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REVISION BIBLIOGRAFICA CUALITATIVA SOBRE EL USO DEL DIAGNÓSTICO EN CASCADA CON CONFIRMACIÓN POR PRUEBAS GENÉTICAS PARA LA HIPERCOLESTEROLEMIA FAMILIAR Y SU UTILIZACIÓN COMO MARCADOR PREDICTIVO DE ENFERMEDAD CARDIOVASCULAR

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Trabajo de Investigación o Tesis Doctoral como requisito para optar el título de Magister en Genética

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RESUMEN

Antecedentes: La Hipercolesterolemia Familiar (HF) es una patología autosómica dominante de una prevalencia a nivel global medida entre 1:250 y 1:600 en sujetos heterocigotos que en su presentación monogénica se ve originada principalmente en mutaciones de tres genes, LDLR, APOB y PCSK9 y que su mayor impacto fisiológico es en metabolismo de los lípidos(LDL-C) con la aparición prematura de un riesgo cardiovascular elevado representado en un proceso aterogénico temprano con formación de placa ateromatosa y eventos por enfermedad arterial coronaria prematura.

La HF tiene un origen genético que desde el punto de vista médico se diagnostica mediante criterios clínicos dejando casi a un lado el diagnóstico genético molecular, es por eso que se realizó una revisión narrativa de la literatura sobre el diagnóstico de la HF por análisis genético en sujetos índice por evento cardiovascular prematuro y el tamizaje de la familia en cascada en la búsqueda de una herramienta que modifique riesgo cardiovascular de los portadores de la enfermedad.

Objetivos: Objetivo General

Realizar una revisión sistemática de la literatura sobre la hipercolesterolemia familiar y el uso herramientas para el diagnóstico genético, como factores modificadores del riesgo para enfermedad cardiovascular con la identificación de casos y portadores de la enfermedad, desde un paciente índice.

Objetivo específicos

- Validar el diagnóstico en cascada como método acertado para la identificación de nuevos casos de HF.
- Calificar el impacto del diagnóstico genético en el manejo preventivo de la HF como un factor desencadénate de riesgo cardiovascular.
- Identificar las mutaciones genéticas más reportadas en la literatura como causantes de HF.

Materiales y Métodos: Revisión bibliográfica de una búsqueda en PUBMED utilizando como primer filtro el término *Hipercolesterolemia Familiar*, que como resultado inicial arrojó 3.569 publicaciones y al agregar el segundo filtro para la *detección de mutaciones* redujo su número a 128 publicaciones; el tercer filtro fue agregar el término de *tamizaje por cascada* lo que redujo a 28 publicaciones y por último se filtraron las publicaciones– por año entre 2010 y 2020 encontrando un total de 25 publicaciones que, al aplicar los criterios de inclusión y exclusión definidos, solo 7 documentos fueron escogidos para su revisión y análisis. La población de sujetos que conformó la muestra analizada en los 7 documentos que quedaron para la revisión final fue de 67.160 sujetos.

Resultados: La revisión bibliográfica de los siete documentos que cumplieron los criterios de inclusión muestran que el uso de del cribado en cascada permite la identificación de entre 1.8 a 8 nuevos casos por caso índice. El diagnostico en cascada permite realizar una intervención temprana en pacientes con HF en el punto que no hay manifestaciones fenotípicas y se puede retardar los desenlaces por enfermedad cardiovascular. La combinación de cribado en cascada con diagnostico genético muestra un incremento de la certeza de diagnostica y permite hacer manejo clínico de precisión sobre los pacientes con HF. El realizar diagnostico en genética permite tipificar la patología por territorios ya que no hay gran prevalencia de mutaciones con cobertura global.

Conclusiones: El uso del diagnostico en cascada y la confirmación por estudios genéticos nos permite hacer tratamiento de precisión en la HF. Una patología de tan alta prevalencia requiere que se realicen estudios poblacionales por país para poder caracterizar el comportamiento de esta en

casa país y Colombia no es la excepción. El uso esta combinación de diagnostico es costo efectiva para el sistema de salud al reducir la posibilidad de evento coronario a temprana edad y mejorar la calidad de vida de cada paciente al disminuir el poder deletéreo del colesterol elevado en el organismo. Queda pendiente poder realizar el registro de HF en Colombia con diagnostico confirmatorio por prueba genética.

Palabras clave: Hipercolesterolemia Familiar, Monogénica, Riesgo Cardiovascular, Caso índice, Tamizaje en Cascada, Mutación.

ABSTRACT

Background: Familial Hypercholesterolemia is an autosomal dominant disease with a worldwide prevalence measure between 1:250 to 1:600 on heterozygous subjects that on her monogenic presentation has an origen mainly on three genes LDLR, APOB and PCSK9, with the biggest physiological impact on the metabolism of lipids (LDL-C) with the premature cardio-vascular risk increases mainly with an early atherogenic process and formation of atherogenic plate and coronary artery disease.

Familial Hypercholesterolemia is a disease with genetic origen that from medical point of view the diagnose is made following clinical criteria's leaving genetic testing at side, that is the reason we made a systematic review of the literature about the diagnose of FH by genetic analysis on index subjects by premature CVD and family cascade screening searching for a tool that helps on modifying the CVD risk of disease carriers.

General Objective:

Create a systematic review of the literature about family hypercholesterolemia and the use of tools for the genetic diagnose, as a factor for the modification of the vascular heart disease risk and the identification of new cases forma n index case.

Objetivo específicos

- Validate the cascade screening diagnose as a Good method of identification of new cases of FH. Validar el diagnóstico en cascada como método acertado para la identificación de nuevos casos de HF.
- Qualify the impact of genetic diagnose on the preventive management of FH as a factor for risk of heart disease.
- Identify most reported genetic mutations on the literature causing FH.
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Materials and Methods: We made a PUBMED search using initially the Familial Hypercholesterolemia with a result of 3.569 publications, then we made an advance search using the term mutation detection and refine the

search to 125, finally we add the term cascade screening leaving 28 documents, a final filter was set on articles between 2010 and 2020 leaving only 25 documents, after applying inclusion and exclusion criteria's 7 articles were left for analysis, the total subjects that made the universe of the 7 articles studied was 67160.

Results: The document revision of the seven documents that fulfill the inclusion criteria shows that the cascade screening allows the identification of new cases for FH on a range of 1.8 to 8 for each index case. The cascade screening allows an earlier intervention on patients with FH from a moment with out phenotypic manifestations of the disease and it can be delay end points of the heart disease. The combination of cascade screening and genetic diagnose shows an increase certainty over diagnose and allows precision clinical treatment on the patient with FH. Due to the lack of prevalence of some specific genetic mutations the genetic testing allows as to map the FH on each country and territory.

Conclusions: The use of the combination of cascade screening with genetic testing allows the precision treatment od FH. A so high prevalence disease needs making populations studies per country so is possible to characterize the behavior on each country including Colombia. The use of the propose combination of testing is cost effective for the health system by the means of reducing the possibility of coronary events at early age and improve the quality of life of each patient with the reducing the effect of high cholesterol on each patient. A pending task is to create the FH register in Colombia with genetic testing as a confirmatory measure.

KeyWords: Familial Hypercholesterolemia, Monogenic, Cardiovascular Risk, Index Case, Cascade Screening, Mutation.

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