International course: Training on strategies to foster solutions of undiagnosed rare disease cases

USE CASE FROM THE INSTITUTO DE SALUD CARLOS III (ISCIII)

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&

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EUROPEAN JOINT PROGRAMME RARE DISEASES

Organised by National Centre for Rare Disease, Istituto Superiore di Sanità, Rome (Italy), April 27-29, 2020

USE CASE FROM THE INSTITUTO DE SALUD CARLOS III

- Spanish undiagnosed RD program SpainUDP
- Diagnostic approach
- Case description
  - ❑ Background
  - ❑ Family history
  - ❑ Prenatal and perinatal history
  - ❑ Clinical symptoms and physical findings
  - ❑ Complementary tests
  - ❑ Previous genetic studies
- Case resolution

SpainUDP
Programa de Casos de Enfermedades Raras Sin Diagnóstico
Undiagnosed Rare Diseases Program

EJP RD

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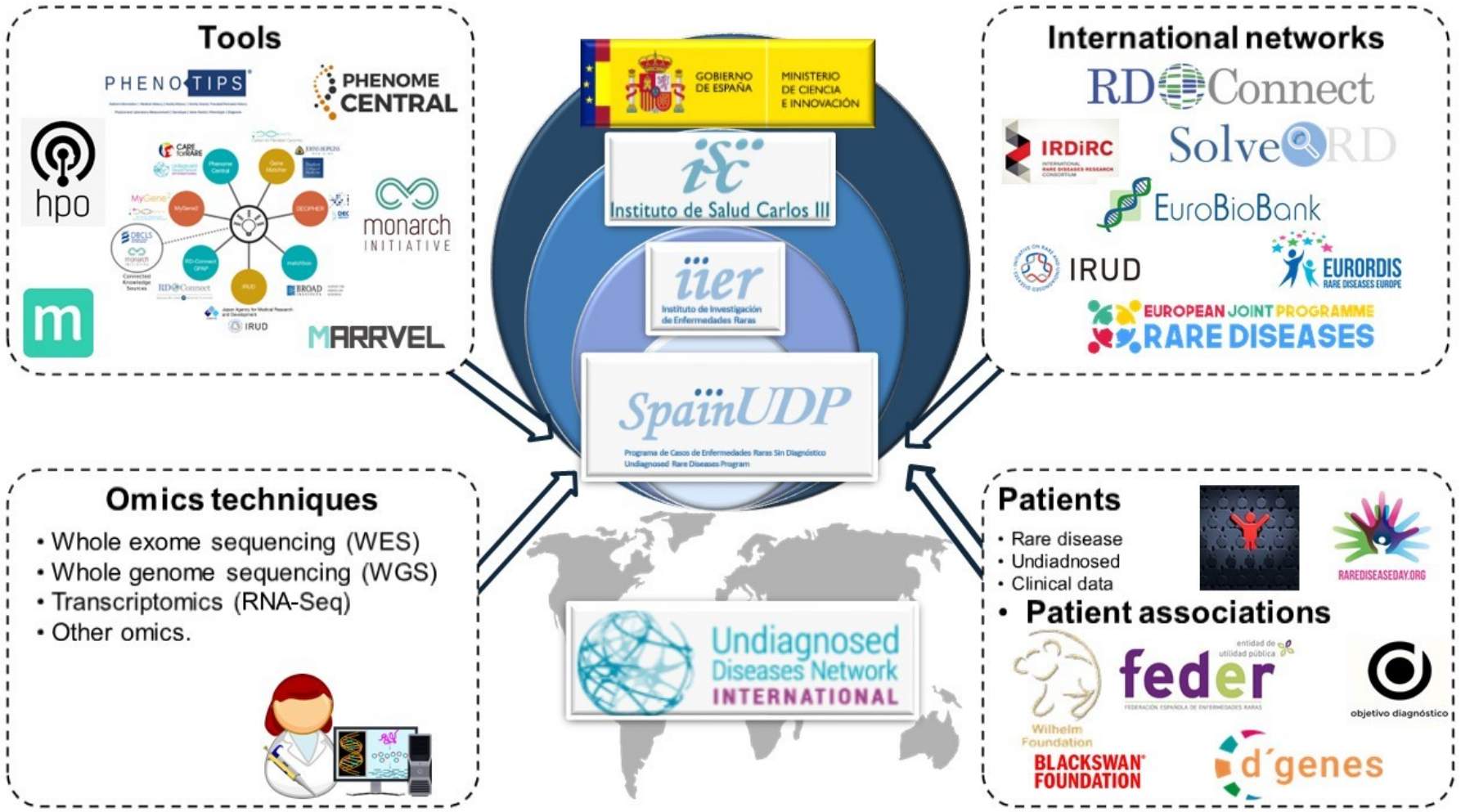
SPAINUDP

THE SPANISH UNDIAGNOSED RARE DISEASES PROGRAM

http://spainudp.isciii.es



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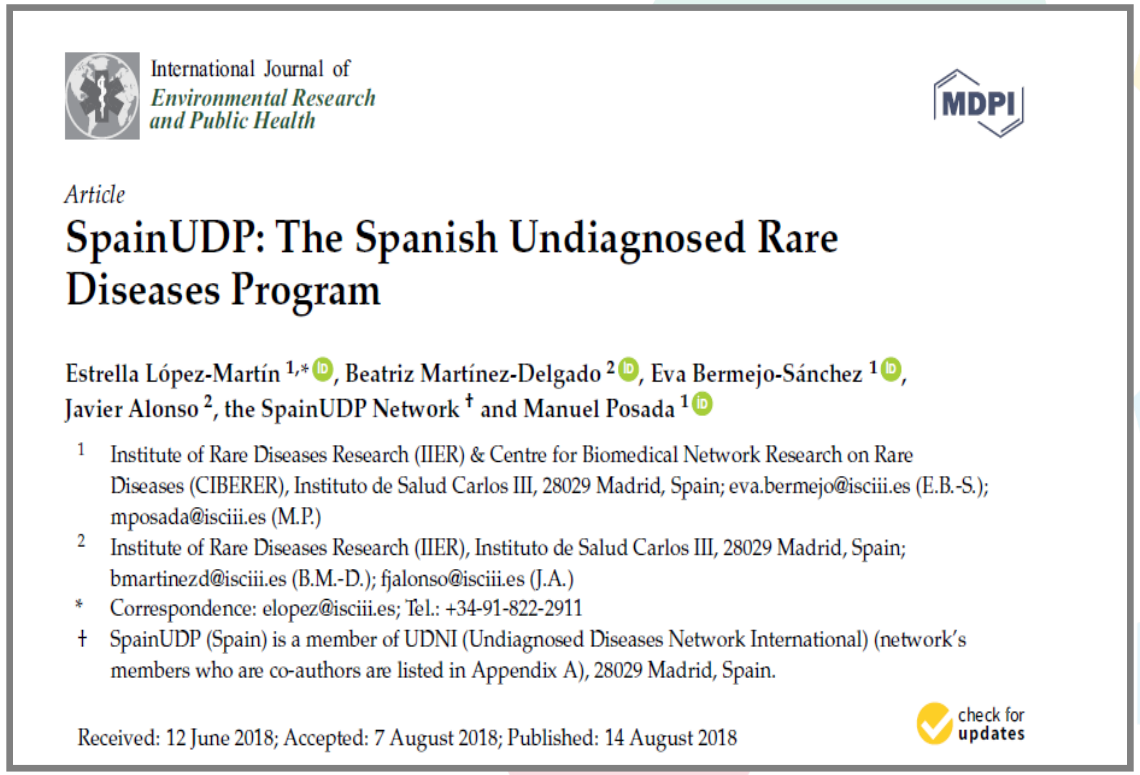
THE SPANISH UNDIAGNOSED RARE DISEASES PROGRAM



International Journal of *Environmental Research and Public Health*

MDPI

Article

SpainUDP: The Spanish Undiagnosed Rare Diseases Program

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check for updates

You can find more information in:

http://spainudp.isciii.es

SpainUDP

Programa de Casos de Enfermedades Raras Sin Diagnóstico
Undiagnosed Rare Diseases Program

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DIAGNOSTIC APPROACH: Process (I)

- **Deep phenotyping in collaboration with:**
  - **Local clinicians**
  - **Patient associations**

Wilhelm Foundation

feder entidad de utilidad pública
FEDERACIÓN ESPAÑOLA DE ENFERMEDADES RARAS

objetivo diagnóstico

BLACKSWAN® FOUNDATION

d´genes

  - **Hospitals supporting UDPs**

SpainUDP
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Undiagnosed Rare Diseases Program

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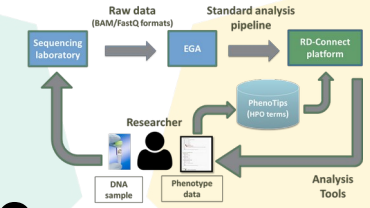
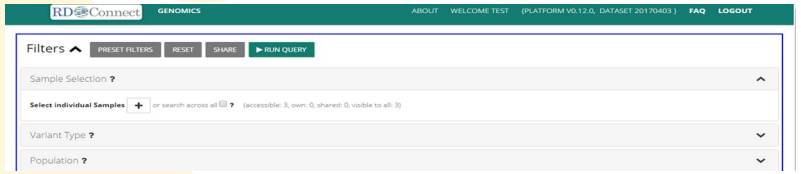
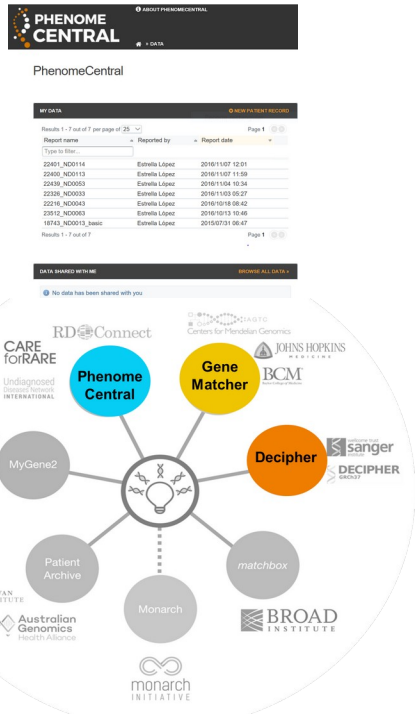
DIAGNOSTIC APPROACH: Process (II)

- WES analysis & confirmation
  - Double check
    - IIER Pipeline
    - RD-Connect Pipeline
  - Candidates confirmation – Sanger
- Other omics
- Functional assays
- Data sharing
  - RD-CONNECT
  - SOLVE-RD
  - Phenome Central → MatchMaker Exchange







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CASE DESCRIPTION: Background

CHILD WITH A NEUROLOGICAL DISEASE

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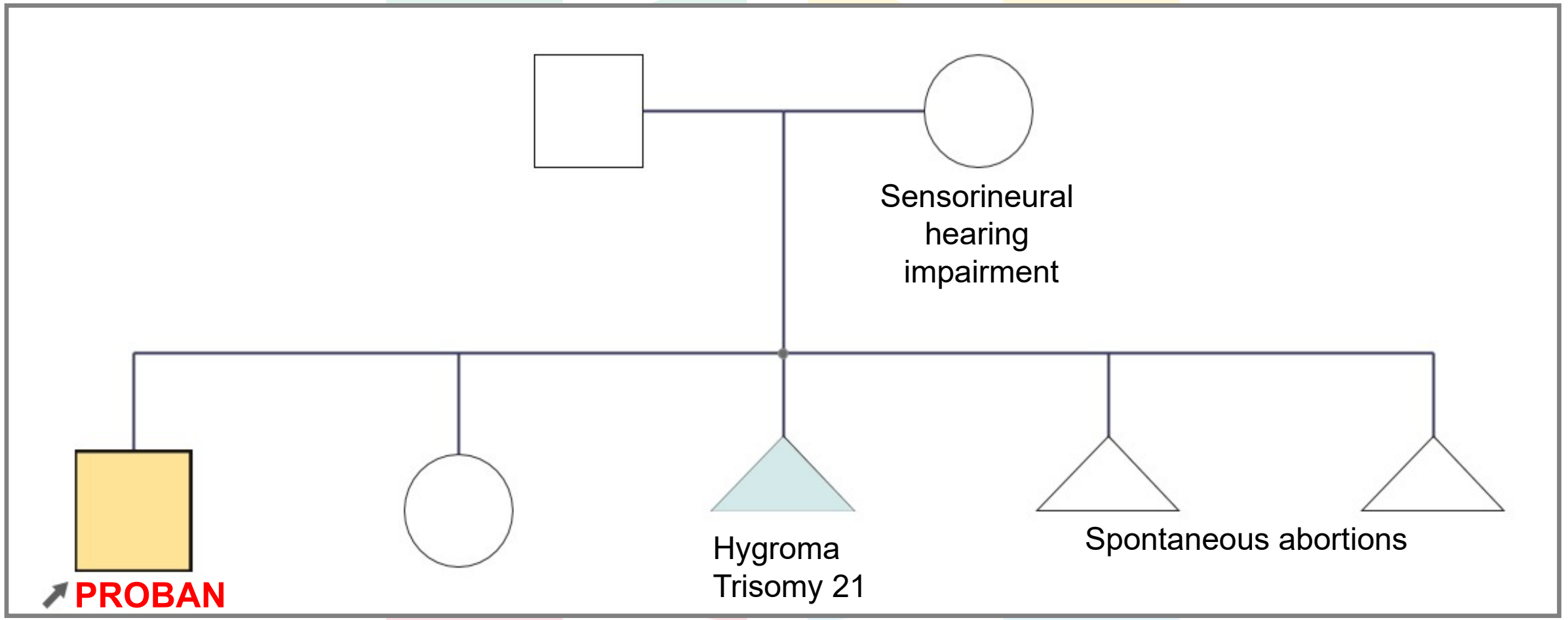
CASE DESCRIPTION: Family history



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CASE DESCRIPTION: Prenatal and perinatal history

Gestation at delivery (weeks)	41
Assisted reproduction:	
NO Conception after fertility medication	
NO Intrauterine insemination (IUI)	
NO In vitro fertilization	
NO Intra-cytoplasmic sperm injection	
NO Gestational surrogacy	
NO Donor egg	
NO Donor sperm	
APGAR score (1 minute)	9
APGAR score (5 minutes)	10

PRENATAL DEVELOPMENT

Decreased fetal movement

Age:	0m	
Weight:	3.22 kg	40th pctl (-0.26SD)
Height:	54.0 cm	! 99th pctl (+2.17SD)
BMI:	11.04	! 2nd pctl (-2.09SD)
Head circumference:	36.0 cm	54th pctl (+0.1SD)

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CASE DESCRIPTION:
Clinical symptoms and physical findings (I)

Age:	**2y 3m**	
Weight:	8.4 kg	!! 0th pctl (-3.63SD)
Height:	84.0 cm	4th pctl (-1.78SD)
BMI:	11.9	!! 0th pctl (-4.0SD)
Head circumference:	46.0 cm	! 1st pctl (-2.47SD)

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CASE DESCRIPTION:
Clinical symptoms and physical findings (II)

- **Craniofacial:**
  - **Microcephaly**
  - **Low-set ears**
  - **Hypertelorism**
  - **Microretrognathia**
  - **Partial lateral cleft palate**
- **Bell-shaped thorax**
- **Dorsal kyphosis**

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CASE DESCRIPTION:
Clinical symptoms and physical findings (III)

- Intellectual disability with severe language impairment
- Global developmental delay
- Generalized muscle weakness
- Diminished osteotendinous reflexes
- Bilateral sensorineural hearing impairment
- Swallowing difficulties
- Happy demeanor
- Epilepsy
- Other: excessive mucus in the upper respiratory ways and gastroesophageal reflux

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CASE DESCRIPTION:
Complementary tests

- Auditory evoked potentials: ↓ auditory capacity, bilateral
- Fundus eye examination and retinoscopy: normal
- Electrocardiogram and Doppler ultrasonography: normal
- Electromyogram: signs of chronic neurogenic affectation
- Electroneurogram: motor conduction altered
- Blood analysis: normal CK, normal thyroid function, hypoglycemia, hypocholesterolemia, ↓LDL, ↑ GOT, ↓GGT
- Cranial magnetic resonance imaging: arachnoid cysts

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CASE DESCRIPTION:
Previous genetic studies

- Karyotype: normal (46,XY)
- Fluorescence in situ hybridization (FISH) for probe 22q11.2: normal
- Array CGH: normal
- Single-gene sequencing for connexin-26 gene: 13:20763686, c.35delG (p.Gly12fs) → pathogenic heterozygous variant (maternal inheritance), associated to deafness AD 3A

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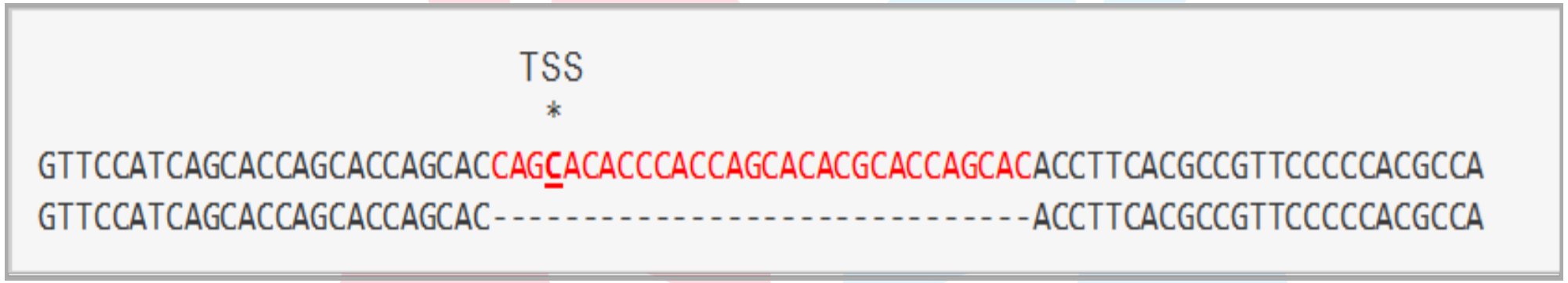
DIAGNOSTIC APPROACH (I)

Results from WES

Candidate gene*: Gene X*
Associated to: Gen X syndrome or Mental retardation, AD XX

De novo 30-bp non-frameshift deletion in exon 9 of the *Gene X*:



Loss of 10 aminoacids in the Gene X protein (p.Gln532_His541del).

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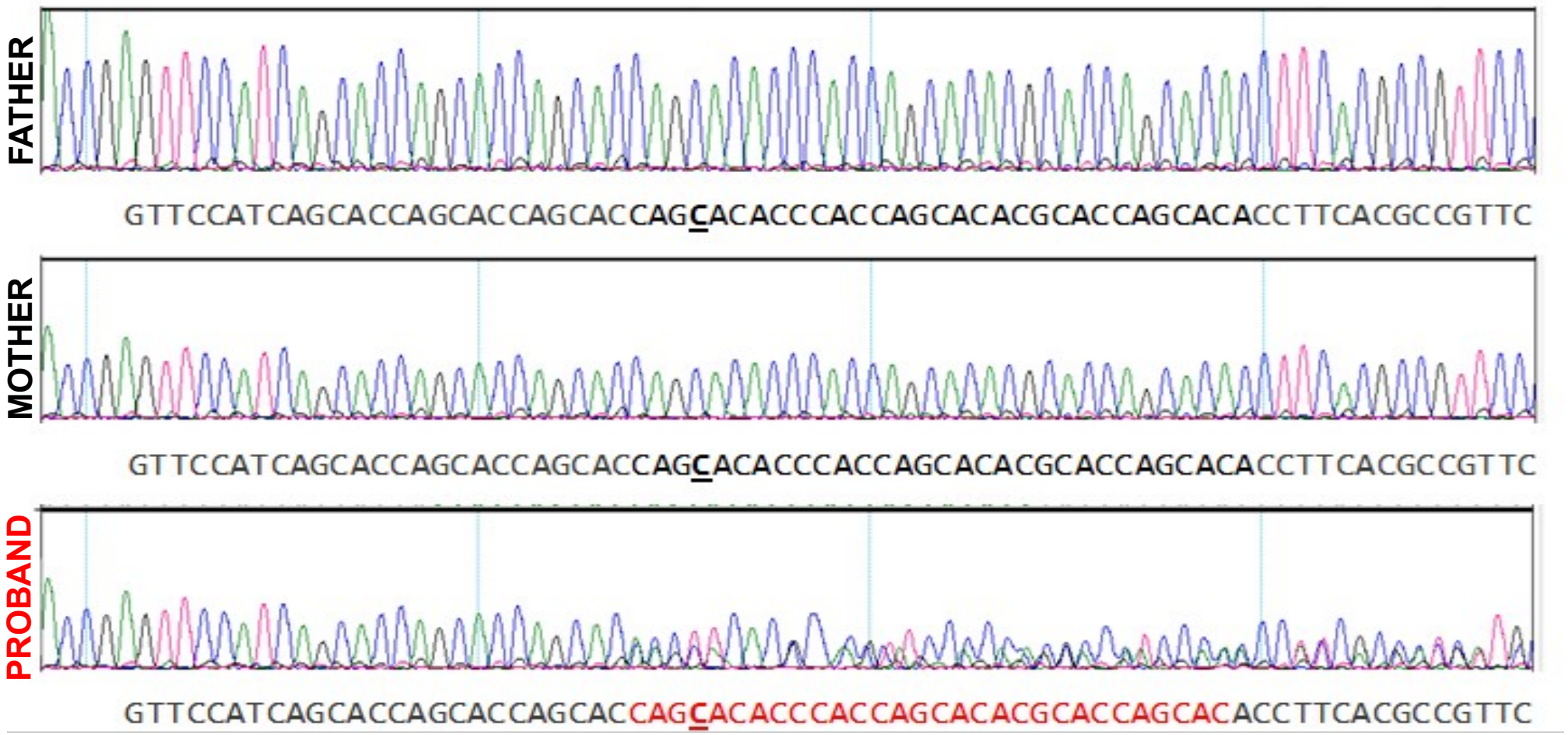
DIAGNOSTIC APPROACH (II)

Confirmation through Sanger sequencing



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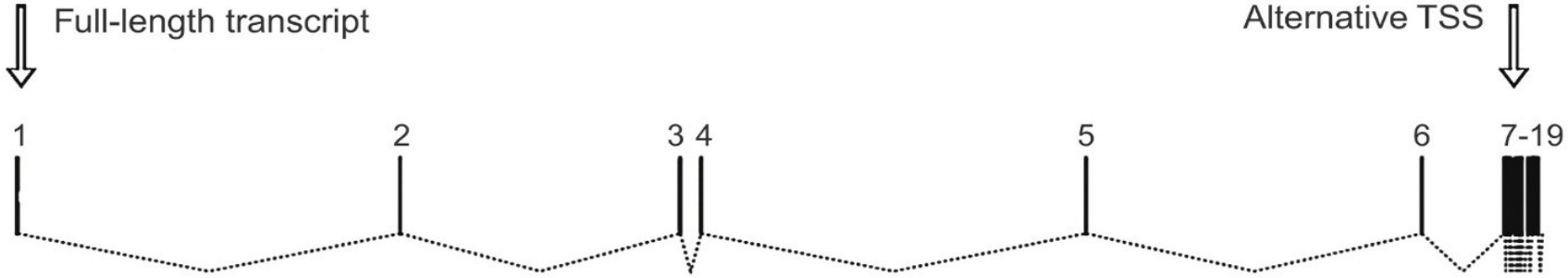
DIAGNOSTIC APPROACH (III)



intron 8 exon 9

gtctccctcttcttctcttccagag AGCAAGACATCTTGCGACAGGAACTGAACACTCGTTTTTTGGCCTCTCAGA

GTGCTGACCGCGGGGCTTCCCTGGGCCCTCCGCCCTACCTGCGGACCGAGTTCCATCAGCACCAGCACCAGCACCAG

*

CACACCCACCAGCACACGCACCAGCACACCTTCACGCCGTTCCCCCCACGCCATCCCACCCACCGCCATC

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DIAGNOSTIC APPROACH (IV)

Results from WES

Candidate gene*: Gene X*
Associated to: Gen X syndrome or Mental retardation, AD XX

De novo 30-bp non-frameshift deletion in exon 9 of the *Gene X*:

Loss of 10 aminoacids in the Gene X protein (p.Gln532_His541del).

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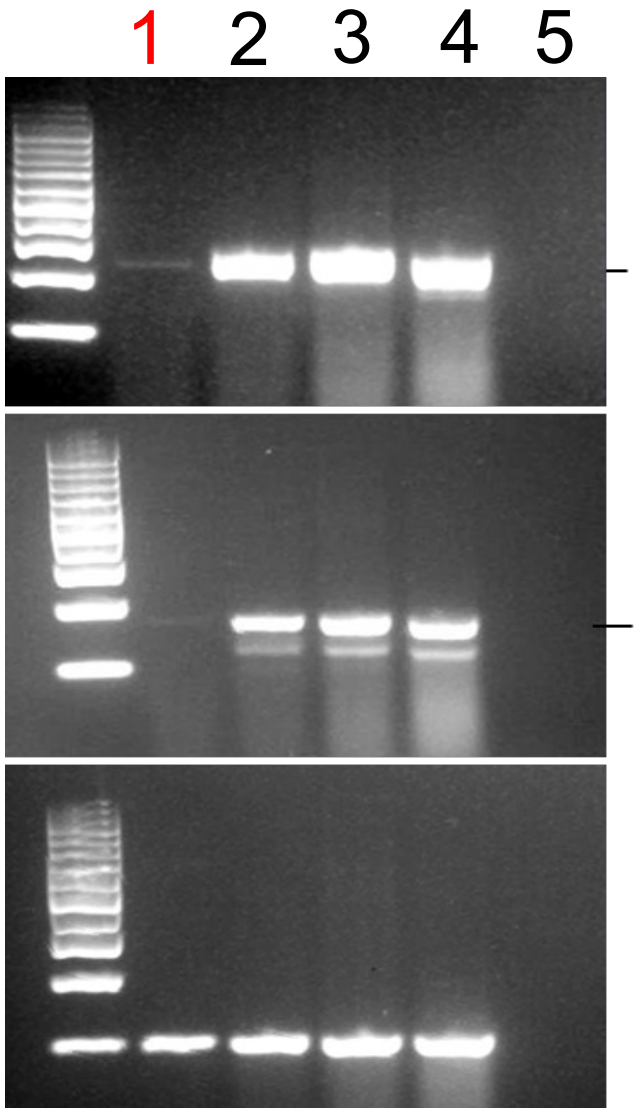
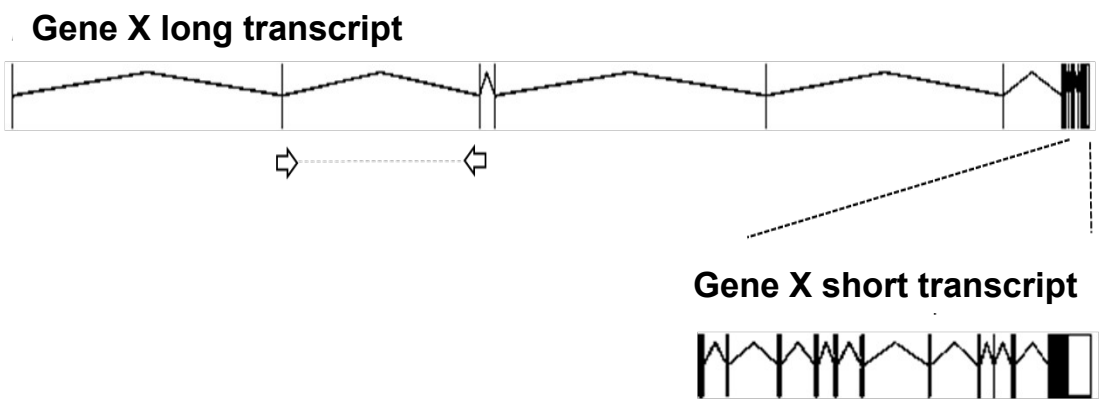
DIAGNOSTIC APPROACH (V)





1. Proband
2. Mother
3. Father
4. Positive control
5. Negative control

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DIAGNOSTIC APPROACH (VI)

Characteristics and Clinical Features	Patient	Published individuals	
		N/Total*	%
General			
Age at examination	3y		
Sex	male		
De novo occurrence	+	18/23	78
Growth and feeding			
Low birth weight	-	10/26	38
Short stature	+	16/30	53
Microcephaly	+	17/28	61
Feeding difficulties	+	15/27	55
Neurodevelopmental			
Intellectual disability/development delay	+	32/32	100
Autism/autistic behavior	-	13/19	68
Sound hypersensitivity	-	5/13	38
Hyperactivity/ADHD	-	4/25	16
Neurological			
Structural brain anomaly	+	7/21	33
Generalized hypotonia	+	13/29	45
High muscle tone/spasticity	-	10/26	38
Dysmorphic features			
Highly arched eyebrows	-	10/27	37
Hypertelorism	+	10/27	37
Proptosis	-	8/27	30
Short palpebral fissures	-	10/27	37
Upslanting palpebral fissures	+	5/26	19
Ptosis	-	11/27	41
Epicanthic fold	-	8/27	30
Strabismus	+	8/28	29
Deep nasal bridge	-	8/27	30
Prominent nasal tip	+	8/27	30
Anteverted nares	+	5/27	19
Short/upturned philtrum	+	14/29	48
Narrow mouth	-	15/26	58
Micro/retrognathia	+	10/26	38
Low-set ears	+	8/26	31
Ear pit	-	2/26	8
Musculoskeletal abnormalities			
Kyphosis/scoliosis	+	5/15	30
Arthrogryposis/shallow palmar creases	-	4/21	19
Tight heel cords	-	6/9	67
Associated birth defects			
Umbilical/inguinal hernia	-	3/30	
Patent foramen ovale/atrial septal defect	-	4/31	

(*) Total with specified data on each specific trait

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CASE RESOLUTION

Conclusions

- Usually, severe phenotypes of Gene X syndrome are related to large deletions in the *Gene X*. However, here we describe a severe phenotype in a patient with a small deletion in the *Gene X*, but affecting to a critical point for its transcription. The presence of this 30-bp deletion in the patient disturbs the expression of not only the short transcript, but also the long Gene X isoform, showing remarkably reduced expression of the *Gene X* in peripheral blood. Also, the patient we describe here shares many of the most distinctive features associated with the Gene X syndrome.

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CASE RESOLUTION

Conclusions

- **These results allow the diagnosis of this patient as Gene X syndrome or Mental Retardation, autosomal dominant XX. In addition, this patient was previously diagnosed as Deafness autosomal dominant 3A.**
- **Difficulties to obtain the correct diagnosis in a patient with pathogenic variants in more than one genetic locus. In this regard, diagnosis process in patients with phenotypic features which could be attributable to either one of the diagnoses (overlapping phenotypes) is particularly challenging.**

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THANK YOU VERY MUCH FOR YOUR ATTENTION¡¡¡

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