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Intervertebral Disc Degeneration Mediates the Causal Effect of Genetically Predicted Diffuse Idiopathic Skeletal Hyperostosis on Spinal Stenosis: Evidence From a Mendelian Randomization Study

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ABSTRACT

Background: Previous studies have noted an association between diffuse idiopathic skeletal hyperostosis (DISH) and spinal stenosis (SS), although causation is unclear. This study used Mendelian randomization (MR) to investigate the causal relationship between the two.

Methods: We utilized large GWAS datasets on DISH and SS to perform a two-sample, bidirectional MR analysis, also quantifying the mediating role of intervertebral disc degeneration (IDD). The inverse variance weighting (IVW) method was the primary approach used to estimate the causal effect size. To ensure the reliability of MR results, we conducted heterogeneity tests, horizontal pleiotropy tests, and the MR-PRESSO test.

Results: The random-effects IVW method indicated that genetically predicted DISH was associated with an increased risk of SS (OR: 1.432; 95% CI: 1.097–1.868; $p = 0.008$), and this association remained significant in the validation dataset (OR: 1.444; 95% CI: 1.208–1.725; $p < 0.001$). Mediation analysis in homogeneous populations showed that IDD partially mediates the causal effect of DISH on SS, with a mediation ratio of 38.39% (95% CI: 2.66–74.13). Sensitivity analyses supported our conclusions.

Conclusions: This study provides causal evidence that genetically determined DISH is associated with an increased risk of SS, with IDD acting as a partial mediator. These findings underscore the importance of spine-protective behaviors and early IDD prevention strategies in patients with DISH to mitigate SS risk.

1 | Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a prevalent systemic disease of unclear origin, typically affecting middle-aged and elderly individuals [1]. The condition manifests as the accumulation of lesions in the bone and ligament tissues of the spine, pelvis, and limbs. A defining characteristic is the ossification of the anterior longitudinal ligament

involving a minimum of four vertebrae in the lower thoracic region [2, 3]. In 1950, French doctors Forestier and Rotes-Querol provided a detailed description of the imaging features and pathological changes observed in patients with this condition. They named it "senile ankylosing hyperostosis" based on the characteristics of the affected population [4]. Diagnostic studies estimate its prevalence at 17.6% using x-ray imaging and between 7.7% and 27.2% with computed tomography [5, 6], with incidences varying from 10% to 40% depending on classification criteria [6–8].

Spinal stenosis (SS), defined as a narrowing of the spinal canal or nerve foramen, is a common cause of damage to the nervous system, especially in the elderly. It results from multifactorial degenerative changes, such as osteophyte formation, ligamentum flavum hypertrophy, and intervertebral disc degeneration [9]. Although DISH is not traditionally categorized as an inflammatory condition, its hallmark ossification can structurally contribute to SS. This may occur through direct invasion into the spinal canal or indirectly via alterations in spinal alignment and mechanical load [10].

Intervertebral disc degeneration (IDD), a key feature of age-related spinal pathology, represents one intermediary factor in this relationship. Degenerative changes such as annular tears, reduced disc height, and osteophyte formation disrupt spinal load distribution, exacerbating segmental instability and pathology [11]. Evidence suggests that DISH may accelerate IDD through abnormal spinal mechanics and systemic metabolic influences, amplifying its structural impact on the spinal canal and promoting stenosis [12]. Kentaro et al. identified DISH as an independent risk factor for severe lumbar spinal stenosis in surgical patients [13]. However, common risk factors such as advanced age, high body mass index (BMI), and diabetes mellitus (DM) complicate analyses, making it difficult to fully disentangle the contributions of DISH to SS.

Mendelian randomization (MR), a novel epidemiological approach, offers a robust method for addressing confounding and reverse causation. MR studies minimize bias through unique mediating instrumental variables (IVs), usually referred to as single-nucleotide polymorphisms (SNPs) [14]. The process of meiosis of genetic material can approximate the randomization process in randomized controlled trials. In this process, allelic segregation occurs, resulting in causal effects that can affect the entire life of an individual [15].

Despite significant advancements in understanding spinal disorders, the genetic predisposition to DISH and its cascading effects on spinal stability and neural compromise remain poorly elucidated. Moreover, the role of IDD as a mediator linking DISH to SS warrants further investigation. To our knowledge, no MR studies have been conducted on the relationship between DISH and SS. Therefore, we performed a bidirectional, two-sample MR analysis to explore the causal association between DISH and SS. Additionally, a two-step MR analysis was conducted to evaluate IDD as a potential mediator in this relationship.

2 | Methods

2.1 | Study Design and Data Sources

In this study, we examined the causal association between DISH and SS. The genome-wide association study (GWAS) summary data for DISH were obtained from a substantial gene association study involving a sample of 33 413 individuals of European descent, utilizing a machine learning model to analyze pathological and genetic features [16]. The source data can be accessed in the GWAS Catalog using the serial number GCST90134532 (https://www.ebi.ac.uk/gwas/home). For SS, GWAS data were derived from an interracial human phenotype study [17], publicly available on the IEU database (https://gwas.mrcieu.ac.uk/), and validated using spinal stenosis phenotype data from the FinnGen database R10 (case = 20 807, control = 294 770). The FinnGen project, initiated in 2017, provides regularly updated statistics, with the latest release on December 18, 2023.

Diagnosis of SS was based on the International Classification of Diseases, 10th Revision (ICD-10) code M48.0. Detailed datasets can be accessed through the FinnGen database's official webpage (https://www.finngen.fi). IDD data were also obtained from the FinnGen database (cases = 41 669; controls = 294 770), classified under ICD-10 code M51. Our MR design was grounded on three key assumptions: (1) the genetic variants exhibit robust associations with the exposures; (2) the genetic variants do not correlate with other confounding factors; and (3) the genetic variants influence the clinical outcome solely through DISH or IDD. The core hypothetical steps and analysis process of this study are shown in Figure 1.

2.2 | Instrumental Variable Selection

We applied a stringent correlation threshold ($p < 5e\text{-}8$) to screen IVs. A corresponding linkage disequilibrium assessment was then performed, excluding SNPs that did not demonstrate independence at a specified threshold level (10 000 kb window with $r2 < 0.001$). To study the causal effects among DISH, SS, and IDD, we extracted the standard deviation (SD) scale effect size and SD for the corresponding SNPs. After meeting the association test threshold, we calculated the F statistic for SNPs, excluding weak IVs (F statistic < 10 is considered to be a weak IV [18]). The formula for calculating the F statistic is $F = R^2 (N-K-1)/(K(1-R^2))$, as described in previous studies [19]. Exposure and outcome data were harmonized before conducting the final MR analysis.

2.3 | Mendelian Randomization Analysis

The causal relationship between DISH and SS was analyzed using bidirectional MR. We used the inverse variance weighting (IVW) method as the primary algorithm because it has the highest statistical power when the horizontal pleiotropy of IVs is not present [20, 21]. The random-effects IVW method is widely used in our study because it can obtain valid estimates in the presence of heterogeneity of IVs [22].

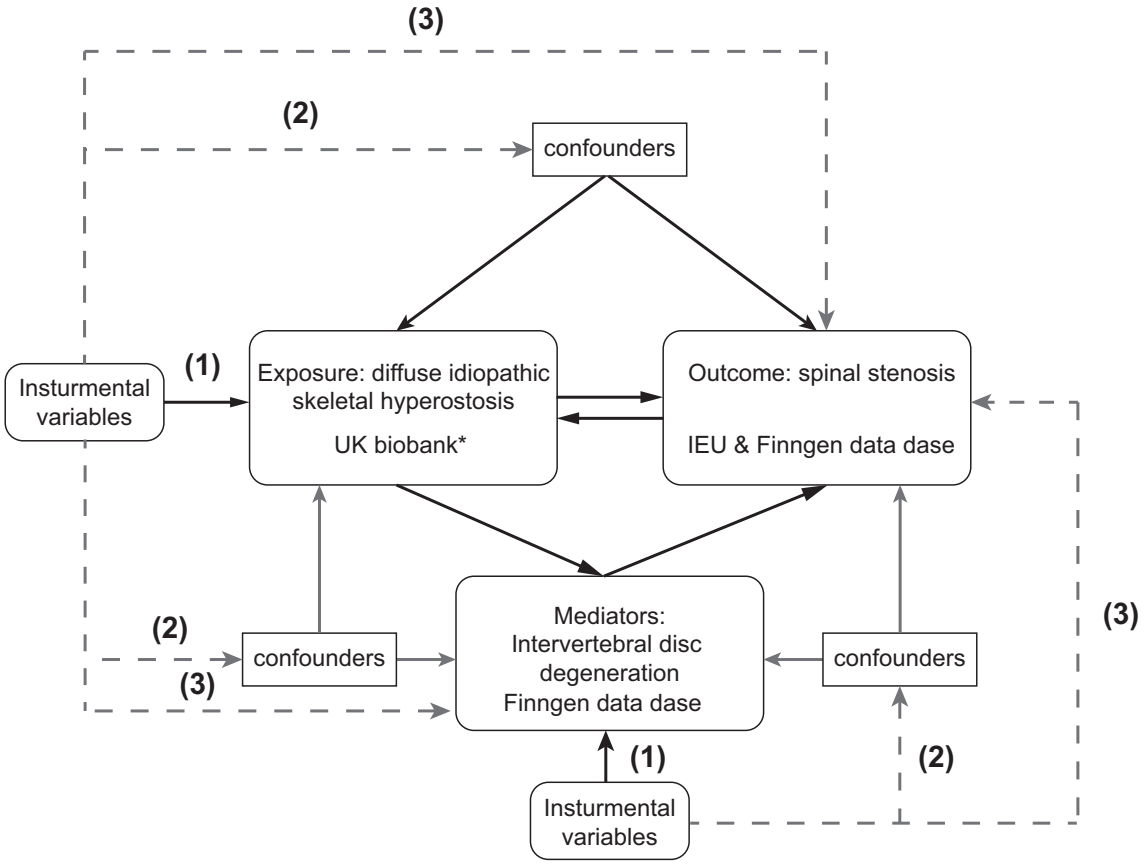

FIGURE 1 | Three key assumptions: (1) the genetic variants exhibit robust associations with DISH or IDD; (2) the genetic variants do not correlate with other confounding factors; and (3) the genetic variants influence the clinical outcome solely through exposures. *: Diagnostic information is obtained based on machine learning and image recognition. DISH: diffuse idiopathic skeletal hyperostosis; IDD: intervertebral disc degeneration.

Additionally, MR-Egger, weighted median, simple mode, and weighted mode methods are adopted to enhance causal inference. To mitigate the potential impact of reverse causality, we conducted a reverse MR analysis by swapping the exposure and outcome. A two-step MR analysis was then performed to investigate potential mediating pathways involving intervertebral disc degeneration.

Cochran's Q statistic was used to evaluate the robustness of the results obtained by the IVW and the MR-Egger methods. A p-value < 0.05 indicated significant heterogeneity among SNPs, suggesting the potential invalidity of some IVs. Next, the horizontal polymorphism of SNPs was evaluated by the MR-Egger intercept. The MR-Egger intercept was used to evaluate the horizontal pleiotropy of SNPs. To visualize potential pleiotropy, we constructed a funnel plot; an approximately symmetric scatter of points in the plot suggests no significant evidence of pleiotropy. To find out whether there are specific SNPs that strongly influence the total causal effect size, we also used the leave-one-out method. The MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) test was used to detect possible outliers. If an SNP significantly impacted the overall effect, it was excluded, and MR analysis was reconducted.

2.4 | Statistical Analysis

The causal coefficient of risk factors on DISH was quantified using odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI). Employing the delta method [23], the intermediate ratio was calculated using the formula ($\beta1*\beta2)/\beta0$, where $\beta0$ represents the causal effect value of DISH on SS, $\beta1$ denotes the causal effect of exposure on mediating factors, and $\beta2$ indicates the causal effect of mediating factors on outcomes. All MR statistical analyses were performed using the TwoSampleMR (version 0.6.4) packages [24] in R version 4.3.3 (2024-02-29 ucrt) [25].

3 | Results

3.1 | Selection of Genetic Instruments

After a stringent screening process, we extracted five IVs independently related to DISH from GWAS summary data, with an average F statistic value of 114.54 (ranging from 94.24 to 173.76). From the IEU database and FinnGen database, we extracted three IVs and 10 IVs strongly correlated with SS, with average F statistic values of 421.59 (ranging from 415.06 to 424.96) and 112.74 (ranging from 100.51 to 129.99), respectively, ensuring no overlap of IVs between the two databases. Following the removal of three SNPs with significant heterogeneity (rsids: rs11873021, rs12308843, and rs6546534) using the MR-PRESSO test, the average F statistic value of the remaining 14 SNPs strongly associated with IDD was 93.00 (range from 79.86 to 133.66). Consequently, we present the analysis results using the remaining 14 SNPs in the validation set. These data indicate that the selected IVs possess reliable statistical power. Detailed information on these genetic variations is

TABLE 1 | MR-PRESSO test results for all significant causal associations.

Exposure	Outcome	SNPs	MR analysis	Causal estimate	SD	T-stat	*p*	RSSobs	*p* for global test
DISH	SS (IEU)	5	Raw	0.359	0.085	4.226	0.013	2.662	0.813
			Outlier-corrected	No outliers detected					
DISH	IDD	5	Raw	0.236	0.089	2.652	0.057	10.445	0.207
			Outlier-corrected	No outliers detected					
IDD	SS (IEU)	5	Raw	0.597	0.108	5.513	< 0.001	39.437	0.013
			Outlier-corrected	No outliers detected					
DISH	SS (FinnGen)	5	Raw	0.367	0.055	6.644	0.003	2.400	0.848
			Outlier-corrected	No outliers detected					
IDD	SS (FinnGen)	17	Raw	0.598	0.089	6.703	< 0.001	57.449	< 0.001
			Outlier-corrected	0.546	0.082	6.658	< 0.001		
IDD	SS (FinnGen)	14[a]	Raw	0.429	0.062	6.909	< 0.001	17.060	0.426
			Outlier-corrected	No outliers detected					

Abbreviations: DISH, diffuse idiopathic skeletal hyperostosis; IDD, intervertebral disc degeneration; MR, Mendelian randomization; SS, spinal stenosis.
[a]Three SNPs were identified as outliers and excluded: rs11873021, rs12308843, and rs6546534.

provided in Supplementary Table 1, and the preimplemented MR-PRESSO results are shown in Table 1.

3.2 | Causal Relationship Between DISH and SS

The results of the preliminary analysis of the IVW method indicated that DISH is associated with an increased risk of SS (OR: 1.432; 95% CI: 1.097–1.868; $p = 0.008$). In contrast, SS did not show a significant causal effect on DISH (OR: 1.104; 95% CI: 0.931–1.309; $p = 0.257$).

Validation with SS data from the FinnGen database yielded similar results (OR: 1.444; 95% CI: 1.208–1.725; $p < 0.001$), while the reverse MR analysis also showed no significant causal effect (OR: 1.031; 95% CI: 0.874–1.217; $p = 0.716$). Figure 2 presents a forest plot depicting bidirectional causality across five different methods. Although the MR-Egger and other algorithms did not achieve nominal significance, the direction of the effect size remained consistent with the IVW estimate, supporting the primary findings.

3.3 | Two-Step MR Analysis

The forest plot of the MR analysis results for IDD as an intermediary factor is illustrated in Figure 3. Initially, we estimated the causal relationship between DISH and IDD, denoted as β1. Using the IVW method, we found a significantly positive association (OR: 1.267; 95% CI: 1.063–1.507; $p = 0.008$). Next, we calculated the causal effect of IDD on SS, denoted as β2. Consistent results were observed in the analysis of outcome data from the IEU database (OR: 1.817; 95% CI: 1.469–2.246; $p < 0.001$) and the FinnGen database (OR: 1.536; 95% CI: 1.360–1.735; $p < 0.001$). Based on these MR analysis results, we performed a mediation analysis to determine the corresponding mediation ratio, as detailed in Table 2. The IVW method indicated that IDD mediated 39.21% of the causal effect of DISH on SS, compared to 27.54% in the validated dataset. Notably, in the mediation analysis results from the IEU dataset, the confidence interval included zero, indicating that the mediation effect of IDD was not significant in this dataset. Given that the IEU dataset comprises a mixed-race population, while the other datasets are predominantly of European origin, we prioritize the causal inferences derived from homogeneous populations.

3.4 | Sensitivity Analysis

Cochran's Q statistics are calculated according to the IVW and MR-Egger methods. We observed that the main heterogeneity was concentrated in the causal effect analysis and reverse causal analysis of IDD on SS, while no significant heterogeneity was found in other steps. Additionally, no evidence of horizontal pleiotropy was detected in the MR analysis steps above. Detailed sensitivity analysis results are provided in Table 3.

Exposure	Outcome	Method	nSNP	Beta	OR (95% CI)	P-value
DISH	SS (IEU)	MR Egger	5	0.010	1.010 (0.456 - 2.239)	0.982
		Weighted median	5	0.273	1.313 (0.960 - 1.796)	0.088
		Simple mode	5	0.329	1.389 (0.920 - 2.098)	0.193
		Weighted mode	5	0.280	1.324 (0.932 - 1.880)	0.193
		IVW	5	0.359	1.432 (1.097 - 1.868)	**0.008**
SS (IEU)	DISH	MR Egger	3	-0.129	0.879 (0.507 - 1.522)	0.725
		Weighted median	3	0.034	1.034 (0.901 - 1.187)	0.633
		Simple mode	3	0.006	1.007 (0.861 - 1.177)	0.943
		Weighted mode	3	0.014	1.014 (0.861 - 1.194)	0.881
		IVW	3	0.099	1.104 (0.931 - 1.309)	0.257
DISH	SS (FinnGen)	MR Egger	5	0.131	1.140 (0.664 - 1.957)	0.666
		Weighted median	5	0.323	1.382 (1.101 - 1.733)	**0.005**
		Simple mode	5	0.330	1.391 (1.030 - 1.876)	0.097
		Weighted mode	5	0.308	1.360 (1.046 - 1.769)	0.083
		IVW	5	0.367	1.444 (1.208 - 1.725)	**<0.001**
SS (FinnGen)	DISH	MR Egger	10	-0.595	0.552 (0.191 - 1.591)	0.303
		Weighted median	10	0.090	1.094 (0.970 - 1.233)	0.144
		Simple mode	10	0.095	1.099 (0.892 - 1.355)	0.399
		Weighted mode	10	0.091	1.096 (0.918 - 1.308)	0.338
		IVW	10	0.031	1.031 (0.874 - 1.217)	0.716

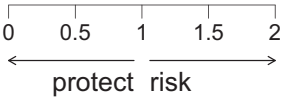

FIGURE 2 | Estimation of causal association under five Mendelian randomization methods. DISH: diffuse idiopathic skeletal hyperostosis; SS: Spinal stenosis; IVW, inverse variance weighting; OR, odds ratio; CI, confidence interval; *p* values < 0.05 are marked bold.

Exposure	Outcome	Method	nSNP	Beta	OR (95% CI)	P-value
DISH	IDD	MR Egger	5	0.130	1.139 (0.628 - 2.069)	0.697
		Weighted median	5	0.228	1.256 (1.069 - 1.476)	**0.005**
		Simple mode	5	0.271	1.312 (1.016 - 1.694)	0.106
		Weighted mode	5	0.239	1.270 (1.049 - 1.536)	0.070
		IVW	5	0.236	1.266 (1.063 - 1.507)	**0.008**
IDD	SS (IEU)	MR Egger	17	1.792	6.002 (1.804 - 19.970)	**0.011**
		Weighted median	17	0.416	1.515 (1.192 - 1.926)	**0.001**
		Simple mode	17	0.367	1.444 (0.838 - 2.487)	0.204
		Weighted mode	17	0.295	1.343 (0.858 - 2.101)	0.215
		IVW	17	0.597	1.817 (1.469 - 2.246)	**<0.001**
IDD	SS (FinnGen)	MR Egger	14	0.375	1.455 (0.645 - 3.285)	0.384
		Weighted median	14	0.390	1.477 (1.240 - 1.760)	**<0.001**
		Simple mode	14	0.399	1.491 (1.118 - 1.989)	**0.018**
		Weighted mode	14	0.337	1.400 (1.099 - 1.784)	**0.017**
		IVW	14	0.429	1.536 (1.360 - 1.735)	**<0.001**

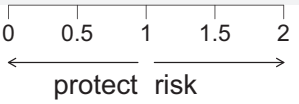

FIGURE 3 | Forest plot of causal association estimation under five methods of disc degeneration as a mediating factor. DISH: diffuse idiopathic skeletal hyperostosis; SS: spinal stenosis; IVW: inverse variance weighting; OR: odds ratio; CI: confidence interval; *p* values < 0.05 are marked bold.

TABLE 2 | The mediation proportion of mediators in the causal relationship between DISH and SS.

Data source	Method	Effect of exposure on outcome β0 (95% CI)	Effect of exposure on mediator[a] β1 (95% CI)	Effect of mediator on outcome β2 (95% CI)	Mediated proportion (%) (95% CI)
IEU	IVW	0.359 (0.093–0.625)	0.236 (0.062–0.410)	0.579 (0.385–0.809)	39.21 (−4.12–82.55)
FinnGen	IVW	0.367 (0.183–0.545)	0.236 (0.062–0.410)	0.598 (0.423–0.773)	38.39 (2.66–74.13)

Abbreviations: DISH, diffuse idiopathic skeletal hyperostosis; IVW, inverse variance weighting; SS, spinal stenosis.
[a]The mediator in this study was intervertebral disc degeneration.

TABLE 3 | Results of heterogeneity test and pleiotropy test.

		Heterogeneity test						Pleiotropy test		
		IVW			MR-Egger			MR-Egger		
Exposure	Outcome	*Q*	*Q*-df	*p*	Q	Q-df	*p*	Intercept	Se	*p*
DISH	SS (IEU)	1.568	4	0.815	0.737	3	0.864	0.022	0.024	0.429
DISH	SS (FinnGen)	1.483	4	0.830	0.660	3	0.883	0.015	0.016	0.431
DISH	IDD	7.546	4	0.110	7.223	3	0.065	0.007	0.018	0.738
IDD	SS (IEU)	33.804	16	0.006	26.828	15	0.030	−0.066	0.033	0.067
IDD	SS (FinnGen)	14.657	13[a]	0.329	14.636	12	0.262	0.003	0.022	0.898

Abbreviations: DISH, diffuse idiopathic skeletal hyperostosis; IDD, intervertebral disc degeneration; IVW, inverse variance weighting; SS, spinal stenosis.
[a]Three SNPs were identified as outliers and excluded: rs11873021, rs12308843, and rs6546534.

To enhance test efficiency, a positive causal association was obtained using the MR-PRESSO method with a seed of 1234, 10 000 iterations, and a threshold of 0.05.

The Global test results indicated that the causal effect of IDD on SS was influenced by heterogeneity in both the IEU dataset (p for Global test = 0.012) and the validation dataset (p for Global test < 0.001). In the IEU dataset, the elimination of outlier IVs was not conducted as MR-PRESSO did not identify any outliers. However, the results are considered credible due to the absence of pleiotropy and the robustness of the random-effects IVW method. A scatter plot of DISH's causal effect on SS and the sensitivity analysis visualizations are shown in Figure 4. In the validation dataset, we eliminated three outlier IVs through repeated testing. In the validation dataset, we identified and eliminated three outlier IVs through repeated testing. Upon recalculating the data postoutlier removal, we found the results remained robust, and the heterogeneity test was passed (p for Global test = 0.426). Visualizations of MR analysis for the other steps are shown in Supplementary Figures 1–5.

4 | Discussion

In this study, we used bidirectional two-sample MR to specifically analyze the potential causal relationship between DISH and SS and to identify potential mediating factors through intermediate analysis. The results of the MR analysis suggest that genetically determined DISH may lead to an increased risk of SS, and the direction of this effect is very consistent across different models. Notably, the reverse MR analysis showed no significant results, confirming the unidirectional nature of this relationship. Furthermore, IDD was identified as a partial mediator, shedding light on the mechanisms linking these conditions.

The causal association between DISH and SS corroborates prior observational studies [13], but the MR analysis provides a more robust framework by mitigating biases from confounding factors and reverse causation. DISH, a noninflammatory spinal disease, predominantly affects the middle and lower thoracic vertebrae and upper lumbar vertebrae, leading to extensive ossification and reduced motion of the surrounding spinal ligaments, thereby altering the spine's normal structure and physiological curvature [26]. Early measurement studies suggested that the mechanism by which DISH may cause SS largely revolves around changes in mechanical stress [27]. In DISH patients, the fusion of affected spinal segments transfers the biomechanical load to adjacent, nonfused segments, resulting in excessive activity and increased stress at the junction between fused and non-fused segments. These mechanical changes can directly lead to IDD or hypertrophy of the ligamentum flavum [28–30], subsequently causing SS. This conclusion is supported by a review of trauma studies, which found that even low levels of external impact tend to destabilize the spine in DISH patients, potentially leading to secondary neurological deficits [31].

Nakasuka et al. [32] and Nakajima et al. [33] suggested that extensive ossification of the anterior longitudinal ligament could lead to a loss of flexibility at the thoracolumbar junction. Long segmental osteophytes increase the mechanical stress of the distal vertebral body and accelerate spinal degeneration. Consequently, DISH may exacerbate IDD. However, measurement techniques for this phenomenon remain inconclusive.

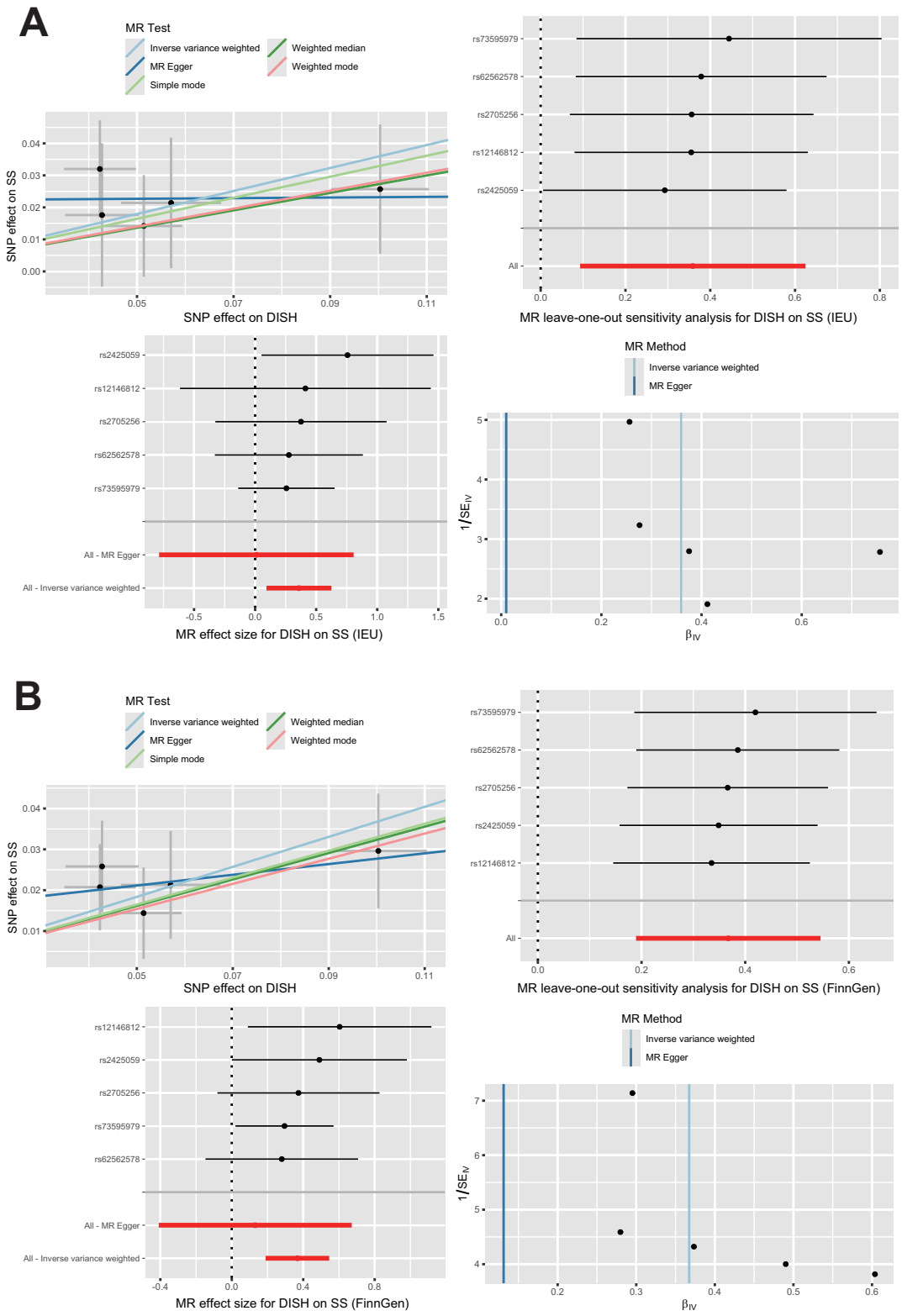

FIGURE 4 | Scatter plot, effect value plot, leave-one-out plot, and funnel plot of the causal effect of DISH on SS. A: Analysis results from the IEU database. B: Validation from the FinnGen database. DISH: diffuse idiopathic skeletal hyperostosis; SS: spinal stenosis.

Kentaro et al. compared preoperative imaging data of 24 SS patients with DISH and 108 without DISH, finding significant reductions in lumbar lordosis and sacral inclination angles in the DISH group [13]. Building on previous studies, Uehara et al. divided DISH patients into cervical, thoracic, and lumbar onset groups, comparing measurement differences within these groups [34]. They found significant differences only in the lumbar spine group, but the small sample size ($n = 13$) limits the generalizability of these results. While finite element modeling and other methods could provide a detailed analysis of stress changes in the spine and intervertebral discs of DISH patients, such models may become overly complex and introduce errors.

The MR analysis effectively used genetic variables to illustrate the mediating role of IDD in this causal relationship.

The genetic underpinnings of SS, DISH, and IDD provide crucial insights into their interconnected pathophysiology. SS is widely recognized as a highly heritable condition, with genetic factors contributing significantly to its development, particularly through pathways involving IDD [35]. Recent studies have identified several loci associated with susceptibility to SS [36, 37], many of which overlap with genes implicated in disc structure and function. Similarly, it is increasingly believed that DISH is a genetic disorder, and associated genes that have been identified include COL6A, ENT1, and FGF2 [38, 39] linked to ectopic ossification. This genetically influenced ossification exacerbates mechanical stress on the spine, accelerating IDD and contributing to SS pathogenesis.

Our study offers new insights into this network of genetic associations. Our findings suggest that IDD acts as a mediating factor in the causal pathway between genetically determined DISH and SS, reinforcing the genetic linkage among these conditions. The genetic correlations between DISH and IDD likely involve shared molecular mechanisms that regulate cartilage and bone metabolism, influencing both ligament ossification in DISH and IDD in SS. These insights underscore the importance of integrating genetic data into the management of spinal disorders.

This study is the first MR analysis to establish a causal link between DISH and SS. Compared to traditional observational studies, the MR analysis reduces the influence of confounding factors and reverse causation, offering more reliable results. Nevertheless, we have to acknowledge a few limitations in the study. First, the SS cohort from the IEU database comprises mixed races, and cross-racial causal inference may introduce some bias, though it allows a broader extrapolation of conclusions. Second, the diagnostic overlap between SS and IDD, due to symptom-based definitions of SS, poses a challenge. Conditions like disc herniation and ligamentum flavum hypertrophy may confound estimates of IDD's mediating effects. Nonetheless, the consistent directional effects across datasets support the robustness of our findings. Third, the reliance on ICD codes for phenotypic classification introduces the potential for misclassification bias. Additionally, while prior studies focus on lumbar SS, the limited evidence on cervical and thoracic stenosis constrains the generalizability of our findings to these regions. Last, the mediating effect of IDD was not consistently significant across datasets, likely due to heterogeneity in GWAS data. While our study supports IDD's mediating role, the effect size should be interpreted cautiously. Future research should explore the association mechanism between DISH and SS by comparing intervertebral disc degeneration severity in DISH patients.

5 | Conclusion

In conclusion, our results establish a unidirectional causal relationship between genetically determined DISH and an increased risk of SS, with IDD identified as a partial mediator. These findings highlight the need for targeted monitoring and management of SS in patients with DISH. Future research should prioritize exploring the genetic underpinnings and shared molecular pathways linking these conditions to refine prevention and therapeutic strategies. Additionally, comparative studies on spinal degeneration severity in DISH patients can further elucidate the mechanisms underlying this association.

Acknowledgments

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Ethics Statement

The data utilized in this study were obtained from publicly accessible databases and do not contain personally identifiable information. As a result, the usual ethical considerations related to the use of human subjects in research do not apply.

Conflicts of Interest

The authors declare no conflicts of interest.

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