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REVIEW

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Skeletal Class III phenotype: Link between animal models and human genetics: A scoping review

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Abstract

This study aimed to identify evidence from animal studies examining genetic variants underlying maxillomandibular discrepancies resulting in a skeletal Class III (SCIII) malocclusion phenotype. Following the Manual for Evidence Synthesis of the JBI and the PRISMA extension for scoping reviews, a participant, concept, context question was formulated and systematic searches were executed in the PubMed, Scopus, WOS, Scielo, Open Gray, and Mednar databases. Of the 779 identified studies, 13 met the selection criteria and were included in the data extraction. The SCIII malocclusion phenotype was described as mandibular prognathism in *the Danio rerio*, *Dicentrarchus labrax*, and *Equus africanus asinus* models; and as maxillary deficiency in *the Felis silvestris catus*, *Canis familiaris*, *Salmo trutta*, and *Mus musculus* models. The identified genetic variants highlight the significance of BMP and TGF-β signaling. Their regulatory pathways and genetic interactions link them to cellular bone regulation events, particularly ossification regulation of postnatal cranial synchondroses. In conclusion, twenty genetic variants associated with the skeletal SCIII malocclusion phenotype were identified in animal models. Their interactions and regulatory pathways corroborate the role of these variants in bone growth, differentiation events, and ossification regulation of postnatal cranial synchondroses.

KEYWORDS
animal model, genetic variants, mandibular prognathism, maxillary deficiency, skeletal Class III malocclusion phenotype

1 | INTRODUCTION

The Skeletal Class III (SCIII) malocclusion phenotype is characterized by a maxillo-mandibular relationship, in which the mandible is relatively positioned more forward than the maxilla. This may be the result of protrusion or hyperplasia of the mandible, hypoplasia of the maxilla, or a combination of both (Singh, 1999). This phenotype has been identified in several vertebrate species other than humans, such as short-nosed dog breeds, rabbits, fishes, and iguanas (Ferraresso et al., 2010). In humans, the negative impacts associated with this condition include masticatory impairments (Bae et al., 2017), temporomandibular disorders, and an overall negative impact on quality of life (Barros et al., 2019; Javed & Bernabé, 2016). Whilst in animals, such as short-nosed dogs, this condition is associated to

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breathing difficulties due to obstructive airway syndrome (Ekenstedt et al., 2020).

The role of genetic mechanisms involved in the expression of this condition has been elucidated in several studies in humans; however, the available evidence remains inconclusive. To date, the most probable inheritance pattern of this condition is thought to be autosomal dominance with incomplete penetrance and variable expression (Bui et al., 2006; Chen et al., 2015; Cruz et al., 2008; Perillo et al., 2015; Rao et al., 2020). Several genetic variants, including *MYO1H* (rs10850110), *BMP3* (rs1390319), *GHR* (rs2973015, rs6184, rs2973015), *FGF7* (rs372127537), *FGF10* (rs593307), and *SNAI3* (rs4287555) have been identified through genetic association studies. For example, a previous systematic review and meta-analysis of genetic association studies (Dehesa-Santos et al., 2021) determined that the presence of the A allele of SNP rs7351083 in *FBN3* increases the predisposition to SCIII malocclusion. In contrast, linkage studies have identified *IGF1*, *HOXC*, *COL2A1* (Frazier-Bowers et al., 2009), *DUSP6* (c.545 C > T; p. Ser182Phe) (Nikopensius et al., 2013), and *ARHGAP21* (Gly1121Ser) as being associated with this condition (Perillo et al., 2015).

As vertebrates, humans and other gnathostome species share common primordial structures, such as the paired maxillary and mandibular prominences, which are derivatives of the first branchial arch originating from the neural crest (Jaruga et al., 2022). Therefore, in human and vertebrate animal models, arches are extensively patterned with signals from the surrounding epithelia, and neural crest cell (NCC) intrinsic information, to accomplish general functions, which have been proven to be highly conserved across species (Mork & Crump, 2015). Animal disease models provide a critical scientific background regarding several conditions essential for understanding the molecular events leading to the development of craniofacial structures and identifying the roles played by specific pathways, facilitating the targeting of potential candidate genes involved in the development of specific phenotypes (Jaruga et al., 2022). Furthermore, the advent of high-throughput technologies has generated considerable large-scale data at various cellular levels, ranging from genomics to proteomics, across different tissues and species (Podder et al., 2021). This knowledge is a percussor for advancements in human research.

This scoping review aimed to identify available evidence from animal studies that examined genetic variants underlying maxillo-mandibular discrepancies resulting in a SCIII malocclusion phenotype.

2 | MATERIAL AND METHODS

This review was conducted following the suggestions of the template and manual for evidence synthesis of the JBI (Peters MG et al., 2020), and the PRISMA extension for scoping reviews (Tricco et al., 2018).

2.1 | Review question

The following participant, concept, context (PCC) question was proposed to select eligible studies: "What available evidence is provided by the animal models regarding genetic variants underlying maxillomandibular discrepancies resulting in the SCIII malocclusion phenotype?"

2.2 | Eligibility criteria

The eligibility criteria for studies to be part of this review were as follows: *Participants*: Studies must involve vertebrate animal subjects, regardless of the species. *Concept*: Studies must involve the identification or characterization of genetic variants that regulate craniofacial structures involved in maxillomandibular discrepancies, resulting in a SCIII malocclusion phenotype in animal subjects. *Context*: No particular context was required, therefore it remained as "open." *Type of sources*: The duration of the study and language in which it was presented were not considered as limitations, as long as they met the above criteria for participants, concept, and context. Eligible studies were limited to functional animal, case-control, and in vivo studies. Functional studies using animal models, identified in the context of human studies, have also been considered. Studies on syndromic conditions, craniofacial malformations, and other diseases that result in SCIII malocclusion, secondary to the disease, were excluded. This was to ensure that specific information pertaining to the SCIII malocclusion phenotype as an isolated trait was obtained for the review. *In vitro* studies, reviews, and opinions were also excluded from the analysis.

2.3 | Search strategy

The search strategy was developed in three stages. The first stage involved an initial search using *PubMed* and *Scopus* databases. The strings of keywords contained in the titles and abstracts of the retrieved papers and their indexed terms were obtained. Then, a second search was performed after incorporating this string of keywords, using the same databases, including *WOS*, *SciELO*, and the gray literature databases *Open Gray* and *Mednar*. The third stage of the search strategy involved a manual search of the reference lists of the identified studies that fulfilled the selection criteria. If necessary, contact with authors of the primary sources was considered and established. The search strategies, including all identified keywords and index terms adapted for each of the consulted databases, are presented in Supporting Information 1.

2.4 | Study/Source of evidence selection

The screening process was divided into three phases: (1) duplicate removal, (2) title and abstract examination, and (3) full-text examination. These were independently performed by two researchers (ADS and CFT). Disagreements were resolved by consensus or by a third reviewer (AIL).

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2.5 | Data extraction

Data extraction was performed by a single reviewer (ADS), and corroborated by a second reviewer (CFT). The preset variables of interest were recorded as follows: authors, year, type of study, animal model, phenotype definition, phenotyping method, genetic variant reported, animal genome location, harboring gene, implication in humans/mammals, human genome location, and closest genes associated with SCIII malocclusion (Cruz et al., 2017; da Fontoura et al., 2015; Marañón-Vásquez et al., 2020; Saito et al., 2017; Sun et al., 2018; Tassopoulou-Fishell et al., 2012; Weaver et al., 2017; Xiong et al., 2017).

2.6 | Interspecies conservation assessment

The orthological relationship between the genes of the animal models and the human genome was determined using the Ensemble 110 database (Martin et al., 2022; Pignatelli et al., 2016). Two scores were attained: the gene order conservation (GOC) score, and the whole genome alignment (WGA) score calculates the alignment coverage over the ortholog pair, assuming that genes that are orthologous to each other will fall within genomic regions that can be aligned with one another. Protein conservation scores were calculated to estimate the evolutionary conservation of the products of each of the identified genes. This analysis was performed using ConSurf (Ashkenazy et al. 2010, 2016; Celniker et al., 2013; Glaser et al., 2003; Landau et al., 2005; Yariv et al., 2023), a bioinformatics tool for estimating evolutionary conservation based on phylogenetic relationships between homologous protein sequences. The *average pairwise distance* (APD) from the multiple sequence alignment of the proteins was acquired to detect evolutionary diversity in the sequences included (Ashkenazy et al., 2010). Additionally, gene function enrichment analysis using all the identified genes orthologs was carried out using the GO (Aleksander et al., 2023; Ashburner et al., 2000) and PANTHER (Thomas et al., 2022) web tools to highlight the possibly overrepresented gene functions. Potential genetic and signaling interactions between the orthologs candidate genes identified across studies were estimated using the GeneMANIA prediction server (Warde-Farley et al., 2010).

3 | RESULTS

3.1 | Search results

Our search strategy retrieved 779 studies, of which 93 were duplicates. Following the PCC criteria, screening by title and abstract yielded 40 articles for a full-text review. Ultimately, 13 studies were included (Babbucci et al., 2016a; Bannasch et al., 2010; Bertolini et al., 2016; Ferraresso et al., 2010; Hünemeier et al., 2009; Marchant et al., 2017; Palmas et al., 2020; Quilez et al., 2011; Rodrigues et al., 2013; Sakata-Goto et al., 2012; Schoenebeck et al., 2012; Sophocleous et al., 2020; Sun et al., 2018) (Figure 1). The reasons for exclusion are compiled and described in *Supporting Information* 2.

The description of the studies included species and genetic variants associated with the SCIII malocclusion phenotype. A summary of the included studies is shown in Table 1. Mandibular prognathism (MP) and

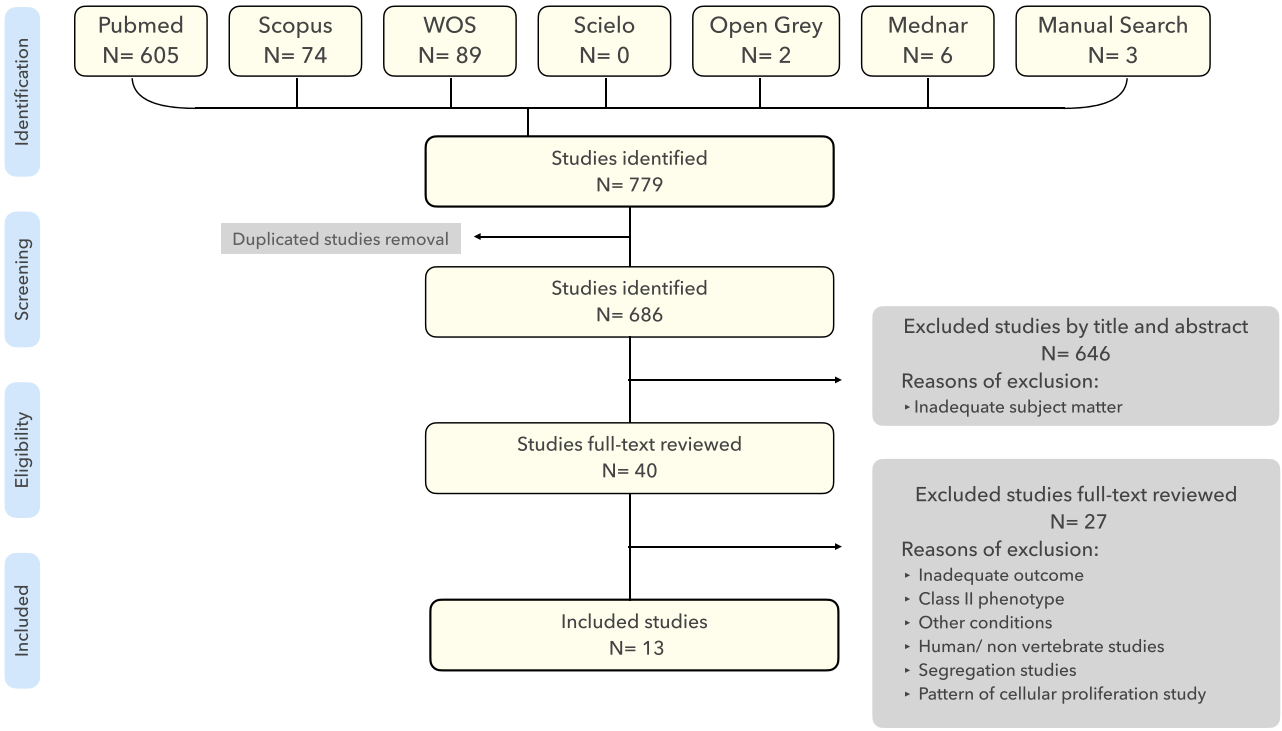

FIGURE 1 PRISMA-ScR flowchart of article retrieval.

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TABLE 1 Studies characteristics.

Year	Author	Study type	Animal model	Phenotype definition	Phenotyping method	Genetic variant/ARN transcript	Result	Animal genome Location	Harboring gene/coding protein	Molecular functions of human homologus genes[a]	Human homologus genome location	Closest genes associated to SCIII malocclusion in humans[b]	Source
Mandibular prognathism													
2010	Ferraresso et al.	mRNA expression study	Seabass (*Dicentrarchus labrax)*	Mandibular prognathism	Not specified-visual inspection	DLPD08826: calcitonin gene-related peptide (*CGRP*)	downregulation in pooled-samplesof deformed mandibles compared to controls	2q31-q32?	*CALCA* (***CGRP***)	***CALCA:*** This gene encodes a membrane protein that functions as part of a receptor complex for a small neuropeptide that increases intracellular cAMP levels. Alternate transcriptional splice variants, encoding different isoforms, have been characterized.	7q11.21	*CALN1* (7q11.22) assoc. MP *COL1A1* rs2249492 (17q21.33)-↑Risk of skeletal class III	Saito et al. (2017). da Fontoura et al. (2015)
						DLPD06176 (Fatty acid-binding protein, brain)*	downregulation in pooled-samples of deformed mandibles compared to controls	CAJNN-U010000003.-1:17,150,885-17,152,589:−1CAJNN-U010000008.-1:20,566,541-20,568,713:1	DLPD06176 (***FABP7***)	***FABP7:*** The gene encodes a small, highly conserved cytoplasmic protein that bind long-chain fatty acids and other hydrophobic ligands. The encoded protein is important in the establishment of the radial glial fiber in the developing brain. Alternative splicing and promoter usage results in multiple transcript variants encoding different isoforms. Pseudogenes of this gene are found on multiple chromosomes.	6q22.31	*TCF21* (6q23.2) assoc. MP*IGF2R* (6q25.3) rs6920141 ↓Go-Pg and Ptm-A measures) rs2277071 ↓maxillary length (Ptm′-A′)	Saito et al. (2017). Marañón-Vásquez et al. (2020)
						DLPD06508 (Synaptosomal-associated protein 25-A)*		CAJNN-U010000008.-1:4,579,431-4,624,439:1CAJNN-U010000019.-1:27,773,604-27,812,169:−1	DLPD06508 (***SNAP25***)	***SNAP25:*** Synaptic vesicle membrane docking and fusion is mediated by SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) located on the vesicle membrane (v-SNAREs) and the target membrane (t-SNAREs). The assembled v-SNARE/	20p12.2	-	

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TABLE 1 (Continued)

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										t-SNARE complex consists of a bundle of four helices, one of which is supplied by v-SNARE and the other three by t-SNARE. For t-SNAREs on the plasma membrane, the protein syntaxin supplies one helix and the protein encoded by this gene contributes the other two. Therefore, this gene product is a presynaptic plasma membrane protein involved in the regulation of neurotransmitter release. Two alternative transcript variants encoding different protein isoforms have been described for this gene.			
						DLPD06320 *			DLPD06320				
						DLPD07001*			DLPD07001				
						DLPD09667*			DLPD09667				
						DLPD14047 (Arrestin-C)*			DLPD14047 (Arrestin-C)				
2016	Babbucci et al.	QTL mapping and GWAS	Seabass (*Dicentrarchus labrax)*	Mandibular prognathism	Visual inspection by two operators independently	L_39743	Hypothesis: might contribute to lower jaw deformity altering patterns of gene expression rather than directly affecting the	**ChrX** (non coding region)Nearest genotyped SNP marker upstream: (L_39728:ChrX:3,348,951) downsteam L_39753, ChrX: 3,540,808)	N.A- cluster of conserved non-coding elements ***PHLDA1*** (closest coding gene)	***PHLDA1***: This gene encodes an evolutionarily conserved proline-histidine rich nuclear protein. The encoded protein may play an important role in the antiapoptotic effects of insulin-like growth factor-1	12q21.2	*MYO1H* (12q24.11) assoc. MP, ↑risk MP and horizontal and vertical maxillo-mandibular discrepancies	Tassopoulou-Fishell et al. (2012). Sun et al. (2018). Cruz et al. (2017)

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							sequence of a protein coding gene. CNE distant enhancers in craniofactal developement						
						L_12903	Significantly downregulated in deformed larvae. Association to mandibular prognathism	Chr17 (coding region)	*SOBP* (habouring gene) *ROCK2* (nearest gene)	***SOBP:*** The protein encoded by this gene is a nuclear zinc finger protein that is involved in development of the cochlea. Defects in this gene have also been linked to intellectual disability. ***ROCK2***: The protein encoded by this gene is a serine/threonine kinase that regulates cytokinesis, smooth muscle contraction, the formation of actin stress fibers and focal adhesions, and the activation of the c-fos serum response element. This protein, which is an isozyme of ROCK1 is a target for the small GTPase Rho.	6q21	*TCF21* (6q23.2) assoc. MP*IGF2R* (6q25.3) rs6920141 ↓Go-Pg and Ptm-A measures) rs2277071 ↓maxillary length (Ptm '-A')	Saito et al. (2017). Marañón-Vásquez et al. (2020)
2018	Sun et al.	Knockdown study of Zebrafish MYO1H Orthologs	Zebrafish (*Danio rerio*)	Mandibular prognathism	Alcian blue staining to visualize the cartilage aspect. measurements on lower jaws in	Paralogous gene: *myo1ha* and *myo1hb*	showed underdeveloped jaw regions and at 5 dpf had a "mandibular jaw downward rotation" (gaped mouth) phenotype	Chr 5(zebrafish)	*myo1ha-myo1hb*	***MYO1H:*** Predicted to enable actin filament binding activity and microfilament motor activity. Predicted to be involved in actin filament organization and vesicle transport along actin filament. Predicted to be part of myosin complex. Predicted to be active in several cellular components, including	12q24.11	*MYO1H* (12q24.11) assoc. MP, ↑risk MP and horizontal and vertical maxillo-mandibular discrepancies	Tassopoulou-Fishell et al. (2012). Sun et al. (2018). Cruz et al. (2017)

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					3 dimensions: the mouth-opening distance), mandible length, and mandible width					actin cytoskeleton; microvillus; and vesicle.			
2013	Rodrigues et al.	Case control study	Zamorano-Leonés donkeys (*Equus africanus asinus*)	Mandibular prognathism	Clinical, oral and dental examinations	*MATN1* (g503G > A)	protector effect in the risk to develop prognathism in donkeys	Region: ENSECA-G000000087-47 (donkey)	*MATN1*	***MATN1:*** This gene encodes a member of von Willebrand factor A domain containing protein family. This family of proteins are thought to be involved in the formation of filamentous networks in the extracellular matrices of various tissues. Mutations of this gene have been associated with variety of inherited chondrodysplasias.	1p36	*MATN1(rs1065755)* ↑*risk MP*	Jang et al. (2010)
Maxillary deficiency													
2009	Hünemeier et al.	Genetic association study	Purebred dogs (Canis familiaris)	Brachycephaly	Classified independently by two trained veterinarians according to head shape	*TCOF1* c.396 C > T (p.Pro117Ser)	C/Pro is found inhomozygosity in several brachycephalic breedsThe T/Ser frequencies obtained were not statistically associated to	CFA4 at 61.902–61.94-2 Mb)	*TCOF1*	***TCOF1:*** This gene encodes a nucleolar protein with a LIS1 homology domain. The protein is involved in ribosomal DNA gene transcription through its interaction with upstream binding factor (UBF). Mutations in this gene have been associated with Treacher Collins	5q32-q33.1	*5p13.1-p12*GHR (rs6184) ↑risk MP.*GHR* (rs297-3015) Increased measures for mandibular sagittal	Sun et al. (2018). Marañón-Vásquez et al. (2020)

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					as dolicho-cephali-c, meso-cephalic or brachy-cephalic		the brachy-cephalic phenotype			syndrome, a disorder which includes abnormal craniofacial development. Multiple transcript variants encoding different isoforms have been found for this gene.		lengths (Co-Gn)	
2010	Bannasch et al.	GWAS (Across Breed Mapping)	Purebred dogs (Canis familiaris)	Brachycephaly	By breeds consid-ered brachy-cephal-ic: Pugs, Boxer and Pe-kinges	*THBS2*, *SMOC2*	association with canine brachy-cephaly	Primary_assembly-Labrador retrieve-r1:56,584,696-56,612,929 reverse strand-Boxer 1:57,192,665-57,221,428 reverse strandPrimar-y_assembly-Labrador retriever 1:56,009,366-56,168,233 forward strand-Boxe-r1:56,617,399-56,777,591 forward strand	*THBS2SMO-C2*	***THBS 2:*** The protein encoded by this gene belongs to the thrombospondin family. It is a disulfide-linked homotrimeric glycoprotein that mediates cell-to-cell and cell to-matrix interactions. This protein has been shown to function as a potent inhibitor of tumor growth and angiogenesis. Studies of the mouse counterpart suggest that this protein may modulate the cell surface properties of mesenchymal cells and be involved in cell adhesion and migration. ***SMOC2***: This gene encodes a member of the SPARC family (secreted protein acidic and rich in cysteine/ osteonectin/BM-40), which are highly expressed during embryogenesis and wound healing. The gene product is a matricellular protein which promotes matrix assembly and can	6q27	*TCF21* (6q23.2) assoc. MP *IGF2R* (6q25.3) rs6920141 ↓Go-Pg and Ptm-A measures) rs2277071 ↓maxillary length (Ptm '-A')	Saito et al. (2017). Marañón-Vásquez et al. (2020)

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										stimulate endothelial cell proliferation and migration, as well as angiogenic activity. Associated with pulmonary function, this secretory gene product contains a Kazal domain, two thymoglobulin type-1 domains, and two EF hand calcium-bindingdomains. The encoded protein may serve as a target for controlling angiogenesis in tumor growth and myocardial ischemia. Alternative splicing results in multiple transcript variants.			
2011	Quilez et al.	GWAS	Purebred dogs (Canis familiaris)	Brachycephaly	By breed: Boxers considerated as brachycephalic	ROH from CFA 26ROH from CFA 1	Selective sweep regions on CFAare candidate for strong artificial selection in the Boxerfor a trait of interest, possibly brachycephaly	– Boxer: 26:8,548,679-9,227,043 bp	ROH from CFA *26*: *HIP1R*, *Q64-F94_CANFA*, *B0FLR1_CANFA*, *AT2A2_CANFA*, *POLE*, *NP_0010-03069.1*-ROH from CFA 1: *THBS2*, *SMOC2*	***HIP1R***: Enables several functions, including phosphatidylinositol phosphate binding activity; phosphatidylinositol-3,4-bisphosphate binding activity; and protein homodimerization activity. Involved in several processes, including positive regulation of signal transduction; protein stabilization; and regulation of organelle organization. Located in clathrin-coated vesicle; cytosol; and ruffle membrane. ***P2RX4***: he product of this gene belongs to the family of purinoceptors for ATP. This receptor functions as	12q24.31	*MYO1H* (12q24.11) assoc. MP, ↑risk MP and horizontal and vertical maxillomandibular discrepancies	Tassopoulou-Fishell et al. (2012). Sun et al. (2018). Cruz et al. (2017)

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										a ligand-gated ion channel with high calcium permeability. The main pharmacological distinction between the members of the purinoceptor family is the relative sensitivity to the antagonists suramin and PPADS. The product of this gene has the lowest sensitivity for these antagonists. Multiple alternatively spliced transcript variants, some protein-coding and some not protein-coding, have been found for this gene. ***P2RX7***: The product of this gene belongs to the family of purinoceptors for ATP. This receptor functions as a ligand-gated ion channel and is responsible for ATP-dependent lysis of macrophages through the formation of membrane pores permeable to large molecules. Activation of this nuclear receptor by ATP in the cytoplasm may be a mechanism by which cellular activity can be coupled to changes in gene expression. Multiple alternatively spliced variants have been identified, most of which fit nonsense-mediated decay (NMD) criteria. ***ATP2A2***: This gene encodes one of the SERCA Ca (2 +)-ATPases, which are intracellular pumps located in the			

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										sarcoplasmic or endoplasmic reticula of the skeletal muscle. This enzyme catalyzes the hydrolysis of ATP coupled with the translocation of calcium from the cytosol into the sarcoplasmic reticulum lumen, and is involved in regulation of the contraction/relaxation cycle. Mutations in this gene cause Darier-White disease, also known as keratosis follicularis, an autosomal dominant skin disorder characterized by loss of adhesion between epidermal cells and abnormal keratinization. Other types of mutations in this gene have been associated with various forms of muscular dystrophies. Alternative splicing results in multiple transcript variants encoding different isoforms. ***POLE***: This gene encodes the catalytic subunit of DNA polymerase epsilon. The enzyme is involved in DNA repair and chromosomal DNA replication. Mutations in this gene have been associated with colorectal cancer 12 and facial dysmorphism, immunodeficiency, livedo, and short			

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										stature. ***MYL2***: This gene encodes a major sarcomeric protein in mammalian striated muscle. The encoded protein plays a role in embryonic heart muscle structure and function, while phosphorylation of the encoded protein is involved in cardiac myosin cycling kinetics, torsion and function in adults. Mutations in this gene are associated with hypertrophic cardiomyopathy 10 and infant-onset myopathy.			
2012	Schoenebeck et al.	GWAS	Purebred dogs (Canis familiaris)	Brachycephaly	Geometric morphometrics (Procrustes fit, PCA, and residuals)	*BMP3*^F452L (missense mutation)	association with canine brachycephaly	Primary_assembly-Labrador retriever-r32:5,237,314-5,263,865 forward strand-Boxer-r32:36,648,399-36,674,930 reverse strand	*BMP3*	***BMP3:*** This gene encodes secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins. Ligands of this family bind various TGF-beta receptors leading to recruitment and activation of SMAD family transcription factors that regulate gene expression. The encoded preproprotein is proteolytically processed to generate each subunit of the disulfide-linked homodimer. This protein suppresses osteoblast differentiation, and negatively regulates bone density, by modulating TGF-beta receptor availability to other ligands.	4q21.21	*BMP3* (rs1495643) Increased asymmetric phenotypic variations in the dental arches with more copies of the rare allele	Weaver et al. (2017)

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2017	Marchant et al.	GWAS (Quantitative Trait Locus)	Purebred and mixed pedigree dogs (Canis familiaris)	Brachycephaly	Geometric morphometrics (Procrustes fit, PCA, and residuals)	*SMOC2*	*SMOC2* dysfunction is responsible for canine brachycephaly	Primary_assembly-Labrador retriever 1:56,009,366-56,168,233 forward strand-Boxer-r1:56,617,399-56,777,591 forward strand	*SMOC2*	***SMOC2***: This gene encodes a member of the SPARC family (secreted protein acidic and rich in cysteine/osteonectin/BM-40), which are highly expressed during embryogenesis and wound healing. The gene product is a matricellular protein which promotes matrix assembly and can stimulate endothelial cell proliferation and migration, as well as angiogenic activity. Associated with pulmonary function, this secretory gene product contains a Kazal domain, two thymoglobulin type-1 domains, and two EF hand calcium-binding domains. The encoded protein may serve as a target for controlling angiogenesis in tumor growth and myocardial ischemia. Alternative splicing results in multiple transcript variants.	6q27	*TCF21* (6q23.2) assoc. MP*IGF2R* (6q25.3) rs6920141 ↓Go-Pg and Ptm-A measures) rs2277071 ↓maxillary length (Ptm′-A′)	Saito et al. (2017). Marañón-Vásquez et al. (2020)
2020	Sophocleous et al.	Genetic association study	Purebred and mixed pedigree dogs (*Canis familiaris*)	Brachycephaly	Pedigree dogs: classified as brachycephalic as reported in other-	*P2RX7* (rs23314-713) (p.Phe103-Leu)	association with brachycephalic breeds	Primary_assembly-Labrador retriever-r26:8224106 forward strand	*P2RX7*	***P2RX7:*** The product of this gene belongs to the family of purinoceptors for ATP. This receptor functions as a ligand-gated ion channel and is responsible for ATP-dependent lysis of macrophages through the formation of membrane pores	12q24.31	*MYO1H* (12q24.11) assoc. MP, ↑risk MP and horizontal and vertical maxillo-mandibular	Tassopoulou-Fishell et al. (2012). Sun et al. (2018). Cruz et al. (2017)

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					studies-Mixed-pedigree dogs: classified as brachycephalic based on known-nancestry and/or display of brachycephalic characteristics					permeable to large molecules.		discrepancies	
2012	Sakata-Goto et al.	Knockout study of inhibitors of the differentiation 2 (Id2)	Mice (*Mus musculus*)	Maxillary hypoplasia	Cephalometrycal analysis: Euclidean Distance Matrix Analysis	Id2	narrower hypertrophic zone andan inhibited proliferative zone in presphenoid synchondrosis (PSS) and spheno-occipital synchondrosis(SOS) with maxillary hypoplasia were identified in the Id2 mutant mice during the	12q	*Id2*	***ID2:*** The protein encoded by this gene belongs to the inhibitor of DNA binding family, members of which are transcriptiona regulators that contain a helix-loop-helix (HLH) domain but not a basic domain. Members of the inhibitor of DNA binding family inhibit the functions of basic helix-loop-helix transcription factors in a dominant-negative manner by suppressing their heterodimerization partners through the HLH domains. This	2p25.1	*SATB2* (2q33.1) rs7593422 assoc. unilateral posterior crossbites	Weaver et al. (2017)

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							postnatal growth period			protein may play a role in negatively regulating cell differentiation. A pseudogene of this gene is located on chromosome 3.			
2016	Bertolini et al.	Selective sweep analysis	Cats (*Felis silvestris catus*)	Brachycephaly	By breeds brachycephalic: Persian, non-Persian and Persian derived breeds	*CHL1*, *CNTN6*	Higher homozygosity in Persiancats and highest divergence from the non-Persian breeds	A2	*CHL1CNTN6*	***CHL1***: The protein encoded by this gene is a member of the L1 gene family of neural cell adhesion molecules. It is a neuralrecognition molecule that may be involved in signal transduction pathways. The deletion of one copy of this gene may be responsible for mental defects in patients with 3p-syndrome. This protein may also play a role in the growth of certain cancers. Alternate splicing results in both coding and noncoding variants. ***CNTN6***: The protein encoded by this gene is a member of the immunoglobulin superfamily. It is a glycosylphosphatidylinositol (GPI)-anchored neuronal membrane protein that functions as a cell adhesion molecule. It may play a role in the formation of axon connections in the developing nervous system. Alternative splicingresults in multiple transcript variants.	3p26.13p26.3	*RASA2* (3q23) assoc. MPFGF12 (3q28) r-s7917605-1 ↑risk MP	Saito et al. (2017). Xiong et al. (2017)

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2020	Palmas et al.	Genetic association study	Mediterranean trout (*Salmo trutta L*)	Pug-headedness	Modified version of the jaw index	Mitochondrial (D-loop) LDH-C1* gene and 11 microsatellites	No association with genetic basis was found	Mitochondrial DNA		Coding the LDH enzyme			

Abbreviations: MP, mandibular prognathism; N.A, not annotated; ROH, region of homocygocity.

[a]According to RefSeq and each study report.

[b]Closest genes identified in genetic association studies; * fold change ratio lower that 0.118.

maxillary deficiency (MD) phenotypes were described in the studies using animal models as follows: fishes, *Dicentrarchus labrax* (Babbucci et al., 2016b; Ferraresso et al., 2010), *Danio rerio* (Sun et al., 2018), *Salmo trutta L* (Palmas et al., 2020), dogs (*Canis familiaris*) (Bannasch et al., 2010; Hünemeier et al., 2009; Marchant et al., 2017; Quilez et al., 2011; Schoenebeck et al., 2012; Sophocleous et al., 2020), cats (*Felis silvestris catus*) (Bertolini et al., 2016), mice (*Mus musculus*) (Sakata-Goto et al., 2012), and donkeys (*Equus africanus asinus*) (Rodrigues et al., 2013). *Danio rerio* (Sun et al., 2018), *Dicentrarchus labrax* (Babbucci et al., 2016b; Ferraresso et al., 2010), and *Equus africanus asinus* (Rodrigues et al., 2013) were used to model the MP phenotype. The MD phenotype was described as brachycephaly in *Felis silvestris catus* (Bertolini et al., 2016) and *Canis familiaris* (Bannasch et al., 2010; Hünemeier et al., 2009; Marchant et al., 2017; Quilez et al., 2011; Schoenebeck et al., 2012; Sophocleous et al., 2020), pug-headedness in *Salmo trutta L* (Palmas et al., 2020), and maxillary deficiency in *Mus musculus* (Sakata-Goto et al., 2012).

3.2 | Findings associated with MP phenotype

The genetic variant matrilin 1 (*MATN1*) (g503G > A) (Rodrigues et al., 2013) showed a preventive effect on MP expression in a case-control study of *Equus africanus asinus* (Table 1), indicating one of the highest levels of homology (Figure 2). A non-synonymous common variant of myosin IH (*MYO1H*), rs3825393, *C > T*, *p. Pro1001Leu*, was significantly associated with MP in a *Danio rerio* model (Sun et al., 2018). In this model, the paralogous genes *myo1ha* and *myo1hb* were knocked down, resulting in an underdeveloped jaw and gaped-mouth phenotype (Table 1). An mRNA expression study using the *Dicentrarchus labrax* model showed that 242 transcripts were differentially expressed in prognathous individuals compared with controls. Table 1 displays the DLPD08826 transcripts corresponding to the calcitonin gene-related peptide (*CALCA*). Its importance was highlighted by the authors, and the other six transcripts that had a fold-change ratio lower than 0.118 (*q* value = 3.275) were used to assess the variability between the experimental and control probes. Finally, in a case-control allelic association analysis of the same model, an association between the MP phenotype and two regions related to the NCC was found, harboring a cluster of conserved noncoding elements and the coding region of *SOBP* (sine oculis-binding protein homolog) (Babbucci et al., 2016b).

3.3 | Findings associated with MD phenotype

In a knockout model of inhibitors of the differentiation 2 gene (*Id2*) in *Mus musculus*, the maxillary hypoplasia phenotype was observed as a result of abnormal endochondral ossification in the cranial base synchondroses during the postnatal growth period (Table 1).

ID2 showed one of the highest homology levels (Figure 2). The pug-head phenotype, characterized by deformation of the

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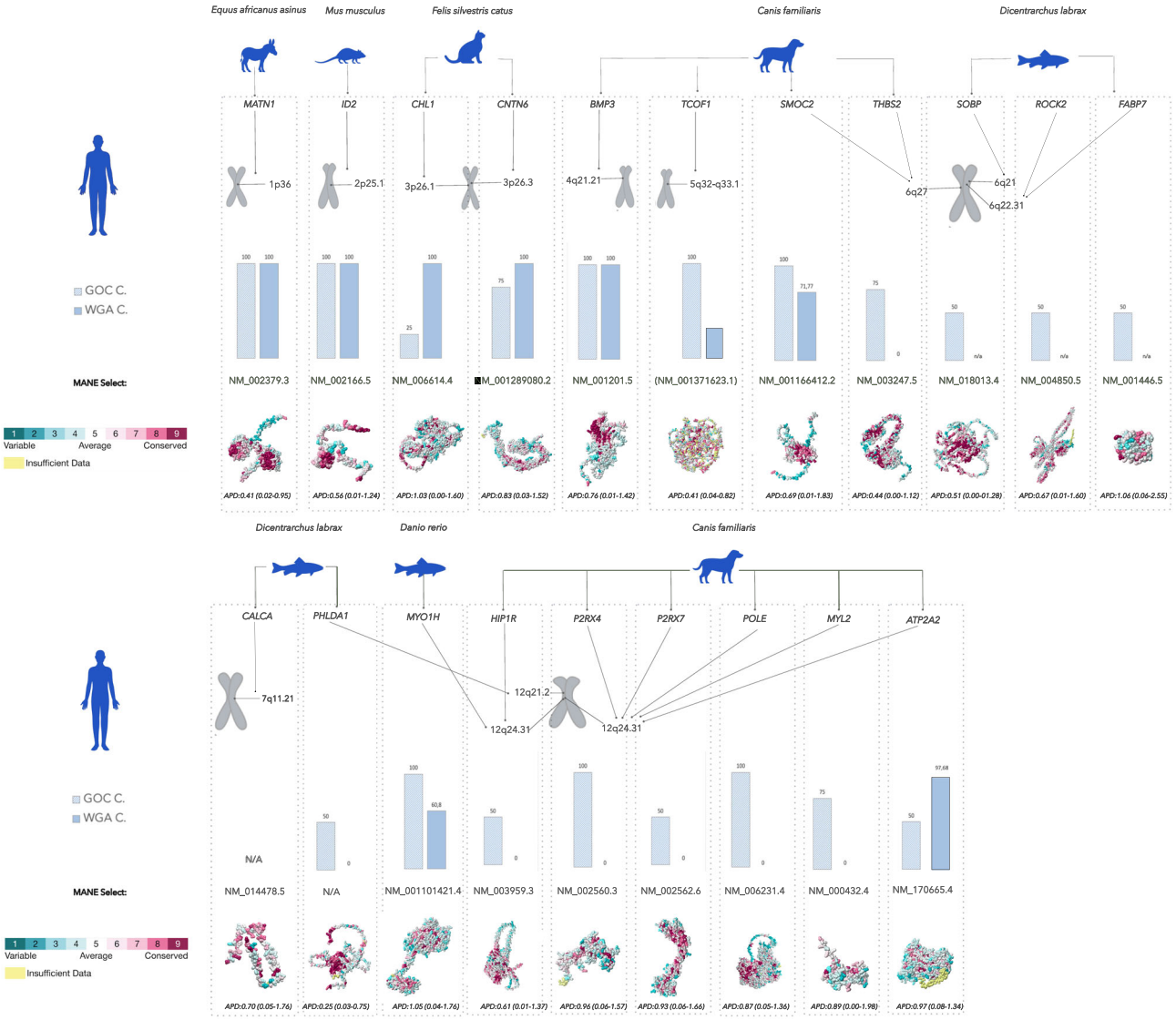

FIGURE 2 Human and animal homologous loci and variants identified. GOC and WGA scores express human and animal gene conservation. The APD score expresses interspecies evolutionary diversity. Detailed information on each protein result can be consulted in Supporting Information 3.

maxilla, premaxilla, infraorbital bones, and ethmoid region, was studied in *Salmo trutta L* (Palmas et al., 2020). No association with the genetic basis was found, and environmental factors during larval development were identified as the most likely factors triggering this malformation. In two genome-wide association studies (GWAS) on purebred *Canis familiaris* (Table 1), brachycephaly, a phenotype characterized by severe shortening of the muzzle, was associated with *THBS2* and *secreted modular calcium-binding protein 2* (*SMOC2*) (Bannasch et al., 2010), and a missense mutation (p. Phe452Leu) (Schoenebeck et al., 2012) in *BMP3*, a highly homologous gene (Figure 2). In a genetic association study, *TCOF1* c.396 C > T (p. Pro117Ser) was found to be associated with brachycephalic breeds (Hünemeier et al., 2009). Two other GWAS on purebred and mixed pedigree *Canis familiaris* found a similar association with *SMOC2* (Marchant et al., 2017) and *P2RX7* (rs23314713), including a variant causing a phenylalanine to leucine change (p. Phe103Leu) (Table 1). Additionally, a GWAS on purebred pedigrees of *Canis familiaris* identified a region of homozygosity (ROH) harboring *HIP1R*, *P2RX4*, *P2RX7*, *ATP2A2*, *POLE*, *and MYL2* as candidates for strong artificial selection for brachycephaly in the boxer pedigree (Quilez et al., 2011) (Table 1). A selective sweep analysis of *Felis silvestris catus* (Bertolini et al., 2016) comparing Persian, non-Persian, and Persian-derived breeds indicated that the region containing the neuronal genes *CHL1*, *CNTN6*, *and LRRN1 had* the highest homozygosity in the Persian breed, which was the brachycephalic phenotype, and had the highest divergence from the non-Persian breeds (Table 1).

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3.4 | Functional interactions

The human homologous locus for each animal variant described above is shown in Figure 2. Among all identified variants, *ID2*, *BMP3*, *and MATN1* showed the highest homology scores (100/100 GOC and WGA scores) between the animal and human genomes. In terms of protein conservation, the average pairwise distance (APD, which represents the average number of replacements between any two sequences in the alignment) oscillated between 0.25 and 1.06. A detailed description of each protein analysis is provided in *Supporting Information* 3. Gene enrichment analysis results are displayed in Table 2, where overexpression of the biological processes surpassing the threshold for FDR ($p > 0.05$) is shown.

A visual representation of the genetic interactions, pathways, co-expression, and shared protein domains of all identified genes, along with software-predicted genes (Warde-Farley et al., 2010), is shown in Figure 3. The identified genes exhibited genetic interactions between *ID2* and *SMOC2*, *THBS2*, and *TCOF1*; *BMP3* and *ROCK2*; and *CNTN6* and *MYO1H*, *SMOC2*, *SOBP*, and *PHLDA1*. Co-expression was observed between *MYL2* and *ATP2A2*, *MYL2* and *POLE*, and *THBS2*, *FABP7*, and *PHLDA1*. *CNTN6* and *CHL1* shared pathways and protein domains, whereas *P2RX7* and *P2RX4* shared protein domains.

3.5 | Discussion

This scoping review aimed to identify available evidence from animal studies that examined the genetic variants underlying maxillomandibular discrepancies resulting in a SCIII malocclusion phenotype.

The MD phenotype, which was associated with *SMOC2*, *TCOF1*, *THBS2*, and *ID2* in dogs and cats, displayed genetic interactions, as depicted in Figure 3. Based on the study by Sakata-Goto et al. (Sakata-Goto et al., 2012). *ID2* (GOC and WGA:100/100), coding for DNA-binding protein inhibitor ID-2 (APD:0.56), interacts with the BMP-Smad signaling pathway. It acts downstream of bone morphogenetic protein (*BMP*) signaling, regulating cartilage formation during postnatal growth and development by enhancing *BMP* signaling and inhibiting Smad7 expression. These are expressed in the proliferating and differentiating chondrocytes of the presphenoid synchondrosis (PSS) and spheno-occipital synchondrosis (SOS). Similarly, *SMOC2* (GOC:100/100; WGA:71.77/100), coding for SPARC-related modular calcium-binding protein 2 (APD:0.69) is related to *BMP* signaling because the matricellular protein SMOC inhibits *BMP* signaling downstream of its receptor (Thomas et al., 2017). *SMOC2*, which was associated with brachycephalic breeds (Bannasch et al., 2010; Marchant et al., 2017; Quilez et al., 2011), has a genetic interaction (Figure 3) with *CNTN6*, which is adjacent to *CHL1* in both the feline and human genomes. These genes were identified in a region of high homozygosity in Persian cats, characterized by an extreme brachycephalic phenotype. Consistently, our enrichment analysis (Table 2) showed *that ID2*, *CNTN6*, and *CHL1* are involved in anatomical structure development and morphogenesis.

BMP3 (GOC and WGA:100/100), coding for bone morphogenetic protein 3 (APD:0.76), a member of the *BMP* family, was associated with the brachycephalic phenotype in canines (Schoenebeck et al., 2012). In addition, our enrichment analysis revealed the involvement of anatomical structural development (Table 2). Bone morphogenetic proteins (BMPs) may play critical roles in mediating chondrocyte proliferation and differentiation, possibly regulating chondrocyte-to-osteoblast transition in synchondroses, as they are expressed in the presumptive central hypertrophic zone of the SOS (Kettunen et al., 2006; Schoenebeck et al., 2012). To test this hypothesis regarding the role of Bmp3 in cranioskeletal development, Schoenebeck et al. used a knockdown zebrafish model and found severe deficiencies in jaw development in knockdown individuals, indicating that Bmp3 is required for zebrafish craniofacial development and that its role in craniofacial development has been prevalent since ancient times (Schoenebeck et al., 2012). Signaling proteins from the BMP subfamily (BMPs) have been reported to influence the development of dentary bone, as ectopic expression of Bmp on the oral side of the mandibular process results in the formation of a mirror-image dentary bone (Fabik et al., 2021). BMPs comprise approximately 20 structurally related members of the transforming growth factor β (TGF-β) superfamily, which are crucial for growth and differentiation events that determine body structure (Wu & Hill, 2009). TGF-β is regulated by the fibrillin protein family, and is primarily associated with the modulation of bone marrow stem cells and bone growth during development. *FBN* genes encode this protein family. A recent meta-analysis showed an overall association between fibrillin-3 precursor gene (*FBN3*–rs7351083) and SCIII malocclusion (Dehesa-Santos et al., 2021).

Regarding the MP phenotype, *MATN1* (GOC and WGA:100/100) coding for cartilage matrix protein (APD:0.41), showed a decreased risk of presenting the MP phenotype in the presence of the g503G > A variant in the animal model (Rodrigues et al., 2013). This result agreed with the preventive effect described in a human study on the presence of the AA genotype of rs20566 (Jang et al., 2010), and was in line with the association of rs1149042 with mandibular retrognathism (Balkhande et al., 2018). In contrast, other human studies have shown an increased risk of mandibular prognathism in the presence of rs1065755 and an association of *MATN1* with SCIII malocclusion in Korean (Jang et al., 2010), Indian (Kulkarni et al., 2021), and Deutero-Malay (Laviana et al., 2021) populations. Similar results were observed for *MYO1H* (GOC:100/100; WGA:60.8/100) coding for unconventional myosin-Ih APD:1.05), in which an increased risk of presenting with MP in the presence of rs3825393, a non-synonymous common variant, C > T, p. Pro1001Leu, was reported by Sun et al. in a knockdown zebrafish model (Sun et al., 2018). Consistent with human studies, *MYO1H* polymorphism rs10850110 has also been associated with MP (Tassopoulou-Fishell et al., 2012) and vertical and horizontal maxillomandibular discrepancies in the Brazilian population (Cruz et al., 2017). Conversely, the same polymorphisms, rs10850110 (Cunha et al., 2019) and rs3825393 (Arun et al., 2016), were also

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TABLE 2 Genetic enrichment analysis. GO biological process complete, describes the type of biological information being analyzed; REFLIST, displays the number of genes in the reference list that are associated with the specific annotation data category; expected value, represents the number of expected genes based on the reference list; Fold Enrichment express the overrepresentation of the genes observed in the uploaded list over the expected; Overrepresentation is indicated with a plus sign; raw *p* value and FDR determined by Fisher's exact test and the Benjamini-Hochberg procedure. To see the genes uploaded distribution per biological category, please refer to the PANTHER database.

GO biological process complete	*Homo sapiens* - REFLIST	Genes uploaded	Expected value	Fold enrichment	Over-representation	Raw *p* value	False discovery rate (FDR)
Positive regulation of interleukin-1 alpha production	7	*CALCA*; *P2RX7*	0.01	>100	+	3.54E-05	4.23E-02
Regulation of multicellular organismal process	2983	*ATP2A2*; *CALCA*; *ID2*; *SMOC2*; *ROCK2*; *THBS2*; *MYL2*; *MATN1*; *P2RX7*; *P2RX4*; *HIP1R*	3.04	3.62	+	5.12E-05	5.30E-02
Regulation of interleukin-1 alpha production	9	*CALCA*; *P2RX7*	0.01	>100	+	5.41E-05	4.94E-02
Regulation of calcium ion transport into cytosol	20	*CALCA*; *P2RX7*; *P2RX4*	0.02	>100	+	1.59E-06	8.25E-03
Response to ischemia	57	*ROCK2*; *P2RX7*; *P2RX4*	0.06	51.6	+	3.01E-05	3.89E-02
Regulation of muscle contraction	169	*ATP2A2*; *CALCA*; *MYL2*; *P2RX4*	0.17	23.21	+	2.57E-05	3.99E-02
Regulation of muscle system process	235	*ATP2A2*; *CALCA*; *ROCK2*; *MYL2*; *P2RX4*	0.24	20.86	+	3.59E-06	1.39E-02
Regulation of system process	569	*ATP2A2*; *CALCA*; *ROCK2*; *MYL2*; *P2RX4*; *HIP1R*	0.58	10.34	+	1.74E-05	3.01E-02
Regulation of heart contraction	203	*ATP2A2*; *CALCA*; *MYL2*; *P2RX4*	0.21	19.32	+	5.17E-05	5.02E-02
Muscle system process	282	*ATP2A2*; *CALCA*; *ROCK2*; *MYL2*; *P2RX4*; *HIP1R*	0.29	17.38	+	8.57E-06	1.66E-02
Multicellular organismal process	6713	*BMP3*; *ATP2A2*; *CALCA*; *ID2*; *CHL1*; *POLE*; *TCOF1*; *ROCK2*; *MYL2*; *CNTN6*; *MATN1*; *P2RX7*; *CHL1*; *FABP7*; *SOBP*; *P2RX4*; *HIP1R*	6.85	2.48	+	7.42E-06	1.65E-02
Blood circulation	403	*CALCA*; *ID2*; *ROCK2*; *MYL2*; *P2RX4*	0.41	12.16	+	4.65E-05	5.15E-02
Anatomical structure morphogenesis	2244	*ID2*; *CHL1*; *TCOF1*; *ROCK2*; *MYL2*; *CNTN6*; *MATN1*; *P2RX7*; *CHL1*; *SOBP*	2.29	4.37	+	2.71E-05	3.82E-02
Anatomical structure development	5201	*BMP3*; *ATP2A2*; *CALCA*; *ID2*; *CHL1*; *POLE*; *TCOF1*; *ROCK2*; *MYL2*; *CNTN6*; *MATN1*; *P2RX7*; *CHL1*; *FABP7*; *SOBP*; *HIP1R*	5.3	3.02	+	1.47E-06	1.14E-02
Developmental process	5702	*BMP3*; *ATP2A2*; *CALCA*; *ID2*; *CHL1*; *POLE*; *TCOF1*; *ROCK2*; *MYL2*; *CNTN6*; *MATN1*; *P2RX7*; *CHL1*; *FABP7*; *SOBP*; *HIP1R*	5.82	2.75	+	5.48E-06	1.70E-02

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TABLE 2 (Continued)

GO biological process complete	*Homo sapiens* - REFLIST	Genes uploaded	Expected value	Fold enrichment	Over-representation	Raw *p* value	False discovery rate (FDR)
System development	3553	*BMP3; CALCA; ID2; CHL1; TCOF1; ROCK2; MYL2; CNTN6; MATN1; P2RX7; CHL1; FABP7; HIP1R*	3.62	3.59	+	6.19E-06	1.60E-02
Multicellular organism development	3966	*BMP3; CALCA; ID2; CHL1; POLE; TCOF1; ROCK2; MYL2; CNTN6; MATN1; P2RX7; CHL1; FABP7; SOBP; HIP1R*	4.05	3.71	+	3.14E-07	4.87E-03

associated with a skeletal Class II phenotype. This evidence suggests that these two genes play key regulatory roles in the sagittal dimension of craniofacial growth (Gershater et al., 2021), and not exclusively in SCIII malocclusion expression.

The complexity of the manifestations of the genes discussed herein is also reflected in their association with other conditions associated with craniofacial or skeletal alterations. *SMOC2* is a candidate gene for craniosynostosis and midface hypoplasia in humans (Marchant et al., 2017). Several studies have established a relationship between premature ossification of the intersphenoid synchondrosis (ISS), SOS, and various forms of craniofacial deformities, which often present craniosynostosis (Hallett et al., 2022). The role of *TCOF1* in the development of Treacher Collins Syndrome has been extensively studied for its participation in regulatory processes related to the facial skeleton and nervous system (Grzanka & Piekiełko-Witkowska, 2021). Consistently, in mouse embryos, the expression of *TCOF1* peaks at E8.5-9.5, and is particularly pronounced in the first pharyngeal arch (which develops into the mandible and maxilla), as well as in the neuroepithelium and developing brain (Grzanka & Piekiełko-Witkowska, 2021).

In this same line, the important roles of TGFβ and BMPs during embryogenesis give rise to a diverse spectrum of skeletal and craniofacial dysmorphologies through mutations in pathway-related genes (Brito et al., 2009; Oka et al., 2007; Wu et al., 2016). BMPs', particularly BMP2', BMP4', and BMP7', are prominently expressed in early craniofacial development (Francis-West et al., 1998), collaborating with FGF, HH, and WNT pathways to regulate key transcription factors crucial for craniofacial skeletogenesis (Karsenty, 2003). Likewise, BMP/GDF (growth differentiation factor) pathway's dysregulation contributes to distinct conditions (Katagiri & Watabe, 2016): BMP/GDF overactivity, stemming from noggin protein loss-of-function or GDF-5 gain-of-function mutations, leads to multiple synostoses syndrome characterized by multiple joints fusion (Dawson et al., 2006; Gong et al., 1999); conversely, BMP/GDF inhibition due to GDF-5 or ALK-6 receptor loss-of-function mutations is linked to brachydactylies (Lehmann et al., 2006; Polinkovsky et al., 1997; Thomas et al., 2017).

Interspecies comparisons have significantly improved in recent years because of the better quality of genome assemblies, orthology mapping between organisms, and increasingly available tissue expression data (Doncheva et al., 2021). However, the application of animal models to humans and the inference of their conclusions has certain limitations.

Comparing human and animal models is still defiant considering that functions, pathways, and protein interactions are still behind the quality of human data (Doncheva et al., 2021). Notably, in this review, the decision to exclude animal models analyzing syndromic conditions or other genetic diseases with SCIII as a secondary trait was made. Although this may produce a reduction in the possibly implicated pathways identified, an analysis of the conserved pathways affecting the SCIII phenotype related to syndromic conditions was attempted.

This review aimed to contribute to the craniofacial research field by gathering evidence from studies on animal models to identify possible susceptible regions in the human genome and postulate

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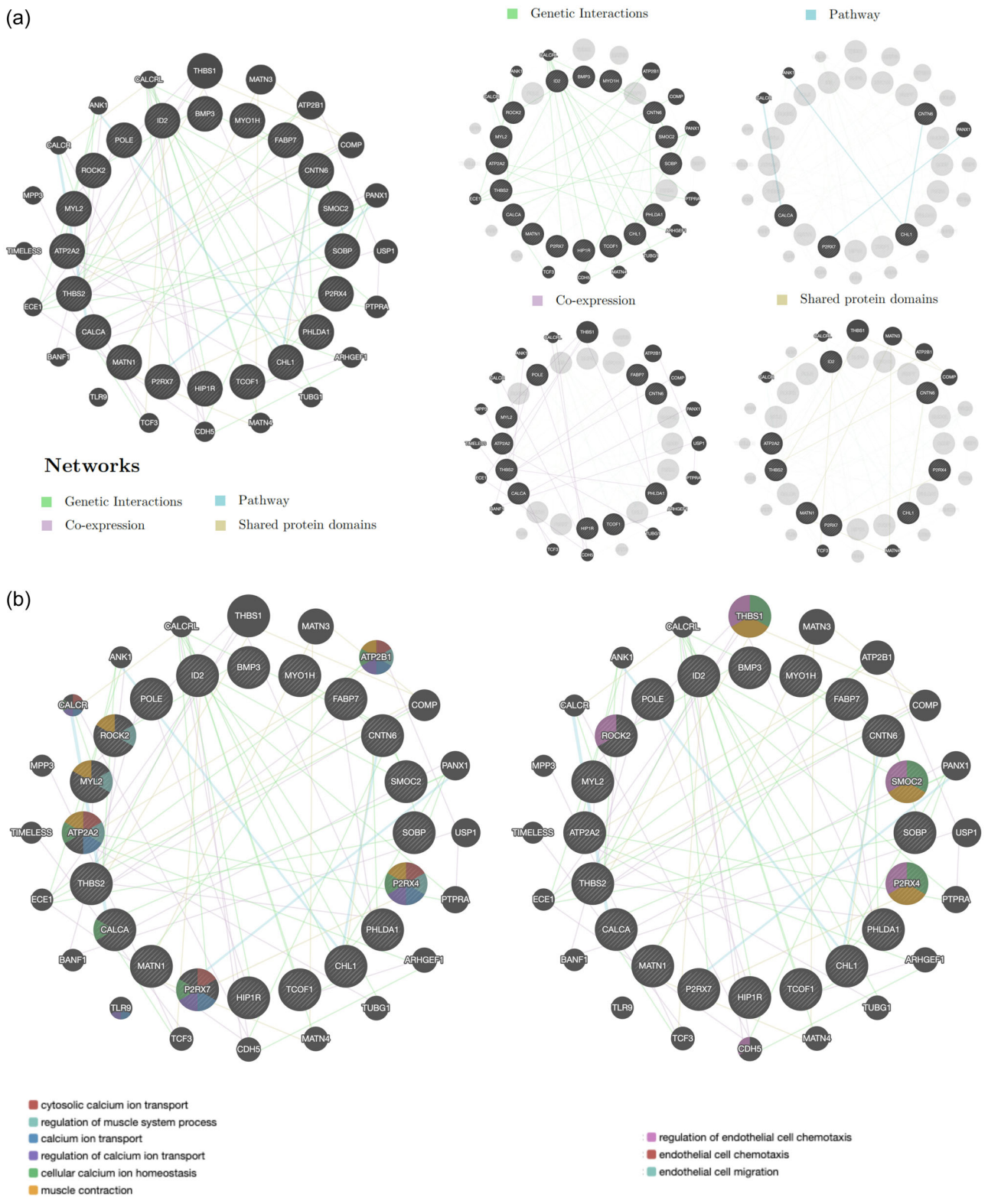

FIGURE 3 Displays 20 identified genes (indicated with stripes) and 20 related genes. (a) Genetic interactions, pathways, co-expression, and shared protein domains are shown. (b) Common functions are shown. Gene networks generated through GeneMANIA.

pathways that are likely responsible for the expression of the SCIII malocclusion phenotype. In conclusion, twenty genetic variants were identified as isolated traits in animal models that studied the SCIII malocclusion phenotype: *MATN1*, *ID2*, *CHL1*, *CNTN6*, *BMP3*, *TCOF1*, *SMOC2*, *THBS2*, *SOBP*, *ROCK2*, *FABP7*, *CALCA*, *PHLDA1*, *MYO1H*, *HIP1R*, *P2RX4*, *P2RX7*, *POLE*, *MYL2 and ATP2A2*. Many of these genes are related to BMP and TGF-β signaling, especially in the regulation of postnatal synchondrosis ossification.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was conducted under a predoctoral contract for research personnel in training (CT63/19-CT64/19). This study was funded by the Complutense University of Madrid and Banco Santander. The authors declare that they have no conflicts of interest. Data used in this study are available upon request from the corresponding author.

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SUPPORTING INFORMATION

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