



ALAG
MENDOZA,
ARGENTINA **2019**

6 AL 9 DE OCTUBRE DE 2019

La arquitectura
del genoma:
su expresión en
los fenotipos
y las poblaciones

SECUENCIACIÓN EXÓMICA DE PACIENTES CHILENOS CON ENFERMEDADES RARAS NO DIAGNOSTICADAS

Exomic sequencing of Chilean patients with rare undiagnosed diseases

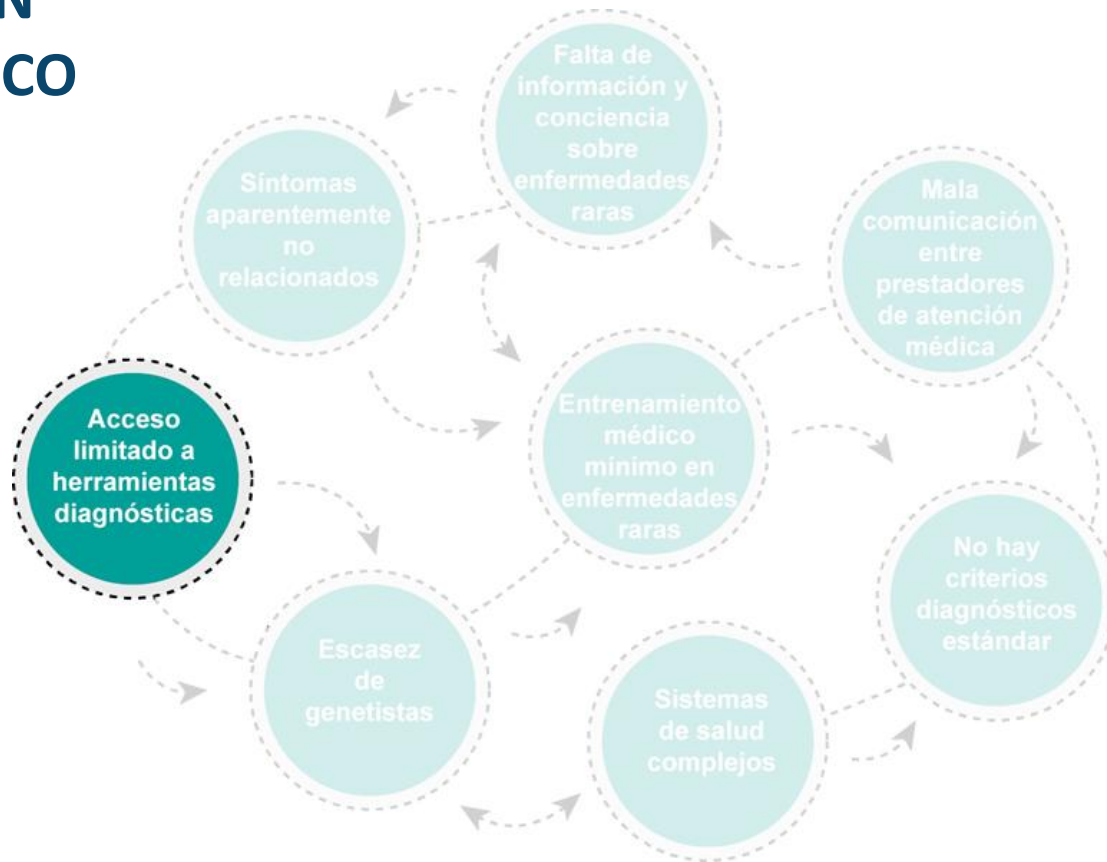
**Gonzalo Encina, Boris Rebolledo, Marcelo Rojas, Cecilia Poli, Luz M. Martin, Esteban San Martín,
Sara Fisher, Sofía Sifaqui, Gabriela Repetto**

Instituto de Ciencias e Innovación en Medicina

Facultad de Medicina - Clínica Alemana

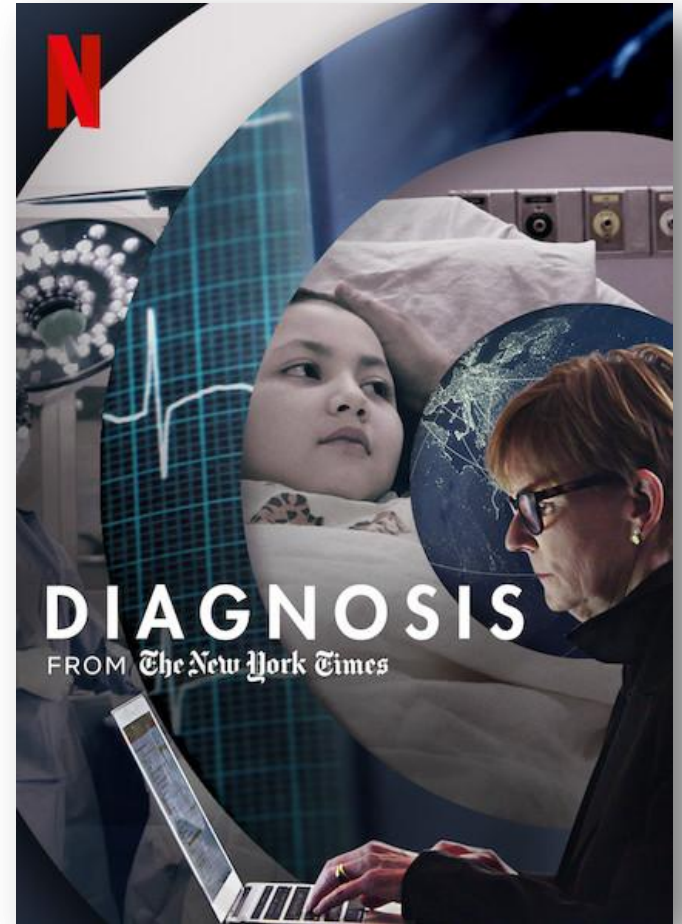
Universidad del Desarrollo

LAS ENFERMEDADES RARAS IMPONEN UN GRAN DESAFÍO DIAGNÓSTICO



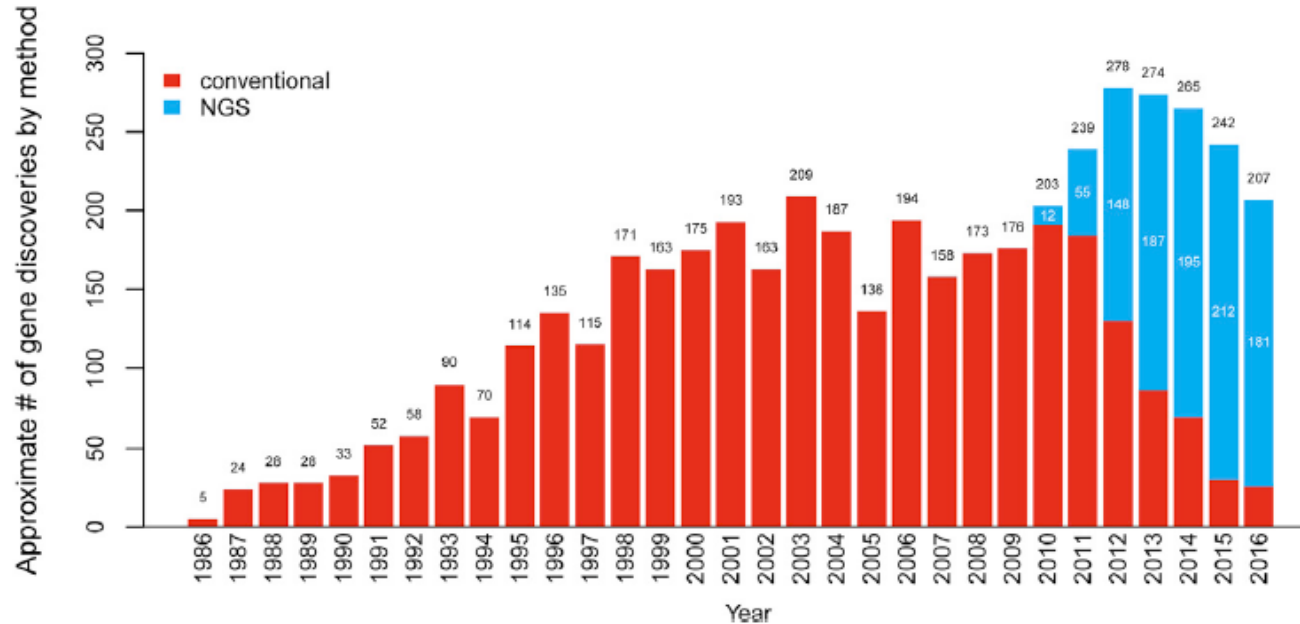
LAS ENFERMEDADES RARAS IMPONEN UN GRAN DESAFÍO DIAGNÓSTICO

Se estima que miles de genes de enfermedades raras y sus mecanismos patogénicos permanecen sin descubrir.

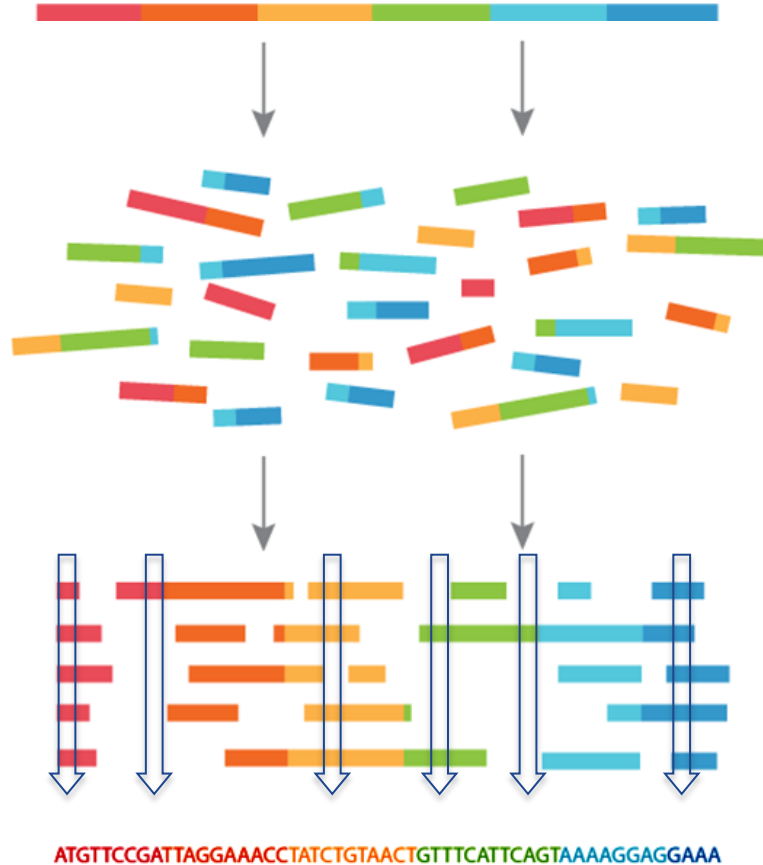


LA SECUENCIACIÓN DE NUEVA GENERACIÓN HA ACELERADO EL DESCUBRIMIENTO DE GENES INVOLUCRADOS EN ENFERMEDADES

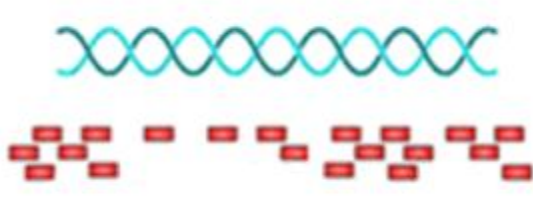
- Desde 2013, con NGS se han descubierto casi tres veces más genes que con los enfoques convencionales.
- A fines del 2017, ~ 5.000 genes involucrados en enfermedades.



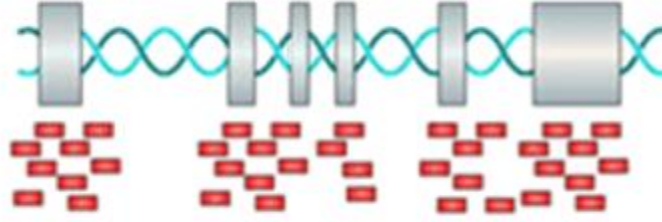
SECUENCIACIÓN DE NUEVA GENERACIÓN



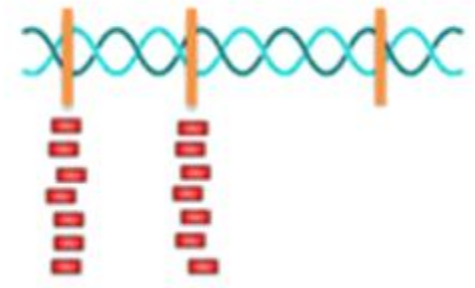
Whole Genome Seq. vs Whole Exome Seq. vs Targeted Gene Seq.



- Profundidad: > 30X
- SNVs, InDels, VE, CNVs
- Variantes codificantes
- Variantes UTRs e intrónicas
- Variantes regulatorias
- Permite descubrir genes no anotados

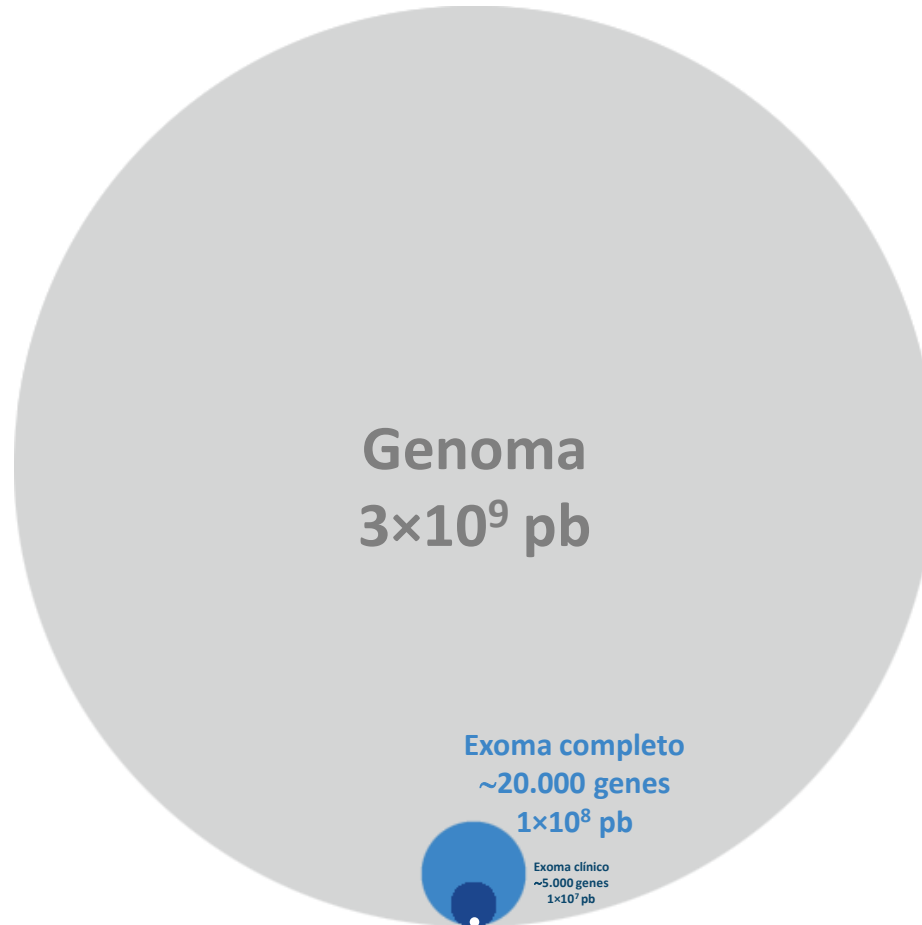


- Profundidad: 50X-100X
- SNPs, InDels, CNVs?
- Variantes codificantes
- Variantes intron-exon
- Permite descubrir genes no asociados a enfermedades

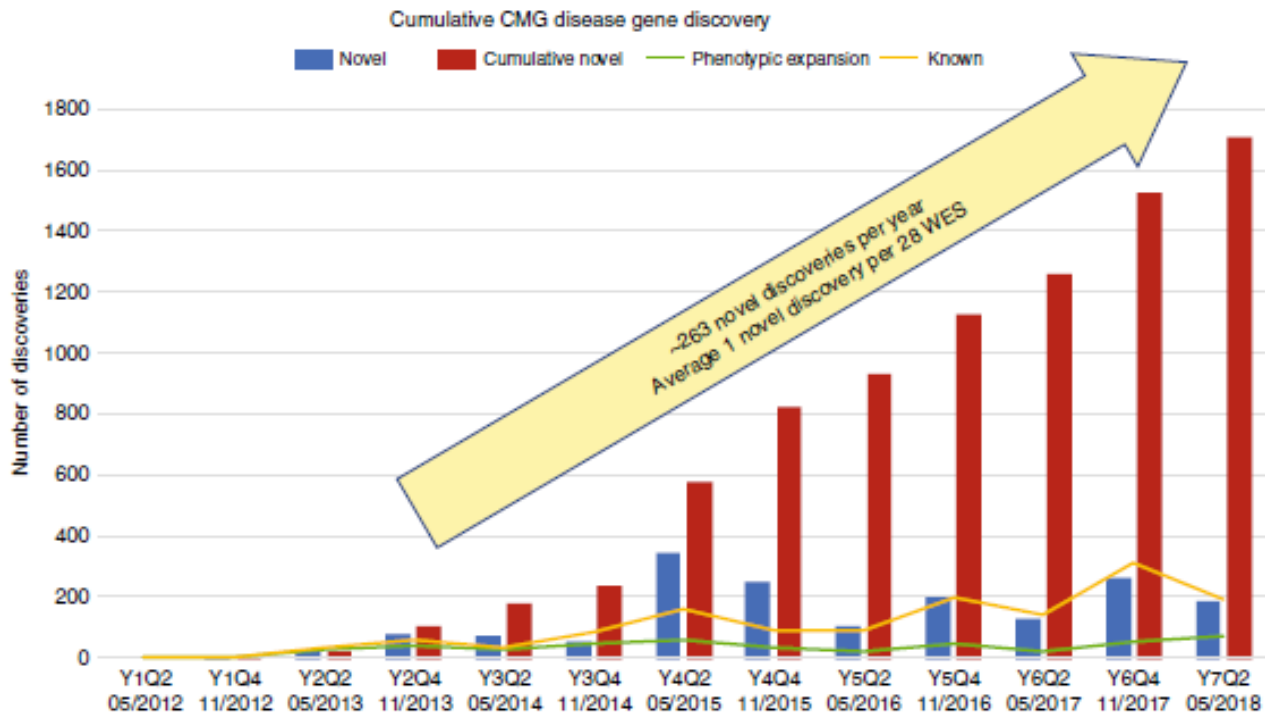


- Profundidad: >500X
- SNPs, InDels
- Variantes codificantes
- Algunas variantes intron-exon
- Permite descubrir variantes en genes asociados a enfermedades

Whole Genome Seq. vs Whole Exome Seq. vs Targeted Gene Seq.



LA SECUENCIACIÓN EXÓMICA HA ACELERADO EL DESCUBRIMIENTO DE GENES INVOLUCRADOS EN ENFERMEDADES



WES: RENDIMIENTO DIAGNÓSTICO 25% -30%

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

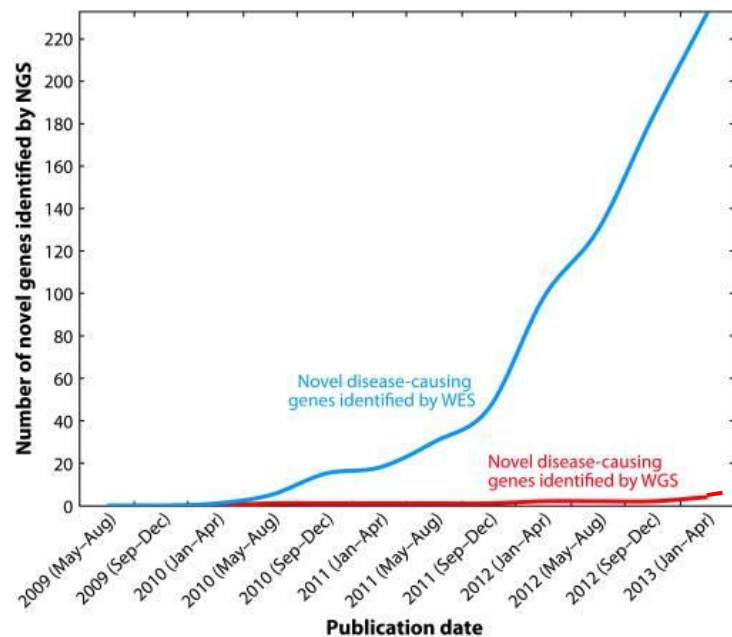
Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D.,
Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S.,
Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D.,
Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D.,
Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D.,
Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D.,
James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D.,
Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.

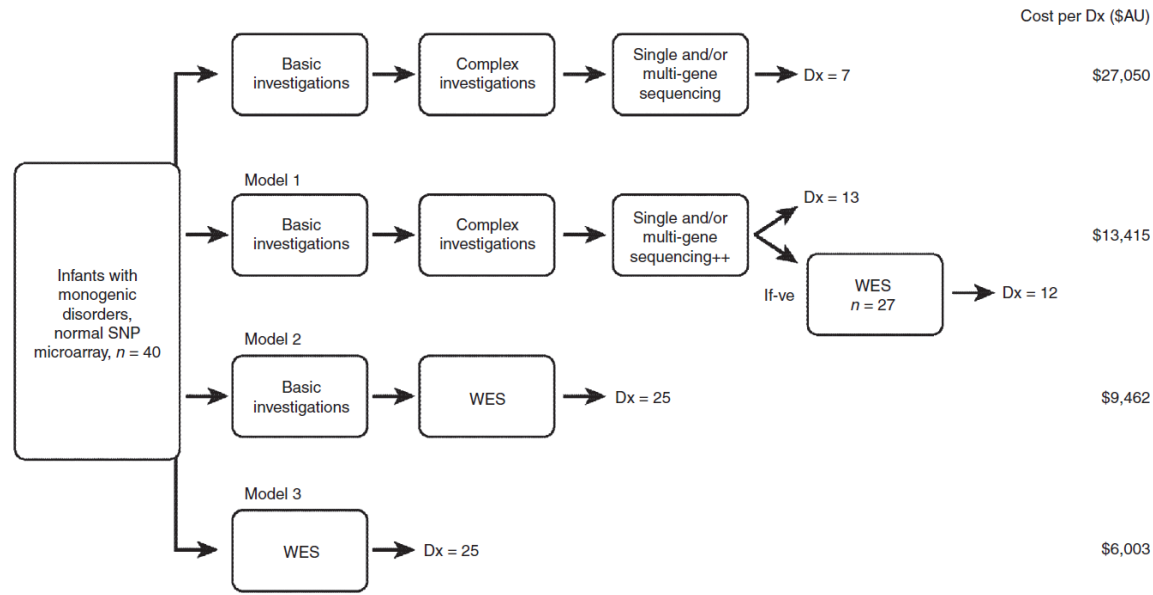
Principalmente para:

- Presentaciones clínicas reconocibles,
- Inicio a edad temprana
- Morbilidad y mortalidad significativas
- Causadas por variantes altamente penetrantes (típicamente codificantes de proteínas).

WES PERMITE DESCUBRIR NUEVOS GENES ASOCIADOS A ENFERMEDADES RARAS



WES AL INICIO DE LA VÍA DIAGNÓSTICA



WGS: Diagnósticos en menos de 10 días

Diagnostics

ORIGINAL ARTICLE

Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children

Lamia Mestek-Boukhibar,¹ Emma Clement,² Wendy D Jones,² Suzanne Drury,³ Louise Ocaka,¹ Andrey Gagunashvili,¹ Polona Le Quesne Stabej,¹ Chiara Bacchelli,¹ Nital Jani,¹ Shamima Rahman,⁴ Lucy Jenkins,⁵ Jane A Hurst,² Maria Bitner-Glindzicz,⁴ Mark Peters,⁶ Philip L Beales,¹ Hywel J Williams¹

WGS: Diagnósticos en < 24 horas

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GENETIC DIAGNOSIS

Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation

Michelle M. Clark¹, Amber Hildreth^{1,2,3}, Sergey Batalov¹, Yan Ding¹, Shimul Chowdhury¹, Kelly Watkins¹, Katarzyna Ellsworth¹, Brandon Camp¹, Cyrielle I. Kint⁴, Calum Yacoubian⁵, Lauge Farnaes^{1,2}, Matthew N. Bainbridge^{1,6}, Curtis Beebe⁷, Joshua J. A. Braun¹, Margaret Bray⁸, Jeanne Carroll^{1,2}, Julie A. Cakici¹, Sara A. Caylor¹, Christina Clarke¹, Mitchell P. Creed⁹, Jennifer Friedman^{1,10}, Alison Frith⁵, Richard Gain⁵, Mary Gaughran¹, Shauna George⁷, Sheldon Gilmer⁷, Joseph Gleeson^{1,10}, Jeremy Gore¹¹, Haiying Grunenwald¹², Raymond L. Hovey¹, Marie L. Janes¹, Kejia Lin⁷, Paul D. McDonagh⁸, Kyle McBride⁷, Patrick Mulrooney¹, Shareef Nahas¹, Daeheon Oh¹, Albert Oriol⁷, Laura Puckett¹, Zia Rady¹, Martin G. Reese¹³, Julie Ryu^{1,2}, Lisa Salz¹, Erica Sanford^{1,2}, Lawrence Stewart⁷, Nathaly Sweeney^{1,2}, Mari Tokita¹, Luca Van Der Kraan¹, Sarah White¹, Kristen Wigby^{1,2}, Brett Williams⁵, Terence Wong¹, Meredith S. Wright¹, Catherine Yamada¹, Peter Schols⁴, John Reynders⁸, Kevin Hall¹², David Dimmock¹, Narayanan Veeraraghavan¹, Thomas Defay⁸, Stephen F. Kingsmore^{1*}

Medicina Genómica en “Países en desarrollo”

Limitaciones:

- Recursos para investigación e infraestructura
- Acceso a conocimiento
- Implementación clínica
- Educación genómica
- Colaboración internacional



Medicina Genómica en “Países en desarrollo”

nature > genetics in medicine > articles > article

Genetics
inMedicine

Article | Published: 02 November 2017

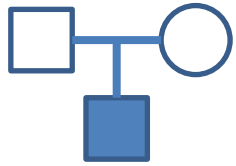
Proband-only medical exome sequencing as a cost-effective first-tier genetic diagnostic test for patients without prior molecular tests and clinical diagnosis in a developing country: the China experience

Xuyun Hu PhD, Niu Li PhD, Yufei Xu MS, Guoqiang Li MS, Tingting Yu PhD, Ru-en Yao PhD, Lijun Fu MD, PhD, Jiwen Wang MD, PhD, Lei Yin MD, PhD, Yong Yin MD, PhD, Ying Wang MD, PhD, Xingming Jin MD, PhD, Xiumin Wang PhD, Jian Wang PhD ✉ & Yiping Shen PhD ✉

Recordemos: WGS vs WES vs TS



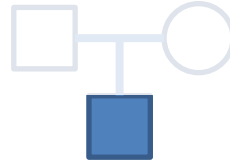
¿Exoma completo o exoma clínico?



WES de tríos

vs

CES solo de probandos



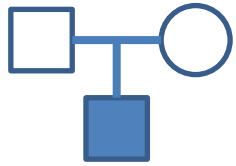
- 20.000 genes x rxn
- Tasa diagnóstica $\approx 30\%$
- Permite descubrir nuevos genes asociados a enfermedades

- 100 secuencias (33 tríos)
- 10 diagnósticos

- 5000 genes x rxn
- Tasa diagnóstica $\approx 25\%$
- Menor costo
- Capacidad existente en Chile
- ¿Menor frecuencia de VUS?

- 100 secuencias
- 25 diagnósticos

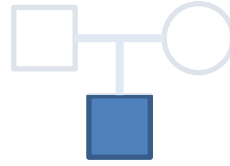
¿Exoma completo o exoma clínico?



**WES
de tríos**

vs

**CES solo de
probandos**



WES/WGS tríos (Baylor o labs clínicos) vs POMES (UDD)

Tasa de detección

Costo

\$/caso detectado

Fenotipos predictores de > % dg

¿Enfermedades nuevas, o variantes nuevas en genes conocidos, propias de la población chilena?

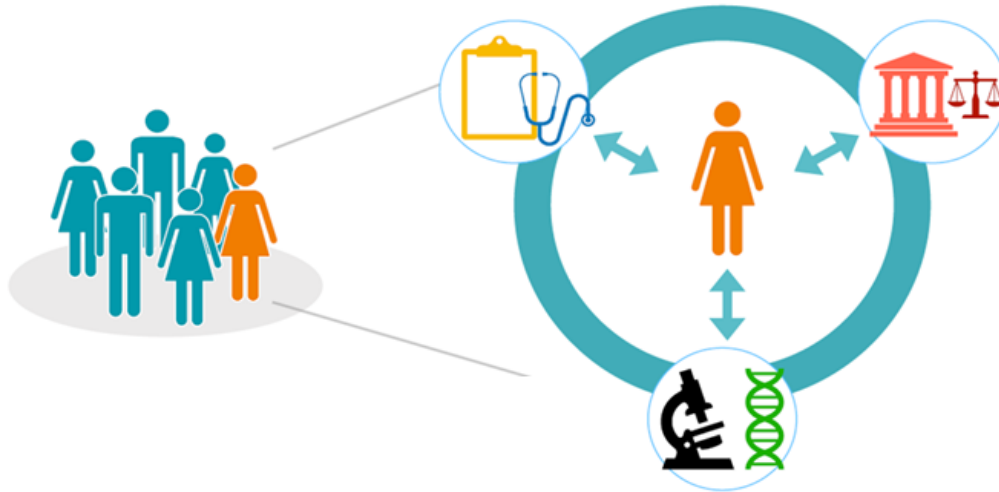
DECIPHERD

Decoding Complex Inherited Phenotypes of Rare Disorders

Decodificando Fenotipos Hereditarios Complejos en Enfermedades Raras

Cuidado clínico de excelencia
a pacientes con EPoF

Proponer y promover políticas
públicas, aspectos regulatorios, éticos y
de participación en EPoF



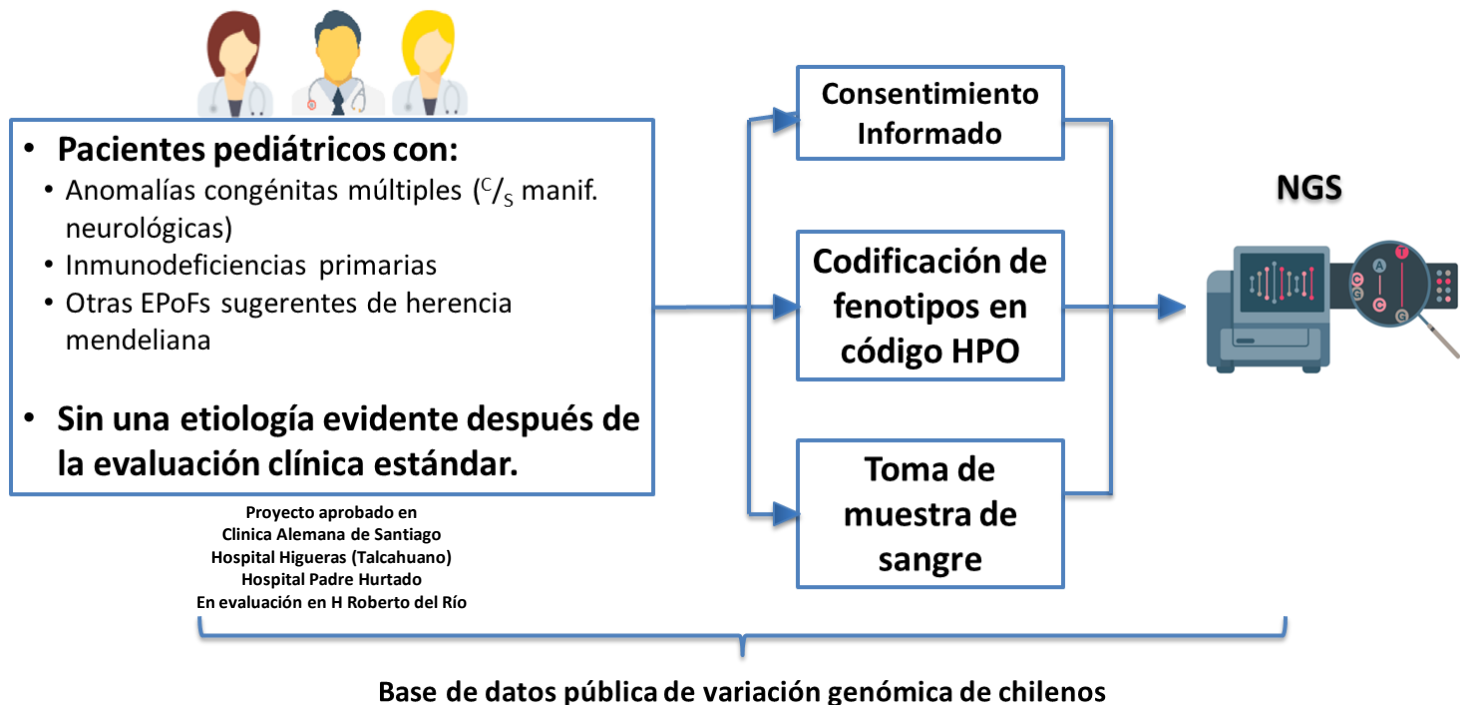
Herramientas genómicas para descubrir nuevas EPoF

Entendimiento de mecanismos y estrategias terapéuticas para EPoF

DECIPHERD

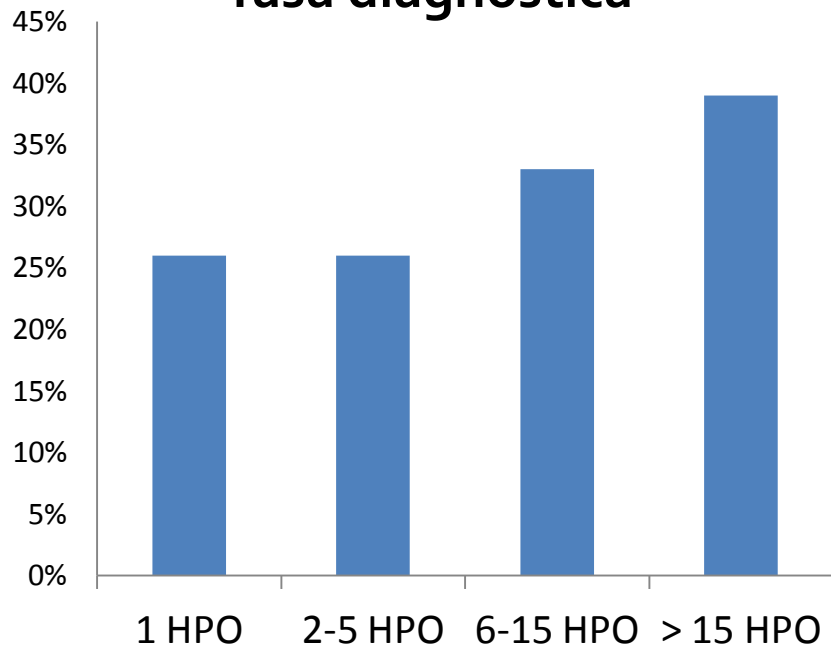
Decoding Complex Inherited Phenotypes of Rare Disorders

Decodificando Fenotipos Hereditarios Complejos en Enfermedades Raras



La tasa diagnóstica aumenta a mayor número de características clínicas (HPO).

Tasa diagnóstica



ARTICLE

Clinical exome sequencing: results from 2819 samples reflecting 1000 families

Daniel Trujillano^{*,1,10}, Aida M Bertoli-Avella^{1,10}, Krishna Kumar Kandaswamy^{1,10}, Maximilian ER Weiss¹, Julia Köster¹, Anett Marais¹, Omid Paknia¹, Rolf Schröder¹, Jose Maria Garcia-Aznar¹, Martin Werber¹, Oliver Brandau¹, Maria Calvo del Castillo¹, Caterina Baldi¹, Karen Wessel¹, Shivendra Kishore¹, Nahid Nahavandi¹, Wafaa Eyaid^{2,3}, Muhammad Talal Al Rifai^{3,4}, Ahmed Al-Rumayyan^{3,4}, Waleed Al-Twajiri^{3,4}, Ali Alothaim^{3,5}, Amal Alhashem⁶, Nouriya Al-Sannaa⁷, Mohammed Al-Balwi^{3,4}, Majid Alfadhel^{2,3}, Arndt Rolfs^{1,8} and Rami Abou Jamra^{*,1,9}

PHENOTIPS

Caracterización fenotípica estandarizada del paciente

PHENO TIPS

Gonzalo Encina Log-out

data P0000004

Create Browse Search

P0000004

Reported by Sara Fischer on 2019/06/02 20:27 · Last modified on 2019/06/04 11:33

Edit Jump to More actions

This record is owned by Sara Fischer and is open

Clinical symptoms and physical findings

GROWTH PARAMETERS

Head circumference for age
Microcephaly (<-3SD)
Failure to thrive in infancy

SCALP/SKULL

Abnormal facial shape

EYES

Strabismus

UPPER EXTREMITIES

Small hand

LOWER EXTREMITIES

Small feet
Limited knee extension

NEUROLOGICAL

Hypertonia
Autistic behavior
Global developmental delay
Partial agenesis of the corpus callosum
Cerebral white matter hypoplasia
Cognitive impairment

CARDIOVASCULAR SYSTEM

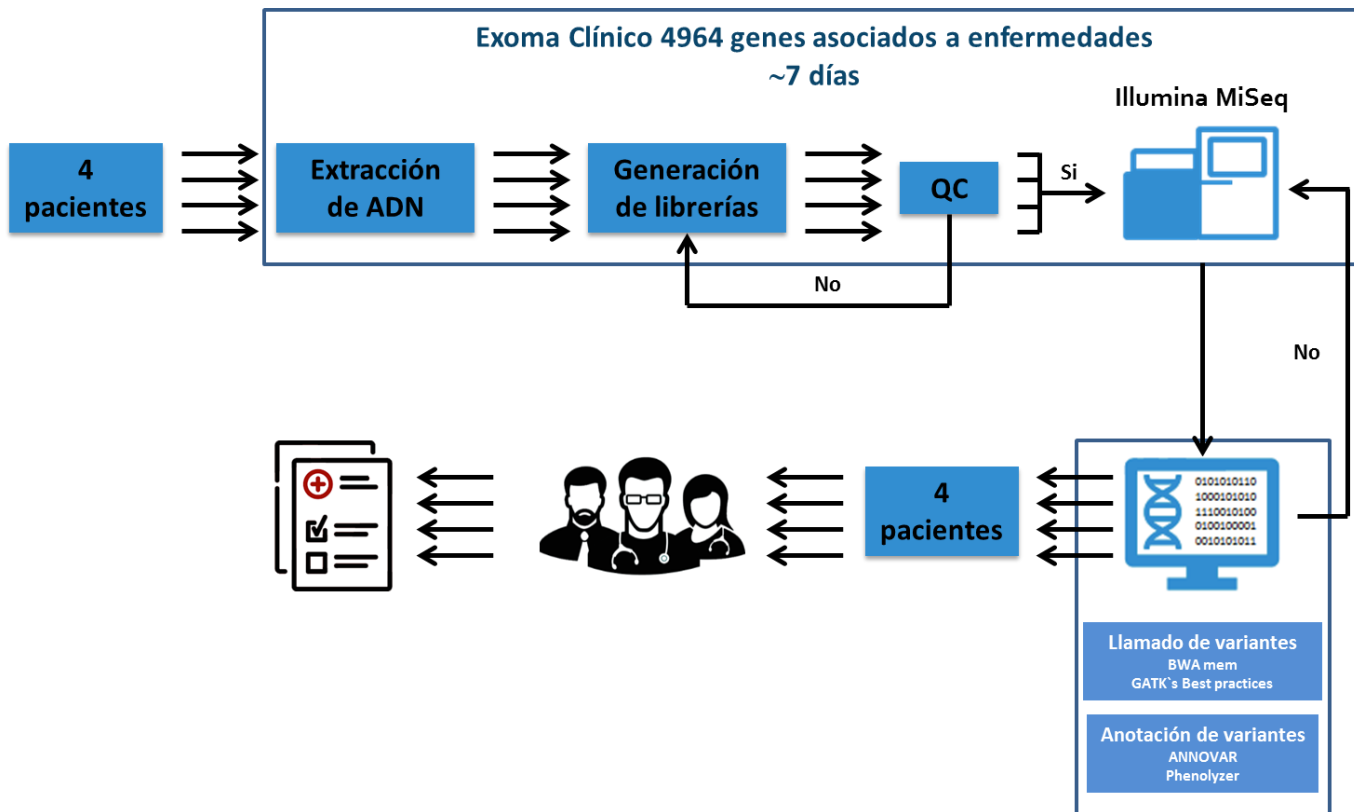
Prolonged QT interval

DIGESTIVE SYSTEM

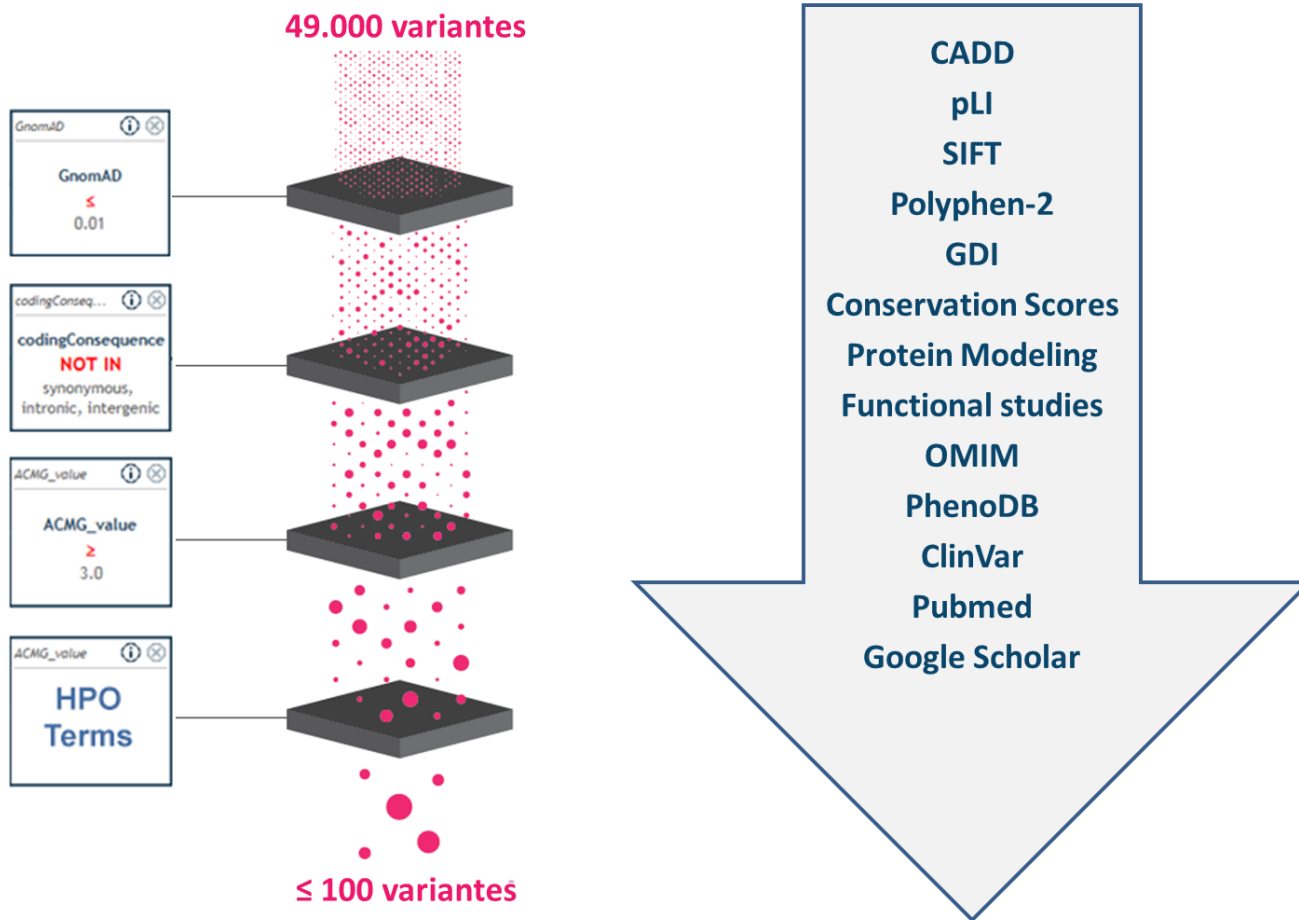
Gastroesophageal reflux

DECIPHERD

Flujo de trabajo multidisciplinario



Filtrado y priorización de variantes

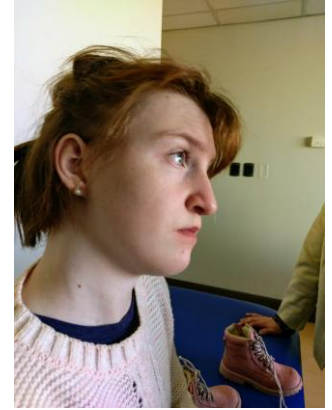


Interpretación clínica de variantes



Caso 1

- **Mujer**
- **14 años**
- **Déficit Cognitivo Severo**
- **Trastorno de la Marcha**
 - Contracturas
 - Ataxia?
- **Dismotilidad Intestinal**
 - Antecedente de 2 obstrucciones intestinales (resección de 1.5 m ID)
- **RNM cerebral**
 - Disgenesia del cuerpo calloso
 - Disminución del volumen de la sustancia blanca
- **Dg: Obs Encefalopatía Neurogastrointestinal Mitocondrial (MNGIE)**



KAT6A c.3385T p.(Arg1129*)

KAT6A = histone acetyl transferase 6

[About](#)[Statistics ▾](#)[Downloads ▾](#)[Contact Us](#)[MIMmatch](#)[Donate ▾](#)[Help ▾](#)[Options ▾](#)View Results as: [Gene Map Table](#)[Clinical Synopsis](#)Display: ☒ Highlights

Search: 'KAT6A '

Results: 8 entries.

[Download As ▾](#)1: * [601408. LYSINE ACETYLTRANSFERASE 6A; KAT6A](#)

MOZ/CBP FUSION GENE, INCLUDED

Cytogenetic location: [8p11.21](#), Genomic coordinates (GRCh38): [8:41,929,478-42,051,987](#)Matching terms: [kat6a](#)[► Gene-Phenotype Relationships](#) [► Links](#)2: * [602410. BROMODOMAIN- AND PHD FINGER-CONTAINING PROTEIN; BRPF1](#)Cytogenetic location: [3p25.3](#), Genomic coordinates (GRCh38): [3:9,731,728-9,748,014](#)Matching terms: [kat6a](#)[► Gene-Phenotype Relationships](#) [► Links](#)3: # [616268. MENTAL RETARDATION, AUTOSOMAL DOMINANT 32; MRD32](#)Cytogenetic location: [8p11.21](#)Matching terms: [kat6a](#)[► Phenotype-Gene Relationships](#) [► Phenotypic Series](#) [► ICD+](#) [► Links](#)4: # [617333. INTELLECTUAL DEVELOPMENTAL DISORDER WITH DYSMORPHIC FACIES AND PTOSIS; IDDDFP](#)Cytogenetic location: [3p25.3](#)Matching terms: [kat6a](#)[► Phenotype-Gene Relationships](#) [► Links](#)

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#616268

[Table of Contents](#)[MIM Entry](#)[Phenotypic Series](#)**CARDIOVASCULAR***Heart*

- Atrial septal defect
- Ventricular septal defect

Vascular

- Patent ductus arteriosus

RESPIRATORY

- Respiratory distress, neonatal

ABDOMEN*Gastrointestinal*

- Feeding difficulties
- Gastrointestinal reflux

SKELETAL*Skull*

- Craniosynostosis

MUSCLE, SOFT TISSUES

- Hypotonia, neonatal

NEUROLOGIC*Central Nervous System*

- Delayed psychomotor development
- Poor or absent speech
- Seizures (rare)

MISCELLANEOUS

- All reported mutations have occurred de novo
- Facial dysmorphic features are variable

MOLECULAR BASIS

- Caused by mutation in the K(lysine) acetyltransferase 6A gene (**KAT6A**, 601408.0001)

External Links**Clinical Resources**[Clinical Trials](#)
[EuroGentest](#)
[GTR](#)
[OrphaNet](#)
[POSSUM](#)

https://amelie.stanford.edu

AMELIE (Automatic Mendelian Literature Evaluation) — [Create new case](#) | [Help](#) | Please cite: <https://doi.org/10.1101/171322>

Bejerano Lab, Stanford

Enter case information

Demo 1 (Wiedemann-Steiner Syndrome)

Demo 2 (Schuurs-Hoeijmakers Syndrome)

Demo 3 (Aicardi-Goutières Syndrome)

Case ID (optional; max 1000 characters)

☐ Upload VCF (Do not load PHI data. Local install version forthcoming)

☒ Enter gene list

Candidate genes (Ensembl ID/HGNC name
(+ optional "dominant"/"all"); **one per line**;
max. 1000 genes; click a demo button for an example)

Case phenotypes
(HPO IDs; max. 1,000 phenotypes;
one per line; see [HPO Browser](#))

Email address to send results link to (optional):

Submit

A movie poster for the film 'Amelie' featuring Audrey Tautou. The poster has a dark background with green star-like speckles. At the top, it says 'She'll change your life.' Below that is a close-up of Audrey Tautou's face, smiling slightly. The text 'Audrey TAUOU' and 'Mathieu KASSOVITZ' is written in a small font. The title 'Amelie' is in a large, stylized yellow font. At the bottom, it says 'A film by JEAN-PIERRE JEUNET'. There is also some small text at the very bottom of the poster.

Whole Exome Sequencing Reveals De Novo Pathogenic Variants in *KAT6A* as a Cause of a Neurodevelopmental Disorder

Francisca Millan,^{1*} Megan T. Cho,¹ Kyle Retterer,¹ Kristin G. Monaghan,¹ Renkui Bai,¹ Patrik Vitazka,¹ David B. Everman,² Brooke Smith,² Brad Angle,³ Victoria Roberts,³ LaDonna Immken,⁴ Honey Nagakura,⁴ Marc DiFazio,⁵ Elliott Sherr,⁶ Eden Haverfield,¹ Bethany Friedman,¹ Aida Telegrafi,¹ Jane Juusola,¹ Wendy K. Chung,⁷ and Sherri Bale¹

¹GeneDx, Gaithersburg, Maryland

²Greenwood Genetic Center, Greenville, South Carolina

³Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

⁴Specially For Children Genetics, Austin, Texas

⁵Children's Outpatient Center of Montgomery County, Rockville, Maryland

⁶Institute of Human Genetics, University of California, San Francisco, California

⁷Departments of Pediatrics and Medicine, Columbia University Medical Center, New York, New York

Manuscript Received: 5 March 2015; Manuscript Accepted: 6 April 2016

TABLE 1. Clinical Characteristics and Sequence Variants Found in Reported Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Novel variant	c.3462delA, p.Gly1155Alafs*21	c.3287delG, p.Cys1096Phefs*27	c.3230delA, p.Asn1077Metfs*46	c.3070C>T, p.Arg1024Ter	c.1928 A>G, p.Asn643Ser	c.3040-1_3040delGA
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo
Gender	Female	Male	Female	Female	Female	Male
Age	2 years	9 years	11 years	5 years	6 years	29 years
Family history	Two unaffected siblings	Two unaffected siblings	Unremarkable	Unaffected younger brother	Unaffected younger maternal half-brother	24 year old sister with ID and autism
Global Developmental Delay/ Intellectual Disability	+	+	+	+	+	+
Motor Development	Sat unsupported at 18 months, non-ambulatory at 2 years	Walked at 24 months	Walked at 24 months	Walked at 19 months	Walked at 19 months	Walked at 22 months
Speech	Non-verbal	Non-verbal	4–5 words at age 7 years	Three words at 5 years	Three words at 3 years	Non-verbal
Hypotonia	+	+	–	+	+	+
Failure to Thrive	+	–	+	–	+	+
Height	5–10th percentile	10–25th percentile	25–50th percentile	>75th percentile	10–25th percentile	10–25th percentile
Weight	25–50th percentile	75th percentile	10–25th percentile	>75th percentile	25–50th percentile	50th percentile
OFC	<3rd percentile	<10th percentile	25th percentile	25–70th percentile	25–50th percentile	50–75th percentile
Microcephaly	– (A)	Mild microcephaly	–	–	–	–
Facial dysmorphism	+	+	+	+	+	+
Congenital heart disease	ASD	–	–	–	–	–
GI	Vomiting, dysphagia	Constipation	Severe GERD Constipation	Resolved GERD	–	Severe GERD in infancy
Brain CT/MRI	N	N	abN ^a	abN ^b	N	abN ^c

DD, Developmental Delay; ID, Intellectual Disability; OFC, Occipito-Frontal Circumference; A, Acquired; C, congenital; ASD, Atrial Septal Defect; MRI, Magnetic Resonance Imaging; N, Normal; abN, abnormal.

^aMicrocephaly, no parenchymal abnormalities.

^bHyperintense signal in posterior periventricular white matter in the T2/FLAIR sequences.

^cMissing olfactory bulb.



Patient 2



Patient 5

Patient 6

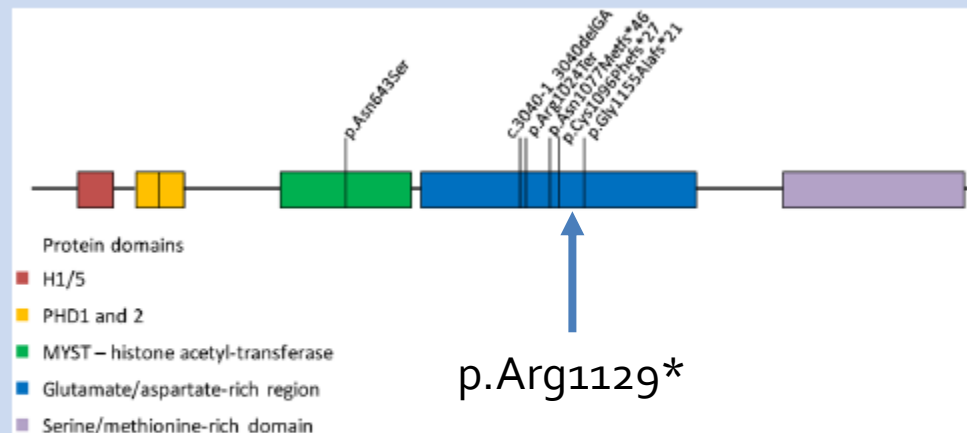
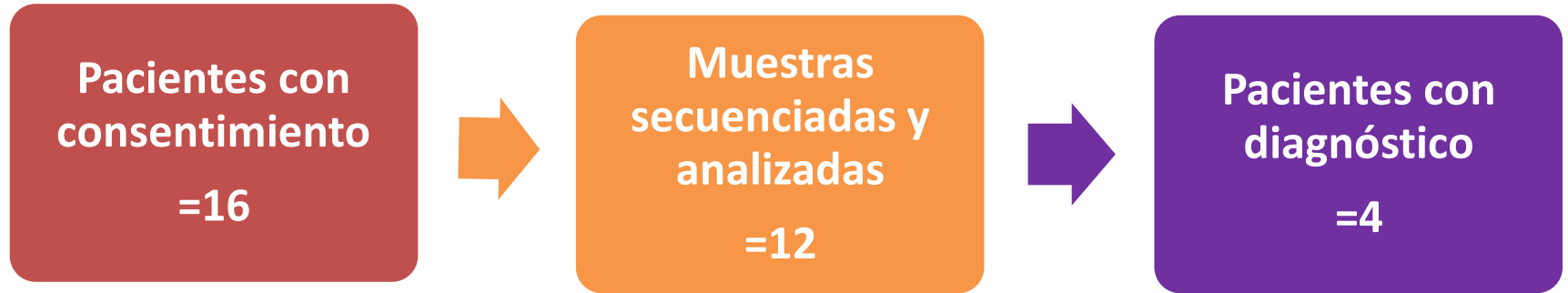


FIG. 2. Schematic representation of *KAT6A* protein and its domains. Vertical lines represent the position at which the sequence variations found in the *KAT6A* gene in the six patients reported here would affect the encoded protein. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>].

FENOTIPO DE LOS PACIENTES Y SU DIAGNÓSTICO

Paciente	Genero	Fenotipo													Diagnóstico
		Neurológico			Dismorfia facial	Ojo, nariz, oreja y boca	Sistema Cardiovascular	Sistema Respiratorio	Sistema Digestivo	Sistema genito-urinario	Sistema musculoesquelético	Sistema endocrino	Sistema inmune	Tegumento	
		DI/ RDSM	Alteración Neuroimagen	Otro											
UDD-001	F	+	+	-	+	+	-	+	+	-	+	-	-	+	DDX3X
UDD-002	M	+	-	+	+	+	-	-	-	-	+	-	-	-	-
UDD-017	F	+	+	+	+	+	+	-	+	-	+	-	-	-	KAT6A
UDD-018	F	+	-	+	+	-	-	-	+	-	+	-	-	-	-
UDD-024	F	+	-	+	+	+	-	+	-	-	-	-	-	-	-
UDD-026	M	+	-	+	+	+	-	-	-	+	+	-	-	+	NFIX
UDD-027	M	+	+	+	+	+	-	-	-	-	-	-	-	-	TCF4
UDD-028	F	-	-	-	+	+	-	-	-	+	+	-	-	-	-
UDD-030	F	-	+	+	+	+	-	-	-	-	+	-	-	-	-
UDD-031	F	+	-	+	+	+	-	-	-	+	+	-	-	+	-
UDD-032	M	+	-	+	+	+	-	-	-	-	+	-	-	-	-
UDD-033	F	-	-	-	-	+	+	-	-	+	-	+	-	-	-

Resumen de resultados iniciales



En resumen

- Hemos identificado 4 variantes en genes *KAT6A*, *TCF4*, *NFIX* y *DDX3X* como probables responsables de las etiologías.
- Nuestros resultados iniciales muestran la factibilidad y utilidad de exomas clínicos para el estudio de niños y adolescentes con enfermedades raras no diagnosticadas.
- Aparentemente podría existir una mayor sensibilidad diagnóstica en pacientes con discapacidad intelectual y/o retraso del desarrollo psicomotor y fenotipos más severos (mayor número de sistemas afectados).
- Relevancia de equipos multidisciplinarios.

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