Informe final

Asistente de investigación

Grupo de Investigación

CIGUR

Línea de investigación

Enfermedades raras

Autor:

Bibiana Alejandra Bayona Gómez, Lina Paola Castro Castillo

Investigador a cargo y/o Director del Grupo de investigación

Carlos M. Restrepo

Informe presentado como requisito para optar por el

título de Pediatra

Bogotá-Colombia

2024

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Escuela de Medicina y Ciencias de la Salud

Universidad Del Rosario

Pediatria

Bogotá- Colombia

2024

Contenido

1 Productos año 1:

1.1 Cursos:

**Se realizaron clases teóricas, para aprender a realizar el análisis de variantes genéticas, la clase fue dada por la Dra. Tatiana y el Dr. Juan Sebastián

1.1.1 Análisis de variantes genéticas:

Es un proceso mediante el cual se identifican, estudian y comprenden las alteraciones o variaciones en el ADN que pueden estar relacionadas con características específicas, como enfermedades hereditarias o rasgos fenotípicos. Las variantes genéticas pueden ser tan pequeñas como un cambio en una sola base del ADN (polimorfismo de un solo nucleótido, o SNP) o involucrar reordenamientos más grandes de secuencias genómicas.

¿Cómo lo realizamos en nuestro estudio?

El análisis de variantes genéticas típicamente sigue estos pasos:

1. **Extracción de ADN**: El ADN se extrae de una muestra biológica, como sangre, saliva o tejido→ en nuestro caso, se tomaron muestras se sangre en las jornadas medicas, se llevaron a análisis genético.

2. **Secuenciación del ADN**: Se utiliza una técnica de secuenciación para leer la secuencia completa del ADN o regiones específicas de interés. Esto puede hacerse mediante secuenciación de nueva generación (NGS) o secuenciación Sanger, entre otros métodos.

3. **Identificación de variantes**: El ADN secuenciado se compara con una referencia genómica para identificar las variantes. Esto incluye SNPs, inserciones, deleciones y otros tipos de variantes estructurales.

3.1 A cada estudiante, se le asignaron 3 o 4 pacientes, para análisis de variantes y selecciones de genes patológicos, probablemente patológicos y benignos.

Con los cuales, posteriormente, se realizaran nuevos análisis, que concordaran con el cuadro clínico del paciente.

4. **Análisis bioinformático**: Los datos obtenidos se analizan utilizando herramientas bioinformáticas que permiten identificar, clasificar y priorizar las variantes en función de su posible relevancia funcional, patogénica o clínica.

5. **Interpretación de variantes**: Finalmente, las variantes identificadas se interpretan en el contexto clínico o de investigación para determinar su posible impacto en la salud, desarrollo de enfermedades o respuesta a tratamientos.

Objetivo de este análisis:

- **Diagnóstico de enfermedades hereditarias**.

- **Identificación de predisposiciones genéticas a enfermedades comunes**.

- **Medicina personalizada**, donde se ajustan tratamientos en función del perfil genético del paciente.

- **Investigación de enfermedades raras** para identificar variantes que puedan estar relacionadas con fenotipos poco comunes.

Este análisis es esencial en la investigación traslacional, ya que facilita la identificación de mutaciones clave y su relación con la enfermedad, lo cual es especialmente relevante para enfermedades raras o en poblaciones con características genéticas particulares, como es el objetivo del estudio.

1.1.2 Realización de genealogías:

Consisten en el estudio y registro de las relaciones familiares a lo largo del tiempo. Es una herramienta importante para investigar la historia familiar y también tiene aplicaciones en genética, antropología y estudios de poblaciones. Las genealogías permiten rastrear antepasados, identificar patrones hereditarios y, en algunos casos, vincular la ascendencia con enfermedades genéticas.

-¿Cómo realizamos las genealogías en nuestro estudio?

-Recopilación de información: El proceso comienza con la obtención de información familiar básica, incluyendo nombres, fechas de nacimiento, matrimonios, defunciones, y lugares. Esta información puede provenir de registros civiles, religiosos, entrevistas con familiares, archivos históricos y bases de datos genealógicas.

Organización de datos: Una vez recopilados los datos, es importante organizarlos de manera clara y estructurada para poder construir el árbol genealógico. Aquí es donde los software especializados son útiles, ya que permiten manejar grandes volúmenes de datos y visualizarlos de manera coherente.

Construcción del árbol genealógico: Se elabora un diagrama o representación gráfica que muestra las conexiones entre las diferentes generaciones. Esto puede incluir tanto líneas ascendentes (ancestros) como descendentes (descendientes).

Verificación y ampliación de la información: Es esencial verificar la exactitud de los datos consultando fuentes oficiales. A medida que la investigación avanza, el árbol genealógico puede ampliarse con nuevas ramas y detalles, incluso incorporando análisis de ADN para descubrir relaciones más remotas o inesperadas.

Software para realizar genealogías

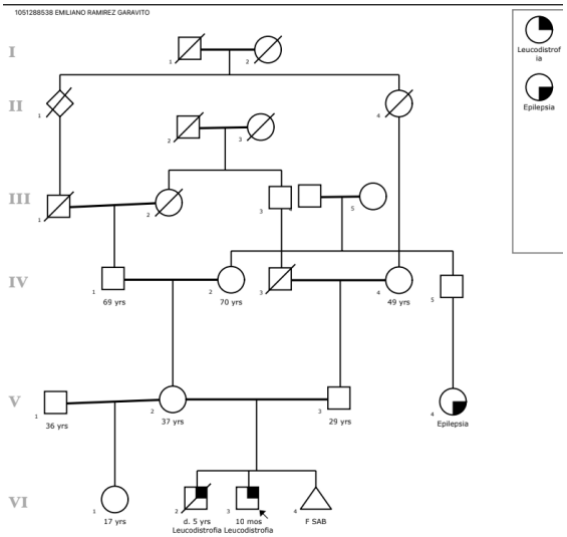
Existen varios programas que facilitan la construcción de genealogías. Algunos permiten almacenar información, generar gráficos y realizar análisis avanzados. A continuación, algunos de los más utilizados:

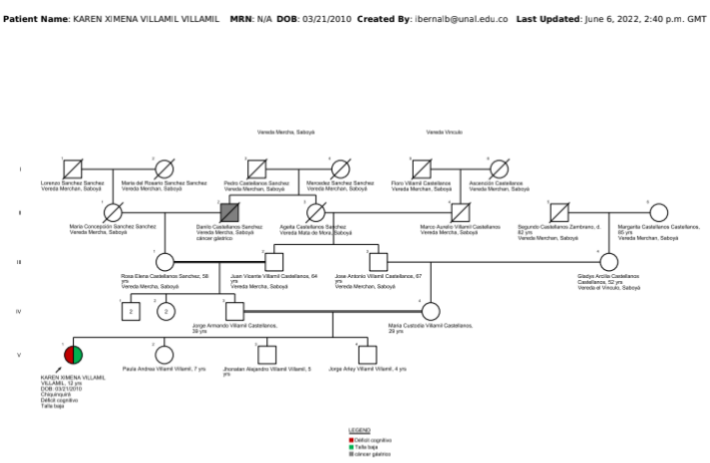
FamilySearch:

- Descripción: Es una plataforma gratuita gestionada por la Iglesia de Jesucristo de los Santos de los Últimos Días que ofrece acceso a una base de datos genealógica enorme. Permite crear y compartir árboles genealógicos.
- Características: Base de datos pública, colaboración con otros usuarios, almacenamiento de documentos e imágenes.
- Ideal para: Usuarios principiantes o investigadores que buscan acceso gratuito a una gran base de datos de genealogía.

Ancestry: (sofware elegido)

- Descripción: Es una de las plataformas más populares para la investigación genealógica, aunque es de pago. Ofrece una vasta base de datos de registros históricos y la opción de realizar pruebas de ADN.
- Características: Herramientas de búsqueda avanzadas, registros históricos, integración con pruebas de ADN para conexiones familiares.
- Ideal para: Usuarios interesados en combinar pruebas de ADN con genealogía tradicional.





1.2 Protocolo/plan del producto a desarrollar

1.2.1 "Un método para identificar enfermedades raras con investigación traslacional en aislados geográficos del departamento de Boyacá explorando la ancestría"

Rol en el proyecto: Coinvestigador

Estoy inscrita en MINCIENCIAS

Funciones:

Colaboración con el investigador principal en la planificación y ejecución del proyecto

Aporto conocimiento en el área de pediatría:

- Realización de historias clínicas en brigadas médicas en Boyacá
- Valoración de pacientes pediátricos
- Recolección y análisis de datos en brigadas-realización de genealogías de pacientes pediátricos
- Publicación de casos clínicos pediátricos, de enfermedades poco prevalentes

El presente informe de investigación describe el desarrollo y objetivos del proyecto titulado **"Un método para identificar enfermedades raras con investigación traslacional en aislados geográficos del departamento de Boyacá explorando la ancestría"**, llevado a cabo por la Universidad Nacional de Colombia, la Universidad del Rosario y la I.P.S Medisens, bajo la financiación y reconocimiento del Ministerio de Ciencia y Tecnología de Colombia.

El objetivo principal del proyecto es estudiar un conjunto de enfermedades raras que afectan a las comunidades del departamento de Boyacá, una región conocida por su alta tasa de consanguinidad, la cual triplica el promedio nacional. Esta característica particular es la razón por la que Boyacá concentra una elevada

cantidad de enfermedades genéticas, muchas de ellas catalogadas como raras o ultra raras. Además, se han identificado patologías sin tratamiento, no diagnosticadas y posiblemente nuevas, lo que subraya la necesidad de investigación en esta zona.

Uno de los aspectos más relevantes de este proyecto es su enfoque en la **investigación traslacional**, que busca aplicar los hallazgos genéticos directamente a la mejora del diagnóstico y tratamiento en las poblaciones afectadas. A través de estudios genéticos detallados y la identificación de patrones familiares mediante el análisis de **isonimias** (apellidos recurrentes en las familias afectadas), el equipo de investigación busca mapear las áreas geográficas donde se agrupan estas enfermedades. Esto permitirá identificar a las poblaciones en mayor riesgo y facilitar la implementación de estrategias de prevención primaria.

El proyecto también tiene como objetivo contribuir a la legislación sobre **enfermedades huérfanas en Colombia**, proponiendo mejoras en el diagnóstico temprano y la optimización de los recursos del sistema de salud, especialmente para patologías de alto costo. La personalización de las estrategias de tratamiento y diagnóstico de acuerdo con las particularidades genéticas y geográficas de estas comunidades es uno de los resultados esperados de la investigación.

Para lograr estos objetivos, el equipo de investigación ha solicitado el acceso a las bases de datos de enfermedades huérfanas con el fin de recolectar información valiosa que permita la identificación de casos no diagnosticados. El proyecto ha sido aprobado tanto por el **Ministerio de Ciencia y Tecnología** como por los comités de ética correspondientes, garantizando el cumplimiento de todas las normativas de confidencialidad y asegurando que las intervenciones genéticas sean aplicadas de manera ética y efectiva.

En resumen, este proyecto tiene el potencial de revolucionar la manera en que se diagnostican y tratan las enfermedades raras en Colombia, enfocándose en una región geográficamente aislada como Boyacá. A través de un enfoque innovador que combina la investigación genética con el análisis poblacional, se espera no solo mejorar la calidad de vida de las comunidades afectadas, sino también aportar al conocimiento global de las enfermedades raras y ultra raras.

1.3 -Participación en seminarios o talleres al interior del Grupo de Investigación para este año:

1.3.1 Jornadas de campo:

Se realiza elaboración de historia clínica, toma de muestras de laboratorio, realización de genealogías.

Fecha	Numero de pacientes /familiar	Actividades
26 de febrero 2022	10 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías

7 de mayo 2022	6 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías
28 de mayo 2022	9 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías
8 de octubre 2022	9 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías
29 de octubre 2022	5 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías

1.3.2 Participación en juntas médicas y reuniones de servicio semanales:

Se realizan reuniones semanales los días martes y miércoles a las 6 o 7 pm, con los genetistas, biología molecular, residentes y estudiantes, para comentar los casos clínicos valorados, seleccionar pacientes para el estudio.

Se adjuntan evidencia en la participación de juntas:

1 de marzo 2022:

Acta N. 3 de reunión virtual del equipo clínico

Fecha: 01/03/2022

Hora: 6:30pm – 8:00pm

Plataforma Virtual: Zoom

Asistentes

1. Erika Jimenez
2. Juan Sebastián Arias
3. Lina Castro
4. Bibiana Bayona
5. Valeria Correa
6. Ingrid Bernal
7. Carlos Restrepo
8. Harvy Velasco

Agenda

1. Presentación de los pacientes valorados en la jornada de consulta médica de genética en la ciudad de Tunja.
2. Definición de realización de estudios moleculares en los casos revisados.
3. Definición de tareas nuevas.

Desarrollo de la agenda

La jornada de valoración de pacientes fue dividida en dos equipos en cabeza del Dr. Carlos Martin Restrepo y la Dra. Ingrid Tatyana Bernal, se realizó la valoración de un total de 10 paciente a los cuales se les realizó historia clínica y árbol genealógico completo.

Todos los integrantes del equipo médico adjuntaron la información de manera ordenada en la base de datos de pacientes evaluados del proyecto, con el objetivo de acceder a la información recolectada de manera ordenada y eficiente.

Cada integrante del equipo médico que participó en la jornada realiza presentación de los pacientes evaluados, indicando si tienen una alta sospecha de patología de origen genético,

antecedentes de consanguinidad en diferentes generaciones y socialización de datos sociodemográficos de interés identificados durante la valoración.

Se define si es necesaria la realización de un estudio molecular en cada caso presentado y que tipo de estudio.

Se determinan las nuevas tareas a realizar del equipo clínico con el objetivo de realizar una nueva jornada de atención de pacientes.

Conclusiones

1. Se define la realización de los siguientes estudios en los pacientes valorados y presentados:
   a. Paciente 1: Solicitar datos crudos a Colcan para reanálisis de exoma
   b. Paciente 4: Realizar exoma + análisis de CNVs
   c. Paciente 5: Análisis de mutación puntual en el paciente y estudio en cascada
   d. Paciente 18: Realización de exoma completo
   e. Paciente 12: Exoma completo comparando datos con el exoma del paciente 17
   f. Paciente 17: Exoma completo comparando datos con el exoma del paciente 12
   g. Paciente 15: Realización de exoma completo
   h. Paciente 16: Realización de exoma completo
   i. Paciente 21: Realización de exoma completo trio con datos de madre y paciente 20
   j. Paciente 20: Realización de exoma completo trio con datos de madre y paciente 20
2. Se divide una nueva base de datos de pacientes con sospecha de patología genética del departamento de Boyacá facilitada por la Dra. Yasmin Sanchez para definir personal a valorar en la segunda jornada médica.
3. Se propone la realización de cartas de presentación a SIVIGILA y diferentes EPS del departamento de Boyacá.

ASISTENTES

NOMBRE	FIRMAS
Carlos Martin Restrepo	
Harvy Mauricio Velasco	

Ingrid Tatyana Bernal	Tatyana Bernal B.
Juan Sebastian Arias	
Lina Paola Castillo	
Bibiana Bayona	Bibiana Bayona
Erika Jimenez	
Valeria Correa	Valeria Correa Martinez

7 de abril 2022:

Acta N. 5 de reunión virtual del equipo clínico

Fecha: 07/04/2022

Hora: 6:00pm – 7:30pm

Plataforma Virtual: Zoom

Asistentes

1. Erika Jimenez
2. Juan Sebastián Arias
3. Lina Castro
4. Bibiana Bayona
5. Ingrid Bernal
6. Carlos Restrepo
7. Harvy Velasco
8. William Usaquen

Agenda

- Presentación de la base de datos de enfermedades huérfanas del SIVIGILA por parte del Dr. William Usaquen.
- Definición de datos relevantes a revisar en la base de datos.

Desarrollo de la agenda

Se realiza la presentación de la base de datos de pacientes del SIVIGILA por parte del Dr. William Usaquén del equipo de poblaciones, quien previamente anonimizó la información con el objetivo de proteger la identidad de los individuos incluidos en esta base.

La información contenida en la base de datos permite definir que regiones del departamento deben ser priorizadas para el abordaje por parte de los diferentes equipos del proyecto, de acuerdo al número de patologías identificadas y el número de individuos afectados.

Se observa que algunas de las patologías incluidas en la base de datos no tienen un origen genético bien establecido o se trata de signos y síntomas que pueden hacer parte de patologías diferentes de origen multifactorial o genético, razón por la cual se decide que el equipo médico realizará una

revisión de cada una de las enfermedades ingresadas en esta base de datos, aclarando si se trata de una patología de origen genético y que mecanismo de herencia tiene cada una de ellas.

Se define programación de una nueva reunión virtual para discutir los hallazgos identificados en la base de datos del SIVIGILA y programación de una nueva jornada de valoración de pacientes.

Conclusiones

1. La base de datos de enfermedades huérfanas del SIVIGILA permite identificar que regiones del departamento deben ser priorizadas para valoración por el equipo médico y el poblacional.
2. Se debe realizar una revisión exhaustiva de la información contenida en la base de datos del SIVIGILA con el objetivo de esclarecer la presencia de patologías genéticas bien establecidas.

ASISTENTES

NOMBRE	FIRMAS
Carlos Martin Restrepo	
Ingrid Tatyana Bernal	Tatyana Bernal B.
Juan Sebastian Arias	
Lina Paola Castillo	

Bibiana Bayona	Bibiana Bayona
Erika Jimenez	
Valeria Correa	Valeria Correa-Martinez
Harvy Velasco	
William Usaquen	

2 Productos año 2:

2.1 Avances del producto de ciencia y tecnología

*** Se encuentra pendiente resultado de estudios genéticos, para enviar a revista***

2.1.1 Enfermedad de McArdle en una familia altamente endogámica con inicio en la infancia.

Ingrid Tatyana Bernal[1], Lina Castro-Castillo[2], Bibiana Bayona-Gomez[2],Juan Sebastian Arias-Florez[3], Valeria Correa-Martinez[4] Sandra Ximena Ramirez[5], William Usaquén-Martínez[6], Lilian Andrea Casas-Vargas[6], Camilo Velandia[7], Nora Contreras Bravo[7], Rodrigo Cabrera[7], Adrien Morel[7], Natalia Santiago-Tovar[7], Cristian Camilo Gaviria-Sabogal[7], Dora Janeth Fonseca-Mendoza[7] and Carlos M. Restrepo[7].

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Introducción

La enfermedad de McArdle, también llamada glucogenosis de tipo V (GSD5), es un trastorno hereditario del metabolismo del glucógeno, que muestra afectación por el músculo esquelético. La enfermedad se origina por una mutación en el gen *PYGM* y causa déficit de función de la miofosforilasa muscular (1). Descrita por

primera vez por McArdle en el año 1951 en una persona con debilidad muscular y mialgias (2); en 1963 se observaron debilidad muscular generalizada y progresiva, además de calambres y reducción o ausencia de la actividad de la enzima fosforilasa muscular con ausencia de mioglobinuria en una pareja de hermanos adultos (3); para el año 2008, se describieron más de 100 mutaciones en el gen *PYGM*, siendo las más comunes, p.Arg50X, seguida por p.Gly205Ser (4). Se presenta un raro caso familiar con, al menos, cuatro personas afectadas, incluyendo un caso infantil de GSD5 en una familia altamente endogámica.

Métodos:

El caso índice es un niño de 9 años, natural de Saboya (Boyacá) y fruto de la primera gestación a término (40.5 semanas), y sin complicaciones. PN 3.760 gramos (P:62), Talla 51 cm (P26). El desarrollo mostró: sostén cefálico: 5 meses. gateó a los 10, marcha a los 15, inicio del lenguaje 12 y control de esfínteres a los 12 meses. Actualmente cursa tercer grado en la primaria, pero refiere tener dificultades en los dictados y lecturas aunque con un rendimiento en matemáticas adecuado. Se han observado dificultades del aprendizaje, identificadas como dislexia y alexia, además de problemas de atención y lectura. En seguimiento por neuropediatría y recibe manejo con terapia del lenguaje y ocupacional con escasa mejoría, por lo que fue remitido a genética.

Los padres tienen 32 (p) y 28 años, son consanguíneos, primos hermanos. El padre es sano y la madre presenta debilidad muscular de etiología no identificada y sus padres, son consanguíneos. El abuelo materno y un tío materno también se identifican con debilidad muscular, sin diagnóstico..

Al examen físico se observó: Talla 103 cm (), Peso: (), se observó hábito asténico, magro, braqui turricefalia, frente amplia, telecanto marcado (**Figura 1A**), orejas rotadas posteriormente (**Figura 1B**), tórax longilíneo, tendencia *pectus excavatum*, asimetría de los pezones siendo el izquierdo de implantación baja, abdomen normal, genitales masculinos infantiles, extremidades simétricas, con hipotrofia de la masa muscular generalizada (**Figura 1C**), escápulas aladas, tendencia a la cifosis dorsal y lordosis lumbar **(Figura 1D)** y el grupo familiar (**Figura 1E**)

Estudios moleculares.

Debido a que las personas fueron evaluadas en un hospital local, no se contaba con recursos de electrofisiología para evaluar debilidad muscular, por lo que se decidió realizar directamente estudios moleculares en el ADN basados en un exoma de diagnóstico. Después de aceptar participar en el proyecto de investigación y obtener un consentimiento y asentimiento informados, se tomaron muestras de sangre por venopunción, seguida de la extracción del ADN genómico de cada persona de la familia. Con el mismo consentimiento, se tomaron fotografías médicas de los afectados y del grupo familiar.

Resultados.

Se presenta la genealogía de tres generaciones donde se evidencias los miembros del grupo familiar, afectados y sanos (Figura 2).

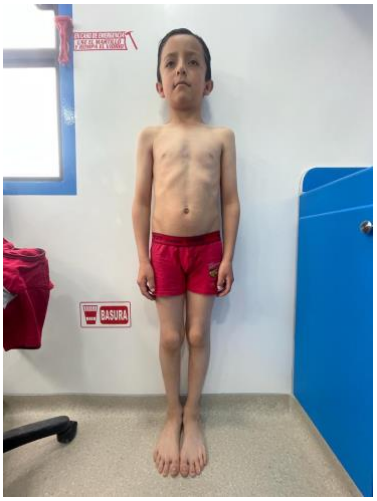

Foto con autorización de los padres. Para caso clínico

Discusión:

La enfermedad de McArdle o GSD5, es un trastorno hereditario raro del metabolismo del glucógeno con preferencia de afección por el músculo esquelético. La enfermedad se origina por mutaciones homocigotas o heterocigotas compuestas en el gen *PYGM*, localizado en el cromosoma 11q13, aunque se han informado

algunos casos con herencia pseudo dominante (5). Los afectados con GSD5 presentan disfunción o ausencia de la expresión de la isoforma muscular de la glucógeno fosforilasa (*PYGM),* una encargada de descomponer el glucógeno a glucosa 1 fosfato en las células musculares (1,6). La deficiencia de miofosforilasa muscular ocasiona xxxxxxxxx, el glucógeno no se descompone adecuadamente en las células musculares, lo que interfiere con su función (7).

La prevalencia es aproximadamente de 1 en 100.000 pacientes en EEUU y de 1 en 167.000 en población española (6,7). La herencia es autosómica recesiva y suele presentarse en la edad adulta (6,7).

Los síntomas suelen estar presentes en la primera década de la vida (infancia) y suelen diagnosticarse hasta la etapa adulta (6,7).

Todos los pacientes con deficiencia de miofosforilasa desarrollan rigidez, fatiga, dolor y/o debilidad muscular que puede ser inducida por períodos breves de ejercicio intenso como el ejercicio isométrico (levantamiento de pesas) o ejercicio dinámico menos intenso pero sostenido (trotar); la afectación del músculo es variable pero la intolerancia al ejercicio empeora con el tiempo (7).

También experimentan el fenómeno llamado "segundo aire", definiendo la mejoría de las mialgias, rigidez muscular, fatiga inicial y la taquicardia después de aproximadamente 10 minutos de ejercicio; y este fenómeno se explica por un aumento del flujo sanguíneo, una mayor liberación de ácidos grasos libres con la activación simultánea del metabolismo de los ácidos grasos y una mayor utilización de la glucosa hepática (8).

Se ha observado debilidad fija que afecta más los músculos proximales que a los distales (9) e intolerancia al ejercicio (7). En pacientes sin actividad física regular se encontró menor masa magra, contenido mineral óseo y densidad ósea (10); y en otros pacientes dolor muscular como un síntoma clínico importante, aunque no relacionado con la edad o la duración de la enfermedad (7).

El diagnóstico se realiza por pruebas genéticas con análisis del ADN en tejido muscular, con inmunohistoquímica y análisis bioquímico (4); son el método más razonable y eficaz para confirmar un diagnóstico en pacientes con síntomas clínicos constantes (7). Una opción funcional y mínimamente invasiva para el diagnóstico de la sospecha de deficiencia de miofosforilasa implica la prueba de ejercicio de los músculos del antebrazo no isquémica; y se pueden encontrar elevaciones en reposo de la creatina quinasa (CK) y episodios de rabdomiólisis (7).

Se han descrito distintas formas; la más común llamada p.Arg50X se encuentra en el norte de Europa y Norteamérica y la segunda en frecuencia p.Gly205Ser en Norteamérica y población hispánica (4).

El tratamiento incluye evitar dietas bajas en carbohidratos y ejercicios aeróbicos de bajos a moderados (6). Se realizara asesoria genética y cuando se tenga mutación identificada se dará prevención en caso de querer hijos, iniciativa de medicacion por empresas farmaceuticas

buscar iniciativas de administracion de glucosa 1 fosfato para evitar el consumo de glucogeno.

Conflictos de interés:

No se reportan conflictos de interés

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2.2 * Actividades desarrolladas (obtención de cartas de aprobación por parte de los Comités, recolección de datos, análisis)

2.2.1 Avance de trabajo de campo:

2.2.1.1 Jornadas de campo

Se realiza elaboración de historia clínica, toma de muestras de laboratorio, realización de genealogías.

Fecha	Numero de pacientes /familiar	Actividades
18 de marzo 2023	1 familia completa 1 Paciente	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías
27-30 de marzo 2023	6 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías
15-18 de mayo 2023	13 pacientes	Realización de historia clínica Toma de muestras de laboratorio Realización de genealogías

*2.2.1.2 * Análisis parcial de datos*

2.2.1.2.1 Selección de variantes:

Seleccionar variantes patológicas o probablemente patológicas, de pacientes valorados en jornadas de campo

-Se tenían de 3 a 4 pacientes por mes.

-Según los hallazgos, se seleccionaban los pacientes, en quienes el gen concordaba con el cuadro clínico.

-Con estos resultados, las variantes patológicas, nuevas o no rpeortadas en la literatura, se seleccionaban para publicación de casos (pacientes pediátricos).

2.2.1.2.2 Selección de términos HPO

El término HPO (Human Phenotype Ontology) **usado para describir de manera estandarizada los** fenotipos humanos**,** es decir, las características observables relacionadas con enfermedades genéticas o condiciones

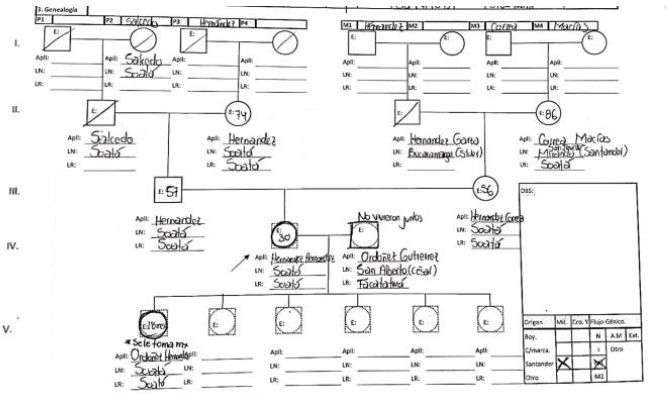
médicas. La HPO proporciona un vocabulario común y estructurado que permite la anotación precisa de los rasgos fenotípicos que se presentan en los individuos.

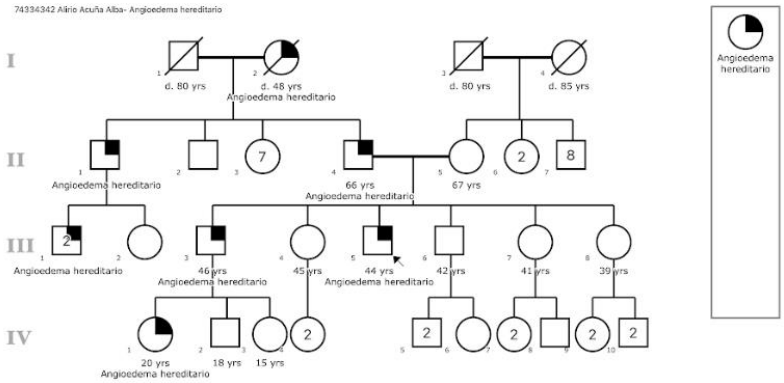
HPO	HP_0000278	HP_0000293	HP_0000316	HP_0000430	HP_0001250	HP_0001252	HP_0001263	HP_0001347	HP_0001763	HP_0002066	HP_0007427
Termino	**Retrognathia**	**Full cheeks**	**Hypertelorism**	**Underdeveloped nasal alae**	**Seizure**	**Hypotonia**	**Global developmental delay**	**Hyperreflexia**	**Pes planus**	**Gait ataxia**	**Reticulated skin pigmentation**
	AARS1	ACTB	ABCD4	ALG9	AAAS	AAAS	AAAS	AAAS	ABL1	AASS	DKC1
	ABAT	ACTG1	ACOX1	ALX1	AARS1	AARS1	AARS1	AARS1	ACTA2	ABCA2	KRT14
	ACTA1	AFF4	ACTA1	ALX4	AASS	AASS	AASS	AARS2	ADGRV1	ACOX2	KRT5
	ACTA2	AGL	ACTA2	ANKRD11	ABAT	ABAT	ABAT	AASS	ADNP	ADAR	NHP2
	ACTB	AIP	ACTB	ASXL3	ABCA2	ABCB7	ABCA2	ABAT	AEBP1	ADSL	TERT
	ACTG1	ASXL1	ACTG1	ATP6V1B2	ABCA5	ABCC8	ABCB7	ABCA4	AFF3	AFG3L2	TINF2
	ADAMTS2	ATP7A	ACTL6B	BCR	ABCA7	ABCC9	ABCC6	ABCB7	AGA	ALDH18A1	
	ADAMTS3	B9D1	ACY1	BICRA	ABCC6	ABCD4	ABCC8	ABCC8	AHCY	ANO10	
	ADAMTSL2	B9D2	ADA2	BRCA1	ABCC8	ACACA	ABCD4	ABCC9	ALDH18A1	AP1S2	
	AGRN	BICRA	ADAMTS3	CENPJ	ABCD1	ACAD8	ABHD16A	ABCD1	ALG14	AP2M1	
	ALG11	BMP2	ADAT3	CKAP2L	ABHD16A	ACAD9	ABHD5	ABHD12	ALG2	APTX	
	ALG13	BRAF	ADGRG6	CLP1	ACADM	ACADM	ABL1	ABHD16A	ALMS1	ARCN1	
	ALG9	CC2D2A	ADK	COL3A1	ACADS	ACADS	ACAD8	ACOX1	AMMECR1	ARID1B	
	AMER1	CCDC88A	ADNP	CREBBP	ACADSB	ACADSB	ACADM	ACSL4	ANOS1	ARSA	
	AP3D1	CDC42BPB	AFF3	CRKL	ACADVL	ACADVL	ACADS	ACTA1	AP1G1	ATAD3A	
	ARCN1	CDK5	AFF4	CTNNB1	ACAT1	ACAT1	ACADSB	ADAR	AP4B1	ATCAY	
	ARID1B	CEP290	AGA	CWC27	ACO2	ACAT2	ACAT2	ADCY5	AP4E1	ATN1	
	ARID2	CLCF1	AHDC1	DDB1	ACOX1	ACER3	ACD	ADGRG1	AP4M1	ATP13A2	
	ARNT2	CLCN3	AIFM1	DDR2	ACP5	ACO2	ACO2	ADSL	AP4S1	ATP1A2	
	ASPH	CPE	AKT1	DGCR2	ACSF3	ACOX1	ACOX1	AFG3L2	APC2	ATP1A3	
	ASXL1	CREBBP	AKT3	DGCR6	ACTA2	ACSF3	ACOX2	AGBL5	ARX	ATXN10	
	ASXL2	CRLF1	ALDH18A1	DGCR8	ACTB	ACSL4	ACP5	AGTPBP1	ASPH	ATXN2	
	ASXL3	CSPP1	ALDH6A1	DYRK1A	ACTG1	ACTA1	ACSF3	AHI1	ASXL3	ATXN3	
	ATG7	DDB1	ALG1	EDA	ACTL6B	ACTB	ACTA1	AHR	ATP1A2	ATXN8	
	ATP6V0A2	DLK1	ALG13	EDEM3	ACVR1	ACTL6B	ACTB	AIFM1	ATP1A3	ATXN8OS	
	ATP6V1A	DPM1	ALG6	EDN3	ACVRL1	ACTN2	ACTG1	AIMP2	ATP6AP2	B9D1	
	ATPAF2	DPYD	ALG8	EDNRB	ACY1	ACY1	ACTL6B	ALDH18A1	ATP6V0A2	BEAN1	

2.2.1.2.3 Elaboración de genalogias

Se realizaron genealogías, para cada paciente valorado en jornadas de campo, se realizaorn de forma manual inicialmente, posterior se pasaron con el uso de sofware.

-Estos fueron elaborados, para ser presentados en la publicación a MINCIENCIAS, sobre ancestrias, consanguinidad y relación con enfermedades genéticas.





2.3 Reporte de caso clínico:

**Se encuentra en finalización, aun esta pendiente el resultado de análisis genético:

2.3.1 A new MAP1B heterozygous gene mutation related with a novel type of epilepsy or periventricular nodular heterotopia 9?

A new MAP1B heterozygous gene mutation related with epileptic-dyskinetic encephalopathy in two brothers

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Key words

Epilepsy; Developmental Disabilities; Genetics; Movement Disorders

INTRODUCTION

Developmental and epileptic encephalopathies are a group of severe epilepsies characterized by **developmental slowing or regression** that may or may not be directly related to the seizures (McTague, 2016)(Guerrini, 2023). They are heterogeneous in seizure types, onset age, epileptiform activity on EEG and etiology. Some encephalopathies have been related to specific ages, genes and clinical patterns, such as West or Dravet syndromes, however, there are many others that don't fit into any syndrome yet, even though research in the field is rapidly growing. The genetic basis of this group of diseases is found in approximately 24% of the cases and includes structural, chromosomal and metabolic alterations; among structural, de novo variants are the most commonly reported. It has been described that the clinical heterogeneity can be explained by somatic and gonadal mosaicism within members of the same family, despite having the same mutation, a phenomenon that has been proved in patients with Dravet syndrome. (McTague, 2016)(Guerrini, 2023)

Comorbidities in patients with epileptic encephalopathies are common, and include autonomic, motor and behavioral alterations (Guerrini, 2023). Among them, epileptic-dyskinetic encephalopathies are genetically heterogeneous early onset epileptic encephalopathies with involuntary **hyperkinetic movements** that are accompanied by severe developmental delay. The common pathological mechanisms between epileptic encephalopathies and these involuntary movements has been related to alteration of NMDA and AMPA receptors functioning, but is not totally understood yet. Nonetheless, the genetic overlap of epileptic encephalopathies, dyskinetic movements with child onset and developmental delay becomes clearer everyday (Arisaka, 2021) (Carecchio, 2017)

On the other hand, Microtubule-associated protein 1B (MAP1B) is a gene which codifies for a protein mainly expressed in the neuronal soma, dendrites and axons during neuronal development that regulates microtubule dynamics, playing a critical role in cone and axon growth. Variants in this gene have been associated with Periventricular Nodular Heterotopia 9 (PVNH-9), an autosomal dominant disorder with high penetrance and variable expressivity, characterized by predominantly frontal nodules, along with variable degrees of cognitive impairment, epilepsy and dysmorphic features in some cases. Its relation with epileptic encephalopathy and dyskinetic movements has not been clearly explored, although the case reports show a pattern of epilepsy and developmental regression or intellectual disability.

In this report, we present two brothers with developmental regression, global developmental delay, seizures and dyskinetic movements. We found a novel mutation in the MAP1B gene in the younger brother, here we propose a new phenotype of epileptic-dyskinetic encephalopathy for the MAP1B gene.

This study is part of an overarching project titled "Method for Identifying Rare Diseases through Translational Research in Geographical Isolates of the Boyacá Department, Exploring Ancestry." The comprehensive aim of this project is to identify isonymy and ancestry patterns within the population of Boyacá, a region characterized by an endogamy rate of 15.7% and presenting various clusters of undiagnosed, untreated, and potentially novel genetic pathologies. The objective of this study is to propose

a predictive risk model for the emergence/presentation of genetic pathologies based on the correlation between genetic-isonymic population analyses and diagnosed orphan diseases. This research aims to contribute to the development of Colombia's orphan disease law by proposing strategies for primary prevention, optimization of diagnosis, and management of pathologies.

CASE DESCRIPTION

Case I

A 10 year-old, male patient from Tunja-Boyacá-Colombia, product of the second pregnancy of an 18-year-old teenage mother. He was born at 40 weeks, delivered by cesarean section, the birth parameters were weight 3080 grams (+0.98 SD) and length 51 cm (+0.66 SD).

His neurodevelopment was normal until 12 months, with head support at 3 months, rolling at 7 months, sitting at 9 months and crawling and standing at 12 months. At this moment he loses the ability to crawl and stand, without regaining motor skills, which leads to permanent prostration.

At 2 years of age, he presented episodes of gaze deviation, perioral cyanosis, tonic posture and clonic movements and myoclonias; considered that corresponded to seizure episodes. Brain magnetic resonance was performed which did not report any nervous central system anomalies and the electroencephalogram showed ocassional paracentral epileptic activity (Table 3).

Since the first episode, levetiracetam was prescribed with no clinical improvement, therefore the therapy is changed to valproic acid and clobazam, managing to control the epilepsy, with the last documented seizures at 5 years of age.

The patient has remained with some dyskinesia (involuntary movements) and tonic posture, with behavioral impairment given by self injurious behavior characterized by usual scratching of his face and biting on his hands that causes bleeding. Additionally, he has severe sleep apnea.

The patient does not present dysmorphic features. On physical examination he is hypotonic, has generalized hypotrophy and ankylosed joints. Deep tendon reflexes are absent in the lower limbs and with hyporeflexia in the upper limbs. Besides,he shows wounds on his hands and fingers, due to biting, he has no interaction with the examiner, does not follow simple orders or utter words; currently he has a degree of total dependency.

It has a clinical exome report with four variants of uncertain significance, making it impossible to classify the patient (Supplementary Table 1).

Date	Test	Outcome
19/03/2020	Clinical exome (4800 genes)	VUS heterozygous KIAA c.1979T>C p.Ile660Thr, rs778849569. VUS heterozygous ADAM22 c.2680G>A p.Val894Met, rs182800008. VUS heterozygous SYNE2 c.5423C>G p.Thr1808Ser, rs780659094. VUS heterocigota PLCB1 c.724G>A p.Val242Ile, rs200567140. VUS heterozygous ZFYVE26 c.5980G>A p.Gly1994Ser, rs765067264.

Supplementary Table 1: Clinical exome year 2020: 4 VUS variables (uncertain significance)

Due to the clinical characteristics and family history, the patient has undergone two genetic tests, the first one performed in 2020 were five variants were identified in the genes KIAA, ADAM22, SYNE2, PLCB1 and ZFYCE26, all of them classified as variants of uncertain significance according to ACMG criteria and did not explain his clinical features (table #2), and the second one was carried out in 2022 with a new phenotypic approach that allowed the identification of a probably pathogenic heterozygous variant in the *MAP1B* gene (c.6171T>G, p.Tyr2057X) (table #1).

Gene	Variant	Zygosity	Clinical Significance	PHENOTYPE
MAP1B (NM_005909.5)	c.6171T>G (p.Tyr2057Ter)	Heterozygous	Probably pathogenic	Periventricular heterotopiar 9 (MIM #618918/AD) Autosomal dominant hearing loss 83 (MIM #618918/AD)

Table 1: DNA sequencing 2023: Probably pathogenic variables.

MAP1B [NM_005909.5]: heterozygous c.6171T>G (pTyr2057Ter).

The family history is noteworthy, his older brother had neurodevelopmental delay and severe epilepsy that led to prolonged hospitalization and subsequent death ("description of the patient in case #2").No history of consanguinity but they live in the same neighborhood; was not found and there is no information on cognitive impairment in the parents or neuroimaging studies performed on them (Image 1).

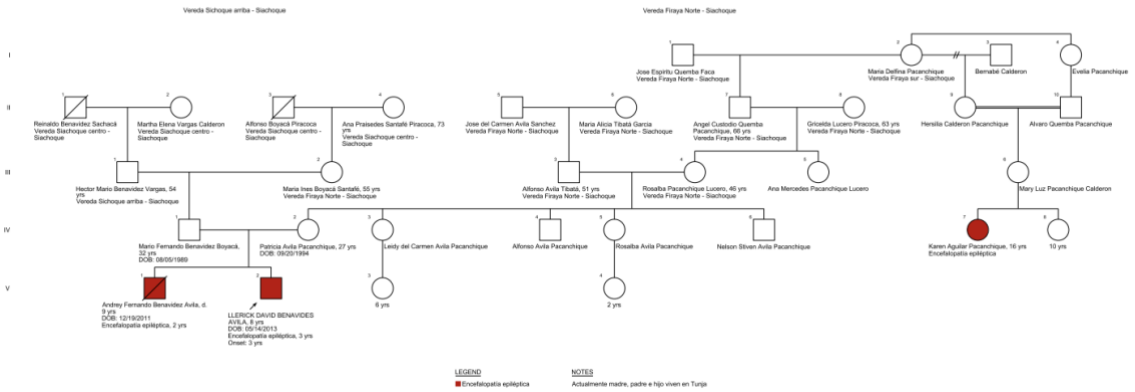

Image 1: Family tree. There is evidence of an affected patient and the deceased affected brother.

Case II

This is the deceased brother. He was the result of a first pregnancy, delivered by cesarean section due to oligohydramnios.

Course with delay in neurodevelopment and language disorder from the first years of life; He remained with frequent abnormal and involuntary movements in addition to myoclonus in the face and extremities, an electroencephalogram was taken and he was diagnosed with epileptic encephalopathy + refractory epilepsy since he was 4 years old (*Table 3*).

He was under follow-up for suspected genetic disease such as congenital muscular dystrophy due to symptoms of central and peripheral nervous system involvement with abnormally high CPK.

In the physical examination; patient without dysmorphic features; At a neurological level, it performs visual and auditory monitoring, he does not emit language, motor stereotypies and sounds are evident quadriaparetic attitude, very hypotonic, hypotrophic, hyporeflexia and with bilateral Babinski; with the need to use a neurological wheelchair to obtain an apparently adequate position.

Test / Study	**Patient case I**	**Patient case II**
Electroencephalogram	11/11/2014: Waking tracing: No evidence of epileptiform activity 05/09/2022: Sleep tracing with evidence of paracentral	Nov/2016: Waking tracing: No

	epileptiform activity that appears very occasionally.	evidence of epileptiform activity
Brain MRI (Magnetic resonance)	29/10/2014: Within normal limits for the patient's age range	Patient deceased prior to assessment
Polysomnography	10/08/2021: Presence of respiratory events, mostly obstructive. Respiratory event rate: 21.5/h: Severe sleep apnea.	
Auditory evoked potential	05/14/2023: Normal	
Neurological symptoms	-Dyskinesia -Myoclonus -Tonic posture -Behavioral impairment characterized by self injurious behavior (frequently scratching of the face and biting hands that causes bleeding)	-Dyskinesia -Myoclonus affecting the face and extremities -Quadriaparetic -Hypotonic -Hypotrophic -Hyporeflexia
Neurodevelopment	<u>Present:</u> • Head support • Rolling • Sitting • Crawling • Standing • Language <u>Absent:</u> • Walking	<u>Present:</u> • Head support <u>Absent:</u> • Rolling • Sitting • Crawling • Standing • Walking • Language
Molecular Testings	<u>NGS:</u> WES:	

	MAP1B [NM_005909.5]: c.6171T>G (pTyr2057Ter).	Patient deceased prior to assessment

T*able 3: Extension studies, neurological symptoms and neurodevelopment: Case I - II.*

Due to multiple comorbidities, they required hospitalizations at home and in the hospital; they required tracheostomy with continued respiratory therapy and oxygen therapy 24 hours a day; He was also a gastrostomy user, but due to great deterioration and severe epilepsy, he died at 9 years of age.

DISCUSSION

Author	**Liu et al. (2015) Autism and ID**	**Heinzen et al. (2018) PVNH**				**Walters et al. (2018) ID or autism**			**Julca et al. (2019) ID, epilepsy and dysmorphic features**	**Arya et al. (2021) mild ID, photosensitivity, behavioral comorbidities and epilepsy**	**Present study ID and epilepsy**
Pathogenic variant	**arr(hg18)5q13.2 (71,221,928-72,188,118)**	**c.907C>T p.Arg303X**	**c.1594C>T p.Gln532X**	**c.3316C>T p.Arg1106X**	**c.818delC p.Leu274CysfsX4**	**c.2133delG p.Glu712LysfsX10**	**c.3094G>T p.Glu1032X**	**c.4990C>T p.Arg1664X**	**c.2035G>T p.Arg1664X**	**c.6385delG p.Ala2129Profs*107**	**c.6171T>G p.Tyr2057Ter**
Transcript	N/A	NM_005909.3	NM_005909.3	NM_005909.3	NM_005909.3	NM_005909.4	NM_005909.4	NM_005909.4	NM_005909	NM_005909.4	NM_005909.5

#Patients per variant	1	1	1	2	1	7	4	2	1	4	1
Mode of inheritance	De novo	De novo	Paternal	Maternal	Paternal	Maternal	Maternal	Maternal	De novo	Maternal	?
Affected parents	N/A	N/A	No	Yes, PVNH, collapsing episodes, psychiatric disease	ND	Yes (ID)	No	No	N/A	Yes, absence and myoclonic seizures	No?
ID/delays	+	+	+	-	+	+	+	+	+	+	+
Seizures/characteristics	+	+ focal	-	Collapsing episodes but negative EEG	+ focal	+ 1/7	-	-	+ Subclinical, EEG with two bursts of generalized slowing with embedded spikes-focal mechanism with rapid secondary generalization.	+ 1. Febrile and afebrile episodes, EEG with bilateral multi-focal and diffuse epileptiform discharges and photo-convulsive response. 2. Atypical febrile	+ Tonic-clonic seizures

										seizures, EEG with mildly slow background but no epileptiform abnormalities 3.Tonic-clonic fever-triggered seizures. EEG with diffuse epileptiform discharges with bi-frontal amplitude emphasis, and a photo-paroxymal response. 4.Absence and myoclonic seizures	
Seizures age onset	N/D	N/D	N/D	N/D	N/D	N/D	N/A	N/A	N/A	1.Age:2.3 y/o 2.Age:4.6 y/o 3.Age:12.8 y/o 4.N/D	Age: 2 y/o

Treatment/control	N/D	N/D	N/D	N/D	N/D	N/D	N/A	N/A	Oxcarbazepine/controlled	1. Controlled with topiramate and valproic acid (started with levetiracetam which was ineffective) 2.Levetiracetam/controlled 3.Ethosuximide/controlled (started with levetiracetam but changed because of aggression and mood swings) 4.N/D	Started with levetiracetam, which was ineffective. Currently in treatment with valproic acid and clobazam, seizure-free since the age of 5 years.
Microcephaly	+	ND	ND	ND	ND	-			+	-	ND
Brain imaging	Normal MRI	PVNH Thin CC	PVNH	PVNH Thin dysmorphic CC, perisylvian	PVNH	Obtained on 10 patients PVNH 9/10 Small CC and reduced white			PVNH Dysgenesis of CC	PVNH, CC abnormalities and perisylvian polimycrogiria	Normal?

				and polimicrogyria		matter volume 10/10			
Ethnicity	ND	American Indian-Alaska native/european	European	Unknown/european	European	Icelandic	African american	American indian/caucasian	Latin american
Dysmorphic features	ND	Bilateral clinodactyly, pes cavus	ND	-	ND	Evaluated by psychologist?	+	-	-

Table 1. Characteristics of patients described in literature. CC: corpus callosum, ID: intellectual disability, N/A: not applicable N/D: No data, PVNH9: Periventricular Nodular Heterotopia 9

Developmental and epileptic encephalopathies (DEE) are a group of diseases characterized by seizures and developmental involvement. Some authors differentiate developmental encephalopathy (DE), where cognitive function is not affected by epilepsy, from epileptic encephalopathy (EE), a term used for patients who have a direct impact of epileptiform activity in cognition. In EE most of the patients have a continuous deterioration along with non-controlled seizures since early infantile or childhood periods, and the underlying cause is mostly genetic. (Raga, 2021) The prognosis is usually poor, however, there are some syndromes characterized by an specific onset age, epileptiform pattern and type of seizures, which allows a clear treatment and prognosis. However, many patients with EE do not fit into any syndrome and there is still a wide field to be discovered about etiology and pathophysiology. (Hussain, 2018) Comorbities are common, and as seen in our patients, EE can be accompanied by hyperkinetic movement disorders, a heterogenous group of diseases characterized by excess of involuntary movements, and receive the name of epileptic-dyskinetic encephalopathies. Some of the movement alterations are dystonias, choreas and myoclonus, and many patients present with a mixture. Patients with this diagnosis are also seen frequently with neurodevelopmental delay and intellectual disability, and they may not have alterations in neuroimaging or laboratory results. (Arisaka, 2021)

MAP1B is a gene which encodes for a microtubule associated protein essential for neuronal differentiation and migration, promoting tubulin polymerization and crossover. This protein is part of a family of high molecular weight microtubule-binding phosphoproteins, formed by a heavy chain and a light chain and has five main domains, two microtubule-binding domains and two actin-binding domains, located at the N-

terminal end of both chains, and a microtubule assembly help domain in the central region of the heavy chain (PMID: 29432744). It is mainly expressed in the neuronal soma, dendrites, and axons during neuronal development, regulating microtubule dynamics, playing a critical role in cone and axon growth, and axon regeneration (PMID: 29432744, 10649507). In the adult brain, MAP1B expression remains high in areas that retain plasticity such as the olfactory epithelium and bulb, the mossy fibers in the hippocampus and the retinal photoreceptors, areas that maintain neurogenesis and axogenesis throughout life (PMID: 10649507, 30150678); mice with homozygous mutations exhibit corpus callosum absence and multiple alterations in neuronal distribution (Meixner, 2000)(GB Walters, 2018).

Loss of function variants (LoF) result in stable truncated proteins that alter the phosphorylation sites leading to decrease in axonal elongation and branching regulation. It has been established that the loss of MAP1B function, in humans, alters the white matter in a widespread fashion secondary to axonal impairment, a condition that leads to epilepsy or cognitive deficits (PMID: 30150678, 33772511). In MAP1B-deficient murine models, a delay in axon formation is observed, involving alterations in the neuronal growth cone and actin organization, without proper establishment of morphological polarity (PMID: 11891784). Deleterious heterozygous variants in the MAP1B gene are related to Periventricular Nodular Heterotopia type 9 (PVNH9) [PubMed: 29738522], [PubMed: 30150678] and with sensorineural hearing loss (DFNA83) (PMID: 33268592), an autosomal dominant disorder with high penetrance and variable expressivity, characterized by predominantly frontal nodules, distinguishing it from the classical FLNA-caused PVNH (Vriend, 2021) There have been some studies with Whole Genome Sequencing (WES) that have found patients with mutations in MAP1B, presenting different phenotypes: Heinzen et al. (2018) described 4 non-related probands with PVNH9 identifying nonsense or frameshift heterozygous mutations in MAP1B by whole exome sequencing (WES) and confirming them by Sanger sequencing. One patient had a de novo mutation, two non-related patients inherited variants from their non-affected parents that didn't have brain imaging, the last patient inherited a variant from his mother who had similar but less severe structural abnormalities in brain imaging. None of these variants were described in GnomAD database.They didn't make any functional study of the variant nor did they study patients' cells, but it was predicted that all of them caused a premature termination and loss of function (LoF). The patients' clinical presentation was varied including seizures, cognitive impairment and dysmorphic facies. Severity and dysmorphic features differed among patients, some of them had a mild or subclinical presentation while others had a more severe disease. Neuroimaging findings were also different, with some patients showing bilateral anterior PVNH and perisylvian and deep insular polymicrogyria. Interestingly, in one family both mother and son presented with similar neuroimaging findings, suggesting a genetic link in the disease manifestation.

In affected members of three Icelandic families with PVNH9 Walters et al. (2018) identified three heterozygous nonsense or frameshift different variants in exon 5 of MAP1B gene. The variants, identified by whole genome sequencing and confirmed by Sanger sequencing, segregated with the disease in the families although there was variable expressivity. None of the variants were present in public databases, including gnomAD. Variant expression in HeLa cells demonstrated the production of truncated proteins, all the variants lead to LC1 protein domain absence.

In a 7-years old kid with PVNH9 Julca et al. (2019) identified a nonsense heterozygous de novo variant in MAP1B (E679X; 157129.0007). The variant was found by whole exome sequencing; there were no functional or cell studies. Finally, in 2021 Arya et al. described four family members, three siblings and their mother, who had PVNH and a combination of different types of seizures along with behavioral characteristics, giving a wider insight of the convulsive phenotype of the disease.

The heterozygous variant NM_005909.5: c.6171T>G (p.Tyr2057Ter) was identified in the patient, in the MAP1B gene, which generates a premature stop codon in exon 5 of 7, possibly leading to degradation of the protein by the NMD (Nonsense mediated decay) system.

Deleterious variants downstream of the Y2057X variant associated with periventricular heterotopia and neurological symptoms have been described in the genetic variants databases (ClinVar) and in the literature (PMID: 37460233), most of them are Loss-of-function variants. Loss of function variants (LoF) result in stable truncated proteins that alter the phosphorylation sites leading to decrease in axonal elongation and branching regulation (PMID: 30150678).

ClinGen aún no ha publicado curaciones para el gen MAP1B, en bases de datos como UniProt, ClinVar, LOVD, MitoMap, VarSome & PubMed basado en la información de Varsome se han descrito 13 variantes nonsense que son patogénicas y probablemente patogénicas en comparación con 0 variantes descritas como benignas o probablemente benignas. En gnomAD v4.1.0 actualmente tiene un puntaje pLI=1, con un intervalo de pérdida de función observada/fracción de límite superior esperada 0,21 (0,17 - 0.28), que sugiere sensibilidad a dosis, con aumento en la probabilidad de ser intolerante a la pérdida de función. De acuerdo a Dechiper el valor sHet (Coeficiente de selección de variantes heterocigotas con pérdida de función) es de 0.099 demostrando una mayor sensibilidad a dosis y el valor de pHaplo (Predicted Probability of Haploinsufficiency) es de 0.99, que indica que los tamaños de efecto promedio de las deleciones son tan fuertes como la pérdida de función de genes que se sabe que están restringidos contra variantes truncadas de proteínas (razón impar ≥2,7) (Karczewski et al., 2020).

CONCLUSION

PVNH9 affected patients showed an anterior frontal or perisylvian predominant heterotopia, polymicrogyria, reduction in white matter volume, thin corpus callosum impaired intellectual development, learning disabilities and behavior abnormalities, lower and variable IQ and some patients showed a focal origin seizure and other EEG abnormalities; variable expression and incomplete penetrance was argued for some patients [PubMed: 29738522].

Hay una tesis que describe el fenotipo epiléptico de la PVNH. Dividieron 10 pacientes en PVNH simple o plus, dependiendo de si tenían otras malformaciones asociadas. Dicen que la literatura describe que alrededor de 80% de los pacientes con PVNH tienen epilepsia farmacorresistente, pero ellos encontraron que ninguno de sus pacientes con PVNH sola la tenía, solamente los que tenían malformaciones asociadas. No hablan de los pacientes con diagnóstico de PVNH sin malformaciones en la RMN. En el artículo de la tabla que tiene RMN normal no hacen diagnóstico de PVNH

He was the product of the second pregnancy of an 18-year-old teenage mother, it was a controlled pregnancy with negative STORCH. He was born at 40 weeks, delivery by cesarean section, birth weight of 3080 grams and height of 51 cm, which were appropriate for age.

At 2 years of age, he presented episodes of gaze deviation, perioral cyanosis, tonic posture, and clonic movements; and according to neuropediatrics, despite normal extension studies (table #1), they considered that the characteristics of these events corresponded to seizure episodes secondary to generalized epilepsy; since then, management was started with levetiracetam, but when there was no improvement, the anticonvulsant was changed to valproic acid and clobazam, with the last episode at 5 years of age. Since that moment he has remained with some involuntary movements and tonic posture. Sometimes he presents self-harm (scratches on the face, bites on the hands with bleeding).

It should be noted that he has a significant family history of a brother who presented a similar clinical picture of delay in neurodevelopment and epilepsy that resulted in prolonged hospitalization and subsequent death. And he has no known history of perinatal noxa or consanguinity (Image #1).

He has been evaluated by multiple specialists, including pulmonology for severe sleep apnea.

Currently, the patient does not have characteristic features, his extremities are hypotrophic with spasticity, he has wounds on his hands, he has no interaction with the examiner, he does not follow orders or utter words; That is why he is not in school and has a degree of total dependency.

Due to the clinical characteristics and family history, it was decided to perform a DNA study using complete NGS sequencing; where a heterozygous probably pathogenic variant was identified in the MAP1B gene, and three variants of uncertain significance (table #3). This makes the case report interesting because it is a pathological variable that has not been described worldwide and could be very useful for the diagnosis and treatment of epilepsy.

ClinGen aún no ha publicado curaciones para el gen MAP1B, en bases de datos como UniProt, ClinVar, LOVD, MitoMap, VarSome & PubMed basado en la información de Varsome se han descrito 13 variantes nonsense que son patogénicas y probablemente patogénicas en comparación con 0 variantes descritas como benignas o probablemente benignas. En gnomAD v4.1.0 actualmente tiene un puntaje pLI=1, que es un puntaje elevado lo que haría más probable que sea sensible a la dosis, con un intervalo de pérdida de función observada/fracción de límite superior esperada 0,21 (0,17 - 0.28), los genes con un valor bajo es más probable que sea sensible a la dosis demostrando aumento en la probabilidad de ser intolerante a la pérdida de función. Se revisan en Dechiper varios scores predictivos de los cuales se destaca: El valor sHet (Coeficiente de selección de variantes heterocigotas con pérdida de función) es de 0.099 demostrando que es mas sensible a la dosis (Los genes con valores mayores (más cercanos a uno) son más intolerantes a las mutaciones). El valor de pHaplo (Predicted Probability of Haploinsufficiency) es de 0.99, esto debido a que las puntuaciones de pHaplo ≥0,86 indican que los tamaños de efecto promedio de las deleciones son tan fuertes como la pérdida de función de genes que se sabe que están restringidos contra variantes truncadas de proteínas (razón impar ≥2,7) (Karczewski et al., 2020).

Neuronal heterotopias are alterations of neuronal migration that result in neurodevelopmental disorders, which may or may not be syndromic, and are often associated with convulsive episodes. These disorders are classified based on their location, morphology and the associated structural alterations.

Periventricular nodular heterotopia (PVNH) is the most common neuronal heterotopia, characterized by abnormal nodules of gray matter around the lateral ventricles (PMID: 37119372, 35952334, Vriend, 2021). The most common clinical feature associated with PVNH is epilepsy, in which its time of onset and severity depends on the number and distribution of nodules and the presence of other brain anomalies. Affected patients also show other neurological symptoms such as learning difficulties and variable developmental impairment (PMID: 37119372).

PVNH9 is an autosomal dominant disorder with high penetrance and variable expressivity, characterized by predominantly frontal nodules, distinguishing it from PVNH genetical causes (Vriend, 2021). The individuals described with MAP1B mutations show variable degrees of neurological impairment, including cognitive impairment, epilepsy, and some have shown dysmorphic features (PMID: 29738522, 31317654).

PVNH is associated with epilepsy in 80-90% of cases due to foci in heterotopias or underlying gray matter. A thesis divided a group of 100 patients with PVNH and seizures in two groups depending on associated malformations, finding that PVNH-only patients had a higher proportion of focal seizures and no resistance to treatment, while about one quarter of patients who had additional structural alterations also had drug-resistant epilepsy, with generalized seizures being more common. The age of onset in this study was around 7.9 years and 33% had familial history of seizures. In both groups, therapy with clobazam had the greatest efficacy as monotherapy, and levetiracetam was the drug most associated with seizure control in polytherapy.(Pallioti, 2022) However, as seen in Table 1, PVNH-9 shows a different prevalence of epilepsy and there has not been a wide characterization of convulsive episodes. Specifically for this disease 2021 Arya et al. described four family members, three siblings and their mother, who had PVNH and a combination of different types of seizures along with behavioral characteristics, giving a wider insight of the convulsive phenotype of the disease.

Only one paper (Arya et al., 2021) described four family members, three siblings and their mother, who had PVNH and a combination of different types of seizures along with behavioral characteristics, giving a wider insight of the convulsive phenotype of the disease. In our patient, tonic-clonic seizures did not respond to levetiracetam and had to be changed to valproic acid and clobazam, similar to patients described by Arya et al. (2021).

3 Productos año 3:

3.1 - Artículos académicos:

**Articulo publicado en revista PLOS ONE

Evidencia:

PLOS ONE

RESEARCH ARTICLE

Phenotypic and molecular characterization of the largest worldwide cluster of hereditary angioedema type 1

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Abstract

Hereditary angioedema type 1 (HAE1) is a rare, genetically heterogeneous, and autosomal dominant disease. It is a highly variable, insidious, and potentially life-threatening condition, characterized by sudden local, often asymmetric, and episodic subcutaneous and submucosal swelling, caused by pathogenic molecular variants in the *SERPING1* gene, which codes for C1-Inhibitor protein. This study performed the phenotypic and molecular characterization of a HAE1 cluster that includes the largest number of affected worldwide. A geographically HAE1 cluster was found in the northeast Colombian department of Boyaca, which accounts for four unrelated families, with 79 suspected to be affected members. Next-Generation Sequencing (NGS) was performed in 2 out of 4 families (Family 1 and Family 4), identifying the variants c.1420C>T and c.1238T>G, respectively. The latter corresponds to a novel mutation. For Families 2 and 3, the c.1417G>A variant was confirmed by Sanger sequencing. This variant had been previously reported to the patient prior to the beginning of this study. Using deep-learning methods, the structure of the C1-Inhibitor protein, p. Gln474* and p.Met413Arg was predicted, and we propose the molecular mechanism related to the etiology of the disease. Using Sanger sequencing, family segregation analysis was performed on 44 individuals belonging to the families analyzed. The identification of this cluster and its molecular analysis will allow the timely identification of new cases and the establishment of adequate treatment strategies. Our results establish the importance of performing population genetic studies in a multi-cluster region for genetic diseases.

OPEN ACCESS

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Data Availability Statement: All .vcf files are available from the github.com at URL: https://github.com/ANGIOEDEMA-Type1/HAE1.

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3.2 Escritura de casos clínicos:

** Caso clínico para publicar, pendiente resultados genéticos definitivos, hermano fallecido.

3.2.1 A novel *PEX5* variant associated with Zellweger syndrome in a highly endogamic family Zellweger spectrum disorders

Authors:

Ingrid Tatyana Bernal, Juan Sebastian Arias-Florez, Sandra Ximena Ramirez, Bibiana Bayona-Gomez, Lina Castro-Castillo, Valeria Correa-Martinez, Yasmín Sanchez-Gomez, William Usaquén-Martínez, Lilian Andrea Casas-Vargas,Natalia Santiago-Tovar, Cristian Camilo Gaviria-Sabogal, Nora Contreras Bravo, Rodrigo Cabrera, Adrien Morel, Dora Janeth Fonseca-Mendoza, Carlos M. Restrepo.

Abstract.

The Zellweger spectrum disorders (ZSDs) are a heterogeneous group of autosomal recessive disorders characterized by a defect in peroxisome formation and are caused by mutations in one of 13 PEX genes [1–3]. Clinically, ZSDs are highly heterogeneous, but the core features are dysfunction, developmental delay, various neurological abnormalities, adrenocortical dysfunction and hearing- and vision impairment [4]. This study presents a case of a male patient with consanguinity history that presents a tonic-clonic seizure at 18 days of birth, with recurrence at two months and symptom remission with oxcarbazepine and levetiracetam. The patient showed global developmental delay, with neuroimaging revealing asymmetric polymicrogyria and cortical alterations. Notably, there is a family history of a deceased brother who died at age 5 with epilepsy and apparent leukodystrophy. The clinical features in both patients are highly suggestive of a peroxisomal disorder (Zellweger syndrome (ZS)), which is consistent with the findings in the trio exome where a homozygous variant in PEX5 gene was identified.

Keywords.

Zellweger spectrum disorder, ZSD, Peroxisome biogenesis disorder, PBD, Zellweger syndrome, Neonatal adrenoleukodystrophy, Heimler syndrome, Very long chain fatty acids, VLCFA, mutation

Introduction.

Zellweger syndrome (ZS) is a rare autosomal recessive disease with onset in the neonatal period, associated with severe dysfunctions of the central nervous system, liver and kidneys. Other common clinical manifestations are neuronal migration disorders, early-onset seizures, characteristic facial features, muscle weakness, developmental delay and renal cysts. Skeletal findings that resemble chondrodysplasia punctata, and severe liver disease; death occurs within the first year of life [4- 6, 14, 17, 18].
ZS is caused by mutations in at least one of several *PEX* genes, which encodes peroxisome assembly proteins involved in complex catabolic and anabolic processes. Metabolic dysfunction is expressed by very long-chain fatty acids (VLCFAs) accumulation, phytanic and pristanic acids and C27-bile acid intermediates deficiencies; plasmalogens in erythrocytes are common [19, 20].

We describe here an inbreed previously undiagnosed family with two affected patients with a novel *PEX5* gene mutation. Early-onset seizures, white matter anomalies in brain MRI and global developmental delay and other clinical findings are consistent with ZS and a 5 years older undiagnosed brother, with epileptic leukoencephalopathy.

Cases report

Index case (VI-2) is a male, born from the second pregnancy, with transient unknown fever at eight weeks. He was delivered via cesarean section following a premature membrane rupture. Birth weight was 2,590 gr (-1.07 z). and height was 49 cm (-0.47 z). At 18 days, he debuted with gaze deviation and tonic seizure; at two months the seizures were generalized tonic-clonic seizures with cyanosis. Treatment with oxcarbazepine and levetiracetam was initiated, leading to seizure remission. At 4 months, the patient developed social smiling, managed to take his hands to his mouth and later he was able to grab things with one hand, and produce monosyllables but he was unable to support his head and maintain sitting position. The patient presented global hypotonia, and distinctive facial features including brachycephaly, broad forehead, midfacial hypoplasia, medially spaced eyebrows, ocular proptosis, a small nose, a short and deep philtrum, a cupid's bow upper lip, downward-slanting commissures, and small ears. A magnetic resonance imaging (MRI) scan revealed asymmetric polymicrogyria with more extensive involvement on the left side along with other cortical alterations, which indicates cortical encephalopathy.

The patient's older brother (VI-3) presented severe global developmental delay, focal epilepsy and leukodystrophy, and died at 5 years without diagnosis prior to our assessment.

Their parents aged 37 (F) and 29 years were consanguineous (second cousins) and their grandparents were first cousins as well (Figure 1A). The couple had three children: the patient, his older brother who died at the age of five due to respiratory complications, and a spontaneous abortion was documented at eight weeks. Additionally, a maternal second grade cousin reported a history of epilepsy.

Whole exome sequencing was performed identifying a frameshift homozygous variant in PEX5 gene [NM_001131025.2]:c.1897_1900dupACTA p.(Met634Asnfs).

Discussion.

This study is part of an overarching project titled "Method for Identifying Rare Diseases through Translational Research in Geographical Isolates of the Boyacá Department, Exploring Ancestry." The comprehensive aim of this project is to identify isonymy and ancestry patterns within the population of Boyacá, a region characterized by an endogamy rate of 15.7% and presenting various clusters of undiagnosed, untreated, and potentially novel genetic pathologies. The objective of this study is to propose a predictive risk model for the emergence/presentation of genetic pathologies based on the correlation between genetic-isonymic population analyses and diagnosed orphan diseases. This research aims to contribute to the development of

Colombia's orphan disease law by proposing strategies for primary prevention, optimization of diagnosis, and management of pathologies.

Both parents were heterozygous for the same variant [NM_001131025.2]:c.1897_1900dupACTA p.(Met634Asnfs) in PEX5 gene. Based on this genetic profile and a thorough family history of neurological disorders, the evidence suggests the presence of an autosomal recessive peroxisome biogenesis disorder.

The incidence of ZSDs is estimated to be 1 in 50.000 newborns in the United States [14]. It is presumed that ZSDs occur worldwide, but the incidence may differ between regions. For example, the incidence of (classic) Zellweger syndrome in the French-Canadian region of Quebec was estimated to be 1 in 12 [15]. A much lower incidence is reported in Japan, with an estimated incidence of 1 in 500.000 births [16].

ZSDs represent the predominant types of peroxisome biogenesis disorders (PBDs), stemming from mutations in the PEX1 gene, which accounts for approximately 60% of all PBD cases [5]. This spectrum entails a clinical continuum of various phenotypes, ranging from the most severe manifestation known as Zellweger syndrome (ZS); to milder forms such as neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD), and Heimler syndrome (HS) [5–9]. Although these conditions were previously identified before the full understanding of the biochemical and molecular underpinnings, the term "ZSD" now encompasses all individuals with a mutation in one of the ZSD-PEX genes, regardless of their specific phenotype [5–9]. Clinical manifestation in ZSD spans a spectrum of severity and often defies the original categorizations [10].

Bowen et al. described a syndrome with failure to thrive, congenital glaucoma and craniofacial dysmorphic features and early death (before 2 years of age) [4]. In 1965 Smith et al. reported two siblings with comparable multiple congenital malformations, along polycystic kidneys and intrahepatic biliary dysgenesis [11]. Subsequently, in 1967 Passarge et al. introduced the term cerebro-hepato-renal syndrome. But it was Dr. Hans Zellweger, a pediatrician, who contributed leading to the later designation of the syndrome as ZS [12]. It was not until 1973 that the causal association between ZS and peroxisomes was established, when Goldfischer et al. observed the absence of peroxisomes in hepatocytes and renal proximal tubules [13].

Multiple cases of ZS have been reported in consanguinity families, each demonstrating distinct clinical presentations. One case involved a child born to Dutch parents, presenting with hypertelorism, prominent epicanthic folds, and other craniofacial anomalies. Seizures developed and were managed, but the infant died at 4 months of age [21]. In another case, a child born to Italian parents exhibited different facial features and died at 19 days old due to congestive heart failure [21]. Additionally, two siblings born to Ashkenazi Jewish parents presented with hypotonia, developmental delay, and other ZS characteristic features. Metabolic studies indicated a peroxisomal disorder [22]. Another case in Saudi Arabia, a family with four affected

children with ZS [PEX26: c.296G>A (p.Trp99Ter)], who all died around 4 months of age [23]. These cases underscore the clinical variability and complexity of Zellweger syndrome, which is also observed in families with consanguinity.

The homozygous variant identified in the *PEX5* gene was of uncertain clinical significance has been, involving a four-nucleotide duplication at position 1897 of the cDNA, located within exon 16 of the gene. This variant induces a reading frameshift in the protein, resulting in the removal of 0.94% of the protein. It is not predicted to cause mRNA degradation by the NMD (Nonsense Mediated Decay) pathway. The allelic frequency of this variant remains unknown in the GnomAD population database and it has not been reported in clinical databases or in the scientific literature reviewed.

Some studies have documented loss-of-function (LoF) variants in genes associated with peroxisomal biogenesis disorders. Dodt et al. (1995) identified two LoF variants in *PEX5* from patients with neonatal adrenoleukodystrophy (NALD) belonging to complementation group 2. Interestingly, patient cells with the missense variant (Asn489Lys) exhibited a defect only in PTS1 protein import, while those with the nonsense variant (Arg390Ter) displayed deficiencies in importing both PTS1 and PTS2 proteins. This observation suggested a potential dual role for the *PEX5* receptor in mediating the import of both PTS1 and PTS2 targeted proteins (https://doi.org/10.1038/ng0295-115).

Based on these findings, Braverman et al. (1998) investigated *PEX5* expression in the same NALD patients and found that this gene undergoes alternative splicing, resulting in two transcripts: one containing an additional 111-bp exon and another lacking it. Notably, fibroblasts from the patient with the nonsense variant displayed significantly reduced levels of both *PEX5* transcript and protein compared to the patient with the missense variant. Further functional studies provided clarity on the role of *PEX5* isoforms. Transfecting patient cells with *PEX5* cDNA lacking the additional exon restored PTS1 import but not PTS2 import. Conversely, transfection with the full-length *PEX5* cDNA restored the import of both PTS1 and PTS2 proteins. Additionally, transfection with *PEX5* cDNAs harboring both variants downstream of the additional exon restored PTS2 import but not PTS1 import. These findings collectively suggest that the long isoform of *PEX5* is essential for the peroxisomal import of PTS2 proteins (DOI: 10.1093/hmg/7.8.1195).

Similarly, Ebberink et al. (2010) provided a comprehensive overview of all variants identified in their genetic complementation studies of over 600 skin fibroblast cell lines from patients with Zellweger syndrome spectrum disorders. Specifically, they analyzed thirteen *PEX5* cell lines by sequencing all exons and adjacent intronic regions amplified from genomic DNA (gDNA), and reported five LoF variants located upstream of the variant we reported (doi:10.1002/humu.21388).

Studies have also identified LoF variants in *PEX5* gene associated with Rhizomelic Chondrodysplasia Punctata (RCDP). RCDP, a recessive and often lethal peroxisomal biogenesis disorder, belongs to complementation

group 11 (CG11), the second most common group among the thirteen identified, and is caused by variants in *GNPAT*, *AGPS*, *PEX5* and *PEX7* genes (https://doi.org/10.1038/ng0497-381.)

Unlike other PBDs, RCDP is characterized by skeletal abnormalities like shortened proximal limbs and bone formation issues, along with mental retardation but without the neuronal migration defects typically seen in other PBDs.

Baroy et al. (2015) investigated a Pakistani family with three siblings diagnosed with Rhizomelic Chondrodysplasia Punctata type 5 (RCDP5). The parents were reported to be consanguineous. Whole-exome sequencing identified a homozygous frameshift variant (c.722dupA) in exon 9 (coding exon 7) of the long *PEX5* isoform in all affected siblings. Sanger sequencing confirmed the variant, which co-segregated with the disease within the family. Notably, the same variant was found in an unrelated Pakistani girl with RCDP, also born to consanguineous parents. Notably, studies on cultured fibroblasts from this unrelated girl revealed a defect in PTS2 protein import, and no variants were detected in *PEX7.*

These findings suggest that, similar to *PEX7* variants, loss of the long *PEX5* isoform can lead to peroxisomal dysfunction. This dysfunction is caused by a selective defect in importing PTS2-tagged proteins, resulting in RCDP instead of a more general peroxisome biogenesis disorder (https://doi.org/10.1093/hmg/ddv305).

Descripción del gen y la proteína:

PTS1R (Peroxisomal Target Signal 1 Receptor, also known as PEX-5), is a peroxin, a group of proteins that are essential for the formation of functional peroxisomes, cellular organelles derived from the endoplasmic reticulum that perform multiple metabolic pathways. (https://www.uniprot.org/uniprotkb/P50542/entry#sequences) PTS1R is located in the cytosol and peroxisomes, and is part of both formation and degradation of these organelles. First, it recognizes and binds matrix proteins containing the C-terminal tripeptide peroxisome target sequence (PTS) in order to import them into the peroxisome through an ATP-requiring action, functioning as a receptor. (https://omim.org/entry/600414) On the other hand, during peroxisome degradation known as pexophagy, PTS1R is phosphorylated by ATM and then ubiquitinated at L209 by the peroxisomal E3-ligase, PEX2/10/12, to be recognized by the autophagic adaptor SQSTM1/p62. (PMID: 29622767) (PMID: 26967755)

PTS1R also participates in autophagy regulation outside the peroxisome through inhibition of the mTORC1 pathway, and it has been shown that its absence impairs the cell's ability to start this process under stress situations. (PMID: 29622767)

It is encoded by the PEX-5 gene located at 12p13.31, containing 16 exons. It has multiple isoforms, with two main coding for functional proteins derived from alternative splicing of exon 7: PEX5S (short) and PEX5L (long) The short isoform only imports PTS-1 sequences while the long one also recognizes PTS-2 (PMID: 22871920)

Even though the testis and brain are the tissues with the highest expression, PEX-5 is ubiquitous in human samples, explaining the multiorgan dysfunction seen in patients with Peroxisomal Biogenesis Disorders caused by PEX-5 deleterious variants: Peroxisome Biogenesis Disorder 2A (PBD2A), Peroxisome Biogenesis Disorder 2B (PBD2B) and Rhizomelic Chondrodysplasia Punctata type 5 (RCDP5) (https://www.ncbi.nlm.nih.gov/gene/5830) (https://omim.org/entry/600414) Variants are found in the entire gene, however, exons 12 and 14 have a particularly high number of them, with the most common variant being c.1578T>G (p.N526K) (PMID: 22871920)

Conclusion:

In summary, based on the available evidence, this variant is classified as of uncertain clinical significance.

Deleterious variants in the PEX5 gene (MIM *600414) are known to be linked with peroxisomal biogenesis disorder 2A (Zellweger) (MIM #214110), peroxisomal biogenesis disorder 2B (MIM #202370), and rhizomelic chondrodysplasia punctata type 5 (MIM #616716), all of which exhibit autosomal recessive inheritance.

Descripción de la región, su endogamia y patología genéticas identificadas. Genetica comunitaria.

This study is part of a broader project titled "Method for Identifying Rare Diseases through Translational Research in Geographical Isolates of the Boyacá Department, Exploring Ancestry." The primary objective of this project is to identify isonymy and ancestry patterns within the population of Boyacá. This region, characterized by an endogamy rate of 15.7%, presents various clusters of undiagnosed, untreated, and potentially novel genetic pathologies. The specific aim of this study is to develop a predictive risk model for the emergence and presentation of genetic pathologies. This model will be based on the correlation between genetic-isonymic population analyses and diagnosed orphan diseases. The research is intended to contribute to the development of Colombia's orphan disease law by proposing strategies for primary prevention, optimizing diagnosis, and managing these pathologies.

Boyacá, located in the Andean region of Colombia, is known for its mountainous geography, inter-Andean valleys, and plateaus, as well as its rich cultural heritage, history, and ethnic diversity. Many of its communities have remained relatively isolated due to the rugged terrain, leading to high rates of endogamy, or marriages between relatives. Endogamy in Boyacá has significantly impacted the prevalence of rare genetic diseases. Evidence from various population studies has identified clusters of recessive genetic disorders, such as Sanfilippo syndrome, a type of mucopolysaccharidosis. Velasco et al. (2017) documented a high incidence of this disease in the population.

The presence of genetic disorders in rural populations like those in Boyacá poses a significant public health challenge. These rare diseases, influenced by endogamy and geographic isolation, increase the healthcare and

economic burden in communities with limited access to specialized medical services. Effective identification and management of these conditions are crucial for implementing prevention programs, early diagnosis, and appropriate treatment, thereby reducing associated morbidity and mortality and improving the quality of life for affected individuals.

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3.3 -Participación en seminarios o talleres al interior del Grupo de Investigación para este año:

3.3.1 Reuniones tecnicas

-Participación en reuniones semanales, para valorar resultados obtenidos, cada 8 dias martes y miércoles a las 6 o 7 pm.

3.3.2 Asesoramiento genético

- Durante el último semestre, se iniciaron los asesoramientos genéticos a familiares, con enfermedades genéticas, para valorar diagnóstico, tratamiento, pronostico, manejo en caso de querer más hijos, técnicas de reproducción asistida, riesgo de aparición de nuevas patologías genéticas.

**Durante el semestre se han realizado 4 asesoramientos genéticos.

-Se realizan de forma virtual, via WhatsApp por elección del familiar, con todo el equipo clínico, a cargo de dos profesionales en formación y un genetista.