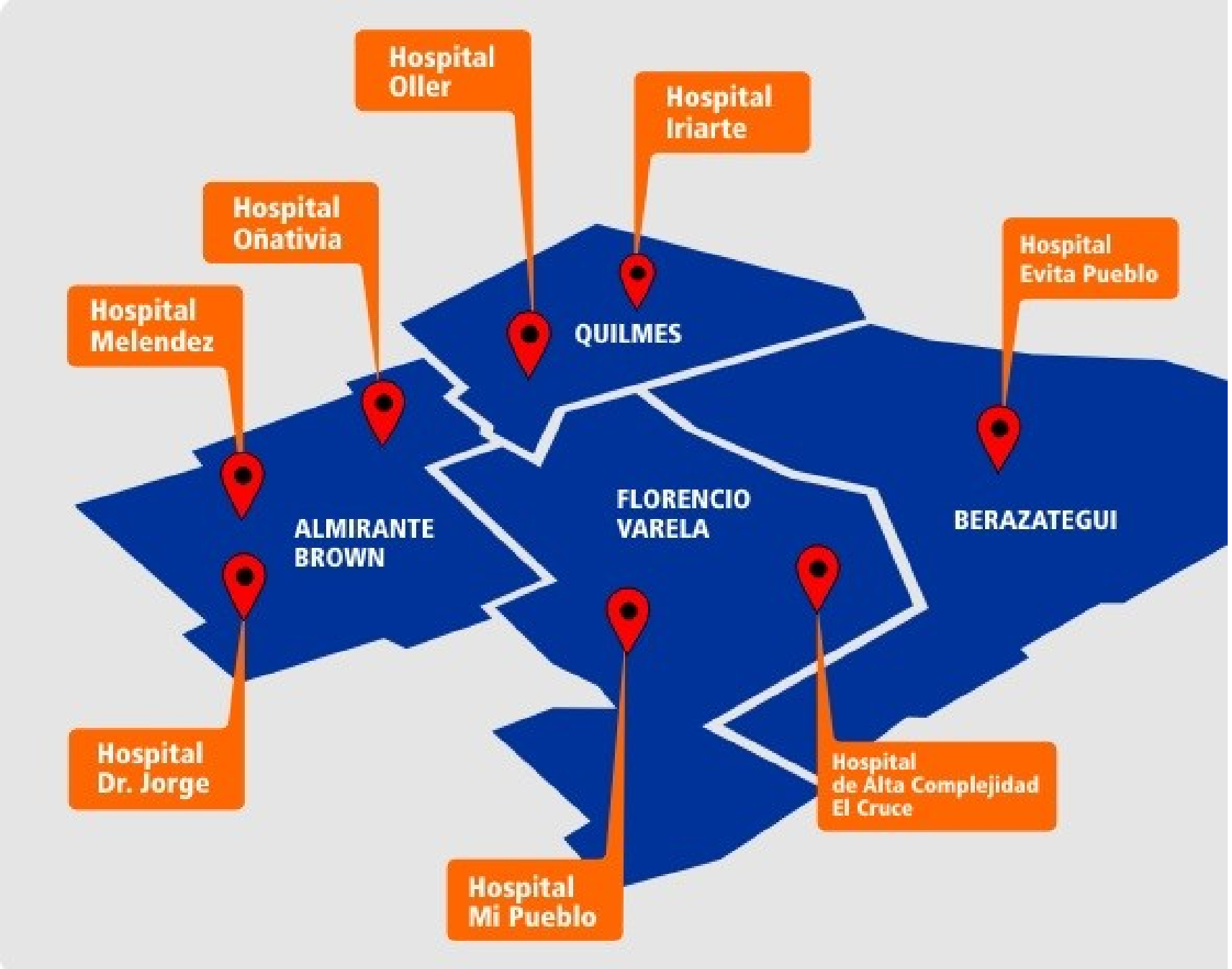


Lancet Neurol. 2019 May ; 18(5): 492–503

Red Sudeste de Hospitales Públicos

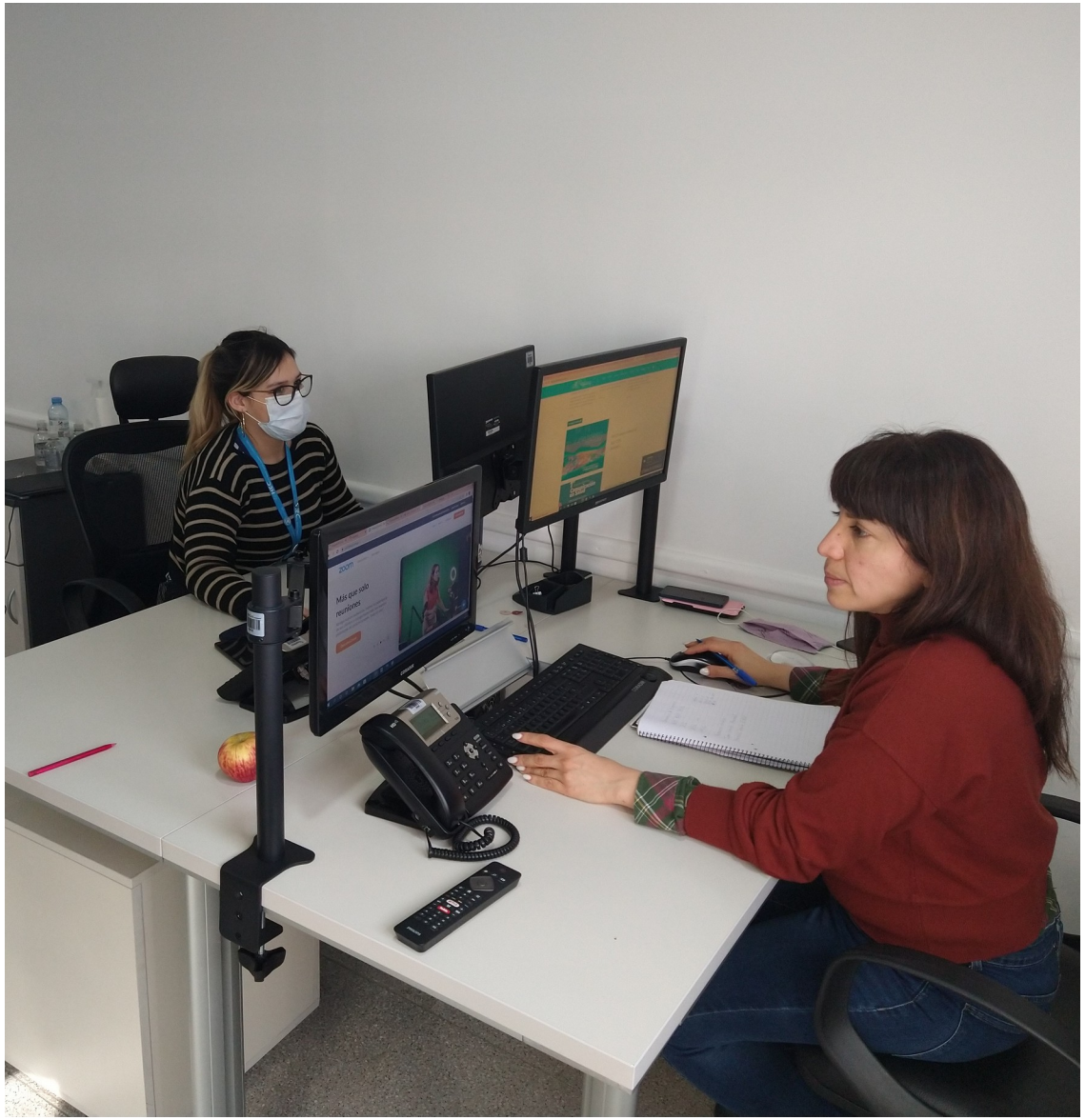


- Auditoría médica de las derivaciones
  - Área de Gestión de Pacientes
- Conurbano Sur:
  - Lomas de Zamora
  - Lanús
  - Avellaneda
  - Esteban Echeverría
- Otros Partidos Bs. As. y Provincias argentinas

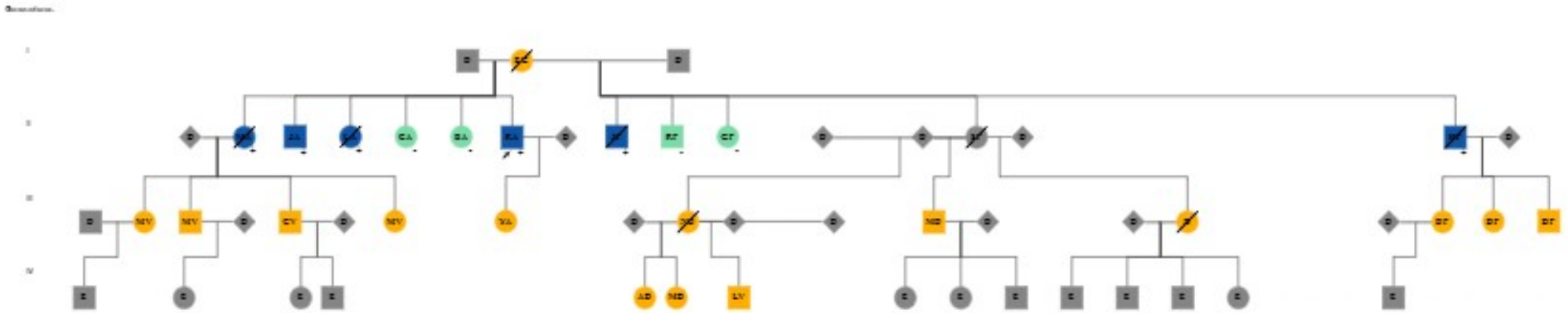


Censo 2010

- Florencio varela 146.704 hab.
- Berazategui 324.244 hab.
- Almirante Brown 552.902 hab.
- Quilmes 582.943 hab.


zoom
Más que solo reuniones


Telemedicina
Conocimiento
Gestión
Salud
ALTA COMPLEJIDAD EN RED
Hospital El Cruce
Dr. Néstor Carlos Kirchner



- Optimizar el relevamiento familiar:
  - ✓ Familias grandes de localidades distantes
  - ✓ Brindar consejo genético
  - ✓ Conexión simultánea con familiares de diferentes localidades

Consultorio de Telemedicina


NEREIDAS R
2022

Genómica y Neurología en el Hospital Público

- Recursos humanos
  - Neurólogo
  - Genetista
  - Bioinformáticos
  - Bioquímicos
- Sector administrativo
- Recursos físicos
  - Secuenciador
  - Laboratorio
  - Estudios de alta complejidad
  - Múltiples disciplinas y especialidades médicas
-

Financiadores de NGS en Consultorio Neurología HEC

- Campaña 100 exomas
  - Bitgenia-FCEyN UBA
- Industria farmacéutica
  - Enfermedad de Pompe
  - Enfermedad de Fabry
  - Enfermedad de Gaucher
  - Niemann-Pick tipo C
  - Lipofuscinosis Ceroidea Neuronal 2
  - Enfermedad de Duchenne
  - Atrofia Muscular Espinal
  - Amiloidosis Hereditaria TTR
  - Trastornos del ciclo de la Urea
  - Defectos de la beta oxidación
  -

- Hospital El Cruce
- Hospital Ramos Mejía
- Hospital Garrahan
- Laboratorios multinacionales de genómica
- Obras sociales/prepagas
-

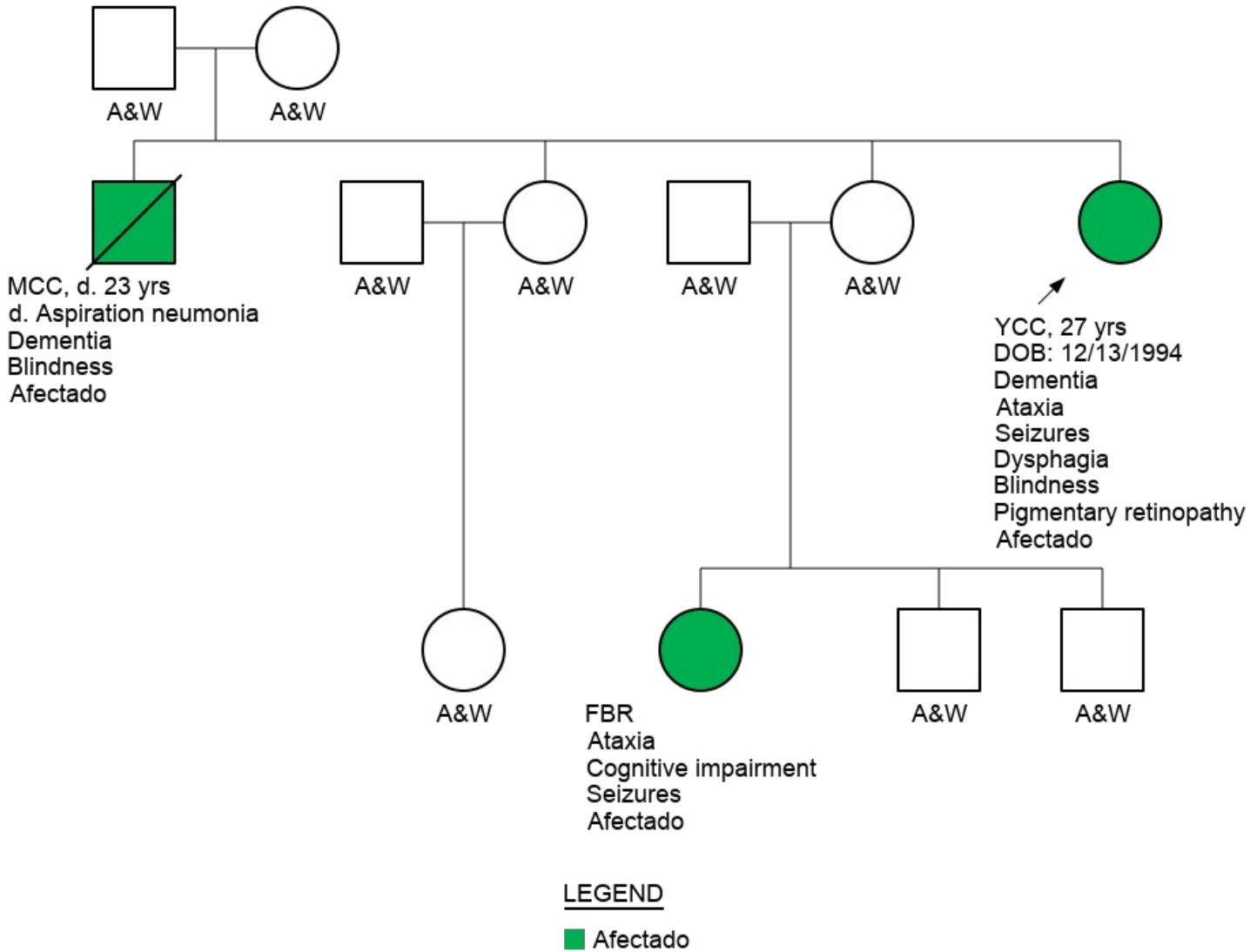
Programa Patrocinado

- Paneles
- Leucodistrofias y Leucoencefalopatías Genéticas
  - 728 genes
- Enfermedades Neuromusculares
  - 230 genes
- Distrofias musculares
  - 60 genes
- Enfermedades Lisosomales
  -

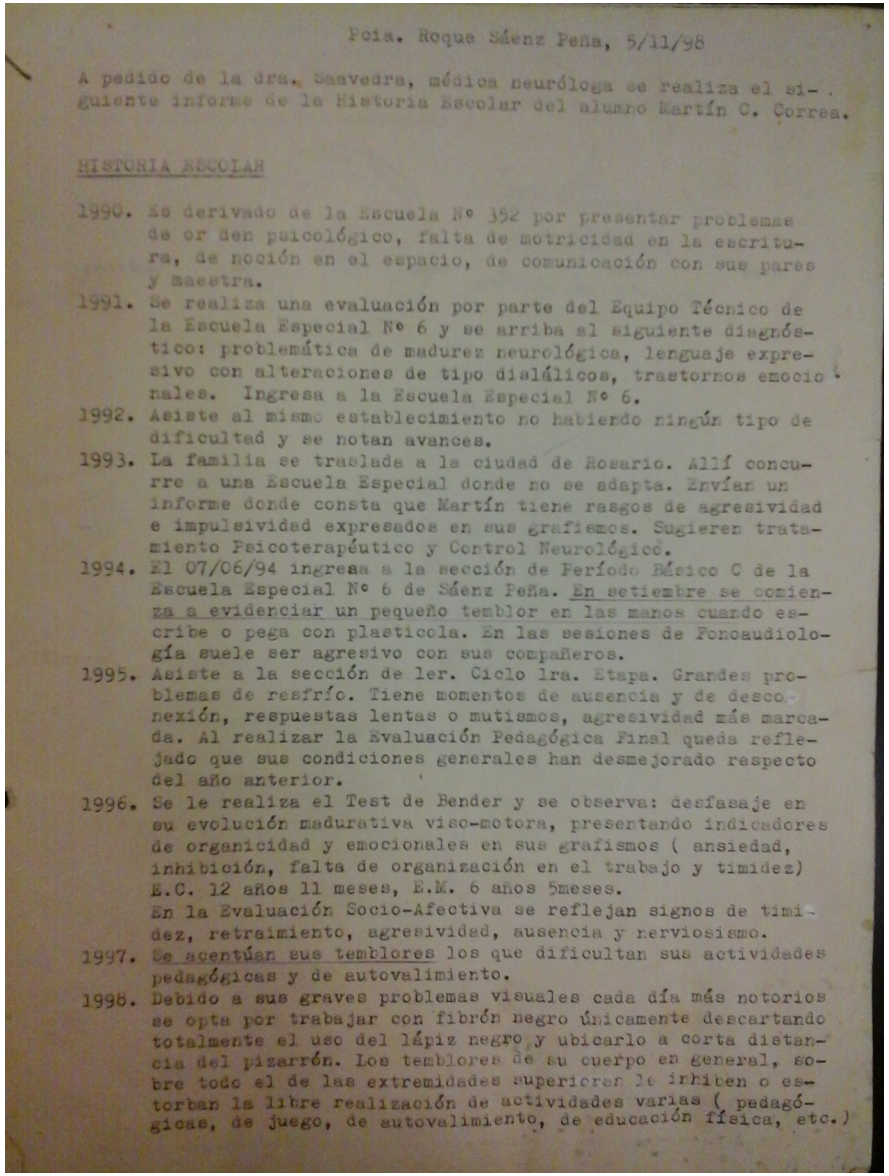
- Resultados en 3-4 semanas
- Resolución de VUS
- Resultado (+)
  - Test a familiares
- Resultado (-)
  - Re-requisition
- Comunicación fluída

Resultados preliminares

- 13/04 → 07/08/2022 = 17
- 9 pacientes (+)
  - Adrenoleucodistrofia (ABCD1) (1)
  - Déficit sistémico de carnitina (SLC22A5) (1)
  - CLN2 (TPP1) (2)
  - Enfermedad de Alexander (GFAP) (1)
  - HDLS (CSF1R) (1)
  - Miopatía relacionada ACTA-1 (2)
  -
- 4 pacientes probable
  - Aicardi (RNASEH2B)
  - MCAD (ACADM)
  - Batten (CLN3)
  - Alexander (GFAP)
-


A&W
A&W
MCC, d. 23 yrs
d. Aspiration neumonia
Dementia
Blindness
Afectado
A&W
A&W
A&W
A&W
YCC, 27 yrs
DOB: 12/13/1994
Dementia
Ataxia
Seizures
Dysphagia
Blindness
Pigmentary retinopathy
Afectado
A&W
FBR
Ataxia
Cognitive impairment
Seizures
Afectado
A&W
A&W
LEGEND
Afectado

Historia Escolar MCC



Pcia. Roque Sáenz Peña, 5/11/98

A pedido de la dra. Saavedra, médica neuróloga se realiza el siguiente informe de la Historia Escolar del alumno Martín C. Correa.

HISTORIA ESCOLAR

1990. Se derivado de la Escuela Nº 352 por presentar problemas de or den psicológico, falta de motricidad en la escritura, de noción en el espacio, de comunicación con sus pares y maestra.

1991. Se realiza una evaluación por parte del Equipo Técnico de la Escuela Especial Nº 6 y se arriba al siguiente diagnóstico: problemática de madurez neurológica, lenguaje expresivo con alteraciones de tipo dislálicos, trastornos emocionales. Ingresa a la Escuela Especial Nº 6.

1992. Asiste al mismo establecimiento no habiendo ningún tipo de dificultad y se notan avances.

1993. La familia se traslada a la ciudad de Rosario. Allí concurre a una Escuela Especial donde no se adapta. Envían un informe donde consta que Martín tiene rasgos de agresividad e impulsividad expresados en sus grafismos. Sugieren tratamiento Psicoterapéutico y Control Neurológico.

1994. El 07/06/94 ingresa a la sección de Período Básico C de la Escuela Especial Nº 6 de Sáenz Peña. En setiembre se comienza a evidenciar un pequeño temblor en las manos cuando escribe o pega con plasticola. En las sesiones de Fonoaudiología suele ser agresivo con sus compañeros.

1995. Asiste a la sección de 1er. Ciclo 1ra. Etapa. Grandes problemas de resfrío. Tiene momentos de ausencia y de desconexión, respuestas lentas o mutismos, agresividad más marcada. Al realizar la Evaluación Pedagógica Final queda reflejado que sus condiciones generales han desmejorado respecto del año anterior.

1996. Se le realiza el Test de Bender y se observa: desfasaje en su evolución madurativa viso-motora, presentando indicadores de organicidad y emocionales en sus grafismos (ansiedad, inhibición, falta de organización en el trabajo y timidez) E.C. 12 años 11 meses, E.M. 6 años 5meses.
En la Evaluación Socio-Afectiva se reflejan signos de timidez, retraimiento, agresividad, ausencia y nerviosismo.

1997. Se acentúan sus temblores los que dificultan sus actividades pedagógicas y de autovalimiento.

1998. Debido a sus graves problemas visuales cada día más notorios se opta por trabajar con fibrón negro únicamente descartando totalmente el uso del lápiz negro y ubicarlo a corta distancia del pizarrón. Los temblores de su cuerpo en general, sobre todo el de las extremidades superiores le inhiben o estorban la libre realización de actividades varias (pedagógicas, de juego, de autovalimiento, de educación física, etc.)

- **1990:** *“…derivado por problemas psicológicos, de la escritura, y comunicación…”.*
- **1991:** *“…diagnóstico: trastornos madurez neurológica, expresivo, y emocionales…”.*
- **1993:** *“…agresividad e impulsividad expresados en sus grafismos…”.*
- **1994:** *“…temblor al escribir o pegar con plasticola…agresividad con compañeros…”.*
- **1995:** *“…momentos de ausencias, desconexión, respuestas lentas o mutismo, agresividad más marcada…”.*
- **1996:** *“…Test de Bender: desfasaje evolución madurativa visuo-motora… indicadores de organicidad y emocionales en sus grafismos…Edad cronológica 12 años y 11 meses, edad madurativa 6 años y 5 meses…”.*
- **1997:** *“acentúan sus temblores…”.*
- **1998:** *“…graves problemas visuales cada día más notorios…trabajar con fibrón*

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
TPP1	c.1340G>A (p.Arg447His)	heterozygous	PATHOGENIC
TPP1	c.196C>T (p.Gln66*)	heterozygous	PATHOGENIC

TPP1, Exon 11, c.1340G>A (p.Arg447His), heterozygous, PATHOGENIC

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 447 of the TPP1 protein (p.Arg447His).
- This variant is present in population databases (rs119455956, gnomAD 0.002%).
- This missense change has been observed in individual(s) with neuronal ceroid lipofuscinosis (PMID: 10330339, 20340139). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant. It has also been observed to segregate with disease in related individuals.
- ClinVar contains an entry for this variant (Variation ID: 2645).
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is expected to disrupt TPP1 protein function.
- Experimental studies have shown that this missense change affects TPP1 function (PMID: 20340139).
- For these reasons, this variant has been classified as Pathogenic.

TPP1, Exon 3, c.196C>T (p.Gln66*), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Gln66*) in the TPP1 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in TPP1 are known to be pathogenic (PMID: 10330339).
- This variant is present in population databases (rs759080581, gnomAD 0.003%).
- This premature translational stop signal has been observed in individuals with neuronal ceroid lipofuscinosis (PMID: 10330339, 23266810).
- ClinVar contains an entry for this variant (Variation ID: 207564).
- Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- For these reasons, this variant has been classified as Pathogenic.

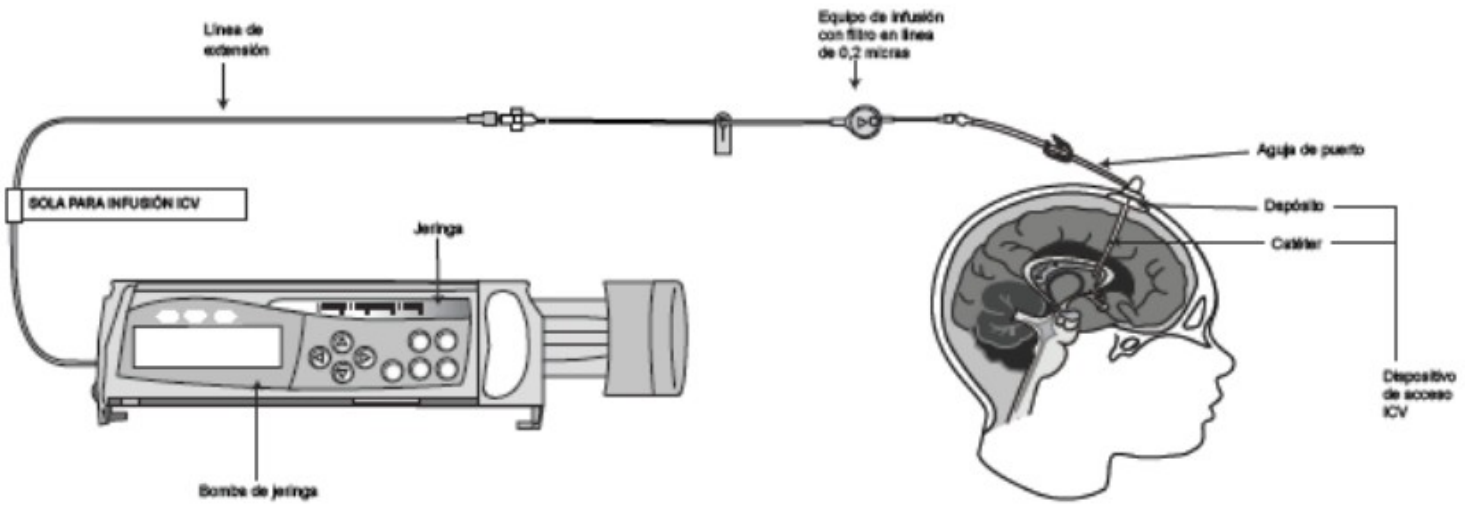
Tripeptidil-Peptidasa-1 en gotas de sangre

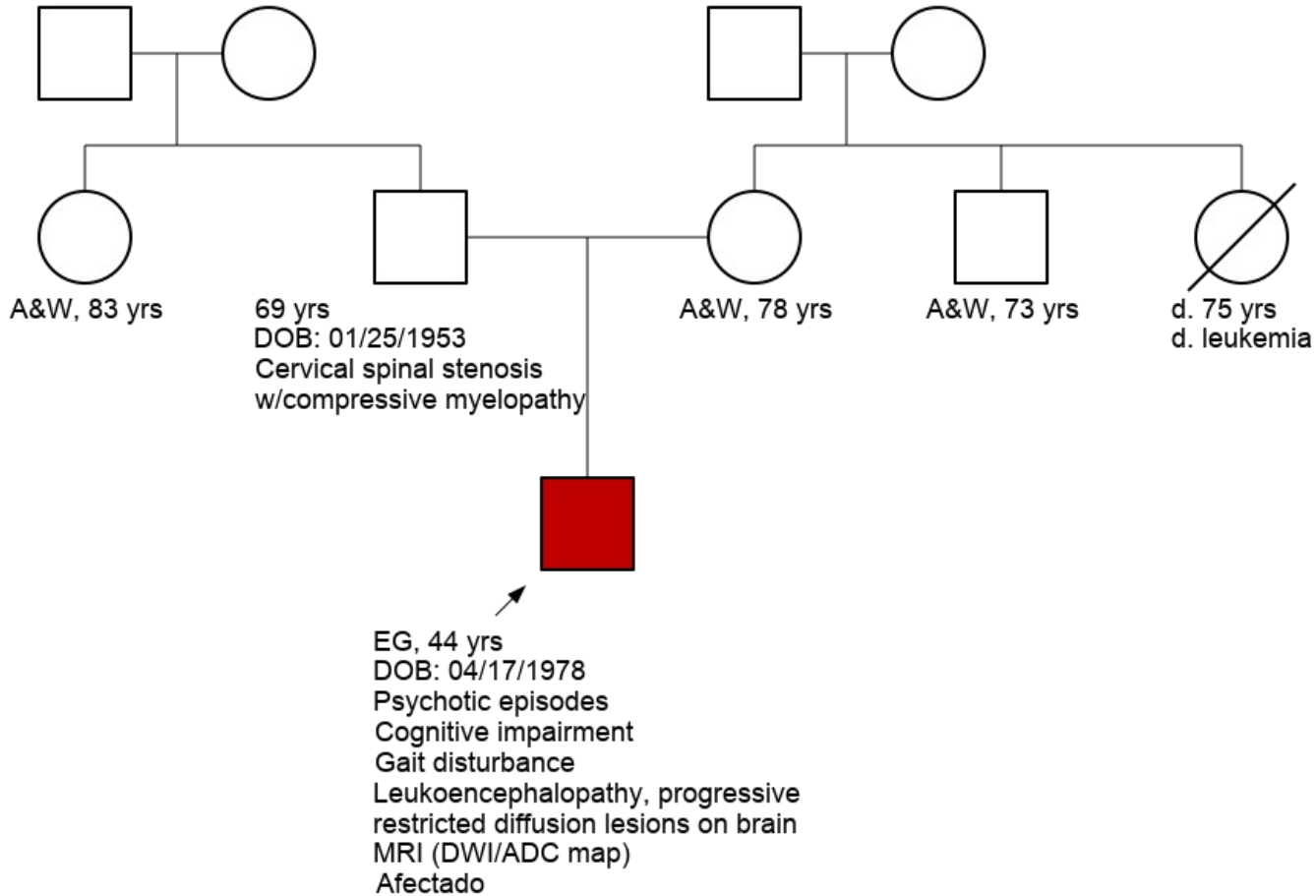
- YCC
  - 0,0 pmol/h/punch
- FBR
  - 0,0 pmol/h/punch
- Valores de referencia
  - 47,0-279,0

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Study of Intraventricular Cerliponase Alfa for CLN2 Disease




A&W, 83 yrs
69 yrs
DOB: 01/25/1953
Cervical spinal stenosis
w/compressive myelopathy
A&W, 78 yrs
A&W, 73 yrs
d. 75 yrs
d. leukemia
EG, 44 yrs
DOB: 04/17/1978
Psychotic episodes
Cognitive impairment
Gait disturbance
Leukoencephalopathy, progressive
restricted diffusion lesions on brain
MRI (DWI/ADC map)
Afectado
LEGEND
Afectado

- 10/2021
  - Alteración del lenguaje + desorientación en la vía pública
    - Internación en Clínica de Obra Social
      - Laboratorio sp
      - Serologías negativas
      - Colagenograma negativo
      - IgM beta-2 glicoproteína (+)
      - LCR
        - Proteínas 63 mg/dl, resto

- RMN de encéfalo
  - Aumento focal de la señal en T2, FLAIR lóbulos parietales y SB periventricular
  - Aumento en DWI y leve caída en ADC Map
- RMN de columna sp
- ETE con FOP
  - Colocación dispositivo de cierre

- 2° internación del 10 al 17/01/2022
  - Deterioro cognitivo-conductual
  - LCR con aumento de proteínas en LCR (65 mg/dl)
  - RMN de encéfalo
    - Lesiones focales de SB periventriculares y subcorticales bihemisféricas
  - Sospechan CADASIL
    -

Secuenciación Completa del Exoma

AARS1, AARS2, ABCA7,ABCC6,ABCD1, ACOX1, ADAR, ADPRHL2, AIMP1, AIMP2, ALDH3A2,ALS2,AMACR, ANG, ANXA11, APOE, APOPT1, APP, ARSA, ASPA, ATL1, ATP7B, ATXN2, BCAP31, BICD2, BOLA3, BSCL2, CACNA1C,CARS2, CBS, CCNF, CD59, CECR1, CHCHD10, CHMP2B, CLCN2, COASY, COL3A1,COL4A1, COL4A2, COLGAT1, COX10, COX15, COX6B1, CP, CSF1R, CST3,CTC1, CTSA, CYLD, CYP27A1, DARS1, DARS2, DCTN1, EARS2, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EMC1, EPRS1,ERBB4, ERCC6, ERCC8, FA2H, FAM126A, FARS2, FBF1,FBN1,FIG4, FKRP, FKTN, FLNA, FOLR1, FOXC1, FOXRED1, FTL, FUCA1, FUS, GALC, GAN, GBE1, GCDH, GEMIN4, GFAP, GFM1, GJC2, GLA, GLB1, GLE1, GLRX5, GMPPB, GRN, HEPACAM, HEXA, HIKESHI, HSD17B4, HSPD1,HTRA1, IBA57, IDS, IFIH1, ISCA1, ISCA2, ITM2B,KARS1, KCNT1, KIF5A, L2HGDH, LAMA2, LARGE1, LIPT2, LMNB1, LRPPRC, LYRM7, MAP3K6, MARS2, MCOLN1, MLC1, MPV17, MRPL38, MTFMT, MTHFS, NACC1, NARS2, NAXE, NDUFS1, NDUFV1, NEU1, NFU1, NKX6-2, ***NOTCH3****, NPC1, NPC2, NUBPL, OCLN, OTC, PC, PET100, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PHGDH, PHYH, PLA2G6, PLAA, PLEKHG2, PLP1, PMPCB, POLG, POLR1C, POLR3A, POLR3B, POLR3K, POMGNT1, POMT1, POMT2, PPT1, PRNP PSAP, PSAT1, PSEN1, PSEN2, PYCR2, QARS1, RAB11B, RARS1, RARS2, RNASEH2A, RNASEH2B, RNASEH2C, RNASET2, SAMHD1, SCP2, SDHA, SDHAF1, SLC16A2, SLC17A5, SLC1A4, SLC25A12, SLC2A10,SLC33A1, SNORD118, SOX10, SPG11, SPTAN1, SQSTM1, STN1, SUMF1, SURF1, TACO1, TAF15,TARS2, TARDBP, TBCD, TBCK, TBK1,TGFB1,TGFB2, TGFBR1, TGFBR2, TFG,TMEM106B, TPP1, TRAPPC12, TRAPPC6B, TRAPPC9, TREM2, TRIM65, TRIM47,TREX1, TUBA4A,TUBB4A, TUFM, TYMP, TYROBP, UBE3A, UBQLN2, UBTF, UFC1, UFM1,UPF3B, VAPB,VARS1, VARS2, VCP,VPS11, WARS2, WSHC5,WBP2,WDR45, WDR45B, ZFYVE26*

Secuenciación Completa del Exoma

Resultados Principales

Se ha detectado la variante patogénica en el gen ABCD1 (ATP Binding Cassette Sub Family D Member 1), causal de adrenoleucodistrofia, adrenomieloneuropatía y otros fenotipos variables detallados en OMIM #300100. Esta variante patogénica figura entre las identificadas en la base de datos gen específica "ALD Variant Database". La variante identificada en el gen ABCD1 es consistente con los hallazgos clínicos que orientaron hacia una leucoencefalopatía hereditaria.

Gen	Variante	c.DNA	cigosidad	clasif. ACMG.	Clasif.ClinVar
ABCD1	p.Q567*	c.1699C>T	hemicigota	Patogénica	Patogénica

Evaluación en HEC 19/07/2022

- Deterioro cognitivo
- Marcha espástica
- Disartria
- Estudios complementarios
  - Laboratorio de rutina y específico sp
    - Se descarta Addison
  - Dosaje de AGCML

RMN de encéfalo 3T

- Afectación de la sustancia blanca periventricular y profunda frontoparietal bilateral
  - ↑ señal Flair y T2 de aspecto confluente
  - ↑ señal T1 y DWI, con leve caída de la señal en el mapa de ADC
  - afectación del cuerpo calloso (esplenio y rodilla)
  - afectación del sector anterior del tronco y unión calloso-septal
-

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CSF1R	c.2545T>G (p.Phe849Val)	heterozygous	Uncertain Significance

- This sequence change replaces phenylalanine, which is neutral and non-polar, with valine, which is neutral and non-polar, at codon 849 of the CSF1R protein (p.Phe849Val).
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with CSF1R-related conditions.
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is expected to disrupt CSF1R protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

- Dear Cristian Ricardo Calandra,
- Thank you very much for your inquiry and for the clinical information you have shared. Our scientists reviewed this information and have noted your patient as a case report for HDLS. However, at this time we continue require additional evidence to be able to reclassify this variant. Testing the patient’s parents is an option (if they are available and interested), and their test results might potentially contribute evidence to our interpretation of this variant. Overall, we are able to offer CSF1R VUS testing for two relatives of your choice at no additional charge… In addition, I am conferring with our scientists regarding the ABCD1 variant and I will update you promptly once I have more information. Please let us know if you have any other questions or concerns. Best regards, Sansan Lee, MS, Licensed, Certified Genetic Counselor

- Dear Cristian,
- Regarding the ABCD1, c.1699C>T (p.Gln567*) variant, this variant is within the guaranteed analysis range of our ABCD1 test and would be detected if present. Therefore, your patient tested negative for this variant at our lab. Further, our scientists conducted a sample audit and found that your patient’s tube scan matched the requisition form with name and birthdate. Also, the lab process had no issues, there are no QC errors, contamination value is 0, and ploidy matched gender. There is no evidence of sample swap here at Invitae. I hope this information is helpful. Please let us know if you have other questions. Best regards, Sansan

Study Description

Go to

Brief Summary:

The purpose of this study is to measure the effect of Hematopoietic Stem Cell Transplantation (HSCT) on symptoms of CSF1R-related Leukoencephalopathy.

Condition or disease
CSF1R-related Leukoencephalopathy
ALSP
POLD
Hematopoietic Stem Cell Transplantation

Study Design

Go to

Study Type :	Observational
Estimated Enrollment :	20 participants
Observational Model:	Case-Only
Time Perspective:	Prospective
Official Title:	Longitudinal Assessment of **CSF1R**-Related Leukoencephalopathy Following Stem Cell Transplantation
Actual Study Start Date :	July 21, 2020
Estimated Primary Completion Date :	December 30, 2025
Estimated Study Completion Date :	December 30, 2026

Groups and Cohorts

Go to

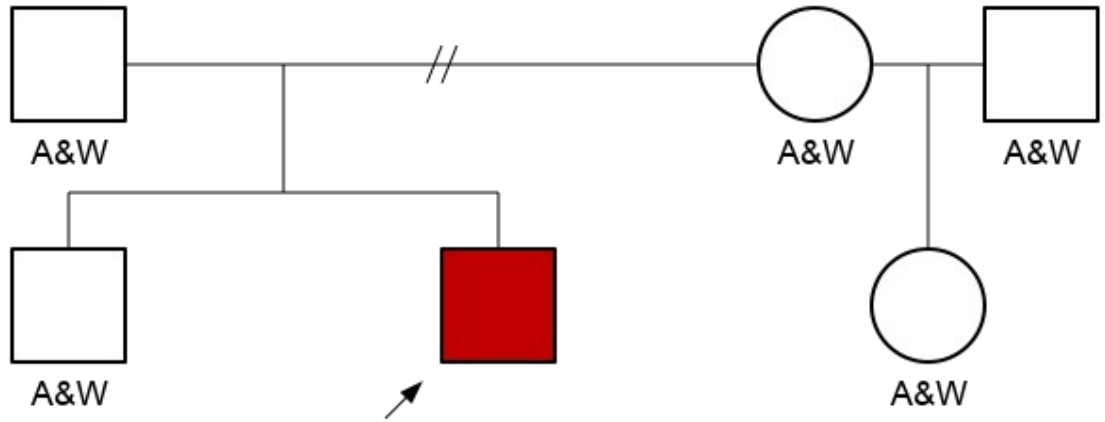
Outcome Measures

Go to

Primary Outcome Measures :

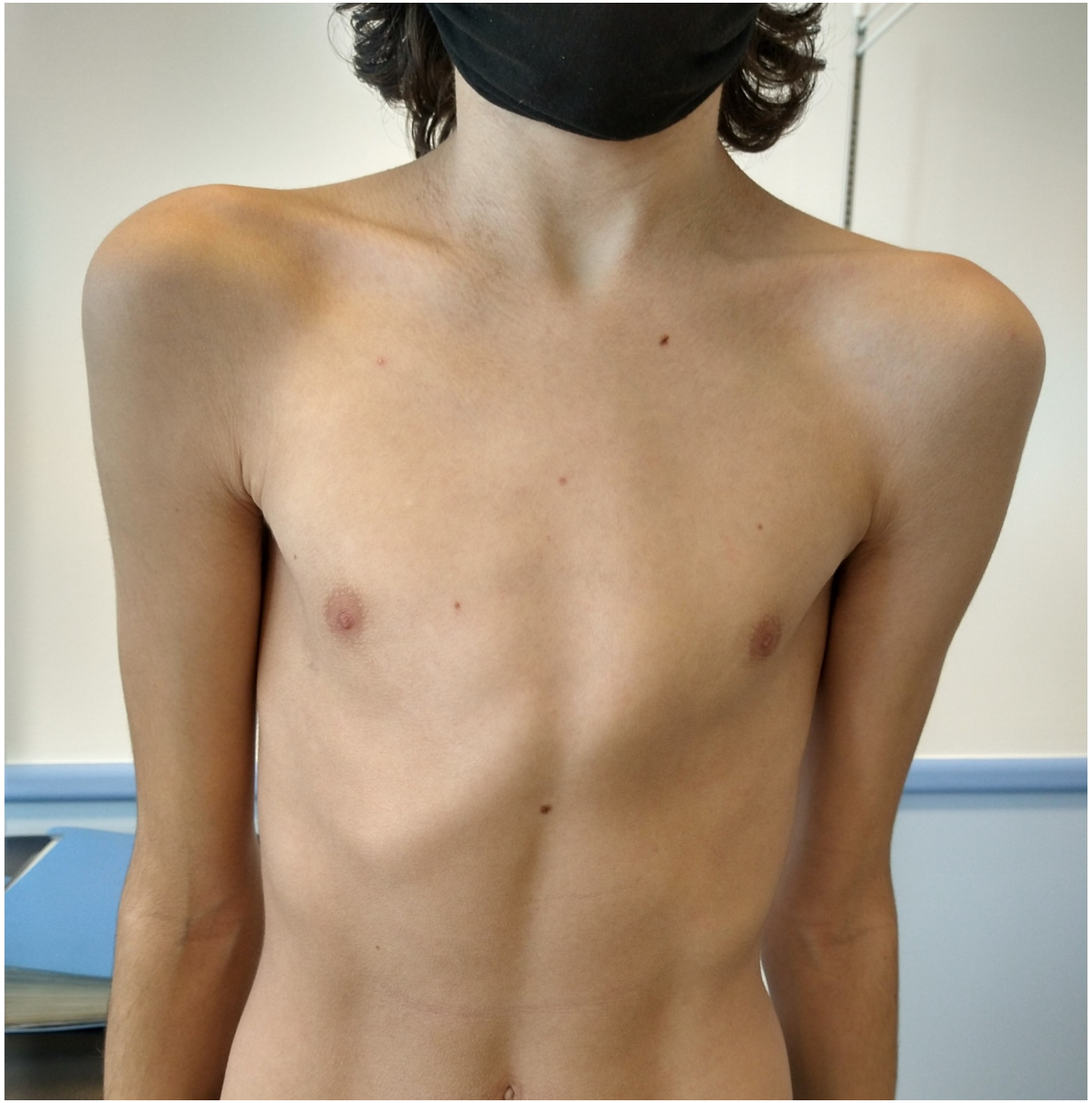
1. Improvement in cognitive and motor function [Time Frame: Through study completion, approximately 5 years]

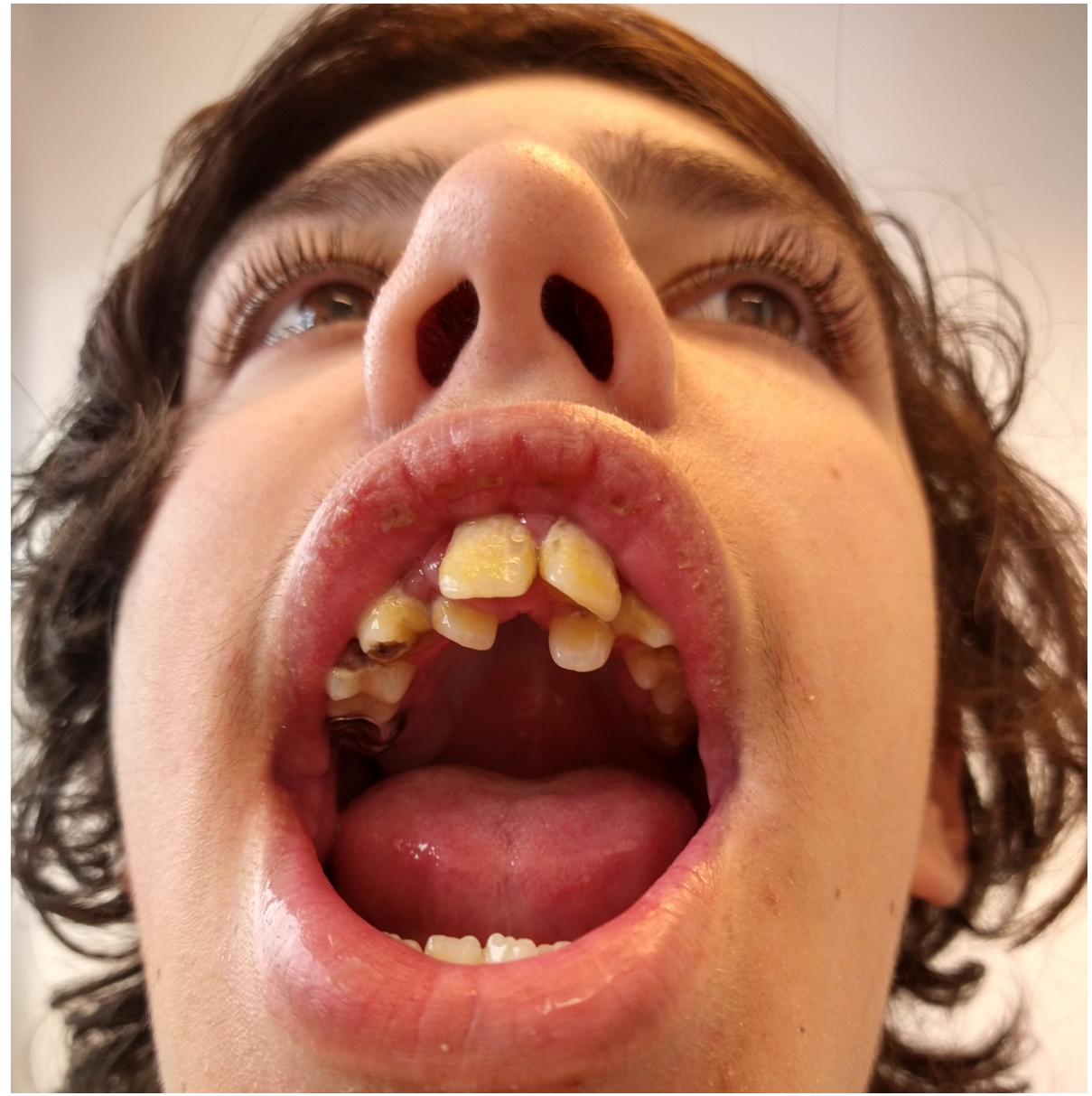
   Number of participants to demonstrate stability/improvements in cognitive and motor function by detailed clinical assessment and radiographic markers of disease.

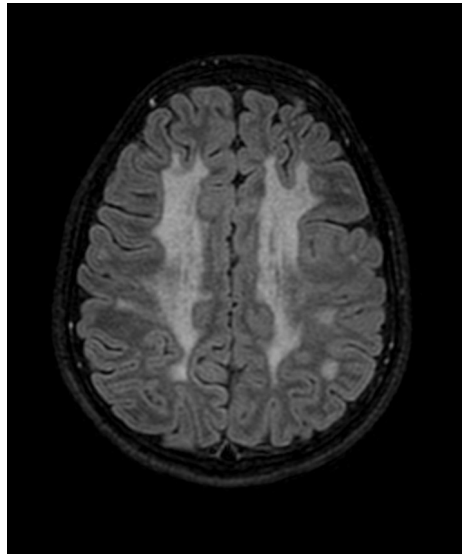


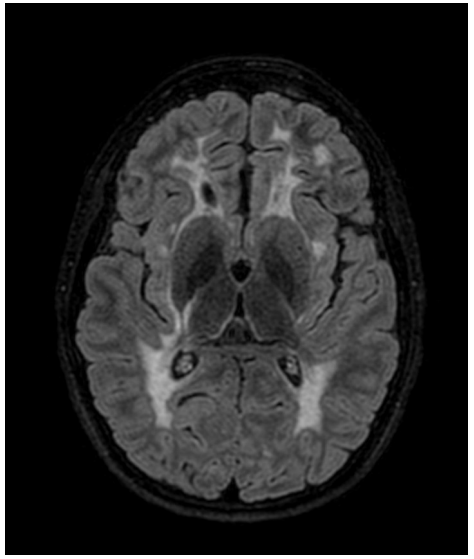
LEGEND

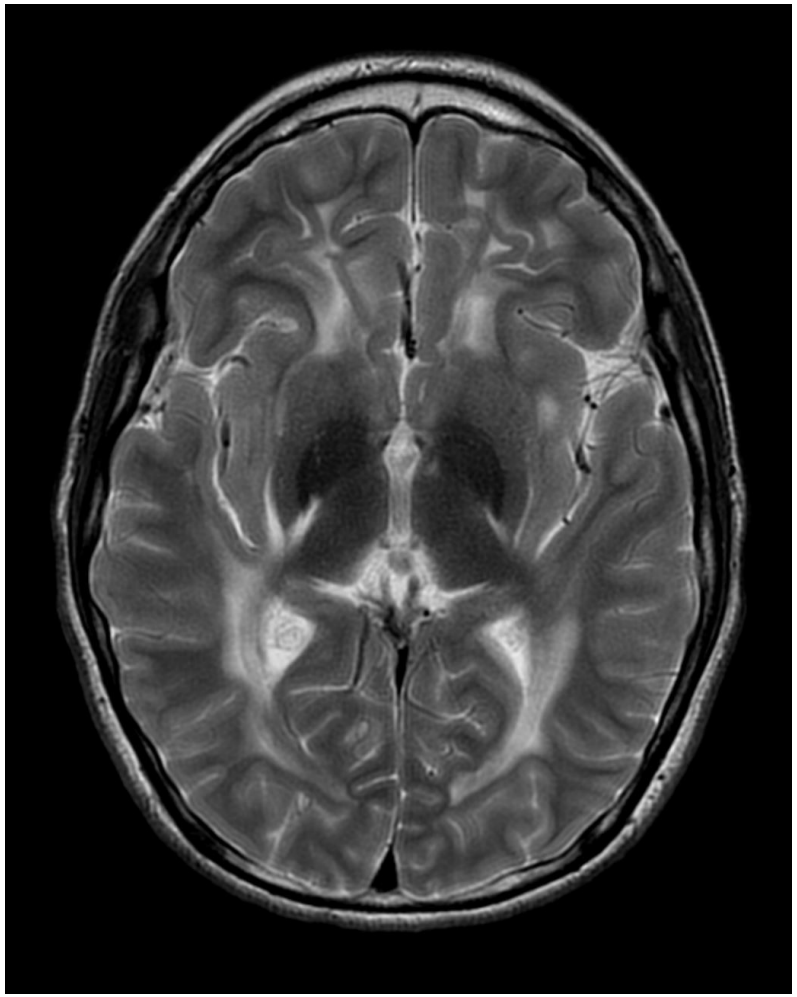
Afectado

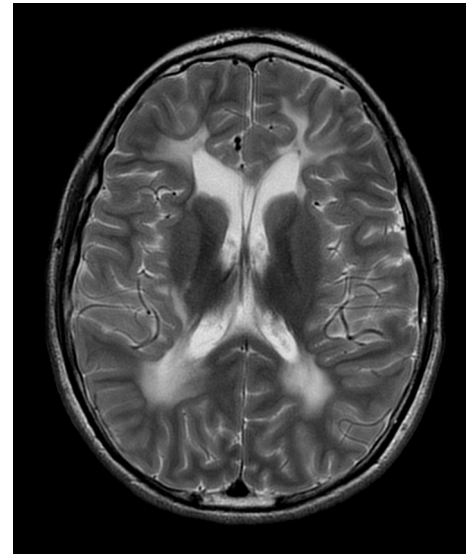


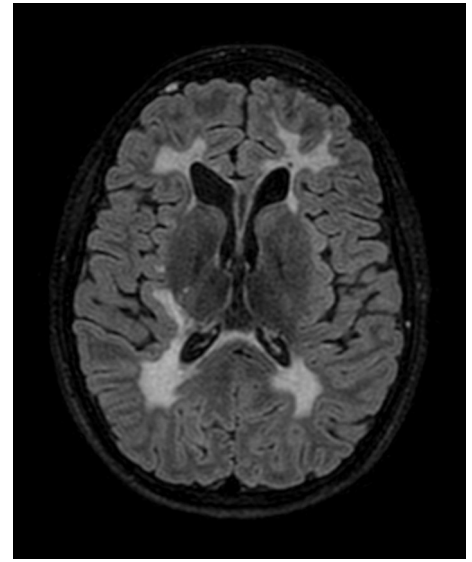












One Pathogenic variant identified in GFAP. GFAP is associated with autosomal dominant Alexander disease.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
GFAP	c.1246C>T (p.Arg416Trp)	heterozygous	PATHOGENIC

GFAP, Exon 8, c.1246C>T (p.Arg416Trp), heterozygous, PATHOGENIC

- This sequence change replaces arginine, which is basic and polar, with tryptophan, which is neutral and slightly polar, at codon 416 of the GFAP protein (p.Arg416Trp).
- This variant is present in population databases (rs121909717, gnomAD 0.01%).
- This missense change has been observed in individual(s) with Alexander disease (PMID: 11138011, 27814755). In at least one individual the variant was observed to be de novo.
- ClinVar contains an entry for this variant (Variation ID: 16169).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Possibly Damaging"; Align-GVGD: "Class C0").
- Experimental studies have shown that this missense change affects GFAP function (PMID: 16826512).
- For these reasons, this variant has been classified as Pathogenic.

Study Description

Go to

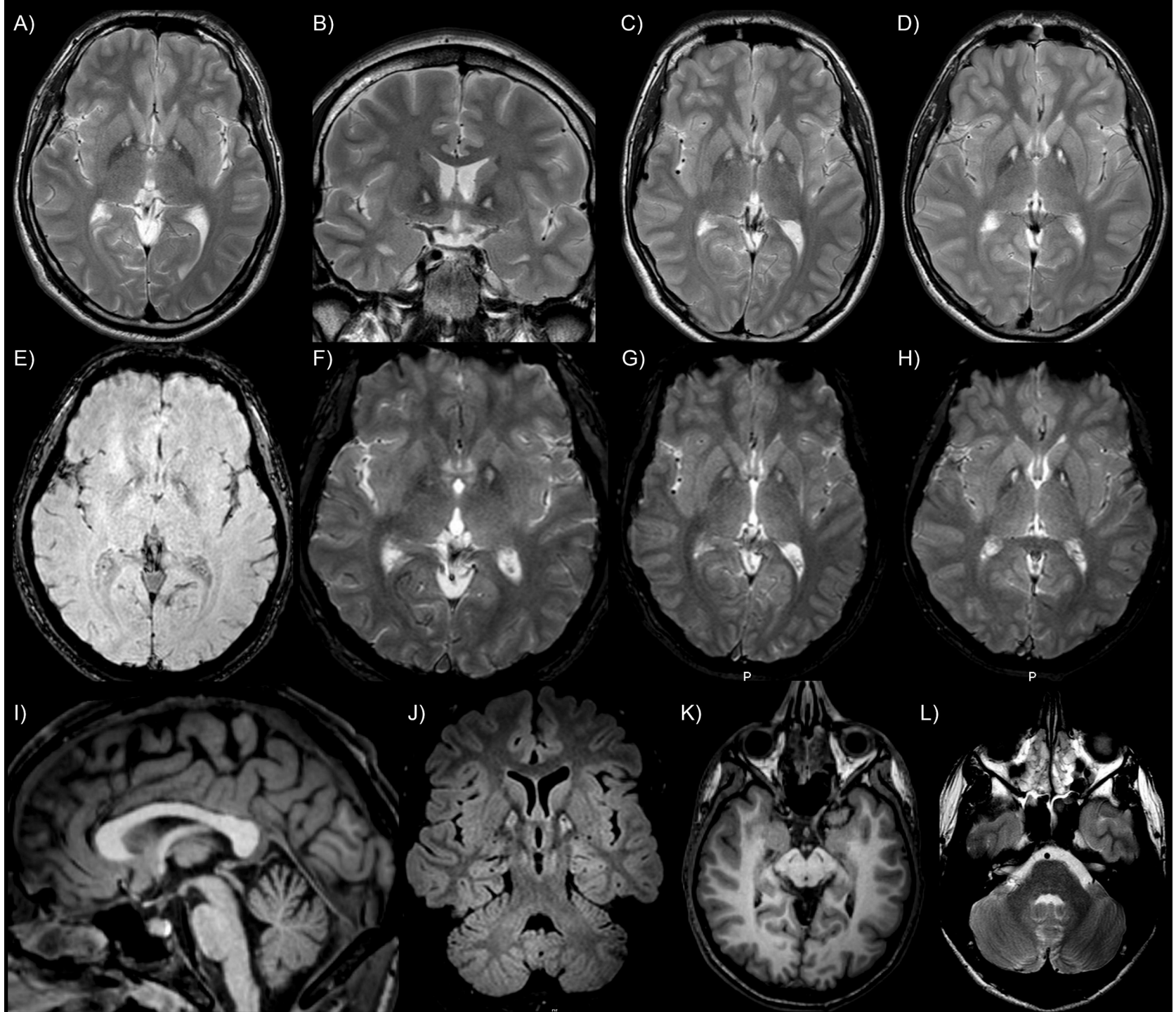
Brief Summary:

The purpose of this study is to evaluate the safety and efficacy of ION373 in improving or stabilizing gross motor function across the full range of affected domains in patients with AxD.

Condition or disease	Intervention/treatment	Phase
Alexander Disease	Drug: ION373 Drug: Placebo	Phase 3

Detailed Description:

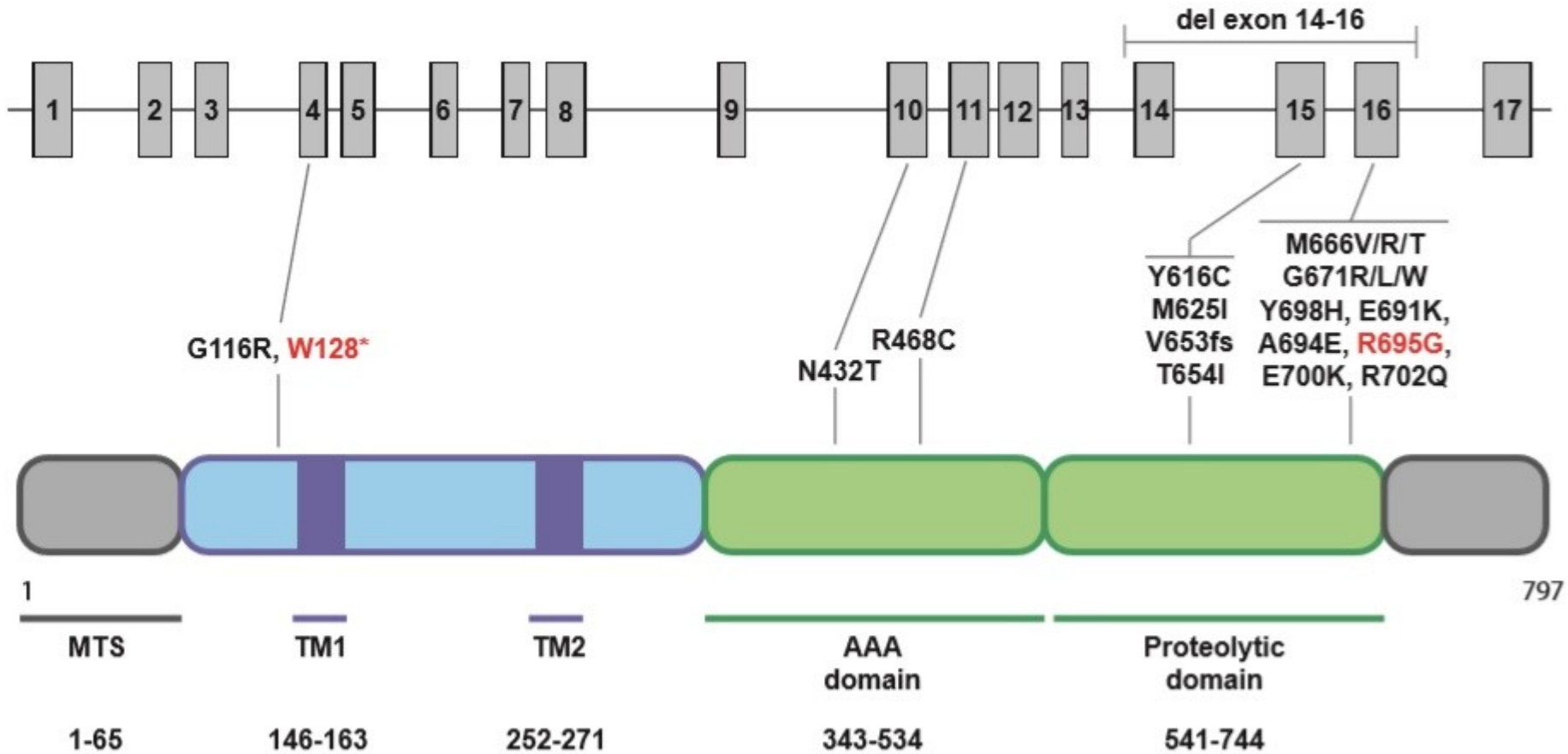
This is a Phase 1-3, multi-center, double-blind, placebo-controlled, multiple-ascending dose (MAD) study in up to 58 patients with AxD. Participants will be randomized in a 2:1 ratio to receive ION373 or matching placebo for a 60-week double-blind treatment period; then all participants will receive ION373 for a 60-week open-label treatment period. Multiple dose cohorts will be evaluated in the study. Cohorts will be enrolled sequentially. The initial participants in each dose cohort must be at least 8 years of age at the time of Screening.


A)
B)
C)
D)
E)
F)
G)
H)
P
P
I)
J)
K)
L)

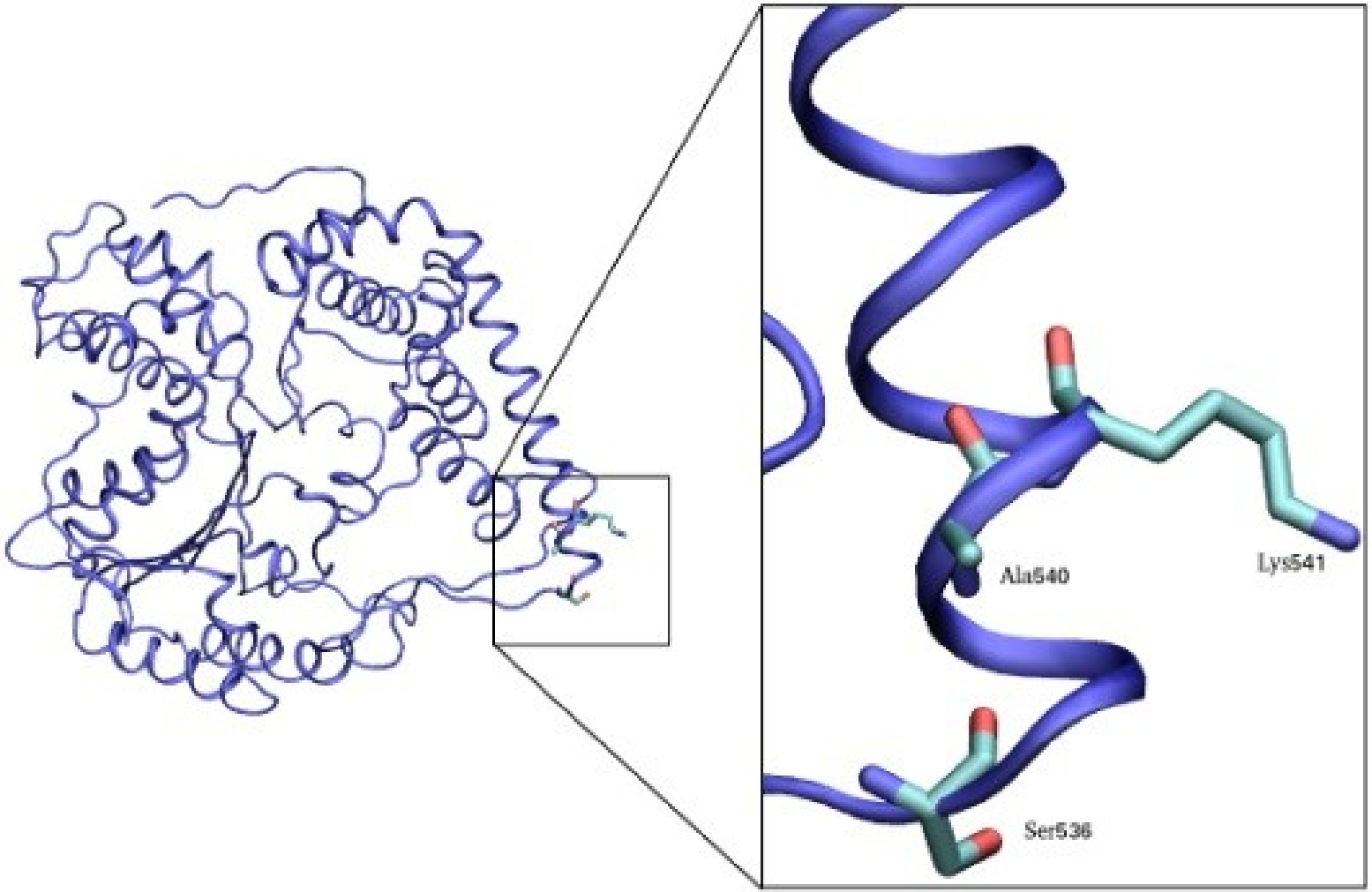
Posición	Gen	Variación nucleotídica	Cambio de aminoácido	Efecto	Cigosidad	Cob.	Info Externa
18:12337432	AFG3L2	T -> C c.2083A>G	p.Arg695Gly	Missense variant	HET	36/87	-
18:12367291	AFG3L2	C -> T c.383G>A	p.Trp128*	Stop gained	HET	25/48	-

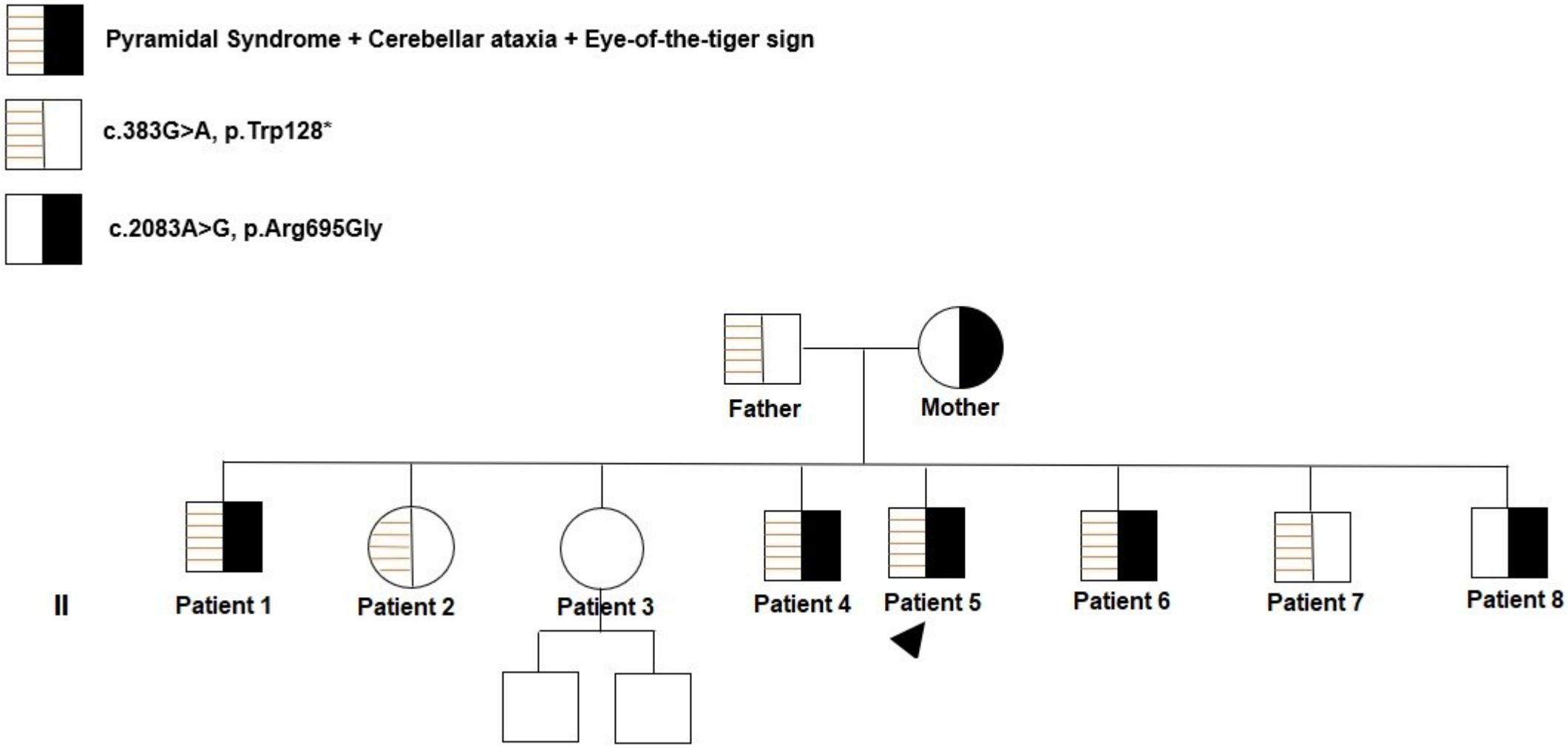
respiratoria (Leonhard, et al., 1999). La variante p.Arg695Gly cae en una posición altamente conservada dentro del dominio proteolítico C-Terminal de la proteasa. Los predictores bioinformaticos SIFT y Mutation Taster la consideran como probablemente patogénica (PP3). No se cuenta con información de frecuencia poblacional en la base de datos ExAC.

La segunda es una variante de alto impacto con predicción patogénica por Mutation Taster que produce la introducción de un codón stop prematuro, resultando en una proteína no funcional.


del exon 14-16
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
G116R, W128*
N432T
R468C
Y616C
M625I
V653fs
T654I
M666V/R/T
G671R/L/W
Y698H, E691K,
A694E, R695G,
E700K, R702Q
1
797
MTS
TM1
TM2
AAA domain
Proteolytic domain
1-65
146-163
252-271
343-534
541-744


695
AFG3-l2(Homo_sapiens) VTQSAYAQIVQFGMNEKVGQISFDLPRQG-----DMVLEKPYSEATARLIDDEVRILIND 707
AFG3-l2(Mus_musculus) VTQSAYAQIVQFGMNEKVGQISFDLPRQG-----DMVLEKPYSEATARMIDDEVRILISD 706
AFG3-l2(Fulmarus_glacialis) VTQSAYAQIVQFGMNEKVGQISFDLPRQG-----DMVLEKPYSEATARLIDEEVRSLINI 573
AFG3-l2(Danio_rerio) VTQSAYAQIVQFGMNEKVGQVSFDLPRQG-----ELVLEKPYSEATARLIDTEVRNLIST 702
Hfl(Basidiobolus_meristosporus) VTKMAYAQITTYGMNNVVGNISFHSPND------EQQFQKPYSEETGRIIDNEARKMIGN 678
FtsH(Escherichia_coli) ATNLARNMVTQWGFSEKLGPLLYAEEEGEVFLGRSVAKAKHMSDETARIIDQEVKALIER 555
FtsH(Thermus_thermophilus) ATELARRMITEWGMHPEFGPVAYAVREDTYLGGYDV---RQYSEETAKRIDEAVRRLIEE 553
AFG3-l1(Mus_musculus) VTQSAYAQIVQFGMSEKLGQVSFDFPRQG-----ETMVEKPYSEATAQLIDEEVRCLVRS 699
AFG3-l1(Rattus_norvegicus) VTQSAYAQIVQFGMSEKLGQVSFDFPRQG-----ETMVEKPYSEATAQLIDEEVRCLVRS 699
AFG3-like(Caenorhabditis_elegans) VTQMAYSQVVKFGMSEKVGPLSFETPAPG-----EMAFDKPYSEATAQLIDQEVRDLVMN 692
AFG3l1(Xenopus_tropicalis) VTQSAYAQIVQFGMSEKLGQVSFDLPRQG-----EMLAEKPYSEATAELIDQEARNLINS 695
Si:ch1073-174d20.2(Danio_rerio) VTQSAYAQIVQFGMSERVGQVSFDLPRQG-----ETVLEKPYSEATAELIDEEVRDLVDR 659


Ala540
Lys541
Ser536

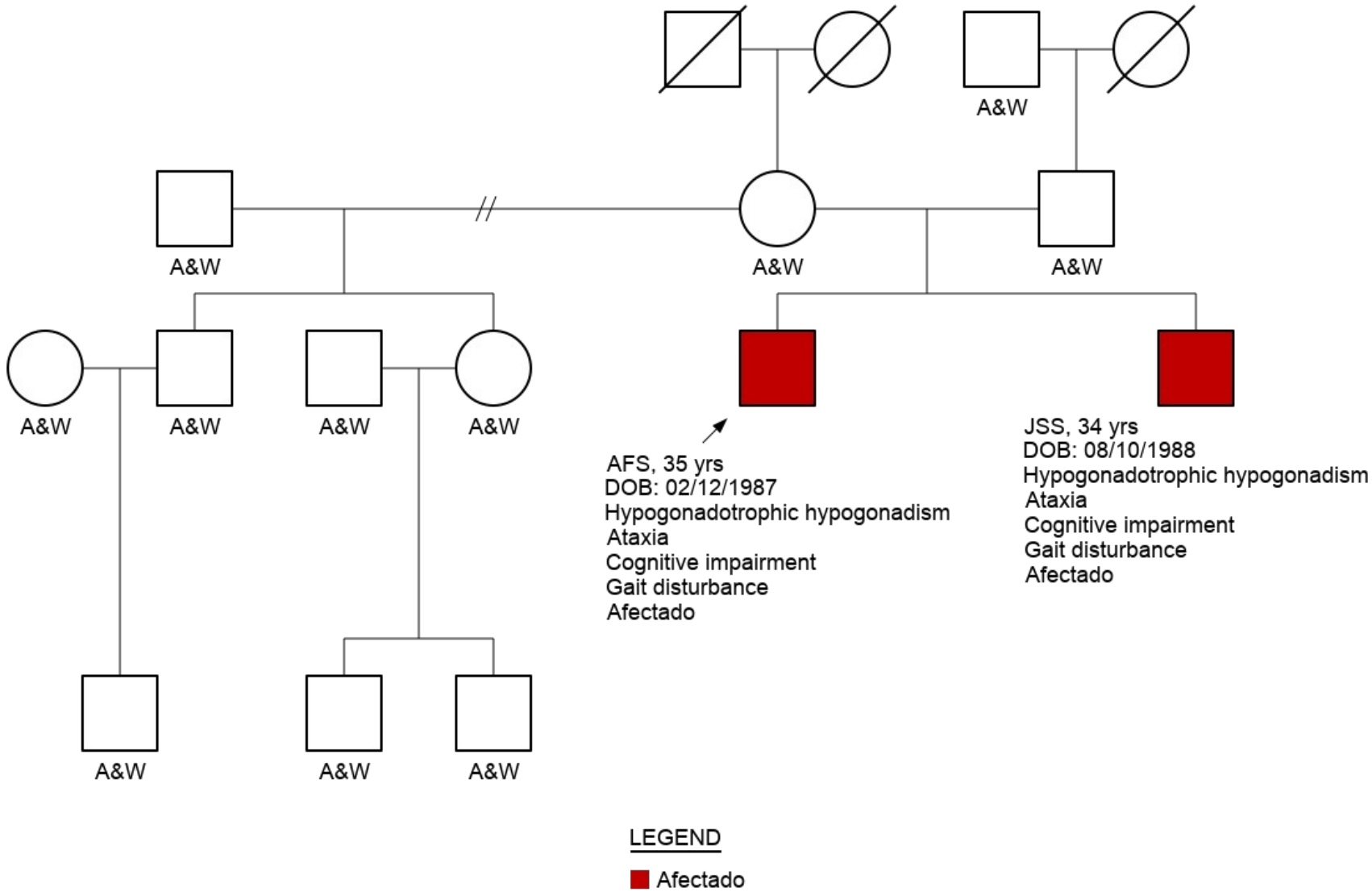

Pyramidal Syndrome + Cerebellar ataxia + Eye-of-the-tiger sign
c.383G>A, p.Trp128*
c.2083A>G, p.Arg695Gly
Father
Mother
II
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8

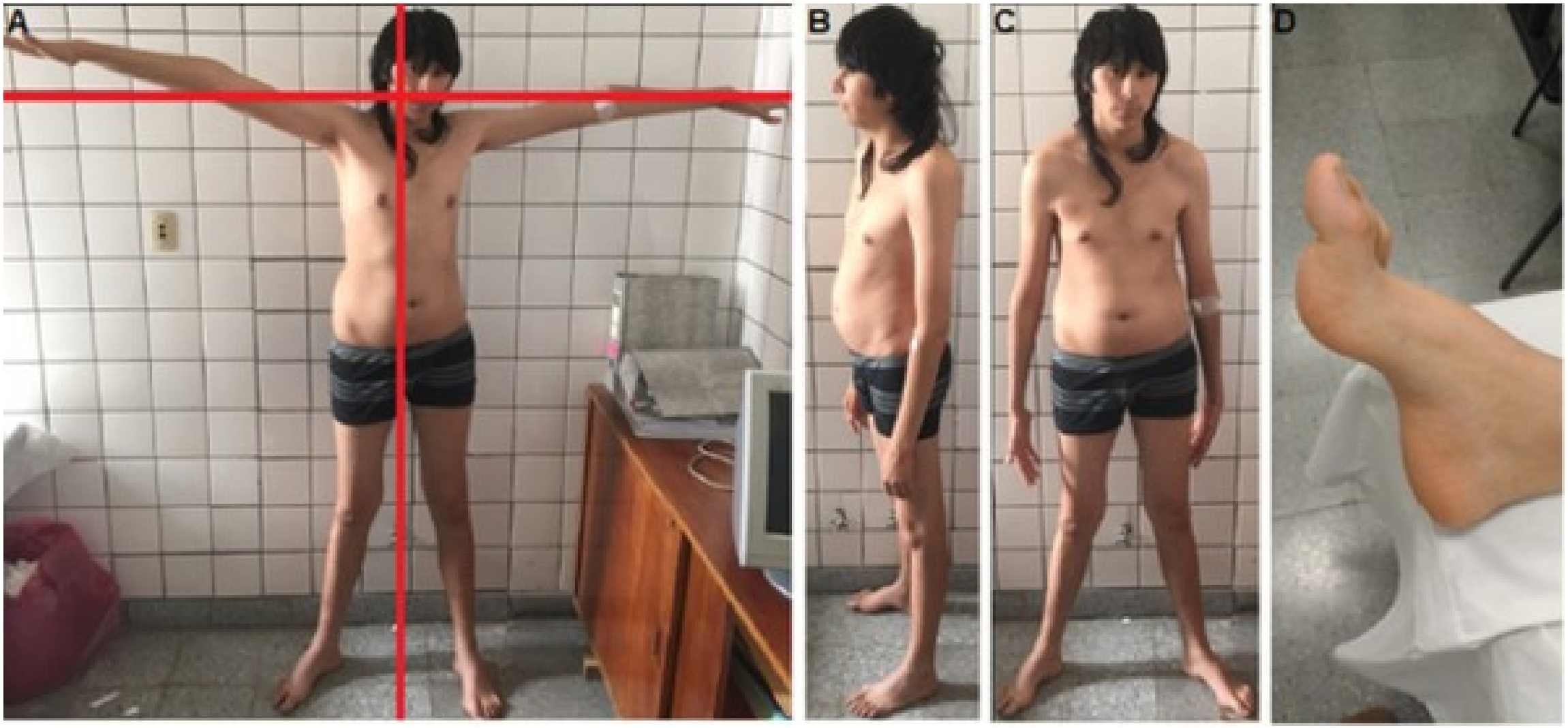
Spastic ataxia with eye-of-the-tiger-like sign in 4 siblings due to novel compound heterozygous AFG3L2 mutation.

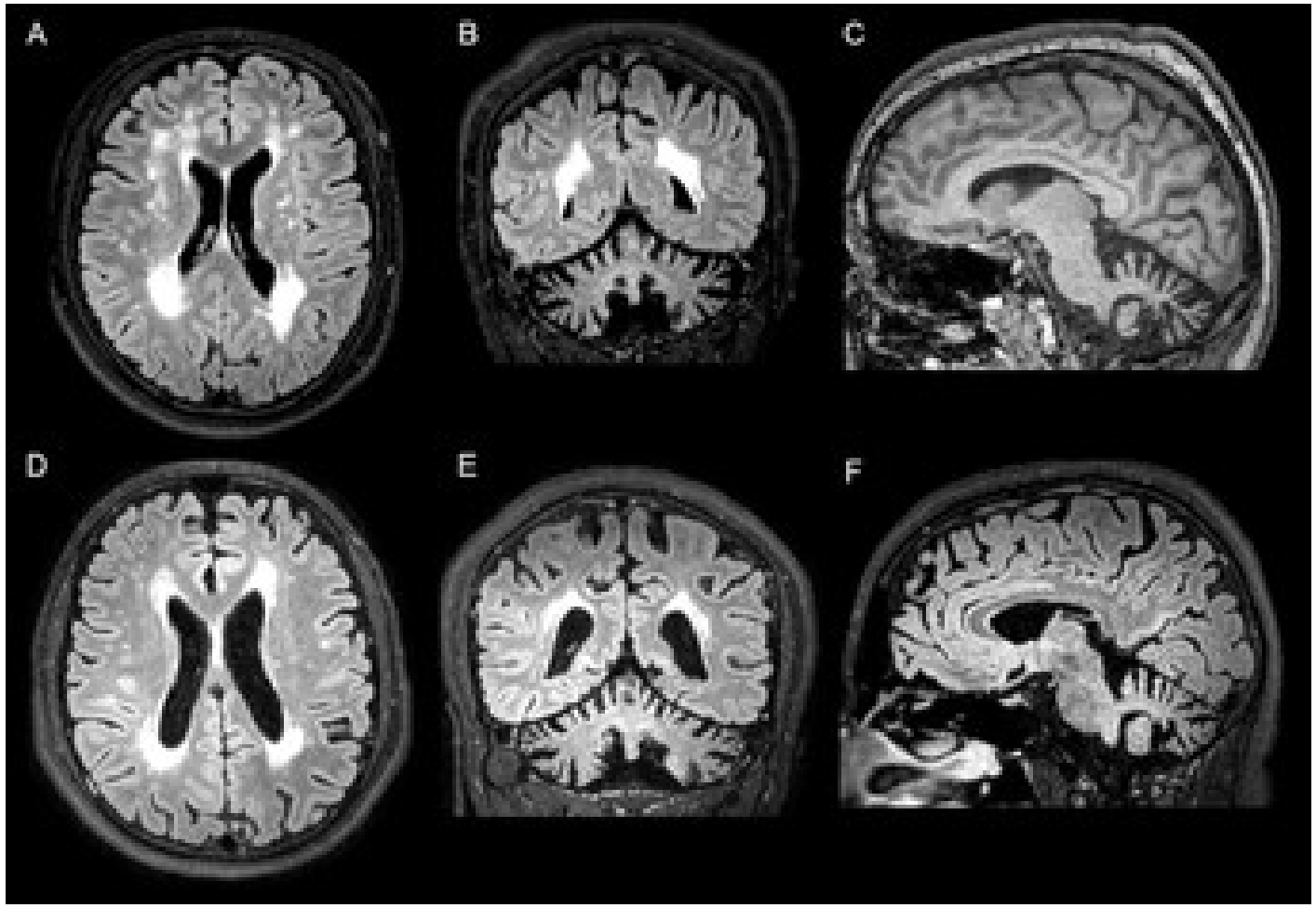
Calandra CR, Buda G, Vishnopolska SA, Oliveri J, Olivieri FA, Pérez Millán MI, Biagioli G, Miquelini LA, Pellene AL, Marti MA.

Parkinsonism Relat Disord. 2020 Apr;73:52-54. doi: 10.1016/j.parkreldis.2020.03.020. Epub 2020 Mar 24.

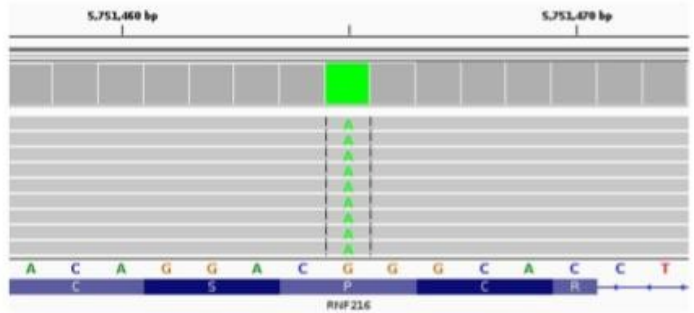
PMID: 32248051 No abstract available.


A&W
A&W
A&W
A&W
A&W
A&W
A&W
A&W
A&W
A&W
AFS, 35 yrs
DOB: 02/12/1987
Hypogonadotrophic hypogonadism
Ataxia
Cognitive impairment
Gait disturbance
Afectado
JSS, 34 yrs
DOB: 08/10/1988
Hypogonadotrophic hypogonadism
Ataxia
Cognitive impairment
Gait disturbance
Afectado
LEGEND
Afectado

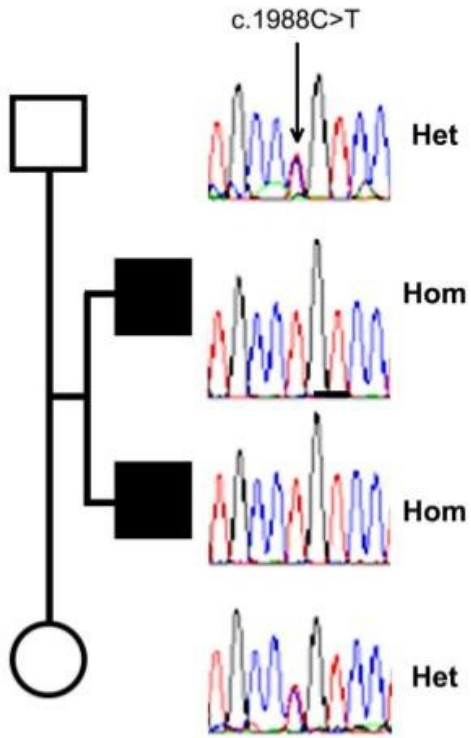

A
B
C
D


A
B
C
D
E
F

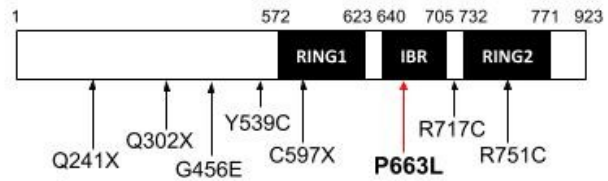
A



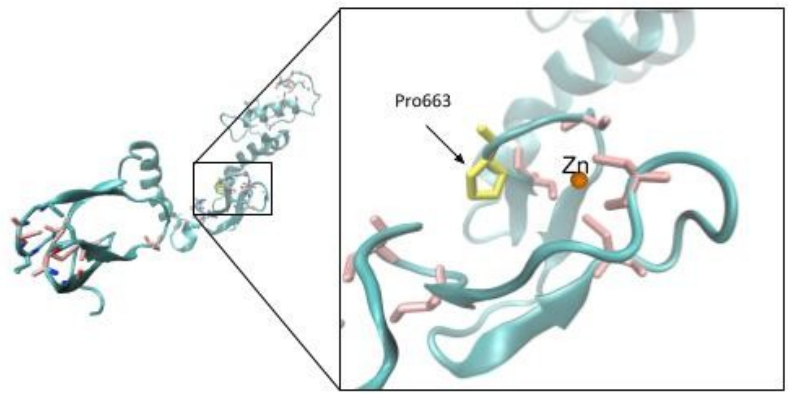
B



C



D



E

663

```
D.rerio         AATCADELVRCPFCNFPALLDKD
X.tropicalis    SAACADQLVRCPSCSFPALLDKD
G.gallus        AAACADELVRCPFCNFPALLDND
M.musculus      AAAYADELVRCPSCSFPALLDSD
M.mulatta       AAAYADELVRCPSCSFPALLDSD
Human           AAAYADELVRCPSCSFPALLDSD
P.troglodites   AAAYADELVRCPSCSFPALLDSD
```

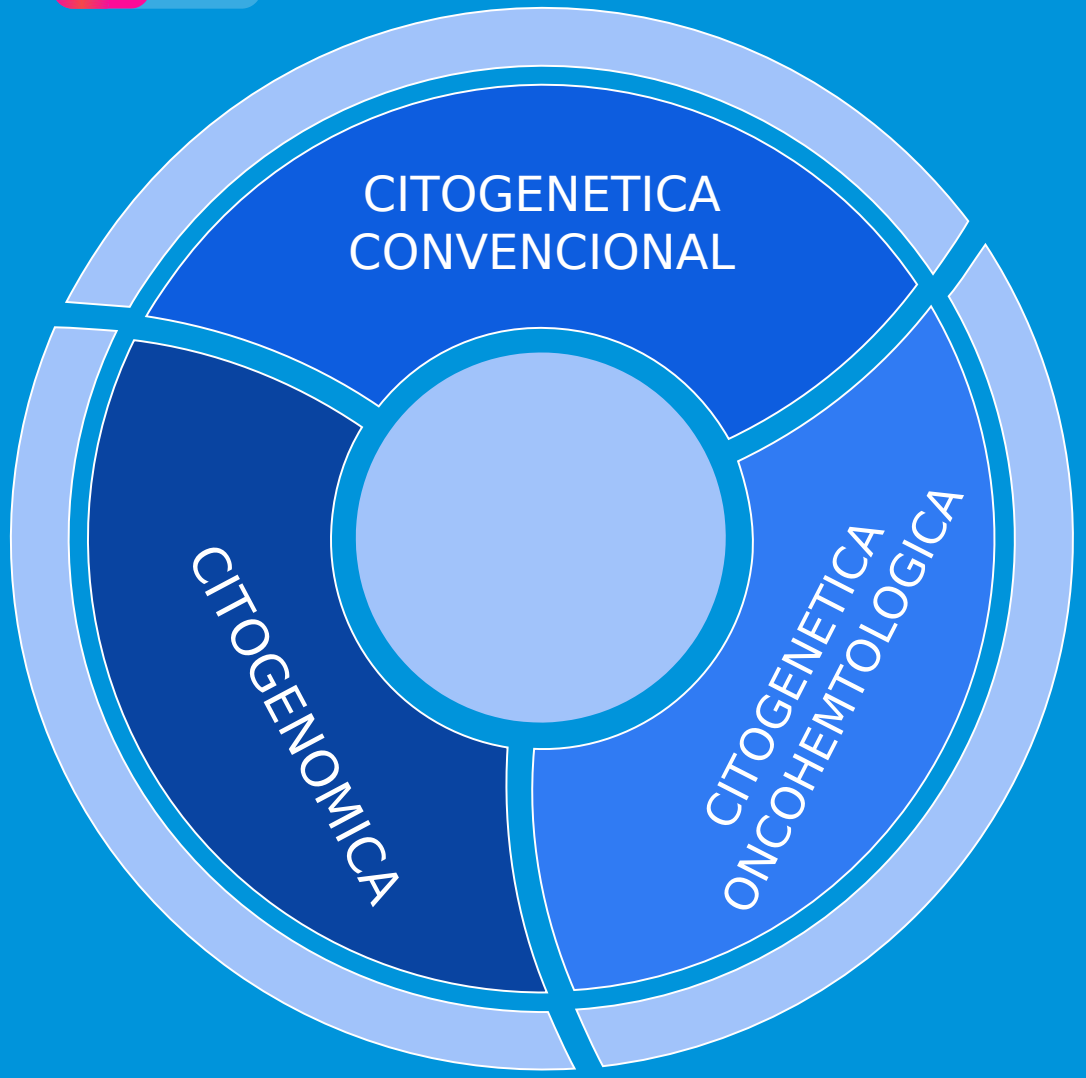
Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Gordon Holmes Syndrome Caused by RNF216 Novel Mutation in 2 Argentinean Siblings

Cristian R. Calandra, MD,[1,] Yamile Mocarbel, MD,[2] Sebastian A. Vishnopolska, MSc,[3,4] Vanessa Toneguzzo, MD,[5] Jaen Oliveri, MD,[6] Enrique Carlos Cazado, MD,[2] German Biagioli, BCs,[3,7] Adrián G. Turjanksi, PhD,[3,4,7] and Marcelo Marti, PhD[3,4,7]*

LABORATORIO CITOGENETICA y CITOGENÓMICA

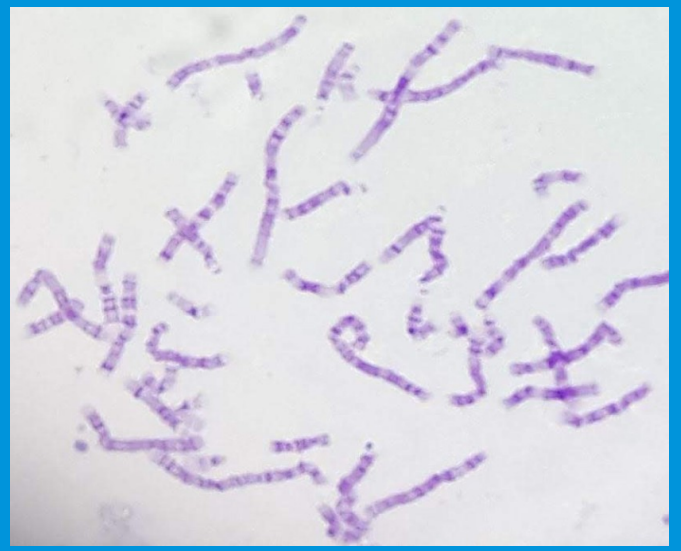


Bioq Soledad Massara
Bioq Brenda Miller
Bioq Vanina Bugatto
Tec. Marina Alegre

HEC humanizado
Dr. Néstor Carlos Kirchner

ANOMALÍAS CONSTITUCIONALES O CONGÉNITAS
Discapacidad intelectual, desórdenes del espectro autista, retraso en el desarrollo, dismorfias, malformaciones congénitas, disgenesia gonadal, genitales ambiguos

ONCOHEMATOLOGÍA
Patologías oncohematológicas en pacientes adultos



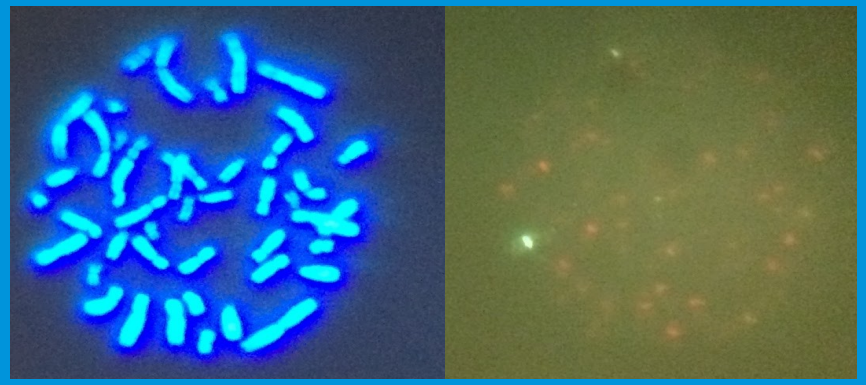
CARIOTIPO

ANOMALÍAS CONSTITUCIONALES O CONGÉNITAS
Desde 2012 – 1800 pacientes estudiados

ONCOHEMATOLOGÍA
Desde 2017 – 700 pacientes estudiados

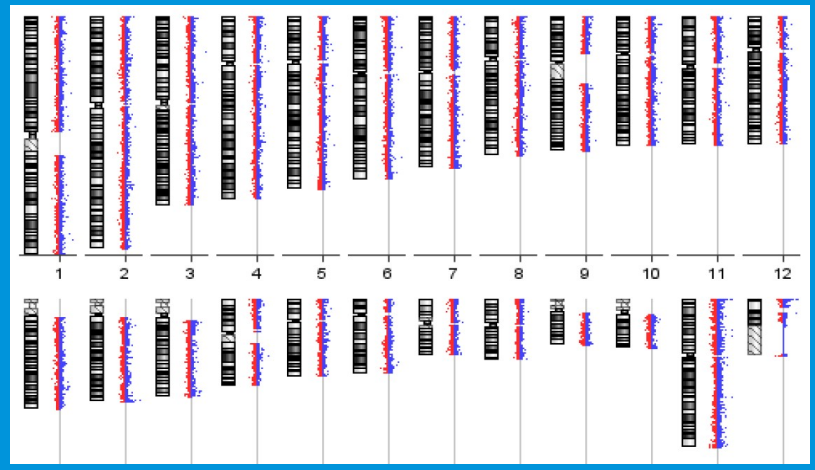
FISH

Desde 2017 - 800 pacientes estudiados



ArrayCGH

Desde 2021 - 24 pacientes estudiados



SERVICIO DE GENETICA CLINICA

humanizado
Dr. Néstor Carlos Kirchner

Paloma Brun

Ana Laura Damia

OTROS SERVICIOS DEL HEC:
UTIP
Endocrinología
Neurología

DERIVACIONES RSVI

Hospital Mi Pueblo, Florencio Varela
Hospital Gandulfo, Lomas de Zamora
Hospital Ana Goitia, Avellaneda
Hospital Oñativia, Alte Brown
Hospital Melendez, Alte Brown
Hospital Iriarte, Quilmes
Hospital Evita, Lanus
Hospital Evita Pueblo, Berazategui

DERIVACIONES Resto del país

Hospital Sor Maria Ludovica, La Plata
Hospital Cuenca Alta, Cañuelas
Hospital Central Mendoza
Cepsi Santiago del Estero

Proyección HEC

2021	2022 (primer semestre)	2022 (segundo semestre)	2023
PRIMER ARRAY PUESTA A PUNTO	3 arrays concluidos (24 pacientes)	4 arrays nuevos (32 pacientes)	8 arrays + Primer array en oncohematologia (72 pacientes) + Puesta a punto MLPA


¿Preguntas?