Int J Mol Epidemiol Genet 2025;16(2):9-15
www.ijmeg.org /ISSN:1948-1756/IJMEG0167110

Original Article

Genetic risk score for cholesteatoma recurrence: using UK Biobank data toward more individualized patient management

Ioannis Michael Vlastos[1], Almomani Mohannad[2,3], John Hajiioannou[3,4], Theodora Chronopoulou[1], Han Peng[5], Kalliopi Gkouskou[6]

[1]Evangelismos General Hospital, Athens, Greece; [2]Mediterranean Hospital of Cyprus, Limassol, Cyprus; [3]Medical School, University of Thessaly, Larissa, Greece; [4]Department of ENT, University Hospital of Larissa, Larissa, Greece; [5]Department of Otorhinolaryngology, Xi'an Jiaotong University, Xi'an, Shaanxi, China; [6]Department of Biology and Genetics, Medical School, Kapodestrian University of Athens, Athens, Greece

Received June 28, 2025; Accepted August 31, 2025; Epub October 15, 2025; Published October 30, 2025

Abstract: Background: Cholesteatoma recurrence is relatively common and often requires repeat surgical interventions, imposing a significant burden on patients and healthcare systems. Although clinical factors such as age, disease aggressiveness, surgical technique, and surgeon experience influence recurrence risk, accurate prediction remains challenging. Genetic Risk Scores (GRS), which aggregate the effects of multiple genetic variants, offer a promising approach to individualized recurrence risk estimation. Objective: To evaluate the contribution of specific genetic variants to cholesteatoma recurrence by constructing a GRS using data from the UK Biobank. Methods: A systematic review of PubMed identified six genes previously associated with cholesteatoma recurrence: KGF (FGF7), KGF-R (FGFR2), MMP9, KRT1, KRT10, and MIF. Corresponding single nucleotide polymorphisms (SNPs) were analyzed using the UK Biobank, a large-scale biomedical database of approximately 500,000 participants. Individuals with recurrent cholesteatoma were identified using ICD-10 code H95.0. SNPs with minor allele frequency <5% or in linkage disequilibrium were excluded. A weighted GRS was calculated by summing the number of risk alleles for each SNP, multiplied by their β coefficients (log odds ratios). Results: A total of 39 SNPs were included in the final GRS calculation. Among 502,164 UK Biobank participants, 55 individuals were identified with recurrent cholesteatoma. The mean GRS for these individuals was 3.86, compared to 3.72 in the general population, indicating a 15.6% relative increase in genetically determined recurrence risk (OR ≈ 1.156). Conclusions: This study demonstrates a modest but measurable contribution of genetic variation to cholesteatoma recurrence. While the effect size is limited, future studies with larger cohorts and genome-wide data may improve predictive accuracy. Even at this stage, the GRS may help guide surgical decision-making and follow-up planning, moving toward more personalized management of cholesteatoma.

Keywords: Genetic risk score, cholesteatoma recurrence, UK Biobank

Introduction

Cholesteatoma recurrence is relatively common, often requiring multiple surgical interventions. It is often debilitating for patients and contributes to increased healthcare costs. Several clinical and surgical factors influence recurrence rates, including the biological aggressiveness of the disease, the age of the patient, the experience of the surgeon, and the surgical technique employed [1-4]. Despite this, predicting which patients are most likely to experience recurrence remains challenging.

An accurate prediction of recurrence risk would be highly valuable in clinical practice. It can enhance shared decision-making with patients, guide follow-up planning, and help guide the choice of surgical technique. Importantly, if recurrence risk could be estimated based on an individual's inherited genetic profile, it allows more personalized treatment strategies. Genetic Risk Scores (GRS), which aggregate the effect of multiple genetic variants across the genome, offer a promising approach to such individualized risk prediction [5, 6].

https://doi.org/10.62347/CRXH8917

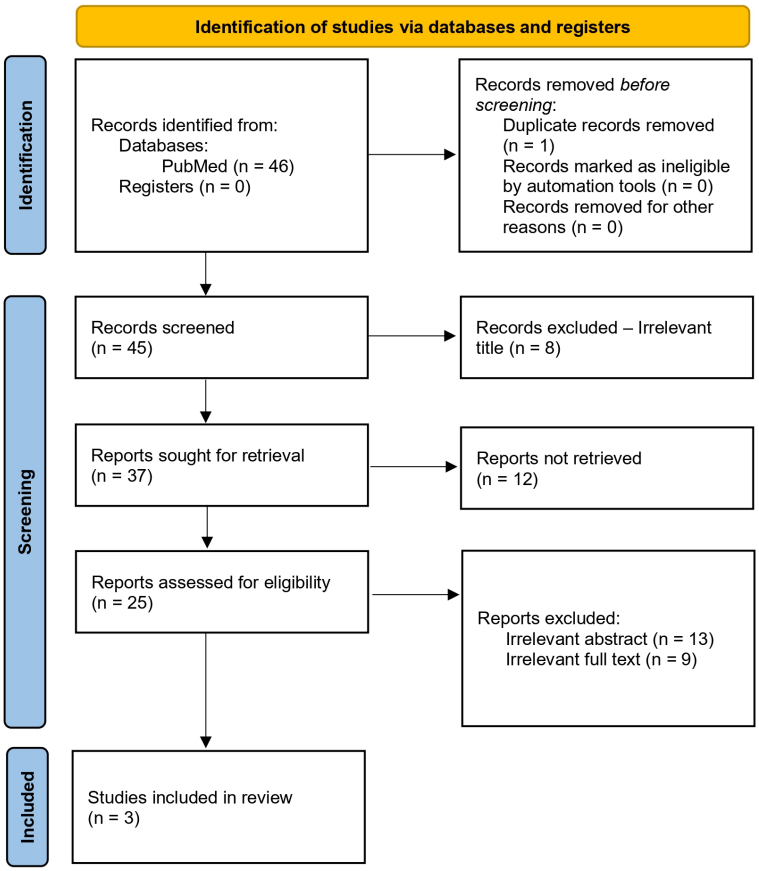

Figure 1. PRISMA diagram of the studies reporting genes that have been correlated to cholesteatoma recurrence.

In a research context, GRS-based prediction not only helps to identify individuals at higher risk but also contributes to a better understanding of disease mechanisms. It facilitates the exploration of gene - environment interactions and enables the stratification of study populations based on genetic susceptibility, which is crucial for targeted interventions and uncovering underlying biological pathways [7-9].

Despite the potential benefits of a GRS in cholesteatoma management, such a score has not yet been developed, primarily for two reasons. First, a GRS requires high-throughput genetic analysis of a large patient cohort, which is difficult and costly to obtain. Second, it demands bioinformatics expertise, a field unfamiliar to the majority of clinicians.

The UK Biobank, one of the largest and most comprehensive biomedical databases in the world, offers an ideal platform for investigating the genetic architecture of complex diseases. In this study, we leverage the UK Biobank to examine specific genes and polymorphisms previously implicated in cholesteatoma recurrence. Using this information, we construct a Genetic Risk Score aimed at evaluating the contribution of genetic variation to recurrence risk. Our findings contribute to the growing field of genomic predictions in otologic diseases and may inform future clinical applications.

Methods

A pubmed systematic review based on terms: “cholesteatoma and recurrence” and “genetic OR genes OR biomarkers” ([recurrence and cholesteatoma and biomarkers] or [recurrence and cholesteatoma and genetic]) was initially conducted with the purpose of retrieving all possible genes or genetic polymorphisms that have been related to cholesteatoma recurrence. Search results are shown in **Figure 1**, depicting a PRISMA type diagram. Genes that have been indirectly related to cholesteatoma recurrence or the whole text of the paper does not support their correlation to recurrence were excluded as irrelevant as we show in our PRISMA diagram. A total of 6 genes through 3 studies [10-12] have been identified by our systematic approach (KGF (FGF7), KGF-R (FGFR2), MMP9, KRT1, KRT10, MIF).

Upon this, single nucleotide polymorphisms (SNPs) of the aforementioned genes implicated in cholesteatoma recurrence were studied in the UK biobank (UKBB). The UKBB is a large-scale biomedical database and research resource containing in-depth genetic, health, and lifestyle information from approximately 500,000 participants across the United Kingdom, aged between 40 and 69 years at the time of recruitment (2006-2010). It also in-

cludes longitudinal follow-up through linkage to electronic health records, e.g. hospital episodes.

For this study, we utilized genotype and phenotypic data from UK Biobank under approved application number (application ID 117308) focusing on genetic variants within candidate genes previously implicated in cholesteatoma recurrence. More specifically, all data was accessed through DNAnexus platform. For each gene a clinical filter of H95.0 (recurrent cholesteatoma of postmastoidectomy cavity) of ICD10 record diagnoses was applied. In all, 55 patients were found with recurrent cholesteatoma out of 502,164 participants. Genotypes were extracted and downloaded as a cmv file for each gene of interest containing alleles frequences in the cohort and in the general population.

The weighted Genetic Risk Score (GRS) based on the genes of interest was calculated as the sum of the number of risk alleles multiplied by their β coefficients (effect size or log-odds ratio for each SNP). Supplementary Figure 1 shows the equations used for this purpose. Those SNPs with an allele frequency of <5% and those that were in linkage disequilibrium (alleles of genetic loci that lie in proximity to each other with strongly associated frequences) were excluded from the calculation of GRS [6].

Results

A total of 39 SNPs were utilized for the formulation of the GRS (**Table 1**). Their allele frequencies in the cohort as well as in the general population and their β coefficient is also shown in this table.

The mean genetic risk score (GRS) for individuals with recurrent cholesteatoma was 3.86, compared to 3.72 in the general population. This corresponds to a relative increase in genetically determined risk of approximately 15.6% (OR = $e^{\Delta GRS}$ = $e^{0.14}$ ≈ 1.156), indicating a modest polygenic contribution to recurrence.

Discussion

Cholesteatoma is a chronically recurrent and locally aggressive condition, marked by uncontrolled epithelial proliferation and progressive bone erosion. Its pathogenesis is thought to involve a persistent inflammatory response that alters key cellular signaling pathways, potentially in conjunction with underlying genetic predispositions. The frequent recurrence and destructive nature of the disease may arise from a complex interplay between genetic susceptibility and local inflammatory mechanisms [13].

In this context, genetic predisposition to recurrence appears to play a meaningful role, potentially influencing the aggressiveness of cholesteatoma. Previous studies have identified specific genes associated with an increased risk of recurrence, namely KGF (FGF7), KGF-R (FGFR2), MMP9, KRT1, KRT10 and MIF.

Of these genes, two (KGF, KGF-R) have a structural role in epidermis, another two are directly implicated in the proliferation of keratin (KRT1, KRT10), whereas MMP9 and MIF are involved in extracellular matrix and in inflammation, indicating the potential involvement of an array of different molecular pathways in the cholesteatoma recurrence.

In more detail, KRT1 (Keratin 1) encodes a structural keratin protein that is essential for the mechanical stability and resilience of stratified epithelia. Polymorphisms in this gene may theoretically alter epithelial cohesion, barrier function, or differentiation capacity, thereby contributing to the abnormal keratin accumulation and architectural disorganization seen in recurrent cholesteatoma [12]. KRT10 (Keratin 10), which is co-expressed with KRT1, plays a complementary role in maintaining epidermal integrity and regulating the balance between proliferation and terminal differentiation [12]. Alterations in these keratins could disrupt epithelial homeostasis, creating a microenvironment more susceptible to pathological keratinization and recurrence.

Keratinocyte Growth Factor (KGF or FGF7) is a key epithelial mitogen that stimulates keratinocyte proliferation and promotes wound healing. In cholesteatoma tissue, its overexpression suggests a contribution to the sustained hyper proliferative state characteristic of the lesion [14]. Such upregulation may not only drive initial growth but also provide a proliferative advantage to residual epithelial cells after surgery, increasing the likelihood of recurrence. Keratinocyte Growth Factor Receptor (KGF-R, also known as FGFR2) mediates the effects of

Table 1. Polymorphisms utilized for the formulation of cholesteatoma recurrence GRS

Gene	RSID	Reference	Alternate	pcontrols	pcases	β coef	GRScontr	GRScas
KGF (FGF7)	["rs16962440"]	T	C	0.651898	0.642857	0.011674	0.015221	0.01501
KGF (FGF7)	["rs12438444"]	T	C	0.714465	0.77381	0.306389	0.437809	0.474174
KGF-R (FGFR2)	["rs1047057"]	G	A	0.558635	0.46	0.007427	0.008298	0.006833
KGF-R (FGFR2)	["rs2278202"]	G	A	0.588496	0.52	0.030226	0.035576	0.031435
KGF-R (FGFR2)	["rs1613776"]	C	T	0.046299	0.08	0.510926	0.047311	0.081748
KGF-R (FGFR2)	["rs2981461"]	C	T	0.565553	0.5	0.017338	0.019612	0.017338
KGF-R (FGFR2)	["rs111564057"]	A	C	0.859956	0.87	0.125624	0.216063	0.218587
KGF-R (FGFR2)	["rs1047100"]	T	C	0.779078	0.73	0.135546	0.211202	0.197898
MMP9	["rs3918251"]	A	G	0.369559	0.38	0.011161	0.008249	0.008482
MMP9	["rs3918253"]	T	C	0.433014	0.42	0.015643	0.013548	0.01314
MMP9	["rs2274755"]	T	G	0.853715	0.86	0.073154	0.124905	0.125824
MMP9	["rs17576"]	A	G	0.357585	0.38	0.025284	0.018082	0.019216
MMP9	["rs3918256"]	A	G	0.432769	0.42	0.015375	0.013308	0.012915
MMP9	["rs2250889"]	C	G	0.04778	0.04	0.339189	0.032413	0.027135
MMP9	["rs13969"]	A	C	0.603257	0.6	0.002762	0.003333	0.003315
MMP9	["rs17577"]	A	G	0.853646	0.86	0.073938	0.126234	0.127174
MMP9	["rs13925"]	A	G	0.855858	0.86	0.048659	0.08329	0.083693
MMP9	["rs20544"]	T	C	0.432561	0.42	0.015147	0.013104	0.012724
KRT1	["rs14024"]	T	C	0.309683	0.31	0.000564	0.000349	0.00035
KRT1	[]	CACCTCCGGAGCCA	CACCTCCGGAGCCGTAGCTGCTACCTCCGGAGCCA	0.530466	0.57	0.03215	0.034109	0.036651
KRT1	["rs698170"]	T	G	0.824655	0.81	0.06234	0.102818	0.100991
KRT1	["rs936958"]	A	G	0.529265	0.57	0.032726	0.034641	0.037308
KRT1	["rs2741159"]	C	A	0.597683	0.67	0.167862	0.200656	0.224934
KRT1	["rs2741158"]	G	A	0.530148	0.57	0.032305	0.034253	0.036828
KRT1	["rs3837476"]	CA	C	0.549635	0.56	0.009202	0.010116	0.010307
KRT1	["rs828367"]	G	A	0.039384	0.05	0.227562	0.017924	0.022756
KRT10	["rs1132367"]	T	C	0.19613	0.2	0.014713	0.005771	0.005885
KRT10	["rs117588718"]	ATAG	ATAA	0.041346	0.06	0.352719	0.029167	0.042326
KRT10	["rs776920005"]	A	AGCTGCCGCCGCCGTATCCGCCGCCGGAGCT	0.117728	0.13	0.085149	0.020049	0.022139
KRT10	[]	AGCCGCCGCTGGAACTGCCGCCGTG	AGCCGCCGCTGGAACTGCCGCCGTGGCCGCCGCTGGAGCTTCCGCCGCCGTG	0.0672	0.09	0.267395	0.035938	0.048131
KRT10	[]	ACTGCCGCCGT	ACTGCCGCCGTGGCCGCCGCCGT	0.719489	0.75	0.14724	0.211875	0.22086
KRT10	["rs17855579"]	A	G	0.318383	0.28	0.147363	0.093836	0.082523
KRT10	["rs1799915"]	C	T	0.198646	0.2	0.005101	0.002027	0.00204
KRT10	["rs6503559"]	C	A	0.235264	0.25	0.041296	0.019431	0.020648
KRT10	["rs1799873"]	A	G	0.317864	0.28	0.145624	0.092577	0.081549
KRT10	["rs77919366"]	C	T	0.236348	0.25	0.038118	0.018018	0.019059
MIF	["rs2096525"]	T	C	0.430111	0.519231	0.018251	0.0157	0.018953
MIF	["rs33958703"]	T	C	0.915448	0.942308	0.706656	1.293814	1.331775
MIF	["rs2070766"]	C	G	0.43264	0.519231	0.016836	0.014568	0.017483
							3.715194	3.860138

KGF and its variants may enhance epithelial responsiveness to proliferative stimuli. This heightened responsiveness may accelerate postoperative epithelial regeneration in a manner that predisposes to regrowth rather than normal repair.

Matrix Metalloproteinase 9 (MMP9) is a zinc-dependent proteolytic enzyme that degrades extracellular matrix components and participates in bone remodeling. Elevated expression of MMP9 in cholesteatoma has been strongly associated with ossicular chain erosion and local tissue destruction. Variants that upregulate MMP9 activity could therefore amplify the aggressiveness of the disease and complicate surgical eradication. Macrophage Migration Inhibitory Factor (MIF) is a proinflammatory cytokine that sustains chronic inflammation and modulates immune responses by inhibiting the anti-inflammatory effects of glucocorticoids and promoting leukocyte recruitment. Its role in cholesteatoma may involve promoting a persistent inflammatory microenvironment that predisposes to tissue damage and recurrence [10]. In cholesteatoma, MIF may perpetuate a persistent inflammatory microenvironment, fueling tissue remodeling, keratinocyte activation, and the cycle of damage and regrowth that underlies recurrence.

While SNPs can influence gene regulation and expression - potentially affecting an individual's susceptibility to certain diseases or traits - the specific effects of rs12438444 and rs1613776 on FGF7 and FGFR2 expression or function are not documented in the relevant genetic databases. In contrast, most of the remaining SNPs are classified as likely benign or non-functional in curated resources such as Varsome. Notably, rs2250889 in MMP9 appears to have significant regulatory potential, being located in an evolutionarily conserved protein-bound region [15], and has been associated with ischemic stroke, glaucoma, and other diseases [16].

Among the 39 SNPs included in the GRS, nine rs-marked polymorphisms appear to contribute more substantially as indicated by their higher β-coefficients (>0.1) (Supplementary Table 1). While SNPs can influence gene regulation and expression, potentially affecting an individual's susceptibility to certain diseases or traits, the specific effects of rs12438444 and rs1613776 on FGF7 and FGFR2 expression or function are not documented in the relevant genetic libraries. Additionally, most of the remaining SNPs are classified as likely benign or non-functional in curated resources such as Varsome. In contrast, rs2250889 in MMP9 seems to exert a significant regulatory potential. It is located in an evolutionarily conserved protein-bound region [15], and it has been associated with ischemic stroke, glaucoma and other diseases [16].

Additional genes have been implicated in cholesteatoma recurrence in previous studies. In some cases, however, the differences in their expression between recurrent and non-recurrent cases did not reach statistical significance, as observed with CYLD [17] and KRT19 [12]. In another study [18], elevated expression levels of TLR-8, NOD-2, IL-12, and TNF-α were noted, but these were primarily attributed to the severity of local inflammatory responses that may necessitate re-operation, instead of being directly linked to the underlying risk of cholesteatoma recurrence itself.

In this study, by leveraging the UK Biobank - one of the largest and most well-curated biobanks in the world - we demonstrate that an array of genes reported in previous studies contributes to cholesteatoma recurrence risk. Their cumulative effect is modest, since individuals with recurrence have 15.6% higher odds attributable to these genetic factors. Nevertheless, as we demonstrated in a previous study on in silico analyses for drug repurposing in cholesteatoma [19], the wealth of knowledge accumulated in the literature and various databases can be effectively leveraged to develop genetic-based predictive tools with real clinical value. Such approaches can optimize the design of more efficient studies, reduce costs, and conserve resources, while also laying the groundwork for future genome-wide investigations and precision otologic care. Over the past decades, many countries have invested heavily in building extensive clinical and genetic datasets, often in the form of national biobanks. In silico and subsequent analyses of these datasets represent a cost-effective strategy for both drug repurposing and the identification of clinically meaningful biomarkers - particularly for conditions such as cholesteatoma, which attract less research

funding due to their relative rarity or lower perceived burden compared with more prevalent or debilitating diseases.

One limitation of this study is that only 55 patients with cholesteatoma recurrence were identified using ICD-10 codes in the UK Biobank. It is possible that additional cases exist within the cohort but were either missed or recorded under alternative diagnoses. However, the potential impact of these missed cases is likely negligible, given the very large overall study population of approximately 500,000 participants.

Another limitation is the relatively small number of recurrence cases, as larger sample sizes are generally required for more accurate estimation of a Genetic Risk Score (GRS). In larger studies, this is referred to as a Polygenic Risk Score (PRS), which can offer more robust predictive power. Nonetheless, a genome-wide association study (GWAS) would have been underpowered, even with a dataset as large as the UK Biobank. For this reason, we limited our analysis to specific genes previously implicated in cholesteatoma recurrence. Genes with indirect or uncertain links to recurrence were not included.

Additionally, the UK Biobank does not provide information on important clinical variables such as the surgeon's experience or the surgical technique used (e.g., canal wall up vs. canal wall down mastoidectomy). However, the data were collected from major tertiary centers across the UK, which increases the likelihood that these patients were treated by experienced surgeons with specialized expertise. Moreover, one key confounding factor - patient age - was appropriately addressed. Recurrence is known to be more common in children, but only adult participants were included in our analysis. All patients were over 40 years old at the time of recruitment, making the presence of congenital cholesteatoma unlikely.

With the availability of larger datasets and the application of more advanced bioinformatic methods, future research is expected to yield more accurate Genetic Risk Scores (GRS) based on a broader set of genetic polymorphisms - as has already been achieved in other complex diseases, such as obesity. In such scenarios, the GRS could become a valuable tool for guiding clinical decision-making, potentially influencing the choice of surgical technique and the timing or frequency of follow-up imaging, such as diffusion-weighted MRI. Even at the current stage, an elevated GRS - derived from the specific polymorphisms analyzed in this study - may support a more aggressive surgical approach (e.g., canal wall down mastoidectomy) or warrant earlier postoperative imaging, particularly in cases managed with a canal wall up technique.

Conclusion

In this study, we developed a Genetic Risk Score (GRS) for cholesteatoma recurrence, drawing on genes previously implicated in the literature and leveraging genetic data from the UK Biobank. Our results indicate a modest yet measurable genetic contribution, with a 15.6% relative increase in genetically determined risk among affected individuals. To our knowledge, this is the first genetics-based predictive tool proposed for this poorly understood otologic condition, demonstrating the feasibility of incorporating genetic risk scores into clinical decision-making pathways for cholesteatoma management.

Disclosure of conflict of interest

None.

Address correspondence to: Ioannis Michael Vlastos, Evangelismos General Hospital, Ipsilantou 45, Athens, Greece. E-mail: giannisvlastos@yahoo.gr

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$$\mathrm{OR} = \frac{p_{\mathrm{cases}}/(1-p_{\mathrm{cases}})}{p_{\mathrm{controls}}/(1-p_{\mathrm{controls}})}$$

$$\beta = \log(\mathrm{OR}) = \log\left(\frac{p_{\mathrm{cases}}(1-p_{\mathrm{controls}})}{p_{\mathrm{controls}}(1-p_{\mathrm{cases}})}\right)$$

$$\mathrm{GRS}_{\mathrm{weighted}} = \sum_{i=1}^{n} \beta_i \cdot G_i$$

Supplementary Figure 1. β-coefficient, which indicates the effect size of each risk allele, can be calculated by the allele frequences of the cohort (*pcases*) and the population (*pcontrols*). *Gi* is the genotype (0, 1, 2) or in other words the number of the risk alleles. Thus β*i***Gi* estimates the average genetic contribution of SNP i to the disease risk and the GRS is the equation of the sums of genetic contribution of the risk alleles.

Supplementary Table 1. Variants with the highest β-coefficients of the cholesteatoma recurrence genetic risk score

Gene	RSID	β coefficient
KGF (FGF7)	rs12438444	0.306389
KGF-R (FGFR2)	rs1613776	0.510926
MMP9	rs2250889	0.339189
KRT1	rs2741159	0.167862
KRT1	rs828367	0.227562
KRT10	rs117588718	0.352719
KRT10	rs17855579	0.147363
KRT10	rs1799873	0.145624
MIF	rs33958703	0.706656