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Genetic Underpinnings of Adolescent Idiopathic Scoliosis: A Review

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ABSTRACT Adolescent Idiopathic Scoliosis (AIS) is a three-dimensional spine deformity with lateral curvature having a Cobb angle exceeding 10° in the individual. It affects about 1-4 percent of adolescents globally and more frequently occurs in females than males. Despite the extensive research carried out on AIS, its aetiology is not known yet. However, several genetic studies suggest the contribution of various genetic variants in the possible aetiology of AIS. This review summarises the genetic association studies, including linkage, candidate as well as genome-wide association studies that were carried out globally on AIS and also categorised the associated genes in different biological pathways such as neurodevelopmental, hormone-related, cartilage and bone development pathways, based on their potential functional roles in the respective pathway, to understand the pathology of the disorder.

INTRODUCTION

The word scoliosis is derived from a Greek letter 'Σκολιωση' (skō'lē-ō'sīs), which means crooked, accompanied by 3D sideways spinal curvature, which is measured by determining the Cobb angle (Cheng et al. 2015). An individual is said to have scoliosis if the Cobb angle is greater than or equal to 10° (Kuznia et al. 2020). The scoliosis curve generally progresses during spinal growth. It is broadly categorised into three types according to the age of onset of the disorder. Infantile scoliosis develops below three years, juvenile scoliosis (three to ten years), and adolescent scoliosis develops after the age of ten years or during puberty (Wajchenberg et al. 2016; Mitsiaki et al. 2022). Some other types of scoliosis are congenital (associated with defects in vertebral formation during foetal development), neuromuscular (related to cerebral palsy, Duchenne muscular dystrophy), and syndrome-related (associated with Marfan syndrome, neurofibromatosis) (Janicki and Alman 2007; Karpe et al. 2020). Scoliosis developed due to an unknown mechanism is classified as an idiopathic type (Cheng et al. 2015; Menger and Sin 2023). AIS is more prevalent among adolescent individuals (Wajchenberg et al. 2016). Globally, a strong genetic association has been found with the development and progression of AIS. The genetic basis of idiopathic scoliosis has been built since the 1920s (Fadzan and Bettany-Saltikov 2017) and witnessed greater prevalence in first-degree relatives of the scoliotic patients as well as by the twin studies that reported a high concordance rate in monozygotic twins than in dizygotic twins (Kesling and Reinker 1997; Cheng et al. 2022). The linkage, candidate gene association, and genome-wide association studies (GWAS) have reported many susceptible genes associated with AIS (Peng et al. 2020). However, the total said variations could only explain 5 percent of the disease heritability, suggesting that most of its genetic heritability is still unknown (Shar-

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ma et al. 2015). The primary reason for undefined heritability is unsubstantial mechanistic interpretations of the current list of candidate genes associated with a lack of data defining their functional roles and interaction as a pathway towards disease pathogenesis.

This review provides a comprehensive overview of the available literature associated with the genetics of AIS, including the GWAS, candidate gene association, and linkage-based studies and their replication studies conducted in different populations of the world. Furthermore, to better understand the etiopathogenesis of AIS, the associated genes are categorised into specific biological pathways based on their potential functional roles.

METHODOLOGY

The current review is an updated comprehensive literature survey of all the genetic association studies conducted on AIS globally.

Search Strategy

The literature survey was conducted on several databases, including PubMed, Google Scholar, GWAS Catalog, GWAS Central, and Web of Science. The "anytime" time filter was used to extract all the genetic associations of AIS. A combination of search terms was used to retrieve the studies from the databases ("Adolescent Idiopathic Scoliosis", "Idiopathic Scoliosis", "Syndrome Related Scoliosis", "Genetic Association Studies", "Case-Control Association", "Linkage Study", "Candidate Genes", "Genome-Wide Association Study", "Family-Based Association Study", "Exome Sequencing", "Replication Study", "Meta-Analysis"). Furthermore, to identify the potentially pertinent studies, the independent screening of article titles and abstracts was done.

Categorisation of Genes Under Biological Pathways

The genes that were found associated with AIS in the extracted studies were categorised under different biological pathways based on the information available in the corresponding study itself or by curating different databases, including "Online Mendelian Inheritance in Man (OMIM)", "Protein Analysis Through Evolutionary Relationships (PANTHER)", and "Kyoto Encyclopedia of Genes and Genomes (KEGG)".

RESULTS

To unravel the AIS aetiology, extensive research has been done globally that suggests the role of genetics in its development. Around 60 AIS susceptibility loci/alleles have been analysed thus far in more than 70 genetic studies via linkage, GWA, and candidate gene association studies in different populations of the world. In Table 1, the researchers have comprehended all these associations along with their possible roles in specific pathways for the pathogenesis of AIS. Around thirty-three genes were studied for AIS susceptibility in multiple ethnicities using linkage, GWAS, and candidate studies, which belong to the different biological pathways. Out of these genes, twelve genes (*MATN1, MATN1-AS1, COL11A2, COL5A2, COL6A3, COL11A1, FBN1, FBN2, DOT1L, CALM1, VDR, AKAP2*) have a role in cartilage and bone development pathway, ten genes (*CHD7, TNIK, MAGI, MEIS1, KCNJ2, CHL1, DSCAM, CNTNAP2, EPHA4, CELSR2*) were found to have a role in neurodevelopmental and axonal pathway, six genes (*LBX1, LBX1AS1, ADGRG6, PAX1, PAX3, SOX6)* belong to other developmental pathway, and five genes (*ESR1, ESR2, IGF-1, LEPR, MTNR1B*) have a role in hormone-related pathway. Most of these AIS susceptible reported belong to cartilage and bone pathways as well as neurodevelopmental pathways, suggesting the major role of these pathways in the AIS aetiology. Of these, the majority of the associated variants are intronic and exhibit low to moderate disease risk, as defined by their odds ratio of less than 2.0. This observation suggests that these variants might not be the actual causative variant for AIS susceptibility but may lie in close proximity/strong LD with actual functional (regulatory or in the exon) variant(s), which strongly recommends fine mapping of the AIS susceptible genomic segments/genes, in order to delineate the actual causative variants. Moreover, there are many disorders that are accompanied with the scoliosis-like phenotype. Several studies have identified different genes/variants associated with such disorders, as comprehended in Table 2.

Table 1: List of the genes/variants categorized under developmental/neurodevelopmental, axon guidance, cartilage development, bone development, and hormonal pathways that were found associated with AIS in different populations of the world

Gene	*SNP/chromosomal locus*	*Chromosomal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
CHD7	8q12	-	Neuro developmental	-	Linkage*	2.72	0.92	52 families of European descent	Associated	(Gao et al. 2007)
	rs4738824	-		-	CGAS	1.03		Bulgarian	Not associated	(Nikolova et al. 2015a)
	rs1017861	Chr 8:60706154		Intronic		2.4	0.0001	Caucasian females	Associated	(Borysiak et al. 2020)
	rs121434341	Chr 8:60706154		Intronic		1.89	0.0018	Chinese Han	Associated	(Wu et al. 2021)
Near SOX9 and KCNJ2	17p11	-	Developmental/neurodevelopmental	-	Linkage*	3.20	-	Three-generation family of Italian ancestry with 11 affected members	Associated	(Salehi et al. 2002)
	17q25	-	-		Linkage*	4.08	-	25 multi-generation AIS families of British descent		Ocaka et al. (2008)
	rs12946942	Chr 17:71240857	-	GWAS	2.21	6.00×10-12		Japanese	Associated	(Miyake et al. 2013)
			-	NA	1.36	7.23×10-13		Japanese, Chinese, Caucasian	Associated	(Takeda et al. 2019)
TNIK	rs9810566	chr3:171153189	Neuro-development	Intron	GWAS	1.19	1.14×10-11	Chinese Han	Associated	(Zhu et al. 2017)
MAGI1	rs7633294	chr3:65650810		Intron		1.20	1.85×10^{-12}			
MEIS1	rs7593846	chr2:66664256		Intron		1.21	1.19 ×10-13			
CHL1	3q12.1	-	Axon guidance		Linkage*	3.00	-	3 large multigenerational IS families with 9-12 affected members		(Edery et al. 2011)

Table 1: Contd...

Gene	*SNP/chromosomal locus*	*Chromosomal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
	rs10510181	Chr 3:149364		Intronic	GWAS	1.37	8.22 × 10?7	Black non Hispanic, white non Hispanic, Hispanic, Latino, Asian, Pacific Islander	Associated	(Sharma et al. 2011)
					Replication study	0.91	0.39	Han Chinese Females	Not associated	(Qiu et al. 2014)
	rs1400180	chr3:129285		Intronic	GWAS	1.30	1.33×10?6	Black non Hispanic, white non Hispanic, Hispanic, Latino, Asian, Pacific Islander	Associated	(Sharma et al. 2011)
					Replication study	NR	NS	Bulgarian	Not associated	(Yablanski et al. 2016a)
	rs2055314, rs331894, rs2272524, rs2272522	chr3:227352, chr3:295083, chr3:349318, chr3:319825		Intronic, Intronic, Intronic, Missense variant	CGAS	NR	0.500, 0.52, 0.532, 0.080	Han Chinese Population	Not associated	(Zhou et al. 2012)
DSCAM	rs2222973	Chr 21:40461957		Intronic	GWAS	0.56	2.26 × 10?5	Black non Hispanic, white non Hispanic, Hispanic, Latino, Asian, Pacific Islander	Associated	(Sharma et al. 2011)
					Replication study	NR	NS	Han Chinese Population	Not associated	(Zhou et al. 2012)
						2.543 (Chi)	0.280	Han Chinese Population	Not associated	(Wu et al. 2015)
CNTNAP2	rs11770843	Chr 7:147098287		Intronic	GWAS	1.75	6.20 × 10?5	Black non Hispanic, white non Hispanic, Hispanic, Latino, Asian, Pacific Islander	Associated	(Sharma et al. 2011)
					Replication	NR	NS	Han Chinese	Not	(Zhou et al. 2012)

Table 1: Contd...

Gene	*SNP/chromosomal locus*	*Chromosomal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
					study			Population	associated	
PAX3/ EPHA4	rs13398147	chr2:221895559	Developmental/ axonal	-	GWAS	1.28	7.59 ×10-13	Chinese girls	Associated	(Zhu et al. 2015)
CELSR2	rs141489111	chr1:109269470cG6859A.	Neuro /axonal	Exon 21	Exome sequencing followed by Case control replication	-	-	Swedish family	Associated	(Einarsdottir et al. 2017)
	rs2281894	chr1:109267922		Synonymous Variant		1.25	0.0001	Swedish-Danish	Associated	
						1.00	0.95	Japan	Not Associated	
ESR1	6p	-		-	Linkage*		1.42	United States white family of French Acadian and English descent	Associated	(Wise et al. 2000)
	rs9340799	chr6:151842246	Hormonal	Intronic	CGAS	NR	0.027	Japanese	Associated	(Masatoshi Inoue et al. 2002)
						NR	0.89	Chinese	Not associated	(Tang et al. 2006)
						2.08	0.005	Chinese	Associated	(Wu et al. 2006)
						NR	<0.001	Chinese	Associated	(Xu et al. 2011)
						0.96	0.988	Japanese	Not associated	(Takahashi et al. 2011c)
						0.90	0.3685	Caucasian females	Not associated	(Janusz et al. 2013)
					NA	1.07	0.51	Multi-ethnic	Not associated	(Yang et al. 2014)
						1.09	0.17	Multi-ethnic	Not associated	(Chen et al. 2014a)
					CGAS	5.13	0.02	Bulgarian	Associated	(Yablanski et al. 2016b)
	rs2234693	chr6:151842200		Intronic	CGAS	NR	0.14	Chinese	Not	(Tang et al.

Table 1: Contd...

Gene	*SNP/chrom-osomal locus*	*Chromo-somal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
									associated	2006)
						NR	0.014	Chinese	Associated	(Zhao et al.
					1.17	0.6046		Caucasian females	Not associated	(Janusz et al. 2013)
					NA	0.93	0.48	Multi-ethnic	Not associated	(Yang et al. 2014)
					CGAS	0.006	2.37	Bulgaria	Associated	al. 2015b) (Nikolova et
						1.51	0.02	Bulgarian	Associated	al. 2016) (Yablanski et
ESR2	rs1256120	chr14:64338283		Non Coding Transcript Variant	CGAS	0.96	0.595	Japanese	Not associated	(Takahashi et al. 2011)
						1.031	0.8707	Caucasian females	Not associated	(Kotwicki et al. 2014)
					NA	1.20	0.36	China, Japan, Polland	Not associated	(Zhao et al. 2017)
	rs4986938	chr14:64233098		Non Coding Transcript Variant	CGAS	1.105	0.7270	Caucasian females	Not associated	(Kotwicki et al. 2014)
IGF-1	12p	-		-	Linkage*	3.2	-	7 multiplex families with AIS of European ancestry	Associated	(Raggio et al. 2009)
rs5742612	Chr12:10 2481086		Intronic	CGAS	0.768 (Chi square)	N		Chinese Females	Associated	(Yeung et al. 2006)
						1.15	0.71	Bulgarian	Not associated	(Nikolova et al. 2015c)
						NR	0.51	Japanese	Not associated	(Takahashi et al. 2011)
						NR	0.006	Korean	Associated	(Moon et al. 2013)
LEPR	rs7799039	-		2KB Upstream Variant	CGAS	1.50	0.27	Hungary	Not associated	(Morocz et al. 2011)
	rs2767485	Chr 1:65513234		Intronic		1.25	0.0118	Chinese	Associated	(Liu et al. 2015b)
MTNR1B	rs7941837	chr11:92966500		-	CGAS	1.31	0.051	Chinese	Associated	(Qiu et al. 2007a)
	rs4753426	chr11:92968430		2KB Upstream Variant	CGAS	1.29	0.015	Chinese	Associated	(Qiu et al. 2007a)
						1.13	0.239	Hungry	Not	(Morocz et al.

Table 1: Contd...

Gene	*SNP/chromosomal locus*	*Chromosomal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
									associated	2011)
						0.94	0.503	Japanese	Not associated	(Takahashi et al. 2011)
					NA	1.11	0.21	Asian or Caucasian	Not associated	(Yang et al. 2015)
	rs10830963	chr11:92975544		Intronic	NA	0.99	0.91	Asian and Caucasian	Not associated	(Yang et al. 2015)
COL11A2, COL5A2, COL6A3, COL11A1	NA	chr6, chr 2, chr 2, chr 1	Cartilage development	Candidate (Exome sequencing)-	4.3, 2.2, 1.6, 2,1		6 × 10?9, 0.01, 0.01, 0.01	European ancestry	Associated	(Haller et al. 2016)
FBN1	rs12916536	chr15:48414374		Intronic	CGAS	0.52	NR	Brazilian	Not associated	(Azevedo et al. 2022)
						0.81	1.10 ×10-4	Chinese	Associated	(Sheng et al. 2019)
FBN1	NA	Chr 15		-	Candidate (Exome sequencing)	4.2	8.14×10?5	European ancestry	Associated	(Buchan et al. 2014)
FBN2	NA	Chr 5		-	Candidate (Exome sequencing)	2.7	0.0054	European ancestry	Associated	(Buchan et al. 2014)
MATN1	intragenic microsatellite (STRP) polymorphism in the 3? untranslated region 3' untranslated region 103bp	Chr 1		-	Linkage#	NR	0.0242	Italian trios	Associated	(Montanaro et al. 2006)
	rs1065755	Chr 1:30715242		Synonymous Variant	CGAS	2.56	0.021	Korean	Associated	(Bae et al. 2012)
MATN1-AS1	rs1149048	chr1:30725886		Non Coding Transcript Variant	CGAS	1.61	0.0001	Chinese	Associated	(Chen et al. 2009)

Table 1: Contd...

Gene	*SNP/chrom-osomal locus*	*Chromo-somal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
						1.17	0.66	Turkish	Not associated	(Yilmaz et al. 2012)
						1.08	0.513	Japanese	Not associated	(Takahashi et al. 2011b)
DOT1L	19p13.3	-	-	-	Linkage#		0.008	11 unrelated Saudi Arabian girls	Associated	(Ali et al. 2011)
	19p13	-	-	-	Linkage*	1.217	-	202 families with 703 affected individuals	Associated	(Alden et al. 2006)
	19p13.3	-	-	-	Linkage*	4.93	-	7 unrelated multiplex families of southern Chinese descent	Associated	(Chan et al. 2002)
	rs12459350	chr19:2176587	Bone development	Intron	CGAS	1.16	0.001	Chinese	Associated	(Mao et al. 2013)
CALM1	rs12885713	chr14:90397013		Intronic	CGAS	4.478 (Chi)	0.034	Chinese	Associated	(Zhao et al. 2009)
	rs2300500	chr14:90399373				0.549	0.0079	Chinese	Associated	(Zhang et al. 2014)
VDR	rs1544410	chr12:47846052		Intronic	CGAS	0.8	0.59	Turkish	Not associated	(Yilmaz et al. 2012)
						4.345	<0.001	Tsinghua University Second Hospita	Associated	(Wang et al. 2016)
				NA	1.67	0.08	Multi ethnic,	Asian	Not associated	(Dai et al. 2018)
				NA	2.12		.009	Multiethnic	Associated	(Yin et al. 2018)
						3.54	<0.00001	Asian	Associated	(Dai et al. 2018)
							Multi ethnic,			
	rs2228670	-		-	CGAS	1.08	0.89	Bulgarian	Not associated	(Nikolova et al. 2015c)
AKAP2	9q31.2-q34.2	-		-	Linkage*	3.64	-	25 multi-generation AIS families of		(Ocaka et al. 2008)

Table 1: Contd...

Gene	SNP/chromosomal locus	Chromosomal	Possible pathway location	Variant type	Study	O.R/LOD	p value	Population	Result	References
		Chr9: c.2645A>C		Exon	Whole exome sequencing	-	-	British descent Chinese Family	Associated	(Li et al. 2016)
					CGAS	NA	-	Chinese	Not associated	(Xu et al. 2017)
LBX1	10q	-	--	-	Linkage*	1.60	-	One large family with seven affected members		(Wise et al. 2000)
	rs11190870	Chr 10:101219450	Developmental	7.5kb downstream of the gene LBX1	GWAS	1.56	1.24×10-19	Japanese	Associated	(Takahashi et al.
					Replication studies	1.85	9.1×10-10 2011a)	Southern Chinese	Associated	(Fan et al. 2012)
						1.51	1.8×10?9	Northern Chinese Han Population	Associated	(Jiang et al. 2013) (Fan et al. 2012)
						1.70	1.17×10-8	Sothern Chinese	Associated	(Gao et al. 2013)
						2.639	4.5610-4	Northern Chinese Han Population	Associated	(Liu et al. 2017)
						0.82	0.00468	French-Canadian Population	Associated	(Nada et al. 2018)
						1.562	0.0005	Chinese	Associated	(Man et al. 2019)
						1.53	7.0×10-18	Scandinavian cohort	Associated	(Grauers et al. 2015)
					NA	2.62	<.001	East Asians	Associated	(Chen et al. 2014b)
						1.66	0.000	Multiple ethnic groups	Associated	(Li et al. 2018)
	rs625039, rs11598564	chr10:101233892 , chr10:101204847		Intronic	CGAS	1.49, and 1.52	5.09×10-5, and 5.54×10-6	Sothern Chinese	Associated	(Gao et al. 2013)
	rs1322331	chr10:101226832		500B Downstream Variant	CGAS	3.349	5.15×10-4	Northern Chinese Han Population	Associated	(Liu et al. 2017)

Table 1: Contd...

Gene	*SNP/chromosomal locus*	*Chromosomal*	*Possible pathway location*	*Variant type*	*Study*	*O.R/LOD*	*p value*	*Population*	*Result*	*References*
	rs1322330	-		-	CGAS	1.42	6.08 ×10-14	Chinese population	Functionally associated with AIS by regulating myogenesis in the paraspinal muscles	(Xu et al. 2021)
LBX1AS1	rs678741	chr10:101237824		Intronic	GWAS	1.44	9.68×10?37	Chinese Girls	Associated	(Zhu et al. 2015)
GPR126 or ADGRG6	6p	-		-	Linkage*	1.42		One large family with seven affected membars		(Wise et al. 2000)
	rs6570507	Chr 6:142358435		Intronic	GWAS	1.28	2.25×10-10	Japanese	Associated	(Kou et al. 2013)
					Replication studies	1.729	0.0035	Chinese	Associated	(Xu et al. 2015)
						1.20	0.007	Chinese	Associated	(Qin et al. 2017)
						1.89	2.68×10?3	Chinese	Associated	(Xu et al. 2019)
					NA	1.22	2.95?× ?10?20	East Asia, Northern Europe and USA	Associated	(Kou et al. 2018)
	rs7774095	Chr 6:142358435		Intronic	CGAS	1.687	0.0078	Chinese	Associated	(Xu et al. 2015)
						1.19	0.013	Chinese	Associated	(Qin et al. 2017)
	rs7755109 rs9403380,	chr6:142429255		Intronic	CGAS	1.687	0.0078	Chinese	Associated	(Xu et al. 2015)
	Chr 6:142358435			Intronic	CGAS	1.17,	0.004,	Chinese	Associated	(Qin et al. 2017)
PAX1	rs6137473	chr20:21904055		-	GWAS	1.3	2.15×10-10	USA, Japanese	Associated	(Sharma et al. 2015)
					Replication studies	1.17	4.6 x 10?6	Chinese	Associated	(Xu et al. 2018)
						1.30	3.12 x 10-3	Northern Chinese Han	Associated	(Liu et al. 2019)
	rs169311	Chr20:21981695		-	CGAS	1.22	2.1 x 10?8	Chinese	Associated	(Xu et al. 2018)
	rs17861031	chr20:21706706	Synonymous Variant		CGAS	0.78	0.05	Northern Chinese Han	Associated	(Liu et al. 2019)
	rs6047663	-	90?kb down-stream of PAX1		GWAS	1.22	1.61x10-15	Chinese Han	Associated	(Zhu et al. 2017)

GWAS: Genome wide association study.
CGAS: Candidate gene association study.
* : Genome wide linkage scan.
# : Linkage analysis using targeted microsatellite.
NR: Not reported
NA : Not Available

Table 2: Syndromes that shows scoliosis like phenotypes

Syndrome	*Gene*	*Feature*
Charge	CHD7	Coloboma, Cranial nerve abnormalities, Choanal atresia, Scoliosis.
Andersen-Tawil Syndrome	KCNJ2	Muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia), and developmental abnormalities including scoliosis.
Horizontal Gaze Palsy with Progressive Scoliosis	Robo 3 (axon guidance)	Affects eyes and have severe scoliosis.
Marfan Syndrome	FBN1	Affects heart and blood vessels, eyes, skin and skeletal system. Symptoms include dolichostenomelia,joint laxity, scoliosis and pectus excavatum or pectus.
Ehlers-Danlos Syndrome	COL5A1, COL5A2,	Loose joints, stretchy skin, muscle fatigue, skeletal abnormalities including scoliosis.
Stickler Syndrome	COL11A1, COL2A1, COL9A1, COL11A2	Distinctive facial features, spinal abnormalities including scoliosis.

DISCUSSION

Genetic Studies of AIS

To unravel the AIS aetiology, extensive research has been done globally that suggests the role of genetics in its development. Around 60 AIS susceptibility loci/alleles have been analysed thus far in more than 70 genetic studies via linkage, GWA, and candidate gene association studies in different world populations. In Table 1, the researchers have comprehended all these associations and their possible roles in specific pathways for the pathogenesis of AIS.

Several susceptible loci for AIS have been discovered using family-based linkage analysis. These studies sought to identify a region of the genome co-segregated through families along with the particular phenotype of interest (Silverman and Palmer 2000). Previous linkage studies conducted on idiopathic scoliosis (IS) were inspired by the hypothesis that IS susceptibility might occur due to the changes in the structural elements of the spine. Therefore, polymorphisms in the *COL1A1*, *COL1A2*, elastin (ELN), and fibrillin 1 (*FBN1*) genes have been examined for AIS susceptibility in the family pedigrees. However, the results of these studies did not indicate any evidence of association of these genes with IS (Miller et al. 1996; Wise et al. 2008). Moreover, linkage studies have identified around 13 AIS-susceptible chromosomal regions harbouring potential causative genes involved in neurodevelopmental, Axon guidance, hormonal, and bone/cartilage developmental pathways.

More than 50 candidate genes association studies (CGAS) have been conducted (mostly in Chinese, Bulgarian and Japanese populations) to understand the genetics of AIS. In candidate gene analysis studies, genes are selected according to the evidence of their involvement in the disease pathogenesis, based on the understating of the basic biology of the disease (Zhu and Zhao 2007). Interestingly, based on AIS linkage signals from the genes involved in neurodevelopmental, Axon guidance, hormonal, and bone/cartilage developmental pathways, around 28 genetic loci/variants have been evaluated for AIS association by CGAS. However, many candidate gene associations replicated poorly across different populations.

GWAS is a chip-based high throughput microarray technology that exploits a genome-wide dense array of tagging single nucleotide polymorphisms (SNP) to map risk loci (usually Linkage Disequilibrium blocks) within the genome (Bush and Moore 2012; Tam et al. 2019). As a powerful strategy to explore the genetics of complex disorders in the population, GWAS have been conducted in different population groups of the world (Chinese, Japanese, Hispanic, Non-Hispanic blacks and whites) and helped in discovering various novel AIS susceptible loci, including *LBX1*, *PAX1*, *GPR126*, *BNC2*, *PAX3*, *BCL2*, *CHL1* genes, which are mainly involved in neurodevelopmental, cartilage/bone developmental and axon guidance pathways (Sharma et al. 2011; Kou et al. 2013; Zhu et al. 2015; Zhu et al. 2017). Interestingly, some of these genes were reported to have a vital role in the pathogenesis of various syndromes in which scoliosis is developed as a secondary phenotypic feature, which confirms their possible role in disease pathogenesis (Table 2).

GWAS assay common SNPs, which define only a subset of genetic predisposition of the complex diseases with low to moderate impact (as per Table 1, the odds ratio is below 2 for AIS). Rare variants with strong functional effects must be analysed for disease association to understand the overall heritability of complex diseases. High-throughput next-generation sequencing technologies make it possible to study the impact of such rare variants on complex diseases. Using whole exome sequencing, several studies have identified strong associations of rare functional variants (odds ratio lie between 2.5-4.5) with severe AI cases (Table 1).

Genes and Their Biological Pathways Associated with AIS

The section below provides a detailed insight into AIS susceptible loci/genes (mentioned in Table 1 and Table 2) and their categorisation into specific biological pathways based on potential functional roles.

Nervous System and AIS

Scoliosis is a common phenotypic feature of neuromuscular or neurological disorders, including Duchenne's muscular dystrophy, spinal muscular atrophy, and many more (Kolb and Kissel 2015; Yiu and Kornberg 2015). Neurological anomalies reported in individuals with AIS support the hypothesis that dysfunction in the nervous system might contribute to the aetiology of the AIS (Krober and Zwolak 2017). Anomalies of the vestibular, visual, postural control, and proprioceptive systems, as well as aberrant structures in the CNS, have been associated with equilibrium disruption and asymmetrical cortical hyperexcitability, which may result in the onset of AIS (Liu et al. 2008). It has been observed that some of the AIS patients do have low-lying cerebellar tonsils, cervicothoracic syrinx, and aberrant cerebrospinal fluid dynamics in the hindbrain. MRI images revealed the reduction of white matter in the brain of AIS patients (Peng et al. 2020). All these studies suggest the association of the nervous system with AIS.

Genes of Neurodevelopment Pathway Associated with AIS

Genes in neurodevelopmental pathways have been previously identified as associated with AIS aetiology. A linkage genome-wide scan on 52 families with familial idiopathic scoliosis (FIS) has identified the association of 8q12 loci with AIS. Further, the fine mapping of the region in 52 families of European ancestry revealed the association of the CHD7 gene with IS. Resequencing exons of *CDH7* further reported that the functional polymorphism disrupted the caudal type transcription binding site (Gao et al. 2007), and this caudal transcription factor has a crucial role in the embryonic axial skeletal development (Subramanian et al. 1995).

In contrast, no association was reported between familial idiopathic scoliosis (FIS) and *CHD7* in European families. Furthermore, a meta-analysis of 52 families (Gao et al. 2007) and 244 families with FIS revealed no correlation between the FIS phenotype and the CHD7 gene (Tilley et al. 2013). However, case-control studies reported variations in *CHD7* that showed an association with AIS in Caucasian females (Borysiak et al. 2020) and in the Chinese population (Wu et al. 2021).

The 188 kbp-long CHD7 gene has 42 exons on chromosome 8 (8q12.2). *CHD7* is a member of the ATP-dependent chromatin remodelling enzymes family and is present in the nucleolus and the nucleoplasm (Hall and Georgell 2007; Zentner et al. 2010). It is highly expressed in different regions of the brain (Hurd et al. 2007; Jamadagni et al. 2021; Reddy et al. 2021). The CHD7 gene regulates the protein formation that organises chromatin to govern developmental pathways. It binds with the promoter of *SOX 4* and *SOX11*. It enhances their expression by remodelling Sox4 and Sox11 promoters to an open chromatin state crucial for neuronal differentiation in neural stem cells (Schnetz et al. 2009; Feng et al. 2013; Schnetz et al. 2010). CHD7 gene mutations produce an abnormally short, non-functional chd7 protein, which disrupts gene expression and causes disrupted neural crest formation (Aramaki et al. 2006). A study discovered that *CHD7* has a tissue-specific effect and is crucial in developing migratory multipotent neural crest cells (Bajpai et al. 2010). Mutations in this gene are primarily related to CHARGE syndrome. This genetic condition develops congenital anomalies such as choanal atresia, coloboma, cardiac abnormalities, growth and development retardation of the individual, genitourinary malformations, and ear abnormalities (Hartshorne et al. 2021). Globally, about 1:16,000 newborns have CHARGE syndrome (Issekutz et al. 2005; Jans-

sen et al. 2012), and about 60 percent of those develop scoliosis as a secondary phenotype, suggesting a link between CHARGE and AIS in terms of aetiology (Gao et al. 2007).

In a GWAS, variants in *MAGI1*, *MEIS1*, and *TNIK* were identified that showed an association with AIS (Zhu et al. 2017). However, these previously reported associations were not further replicated in any other study. MAGI1 protein assembles multiprotein complexes in cell-cell contact areas on the inner plasma membrane surface (Dobrosotskaya et al. 1997; Kotelevets and Chastre 2021). This gene product is a scaffolding protein for the cell-cell junction (Mino et al. 2000; Excoffon et al. 2022). It also functions like a scaffolding molecule for the NGF (neuron growth factor) receptor-mediated signalling cascade (Ito et al. 2013). Magi-I is more abundant in some rat neural tissues, including the dorsal root entry zone of the spinal cord as well as the glomeruli of the adult rat's olfactory bulb (Ito et al. 2012). *MEIS1* (Meis Homeobox 1) gene-encoded homeobox protein belongs to homeodomain-containing TALE (three amino acid loop expansion) proteins (Jiang et al. 2021). Meis1 acts like a DNA-binding cofactor of Hox proteins (Garcia-Cuellar et al. 2015). It is crucial for developing many organs, including the peripheral and central nervous systems. This gene is reportedly associated with restless legs syndrome, a nervous system disorder (Salminen et al. 2019). A recent study suggests its role in cortical development by regulating cell migration and proliferation in the cerebral cortex of the embryo (Isogai et al. 2022). The tnik protein, which has scaffolding and kinase domains, is linked to cell proliferation and postsynaptic signalling. Its expression is highly found in the nervous system (Mahmoudi et al. 2009; Shitashige et al. 2010; Coba et al. 2012). The tnik is a regulatory element for the beta-catenin transcriptional complex (Mahmoudi et al. 2009; Masuda et al. 2015). Further, the Wnt beta-catenin pathway showed highly asymmetric expression in the bilateral paraspinal muscles in individuals with AIS (Zhu et al. 2017). This study highlights the importance of the wnt/beta-catenin pathway in the aetiology of AIS, as these genes (*MAGI1*, *MEIS1*, *TNIK*) had been earlier reported to have some regulatory function in Wnt/beta-catenin pathway (Dobrosotskaya and James 2000; Mahmoudi et al. 2009; Stephens et al. 2010; Masuda et al. 2015). More studies are warranted to evaluate these genes' role in AIS aetiology.

Genes of Axon Guidance Pathway That Are Associated with AIS

Horizontal gaze palsy is a rare autosomal condition marked by a lack of conjugate horizontal eye movements with severe scoliosis. This condition develops due to the mutation in the (*ROBO3*) roundabout guidance receptor 3 gene, which encodes an axon guidance protein (Pinero-Pinto et al. 2020). It is highly expressed in the spinal cord commissural neurons of an embryo (Jen et al. 2004; Sabatier et al. 2004). Like *ROBO3*, *CHL1* (close homolog of L1) also encodes the axon guidance protein (Qiu et al. 2014). Therefore, CHL1 might also have an essential role in AIS pathogenesis. This has been evidenced by a GWAS study where a genetic locus in the juxtaposition of the *CHL1* gene has shown an association with the AIS in non-Hispanic blacks, non-whites and non-Hispanic whites (Sharma et al. 2011). In the same study, the *DSCAM* and *CNTNAP2* gene genetic variants also showed an association with AIS susceptibility (Sharma et al. 2011).

Furthermore, the CHL1 gene did not show any association with AIS in the case-control studies carried out in Han Chinese females (Qiu et al. 2014) and the Bulgarian population (Yablanski et al. 2016a). Chl1 is a neural cell adhesion molecule, which belongs to the immunoglobulin-class 1 family. During development, it is essential for neurite outgrowth, axon guidance, and neuronal differentiation. Chl1 controls the plasticity and activation of synaptic connections in the nervous system (Guseva et al. 2018). *CHL1* is primarily expressed in the neuronal system and is crucial for several neuronal functions, such as axon development, apical dendrite direction, and positioning and migration of neurons (Schmid and Maness 2008; Liu et al. 2011). The absence of Chl1 can cause the somatosensory thalamic axons to lose their topography (Wright et al. 2007). *DSCAM* is located on human chromosome 21 and is an axon guidance molecule in invertebrates and vertebrates (Andrews et al. 2008; Liu et al. 2009). During spinal cord development, *DSCAM* also promotes the projection of the commissural axon and path-finding over the ventral midline to reach the floor plate (Wu et al. 2015). The DSCAM gene knockdown in the embryos of zebrafish results in severe anterior/posterior axis shortening. The partial knockdown of *DSCAM* produces crooked-tailed embryos (Yiml-

amai et al. 2005), suggesting that *DSCAM* might be involved in the development of the scoliotic condition. *CNTNAP2* belongs to the neurexin family, located at chromosome 7q35, and is a cell adhesion molecule in the nervous system at the developing stage (Nakabayashi and Scherer 2001).

Further, *CNTNAP2* promotes the neuron's interaction with the glia during nervous system development and is essential in potassium channel localisation within differentiating axons (Poliak et al. 2003). It encodes neurexin IV, necessary for axon guidance pathways through its interaction with the roundabout molecule (Banerjee et al. 2010). Multiple neurodevelopmental problems, including schizophrenia, epilepsy, autism, and mental retardation, were reported to be associated with *CNTNAP2* mutations (Verkerk et al. 2003; Strauss et al. 2006; Alarcon et al. 2008; Friedman et al. 2008; Zweier et al. 2009). Till now, no direct relation of this gene with AIS development has been reported.

EPHA4 knockdown is another gene of this pathway found implicated with AIS. A GWAS has identified a genetic locus between *EPHA4* and *PAX3*, showing an association with AIS in a group of Chinese girls (Zhu et al. 2015). EPHA4 gene belongs to the EPH receptor subfamily. EPH receptors are thought to have a significant function in the normal regulation of developmental processes, particularly in the nervous system (Frisen and Barbacid 1997; Yang et al. 2018). It controls many axonal guidance processes, including the formation of corticospinal projections (Coonan et al. 2001). Along with axonal guidance, it regulates synaptic plasticity too. Developing neuromuscular circuits may also control the segregation of motor and sensory axons (Gallarda et al. 2008).

CELSR2 is another gene identified to be associated with AIS. Linkage analysis identified a genetic locus located at chromosome 1 with a high risk for IS in a Swedish family in which IS is segregated in the dominant mode of inheritance pattern. Further, the exome sequencing of two affected members has been carried out, which revealed a rare non-synonymous variation in *CELSR2*. This association was not further replicated in the independent cohort of Japan and the US (Einarsdottir et al. 2017). Its expression is primarily observed in the neuronal tissues, such as the occipital pole, temporal lobe, postcentral gyrus, and adult spinal cord. It is essential for axon pathfinding, cilium polarity, and neuronal migration (Boutin et al. 2012; Feng et al. 2012; Qu et al. 2014).

All these pieces of evidence suggest that the axon guidance pathway is vital in the AIS pathogenesis. More studies are warranted to comprehend the importance of axon guidance pathway contribution to AIS.

Genes of Hormone-related Pathways Associated with AIS

The association between hormones and AIS is significant, and this has been established by double-neuro osseous theory, which proposes that during the developmental disharmony between the nervous, somatic as well as autonomic systems in the spine and the trunk, along with the higher levels of the hormones leads to the overgrowth of the skeletal system. Therefore, the dysfunction of one or both mechanisms may lead to the AIS development (Burwell et al. 2009). AIS develops during the growing period of children when there are a lot of hormonal changes inside the body (Sharma et al. 2015). Adolescence is a time of rapid physical development during which the levels of several hormones in the body that control bone growth and development rapidly changes. Various studies identified that AIS patients had abnormal levels of many hormones, indicating the possible role of hormonal factors in the AIS susceptibility (Willner et al. 1976; Kulis et al. 2006; Qiu et al. 2007; Esposito et al. 2009; Machida et al. 2009; Tam et al. 2016). Therefore, the genes with some known function in the various hormone-related pathways were considered potential candidate genes for studies related to AIS. Several studies have reported many hormone receptor genes associated with AIS susceptibility.

Estrogens

Estrogens are steroid hormones that can act via two oestrogen receptors (*ESR1* and *ESR2*) distributed widely in the human body and regulate several developmental processes (Compston 2001; Amenyogbe et al. 2020). Oestrogen receptors are structurally and functionally different (Ascenzi et al. 2006). In humans, these receptors' expression is highly found in bone growth plates (Nilsson et al. 2003; Chagin and Savendahl 2007). Its significant effects on bone development are mediated through ESR1 receptor activation (Maggiolini and Picard 2010; Borjesson et al. 2011). In bone metabolism, oestrogen's most essential effect is to stimulate

bone growth by promoting osteoblast differentiation and osteoclast apoptosis and inhibiting osteoblast apoptosis (Moverare et al. 2003; Nakamura et al. 2007). Low oestrogen levels and delayed menarche can reduce bone mineralisation in females, resulting in an increased risk of bone deformities (Liang et al. 2021). Various abnormal changes have been observed in the oestrogen and its receptor in AIS patients, such as oestrogen concentration in serum, age at menarche, cellular response to oestrogen, and genetic variation in the genes of the oestrogen receptor (Kulis et al. 2006; Letellier et al. 2008). There are two main theories regarding the role of oestrogen in AIS susceptibility. First, its abnormal levels result in delayed puberty in females and bone formation and maturation, which elevates the spine deformity risk (Grivas et al. 2006; Sanders et al. 2007). Secondly, aberrant oestrogen levels directly impact bone metabolism and remodelling, resulting in improper bone growth and development, which increases the risk of AIS. Although estrogens were not thought to be a direct causative factor for AIS due to their role in bone growth and development by interacting with various agents that regulate bone formation and biomechanics (Leboeuf et al. 2009), it was hypothesised that they might contribute to the AIS susceptibility.

The two polymorphism sites Xba I (rs9340799) (Chen et al. 2014a) and Pvu II (rs2234693) (Zhao et al. 2009) in *ESR1*, and Alu I (rs4986938) (Kotwicki et al. 2014), AlwN I (rs1256120) (Zhao et al. 2017) and Rsa I (rs1256049) (Kotwicki et al. 2014) in the ESR2 gene were identified to have an association with idiopathic scoliosis. Xba l (rs9340799) has also shown a significant association with the progression of IS in the Japanese cohort (Inoue et al. 2002), in the Chinese female population (Wu et al. 2006), and in the Bulgarian population (Yablanski et al. 2016b). However, the Xba I (rs9340799) and Pvu II (rs2234693) associations have not been further replicated in a larger female group of Chinese population (Tang et al. 2006) and Caucasian female population (Kotwicki et al. 2014). The genetic variant AlwN I (rs1256120) of *ESR2* was also reported to be associated with spinal curve progression and predisposition in the Chinese cohort (Zhang et al. 2009). However, no significant association has been found in the larger cohort of the Japanese population (Takahashi et al. 2011c) and in Caucasian females (Kotwicki et al. 2014). More studies in different populations could help determine the significance of *ESR* mutations with the susceptibility to AIS.

Growth Hormone-insulin-like Growth Factor-1 Axis

Among the numerous theories regarding the aetiology of AIS, it is believed that AIS occurs due to the abnormal growth pattern of vertebrae (Fadzan and Bettany-Saltikov 2017). The growth hormone and *IGF1* have a crucial role in skeletal development. The level of GH increases during the pubertal stage (Mauras et al. 1987; ROSE et al. 1991). In addition to IGF-1, GH directly impacts various types of bone cells. It increases bone development and remodelling and regulates linear growth and bone mass (Olney 2003). An earlier study reported higher growth hormone levels in AIS individuals during early puberty (Willner et al. 1976).

Furthermore, this was supported by a different study that showed AIS patients had earlier pubertal development than people without AIS (Ylikoski 2003). Growth hormone treatment resulted in scoliosis development and progression (Wang et al. 1997; Park et al. 2021), which suggests the association of AIS development with high growth hormone activity. Further, the IGF-1 gene has been observed to be associated with the severity of spinal deformity in the Chinese population, but no association has been reported with the AIS onset (Yeung et al. 2006). The association of *IGF-1* with AIS susceptibility and its progression was also observed in a small group of the Korean population (Moon et al. 2013). The association was further not replicated in the Japanese (Takahashi et al. 2011b) and Bulgarian population (Nikolova et al. 2015c). Therefore, further studies are required to validate the association of the growth-regulating genes with AIS.

Leptin

Leptin is essential in regulating appetite and bone morphogenesis (Turner et al. 2013; Farooqi and O'Rahilly 2014). Leptin and the soluble leptin receptor (sOB-R) were found to have a crucial role in regulating bone and energy metabolism (Upadhyay et al. 2015). Leptin improves muscle mass by inhibiting troponin degradation and promotes

muscle cell proliferation during muscular development (Sainz et al. 2009). It is a permissive factor regulating pubertal development (Apter 2003). The aetiology of AIS could be linked to leptin and its signalling system. A thin body and a low BMI are common characteristics in women with AIS, which are believed to be connected to leptin and adiponectin. A genetic locus in *LEPR* was also associated with the disease in the Chinese population (Liu et al. 2015b). To validate this association, more studies are required in different populations.

Melatonin

Melatonin is found primarily in all animals and has a role in regulating the biological rhythm of the body. Melatonin secretion levels are low throughout the day and dramatically increase during the night (Zhao et al. 2019). In addition to regulating biological rhythms, melatonin is essential for several biological processes, including bone growth (Tordjman et al. 2017). The pinealectomy in chickens induced severe scoliosis, which first suggested the association of melatonin and AIS. It showed similar biological characteristics to that of idiopathic scoliosis in humans. Melatonin deficiency is a causative agent of this experimental scoliosis (Machida et al. 1995; Fagan et al. 2009). The impaired melatonin signalling was also reported in the cultures of osteoblast prepared from specimens of bones extracted during spine surgeries of the AIS patients (Moreau et al. 2004). Since pinealectomy decreases melatonin release, low circulating melatonin levels have been indicated as a plausible factor in scoliosis development (Girardo et al. 2011). Melatonin receptor 1A and melatonin receptor 1B are the transmembrane receptors through which melatonin exerts biological functions (Gall et al. 2002; Ahmad et al. 2023). The genes encoding the melatonin receptor *MTNR1A* and *MTNR1B* were studied in different populations to find their possible role in the pathogenesis of IS.

According to current evidence, inappropriate downstream *MTNR1B* responses, but not *MTNR1A* responses, may have a possible role in the AIS development. In one earlier study, tag SNP rs4753426 in the *MTNR1B* was found in association with AIS onset in the group Chinese population (Qiu et al. 2007). A meta-analysis study showed that the genetic variant rs4753426 is associated with AIS in Caucasian and Asian populations (Yang et al. 2015b). MTNR1B protein and mRNA levels in AIS patients were considerably lower compared to non-AIS individuals (Liang et al. 2021). In contrast, the level of *MTNR1A* was normal in AIS patients, and no variation in this gene has been observed to have an association with AIS (Morcuende et al. 2003; Qiu et al. 2008; Yim et al. 2013). These studies indicate that melatonin might be a causative factor in the scoliosis development. However, the existing evidence does not support a definitive function of melatonin in AIS.

Other Developmental Genes

Several genetic studies carried out globally using different approaches showed the association of several variants of other genes with the AIS. The most replicated and strongest association with AIS is demonstrated by the variant at 10q24.32 near *LBX1* (Londono et al. 2014). A GWAS study first discovered three variants close to the LBX1 gene in the Japanese population, and the most significant SNP, rs11190870, is present downstream at 7.5 kb of the gene (Takahashi et al. 2011a). This genetic locus was then successfully replicated in Chinese, Scandinavian, French Canadian, and East Asian populations (Fan et al. 2012; Jiang et al. 2013; Gao et al. 2013; Liu et al. 2017; Nada et al. 2018; Man et al. 2019). Another functional variant, rs1322330, present at the promoter site of this gene, has been reported to have an association with AIS in the Chinese population by regulating myogenesis in paraspinal muscles (Xu et al. 2021). *LBX1* encodes a transcription factor known as ladybird homeobox. This gene is expressed specifically during early embryogenesis in the dermomyotome. It regulates the gene expression that directs the lateral migration of the muscle precursor cells and controls their migration potential (Brohmann et al. 2000). It is also essential for dorsal horn specification as well as for somatosensory function (Gross et al. 2002). Thus, *LBX1* could also be involved in AIS neurogenic and myogenic pathogenesis (Wise et al. 2020).

SOX9 encodes a protein crucial in skeletal development (Bi et al. 1999; Lefebvre et al. 2019). The gene encodes the transcription factor involved in chondrogenesis (Dy et al. 2012). Sox9 interacts with Sox5/6 and regulates gene expression related to the growth plate's chondrogenesis (Liu et al. 2015a). The gene is necessary for appropriate spine pat-

terning and development in embryonic mice. It was observed that the removal of *SOX9* in embryonic mice failed to produce well-patterned vertebral bodies or intervertebral disk (IVD) tissues (Akiyama et al. 2002). In skeletally mature mice, it was found that *SOX9* is constantly needed for maintaining the homeostasis of the spine. In contrast, its ablation was found to be causing kyphoscoliosis, disc compression, and IVD degeneration (Henry et al. 2012). This suggests that *SOX9* is associated with spinal abnormalities and scoliotic phenotype, and thus, it has a plausible role in AIS etiopathogenesis. The hypothesis was held firm as the GWAS study in the Japanese population reported common genetic loci rs12946942 near *SOX9* and *KCNJ2* at chromosome 17, which was associated with AIS (Miyake et al. 2013), depicting the importance of this gene in the AIS aetiology.

ADGRG6 or *GPR126* belongs to the adhesion GPCR family and is essential for biological processes, including the migration of cells and their adhesion (Langenhan et al. 2013). The GWAS study reported a genetic variant rs6570507 of *GPR126* associated with AIS in Japanese, European-ancestry populations, and Han Chinese and found delayed ossification of developing spine in the gpr126 knockdown zebrafish model (Kou et al. 2013). This gene is further reported to have an association with AIS in different studies (Xu et al. 2015; Kou et al. 2018; Xu et al. 2019). Another functional locus, rs9403380, has been identified in the southern Chinese population, which regulates the expression of *GPR126* in the paraspinal muscles of AIS patients (Qin et al. 2017). In humans, the expression of *GPR126* was found to be high in cartilages and intervertebral discs. In mouse embryos, its expression was reportedly increased in the spine cartilage, indicating its function in spine development (Kou et al. 2013). It is also essential for the normal axonal myelination and promyelination of differentiating Schwann cell development (Monk et al. 2011; Wise et al. 2020).

PAX3 is another developmental gene found to have an association with AIS. In the neural tube, the *PAX3* controls myogenesis and neurogenesis (Schubert et al. 2001; Young and Wagers 2010). Additionally, *PAX3* mutation might result in spinal column deformity and muscular and neural tube abnormalities (Rong et al. 1992; Boudjadi et al. 2018). The primary lineage that expresses the *PAX3* is the lineage of skeletal muscles. The expression of *PAX3* was initially observed in the paraxial mesoderm during embryonic development and later confined to the dermomyotome. Cells that express *PAX3*, separate from the dermomyotome, in the central body segments develop skeletal muscle. Cells expressing *PAX3* move to other locations, such as the limbs, where they develop into other skeletal muscles (Buckingham and Reliax 2007). Postnatal muscle growth and regeneration during later embryonic stages are regulated by myogenic satellite cells that express *PAX3* and/or *PAX7*. A genetic variant (rs13398147) between *PAX3* and *EPHA4* is identified in a GWAS to be associated with the disease in Chinese ancestry (Zhu et al. 2015). In AIS patients, aberrant expression of *PAX3* was related to abnormal paravertebral muscle development (Qin et al. 2020), suggesting its possible functional role in AIS development.

Similarly, *PAX1* encoded paired box 1 protein is a transcription factor that helps form sclerotome and develop intervertebral discs (Wallin et al. 1994; Wise et al. 2020). The expression of the PAX1 gene is well described during somitogenesis in the growing mice embryo. Its expression was observed in vertebral and intervertebral disc cells and in the precursor cells of the connective tissue surrounding the dorsal root ganglia and spinal nerve (Monsoro-Burq 2003). The deletion and missense mutations in *PAX1* resulted in deformities and malformation of the spine, including scoliosis in the undulated and scoli mouse strains (Adham et al. 2005). Furthermore, the genetic study has also identified the association between the *PAX1* enhancer locus and AIS in the European population. A similar association is also observed in independent ethnic groups like Japanese, North American, and in East Asian female populations. Further, it was found that this association is driven explicitly by the females and not by the males, suggesting it is a sex-specific locus for AIS (Sharma et al. 2015). These studies hint towards the contribution of *PAX1* in AIS pathogenesis.

Genes of Bone and Cartilage Development

Extracellular matrices (ECMs) provide structural and biochemical support to the vertebral column (Wise et al. 2020). Numerous studies have examined these extensively to unravel the aetiology of AIS (Lowe et al. 2000). Scoliosis is the secondary phenotypic characteristic of various disorders of

connective tissues, including Marfan syndrome, spondylocarpotarsal syndrome, stickler syndrome, and Ehlers-Danlos syndrome, indicating the importance of the genes of connective tissues, in the development of AIS. Initially, research was concentrated on the *COL1A1* (Carr et al. 1992), *COL1A2* (Carr et al. 1992; Miller et al. 1996), *COL2A1* (Carr et al. 1992), *FBN1*, and elastin (Miller et al. 1996), which acts as the structural elements of the ECM system. However, none of these genes showed any evidence of association with idiopathic scoliosis in studied populations. However, a recent genome-wide pathway burden study using exome sequencing identified extracellular matrix genes as the prominent class of genes that might contribute to the polygenic nature of AIS.

Marfan syndrome, a connective tissue disorder, develops due to the pathogenic variations in the fibrillin-encoding gene *FBN1* (Coelho and Almeida 2020). However, the mutations in *FBN1* were also observed to be associated with isolated kyphoscoliosis (Zorkol'tseva et al. 2002) as well as with isolated skeletal features like scoliosis (Milewicz et al. 1995; Reyes-Hernandez et al. 2016). Earlier studies identified the fibrillin anomalies in the fibroblasts of AIS patients (Hadley-Miller et al. 1994). However, the linkage analysis studies showed no association of *FBN1* with AIS (Miller et al. 1996). An exome sequencing study identified the association of the rare variants (chr15:48902952, chr15:48826300, chr15:48796007, chr15:48795990, chr15:48784766, chr15:48777634, chr15:48777609, chr15:48773879, chr15:48764870, chr15:48760155, chr15:48741087, chr15:48736768, chr15:48726873, chr15:48725128, chr15:48712949, chr15:48703201, chr5:127873139, chr5:127872157, chr5:127782238, chr5:127713520, chr5:127704904, chr5:127681205, chr5:127674750, chr5:127674724, chr5:127673755, chr5:127671182, chr5:127627260, chr5:127613647, chr5:127609564, and chr5:127607792) in *FBN1* and *FBN2* with curve progression in AIS individuals of the European population (Buchan et al. 2014). Furthermore, the common genetic variant rs12916536 in the FBN1 gene is substantially related to the AIS development in the Chinese population (Sheng et al. 2019). This association was recently replicated in the Brazilian population (de Azevedo et al. 2022).

Matrilin 1 (MATN1), also called cartilage matrix protein, is vital in the ECM assembly in different tissues and is essential for spinal stability (Chen et al. 1999; Zhang et al. 2014a). An intragenic microsatellite variation in the *MATN1* was associated with AIS in 50 Italian trios (Montanaro et al. 2006). Similarly, variation in the promoter of the MATN1 gene has shown an association with AIS susceptibility and progression in the Chinese population (Chen et al. 2009). Another genetic variant in this gene was associated with double curves in patients with AIS in the Korean population (Bae et al. 2012). Matrilin-1 is essential in organising chondrocytes into separate growth plate zones (Chen et al. 1995; Chen et al. 2009). Chondrocyte zonal distribution disruption could result in a musculoskeletal disorder like scoliosis (Goldring et al. 2006). Study on *MATN1* mutant mice showed phenotypes like scoliosis, tail kinks, or kyphosis, making it a potential gene for AIS development (Blank et al. 1999; Giampietro et al. 1999; Chen et al. 2009).

DOT1L gene, located at chromosome position 19p13.3, was reported as a susceptibility locus for AIS by linkage analysis study (Alden et al. 2006; Chen et al. 2009). A case-control study identified a genetic locus rs12459350 in the *DOT1L* associated with AIS susceptibility and peak height velocity during puberty (Mao et al. 2013). The gene DOT1L is an evolutionarily conserved histone methyltransferase and is essential for the chondrogenic cells differentiation and regulation of the cartilage thickness by governing the activity of Wnt target genes (Betancourt et al. 2012). Invitro silencing of the gene DOT1L inhibits chondrogenic differentiation, and the knockdown of the DOT1L gene decreases the collagen and proteoglycan content and mineralisation during the process of chondrogenesis (Betancourt et al. 2012). All this suggests the function of *DOT1L* in cartilage development.

The calmodulin (CaM) protein is encoded by the *CALM1* (calmodulin 1 gene). Calmodulin controls the calcium signal transduction, which regulates downstream calcium signalling, like the contraction of skeletal muscles, agglomeration of platelets, etc. (Liang et al. 2021). It is essential for intercellular communication, cell differentiation, movement, cell proliferation, and other biomechanical and physiological activities (Hanley et al. 1990; Rebas et al. 2012). Initially, in a study, it was reported that the patients with IS had 2.5 times increased calmodulin levels in their platelets, and the calmodulin level was substantially found to be related to the spinal curve severity (Cantaro et al. 1985). The mutation in the *CALM1 was associated* with

the double curve predisposition in the Chinese population (Zhao et al. 2009). Another study identified the three genetic loci rs2300496, rs2300500, and rs3231718 of the CALM1 gene that are associated with AIS (Zhang et al. 2014b). The primary role of calcium signalling is to regulate bone turnover and the regulation of both osteoclasts and osteoblasts (Williams et al. 2010). Calcium calmodulin signalling is also crucial for the response of chondrocytes to mechanical load, which is significant for the normal functioning of the articular (Poulou et al. 2008).

The *VDR* that codes a nuclear receptor for vitamin D metabolites is present at chromosome position 12q12-q14 (Uitterlinden et al. 2002; Gasperini et al. 2023). *VDR* is a significant factor in vitamin D's biological activity and is essential for bone mineral density (BMD) regulation and skeletal metabolism (Uitterlinden et al. 2002; Reid 2017). *VDR* polymorphisms have been reported to be associated with bone disorders, including osteoarthritis and osteoporosis (Martirosyan et al. 2016; Xu et al. 2012). Because of the significant function of *VDR* in the aetiology of many bone disorders, several studies were performed to determine the correlation between *VDR* and AIS aetiology. The VDR gene also showed an association with AIS in different studies. SNP rs1544410 in the VDR gene is reported to be associated with low bone mass and abnormal growth in Asian females (Xia et al. 2007), AIS (Wang et al. 2016), and low lumbar bone mineral density as well as curve predisposition in a female group of Korea (Suh et al. 2010). Moreover, a meta-analysis study reported that the genetic variants rs1544410 and rs7975232 in *VDR* are associated with the AIS aetiology in the Asian population (Yin et al. 2018).

AKAPs are involved in creating signalling complexes that govern the events of temporal and spatial sequencing. The gene AKAP2 interacts with the protein kinase A regulatory unit (McConnachie et al. 2006; Sarma et al. 2015). In previous studies, the gene was associated with Kallmann syndrome and bone deformities (Panza et al. 2007). A linkage study identified the locus on chromosome 9q31.2–q34.2 associated with AIS (Ocaka et al. 2008). Whole exome sequencing showed a significant association of the AKAP2 gene with AIS predisposition in a Chinese family (Li et al. 2016). However, this association has not been further confirmed in the Chinese population cohort (Xu et al. 2017). Its expression is highly detected in the cartilaginous structure of mouse embryos. AKAPs regulate the signalling of cyclic AMP-dependent protein kinase (PKA) in space and time. PKA's dimerization/docking (D/D) domains are firmly bound by the dual-specific AKAP2 and help in the downstream signalling (Sarma et al. 2010). Furthermore, the PKA pathway was reported to regulate bone growth and the anabolic skeletal response (Kao et al. 2013; W. Li et al. 2016).

Status of Scoliosis in India

There is a scanty of information related to the epidemiology of AIS in the Indian population. This paucity of epidemiological evidence of scoliosis explains the disease's obscurity and misconceptions in India. Few epidemiological studies have been conducted in India. One of the prevalence studies of AIS was conducted in Patiala, Punjab, showed the prevalence of AIS as 0.13 percent (Mittal et al. 1987), and the other in Assam reported a prevalence of 0.2 percent (Saikia et al. 2002). Recently, the researchers have carried out an epidemiology study in the Jammu and Kashmir region where a screening of 9500 school children was done. The study reported an overall prevalence of AIS to be 0.61 percent, with lower female predominance (Singh et al. 2022b) in contrast to the global prevalence. This suggests that it might be a result of genetic heterogeneity of the Indian population compared to other populations of the world. So, to unravel the genetic heterogeneity, the researchers have conducted the first genetic study of AIS in the Indian population where in the first phase of the study, the researchers have genotyped the highly replicated SNP rs11190870 nearby *LBX1* in the population of North India (Singh et al. 2022a). Furthermore, the researchers have also evaluated the association of the genetic variants in various previously reported genes in the population of northwest India (the results are still unpublished).

Future Prospective

Large-scale school-based scoliosis screening is warranted in the Indian population to understand the epidemiology of the disease. Genetic studies comprising large sample sizes are pertinent in different population groups of India to unravel the genetic aetiology of scoliosis.

CONCLUSION

Understanding the association of genetic variants with the disease is a crucial objective of genetics. Intuitively, one can anticipate that disease-causing variations cluster into key pathways influencing disease biology. Most of the AIS genetic studies are conducted in the population of East Asian and Caucasian origin. Based on all the genetic studies conducted globally on AIS, it was found that most of the AIS susceptibility loci are associated with the pathways of neurodevelopment and axon guidance, followed by body development, cartilage development, bone development pathways, and hormonal-related pathways. Most of the associated variants are intronic and exhibit low to moderate disease risk, as defined by their odds ratio of less than 2.0. This observation suggests these variants might not be the causative variant for AIS susceptibility but may lie nearby/strong LD with actual functional (regulatory or in the exon) variant(s). It was also observed that many AIS candidate gene associations replicated poorly across different populations. The probable reasons include the lack of power of the study or population stratification issues and genetic heterogeneity in the population.

RECOMMENDATIONS

To unravel the potentially disease-causing variants, it becomes pertinent to conduct large-scale genetic studies in genetically diverse population groups, including South-Asian populations, African, Hispanic, and many more. In addition, based on understanding the possible role of risk alleles in disease-specific pathways, gene-gene, and gene-environmental interaction analysis must be performed to make meaningful mechanistic interpretations of the current list of candidate genes, which may add to the genetic heritability of the disorder. Also, fine map the AIS susceptible genomic segments/genes to delineate the actual causative variants) is strongly recommended. Further, to understand the overall heritability of AIS, rare variants with strong functional impact must be analysed for AIS association, which is successfully feasible using high-throughput next-generation sequencing technologies.

ABBREVIATIONS

AIS: Adolescent Idiopathic Scoliosis
GWAS: Genome-wide association studies
CHD7: Chromodomain helicase DNA-binding protein 7
FIS: Familial idiopathic scoliosis
MAGI1: Membrane-associated guanylate kinase, WW, and PDZ Domain Containing 1
MEIS1: Meis Homeobox 1
TINK: Traf2 and NcK interacting kinase
ROBO3: roundabout guidance receptor 3
CHL1: close homolog of L1
EPHA4: Ephrin type-A receptor 4
IGF1: Insulin-like growth factor-1 axis
ADGRG6: Adhesion G protein-coupled receptor G6
ECMs: Extracellular matrices
MATN1: Matrilin 1
CALM1: Calmodulin 1 gene
VDR: Vitamin D receptor
AKAP: A-kinase anchoring proteins

DECLARATION

All authors declared that this article has not been published or sent to any other publication elsewhere.

AUTHOR CONTRIBUTIONS

SS, ER and VS conceived the study, S and HS wrote the manuscript, and SS, ER, and VS critically reviewed the manuscript.

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