European Journal of Clinical and Experimental Medicine

ONLINE FIRST

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Article type: Review

Received: 18 November 2023

Accepted: 9 January 2024

Published online: 13 February 2024

eISSN: 2544-1361

Eur J Clin Exp Med

doi: 10.15584/ejcem.2024.2.2

Genetic factors contributing to the development of inguinal hernias – a narrative review

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ABSTRACT

Introduction and aim. Inguinal hernias are one of the major disorders in the field of general and visceral surgery and can be viewed as multifactorial diseases. Although the molecular mechanism that led to predistortion to inguinal herniation still remain unclear, is well known that defects leading to improper closure of the inguinal canal during fetal development and mechanisms contributing to weaker muscles of the abdominal wall can greatly increase the risk of developing the latter disease.

Material and methods. A literature search was performed in all major electronic databases using keywords and Boolean operators to retrieve all available literature related to the topic. Due to the narrative nature of the review, there were no specific inclusion and exclusion criteria.

Analysis of the literature. Genetic factors, undoubtedly, can interfere with these mechanisms and therefore play major role in developing hernias. To this end, the present narrative review provides an overview of genes with altered expression and genetic polymorphisms associated with inguinal herniation. Moreover, the results of genome-wide association studies (GWAS) exploring susceptible genetic loci associated with the disease have been reported.

Conclusion. Nevertheless, more case-control studies and GWAS need to be conducted in different ethnic populations so as to provide better insights into the topic.

Keywords. genes, genetics, genome-wide association, inguinal hernias, polymorphisms, studies

Introduction

The inguinal canal is an oblique tubular passage that runs in the lower abdominal wall, exactly above the groin region, containing the spermatic chord in males and the round ligament of the uterus in females. An inguinal hernia is formed when abdominal viscera protrude through the inguinal canal, and is usually presented as bulges in the groin. Inguinal hernias are indeed one of the most prevalent clinical conditions, with a prevalence of approximately 9.61% in men and 1.31% in women globally.[1] They are classified into direct hernias, which are those that are characterized by protrusion through the wall of the inguinal canal, and indirect hernias, which are formed by protrusion through the inguinal ring.[2,3] Indirect inguinal hernias are more common in children and usually occur due to birth defects of the inguinal canal opening that allow the protrusion of abdominal viscera through the canal.[4,5] Direct inguinal hernias, on the other hand, are more common in middle-aged and older patients and are often caused by the weaking of the abdominal musculature.[4]

Today, the only existing method of treating inguinal hernias, is through open or laparoscopic surgery.[6] However, there is still a chance that the hernia reoccurs even after a successful surgical operation, making the disease a heavier burden for the patient.[7] Different factors have been identified that increase the risk of developing direct and indirect inguinal hernias, as well as the risk of post-surgery recurrence.[8,9] Recently, studies have also shown that different genetic factors may also increase the risk of developing both direct and indirect inguinal hernias, suggesting that they can be studied as multifactorial diseases.[4] Indeed, several studies have been able to identify strong inheritance patterns of predisposition to inguinal hernias amongst different families.[10] This would allow clinicians and researchers to gain better insights into the prevention of inguinal hernias and provide patients with more information on the risk of post-surgery recurrence through means of molecular testing.

Aim

The present narrative review, aims to explore the role of genetics in the development of inguinal hernias has been analyzed in detail, with the hope of providing an overview of the current available evidence.

Material and methods

A systematic search was performed in the electronic databases of PubMed, Scopus, EMBASE and Google Scholar to retrieve all available literature on the role of genetic factors in inguinal herniation. A combination of the keywords “Genetics”, “Genes”, “GWAS”, “Inguinal”, “Hernias” and “Herniation” were used in combination with the operators “AND” and “OR”. Due to the narrative nature of the review, there were no specific inclusion and exclusion criteria. Overall, all articles, including original research and reviews, written in the English language and with relevant information were included in the synthesis of the review.

Analysis of the literature

Molecular mechanisms of inguinal hernia development

There are various molecular mechanisms that can increase the predisposition of developing inguinal hernias. A broader understanding of these mechanisms is required in order to comprehend the genetic backgrounds of inguinal herniation.

The role of the extracellular matrix in inguinal hernias

The extracellular matrix (ECM), is one of the important factors contributing to the pathogenesis process of inguinal hernias.[4] Indeed, the composition of the ECM can determine the strength of the lower abdominal wall muscles and therefore contribute to direct herniation.[11] Moreover, research has shown that the ECM plays a crucial role in fetal morphogenesis and thus, defects in the ECM can cause inadequate closure of the inguinal ring, contributing to the formation of indirect hernias, especially in children.[12,13] Two of the main components of the extracellular matrix are collagen and elastin fibers, which have been related to many genetic disorders and predisposition to various diseases.[14] Indeed, regarding inguinal hernias, researchers have discovered that the total quantity of collagen, especially that of type I collagen is significantly less in the fascia transversalis and peritoneal samples of most patients with direct or indirect inguinal hernias.[15] On the other hand, the quantity of collagen type III has been found to be increased in the fascia transversalis of patients with inguinal hernias.[16] It is known that collagen type III is characterized by less mechanical resistance and is associated with fragility and decreased collagen alignment in the ECM.[17] Thereby, a substitution of type I collagen by type III collagen may result in higher predisposition to inguinal hernias. In fact, studies have found that the collagen type I/III ratio is higher in the abdominal wall and peritoneum of patients with inguinal hernias, but no statistically significant difference has been found between patients with direct and indirect hernias.[18] Simultaneously, elastin fiber levels have been found to be decreased in patients with both direct and indirect inguinal hernias and contribute to weaker muscles of the abdominal wall.[18,19] It is also worth mentioning that other proteins and glycoproteins such as fibulins, fibronectin and tenascins are of high significance in the structure and mechanical resistance of the ECM.[20] Indeed, it has been discovered that in patients with direct and indirect inguinal hernias, the expression of fibulin-3 is downregulated.[21] Furthermore, patients with Ehlers-Danlos Syndrome who present tenascin-X deficiency are at a higher risk of developing inguinal hernias.[22] However, regarding fibronectins, no correlation has been yet found with inguinal herniation in human samples.[23]

The role of growth and differentiation factors in inguinal hernias

The formation of the inguinal canal begins around 8 to 10 weeks after gestation and is the route for testicular decent in male fetuses.[24] The formation and closure of the canal, nonetheless, continue until the final stages of gestation up to the third trimester and any defects in the process may result in higher predisposition to indirect inguinal herniation.[24,25] Studies have found that factors contributing to smooth muscle cell

differentiation in the fetus may result in defects of the inguinal canal in children.[26] Moreover, it has been suggested that the production of androgens and epithelial transformation factors contribute to the formation of the inguinal canal, and therefore defects in these mechanisms may result in higher risks of developing indirect inguinal hernias.[27]

Figure 1 presents a summary of the molecular mechanisms contributing to predisposition to inguinal herniation.

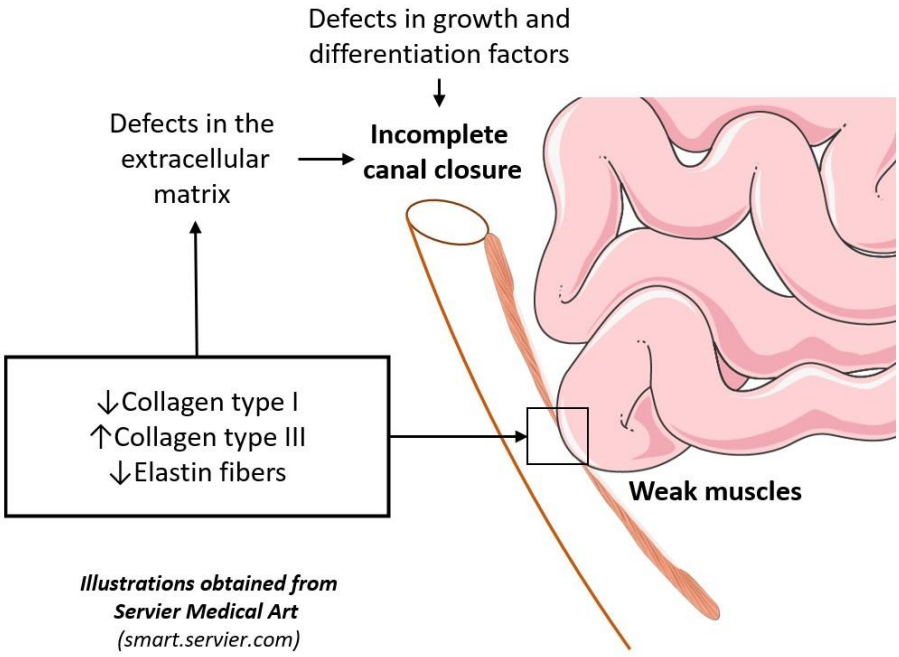

Fig. 1. Molecular mechanisms contributing to predisposition to inguinal herniation

Genes and genetic polymorphisms related to inguinal hernias

In the recent years, many genes have been found to be related to inguinal hernias and some of their polymorphisms have been statistically associated with higher risk of herniation [4]. Hence, these genes have been overviewed in this review article.

Collagen genes

The collagen genes, especially those coding for type I collagen have been found to be associated with both direct and indirect inguinal hernias. Indeed, Sezer et.al found that the +1245G/T polymorphisms in the collagen type I alpha 1 (COL1A1) gene are associated with inguinal herniation, finding approximately fourfold odds of the polymorphisms in patients with direct and indirect inguinal hernias, compared to controls.[28] This polymorphism has also been associated with other conditions such as osteoporosis and predisposition to cruciate ligament injuries and is not specific to the abdominal wall.[29,30] Moreover, a cohort

study in 2022 concluded that the hazard ratio of inguinal herniation was approximately twofold in a population with collagenopathies compared to initially healthy individuals.[31]

The elastin gene

The elastin gene (ELN) codes for the protein tropoelastin is another very significant component of the ECM.[32] A case-control study by Rodrigues et.al identified that the point missense mutation g28197A>G in the ELN gene leading to an amino acid substitution in the hydrophobic domain of tropoelastin, is significantly associated with direct inguinal herniation.[33] It is also worth mentioning that the 2012DeltaG and 2039DeltaC frameshift mutations in the ELN gene have been found to be associated with congenital cutis laxa, a disease reported to increase predisposition to inguinal herniation.[34,35]

Matrix metalloproteinase genes

The matrix metalloproteinase (MMP) genes as well as their tissue inhibitors genes (TIMPs) are known to be linked to the composition of the ECM and collagen expression within the matrix.[36,37] In the case of inguinal hernias, tissue samples obtained from the abdominal wall have shown upregulation of MMP-1, MMP-2, MMP-9 and MMP-13 and simultaneously, downregulation of the inhibitors TIMP-1, TIMP-2 and TIMP-3.[38-40] Nevertheless, a search conducted from inception until May 2023 in the PubMed and SCOPUS databases retrieved no study relating polymorphisms of these genes with inguinal herniation, suggesting that such studies have not been conducted yet.

The Wilms tumor protein gene

The Wilms tumor protein gene (WT1) codes for a transcription factor, responsible for the development of the urogenital system and has been associated with the development of certain malignancies including nephroblastoma and hematological cancers.[41] Interestingly, the rs3809060 polymorphism of the gene has been found to be associated with inguinal hernias, where the GT and TT genotypes increase the risk of herniation in adult males.[42]

The EGF-containing fibulin-like extracellular matrix protein-1 gene

The EGF-containing fibulin-like extracellular matrix protein-1 gene (EFEMP1) is another very significant protein regulating the composition of the extracellular matrix.[43] Peng et.al, discovered that the expression of EFEMP1 is downregulated in the fascia transversalis of patients with direct inguinal hernias compared to apparently healthy controls.[21] Furthermore, it has been discovered that the EFEMP1 rs2009262 polymorphism is associated with inguinal hernias adults, where the TC and CC genotypes in females increase the risk of herniation in adult females.[42]

The T-box transcription factor genes

The T-box transcription factors are a family of proteins vital for embryonic development, including the development of the abdominal cavity and the genitourinary system.[44] The T-box transcription factor 2 (TBX2) and T-box transcription factor 3 (TBX3) genes have been found to be related to predisposition to indirect inguinal hernias.[45,46] In fact, the g.59476307G>C DNA sequence variant (DSV) within the TBX2 promoter gene has been found to be connected with indirect herniation.[45] Similarly, the deletion variant g.4820_4821del within the TBX3 gene promoter, has been found to significantly decrease the promoter's activity and as a result lead to herniation predisposition.[46] These polymorphisms have been found to be correlated to the development of other embryological development disorders such as ventricular septal defects and thus, are not specific only to inguinal herniation risk.[47,48]

The lysyl oxidase like-1 gene

The lysyl oxidase like-1 gene encodes for an enzyme necessary for the biosynthesis of elastin and the cross-linking of collagen molecules.[49] A study by Pascual et.al, discovered that the expression of the enzyme is significantly downregulated in the fascia transversalis of patients with direct inguinal hernias.[50] The downregulation of LOX1, leads to the formation of a mechanically weaker ECM with less elastin fibers and therefore contributes to the process of herniation.[51]

Sirtuin genes

The sirtuin (SIRT) gene family, encoding for a total of seven significant proteins, has been found to contribute to muscle formation and differentiation and act as transcription factors.[52] In the case of inguinal hernias, it has been discovered that expression of the SIRT1 gene is correlated with incomplete closure of the inguinal canal and thus, indirect inguinal herniation. In fact, two DSVs namely g.69644213G>A and g.69644268T>A, and one single nucleotide polymorphism (SNP), g.69643707A>C of the SIRT1 gene, have been found to increase the risk of developing indirect inguinal hernias in a case-control study.[53]

Table 1 summarizes all genetic variations relating to inguinal hernia predisposition.

Table 1. Genetic variations increasing the risk for inguinal herniation

Gene	Variation	Type of variation	Subtype of inguinal hernias associated	References
COL1A1	+1245G/T	Insertion polymorphism	Direct and indirect inguinal hernias	[28]
ELN	g28197A>G	SNP	Direct and indirect inguinal hernias	[33]

WT1	rs3809060	SNP	Direct and indirect inguinal hernias (Males only)	[42]
EFEMP1	rs2009262	SNP	Direct and indirect inguinal hernias (Females only)	[42]
TBX2	g.59476307G>C	DSV	Indirect inguinal hernias	[45]
TBX3	g.4820_4821del	DSV	Indirect inguinal hernias	[46]
SIRT1	g.69644213G>A	DSV	Indirect inguinal hernias	[53]
	g.69644268T>A	DSV	Indirect inguinal hernias	
	g.69643707A>C	SNP	Indirect inguinal hernias	

Genome-wide association studies on inguinal hernias

Several genome-wide association studies (GWAS) have been conducted in order to identify significant genes and susceptible genetic loci related to inguinal hernias. Until today, five GWAS have been conducted in the UK, Japan and the USA, some in multiethnic populations, and they have reported significant results.[54-58] Table 2 summarizes the characteristics of these GWAS.

Table 2. Genome-wide association studies on inguinal hernias

Study	Year	Country	Patients	Controls	Number of loci identified
Jorgenson et al.[54]	2015	USA	5295	67,510	4
Hikino et al.[55]	2021	Japan	1983	172,507	23
Ahmed et al.[56]	2022	UK	18,791	93,955	24
Choquet et al.[57]	2022	USA (multiethnic)	33,491	694,927	63
Fadista et al.[58]	2022	UK	28,707	343,103	69

Overall, numerous susceptibility loci have been identified, out of which some include the genes which had been screened in previous smaller case-control studies, such as ELN, WT1, EFEMP1 and LOX1.[54,55,57,58] Sex-specific genes in males have also been reported to be included as susceptibility loci in inguinal hernias.[57] It is worth mentioning that two studies screened genetic loci for different types of hernias and some susceptibility loci overlapped in different types of herniation.[56,58]

Discussion

Although the molecular mechanisms contributing to inguinal herniation are not yet fully comprehended, it is clear that genetic factors do indeed contribute to the formation of both direct and indirect inguinal

hernias[4]. Moreover, studies have shown that certain genetic polymorphisms associated with inguinal herniation such as the WT1 polymorphism are sex-specific rs3809060 and this could explain the higher prevalence of inguinal herniation amongst males.[42] With so many genetic polymorphisms and susceptibility loci found to be associated with inguinal herniation, the condition can henceforth be viewed as a multifactorial disease. This would mean that surgeons and pathologists could also possibly include means of molecular testing in cases of inguinal hernias to provide themselves and patients with better clinical images.

Nevertheless, there are still some genes such as MMPs and TIMPs which have been shown to present altered expression levels in patients with inguinal hernias, but the relationship between their polymorphisms and inguinal herniation is still unknown.[38,39]

Conclusion

Therefore, more studies need to be conducted in this direction so as to discover whether polymorphisms of the genes are associated with the disease or even discover epigenetic mechanisms which alter their expression. Moreover, the majority of the genome-wide association studies for inguinal hernias, except one multiethnic study in the USA, have been conducted in Caucasian and Asian population. Hence, more studies are required in other ethnic populations so as to decrease the risk of reporting biased results. It is also worth mentioning that most studies are conducted mainly on male populations and thus it is difficult to generalize the results amongst the population, indicating the need for conducting further studies involving both males and females in a normalized distribution.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

Conceptualization, D.K.; Methodology, D.K.; Software, D.K.; Validation, D.K.; Formal Analysis, D.K.; Investigation, D.K.; Resources, D.K.; Data Curation, D.K.; Writing – Original Draft Preparation, D.K.; Writing – Review & Editing, D.K.; Visualization, D.K.; Supervision, D.K.; Project Administration, D.K.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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