

Developmental senescence misregulation in congenital disorders: CHARGE syndrome as a candidate model

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ABSTRACT

Developmental senescence has recently emerged as a physiological program that contributes to tissue remodeling, morphogenesis and growth regulation during vertebrate embryogenesis. While transient and non-pathological under normal conditions, this program requires strict spatial and temporal control. Here we argue that its misregulation represents a source of congenital defects. In particular, we suggest that the deficiency of the chromatin remodeler CHD7, the major genetic cause of CHARGE syndrome, may disrupt the spatiotemporal boundaries of developmental senescence. This hypothesis is supported by several lines of evidence in vertebrate models: first, *CHD7* expression domains during development largely overlap with regions where physiological embryonic senescence has been described. Second, *CHD7* reduction is associated with altered cell proliferation and misregulation of key senescence-related pathways including those driven by p53, p21 and TGFβ. Disruption of this regulatory balance may alter the timing of cellular growth arrest, clearance and tissue differentiation, providing a plausible mechanistic framework for the multisystemic anomalies observed in CHARGE syndrome.

INTRODUCTION

Cellular senescence has long been considered a cell program triggered by telomere attrition, DNA damage or oncogene activation, acting as a tumour-suppressive barrier in adult tissues [1]. However, in the last decade,

a paradigm shift has emerged: senescence is not only a defensive response to stress but also a physiological process during embryogenesis. In mammalian embryos, programmed senescence occurs in defined structures such as the mesonephros, the endolymphatic sac and the apical ectodermal ridge [2, 3]. This developmental

form of senescence is distinct from classical stress-induced senescence: it is transient, spatiotemporally restricted, lacks canonical DNA damage markers, and mechanistically, its regulation implicates TGF β /SMAD and PI3K/FOXO pathways upstream of p21, independently of p16 activation. These cells are later cleared by macrophages enabling tissue remodeling and proper morphogenesis [2, 3].

If developmental senescence is indeed a controlled morphogenetic program, then alterations or defects of its timing or spatial distribution could constitute a driver of morphogenetic defects. Minor shifts in onset or resolution might perturb the balance between proliferation, differentiation and cell elimination in tissues where precise temporal coordination is required, thereby contributing to congenital abnormalities.

CHARGE syndrome provides an illustrative example. Mutations in *CHD7* account for the majority of CHARGE cases [4]. *CHD7* (Chromodomain Helicase DNA-binding protein 7) encodes an ATP-dependent chromatin remodeler that modulates enhancer accessibility and transcriptional competence [5]. Intriguingly, phenotypic defects in CHARGE syndrome (such as inner ear defects, coloboma, olfactory malformations, heart defects, urogenital anomalies and retardation of growth) [6, 7] overlap with embryonic domains in which senescence has been documented [2, 3, 8].

Further supporting this connection, *CHD7* has been implicated in the negative regulation of p53 during mammalian development, and inappropriate p53 activation is sufficient to produce CHARGE-like defects [9, 10]. Additionally, *chd7* zebrafish morphants show upregulation of the cell cycle inhibitors *cdkn1a* (p21), *cdkn2a/b* (p15/p16) and *cdkn1bb* (p27) [11].

Taken together, the convergence between CHARGE models-associated phenotype, the distribution of embryonic senescence, and the known links between *CHD7* and p53/p21 pathways suggest that *CHD7* may regulate the initiation and temporal resolution of developmental senescence.

In this article, we summarize current knowledge on developmental senescence, examine how its misregulation could contribute to congenital defects, and propose that *CHD7* deficiency leads to spatiotemporal miscontrol of senescence in embryonic cell populations. We argue that CHARGE may exemplify a broader class of developmental disorders in which senescence misregulation contributes to pathogenesis. The anatomical and molecular framework underlying this working hypothesis is summarized in Figure 1.

Given the narrative nature of this review, the proposed framework was developed through a focused, non-systematic appraisal of the peer-reviewed literature. In addition to studies specifically addressing developmental senescence, embryonic morphogenesis, neural crest biology, CHARGE syndrome, and *CHD7*, we also considered relevant work on other genes, congenital disorders, and developmental contexts discussed throughout the article, together with key reference literature in the field that has helped shape the conceptual basis of this review. Developmental, molecular, and comparative evidence from different vertebrate models was integrated with the aim of building a biologically grounded and experimentally testable framework. Because the available evidence remains heterogeneous and, in many cases, indirect, this article should be interpreted as a focused conceptual synthesis rather than as a systematic or exhaustive review.

Developmental senescence in morphogenesis and congenital pathology

Insights from vertebrate development reveal that senescence is present more broadly than initially assumed by mammalian models, and that it constitutes a conserved morphogenetic mechanism rather than an isolated evolutionary acquisition [12]. Comparative analyses in birds, amphibians and fish have shown that senescence consistently arises in epithelia and transient organs undergoing structural transitions such as the quail mesonephric tubules [13], the axolotl and *Xenopus* pronephros and the *Xenopus* cement gland [14], or the zebrafish yolk sac and digestive endothelium [15]. These senescent domains share a common developmental logic: they appear only during brief windows of tissue remodeling, facilitate population turnover or organ regression, and are eliminated once their function is complete. This evolutionary conservation suggests that senescence is embedded within ancient developmental modules responsible for sculpting embryonic tissues.

What distinguishes this program in developmental contexts is not merely the arrest of proliferation, but its integration into broader morphogenetic systems. During development, senescent cells contribute to tissue remodeling and patterning by secreting signaling and matrix-remodeling factors that modulate the behavior of neighboring cells [12]. Their clearance by macrophages contributes to the orderly regression of transient embryonic structures, supporting the view that developmental senescence operates as a coordinated program of cell-cycle arrest, signaling, and phagocytic clearance [2]. Given this complexity, even small deviations in the magnitude or distribution of

senescence can have disproportionate developmental effects. Morphogenetic programs that rely on precise spatial confinement of senescent cells (such as the inner ear, limb bud, neural tube or pronephros) appear particularly sensitive to disruptions. Upstream pathways that govern developmental senescence, including TGF β /BMP, ERK, FOXO and miR-based modules, are themselves central to patterning and differentiation, and their misregulation can shift the balance between

proliferation, apoptosis and senescence [2, 3, 12]. The result is not a simple loss of senescence but a re-allocation of arrested cells into inappropriate domains, or an amplification of senescence where it should normally be minimal or transient. Throughout this review, it is important to distinguish physiological developmental senescence from pathological ectopic senescence, as these do not necessarily imply the same consequences.

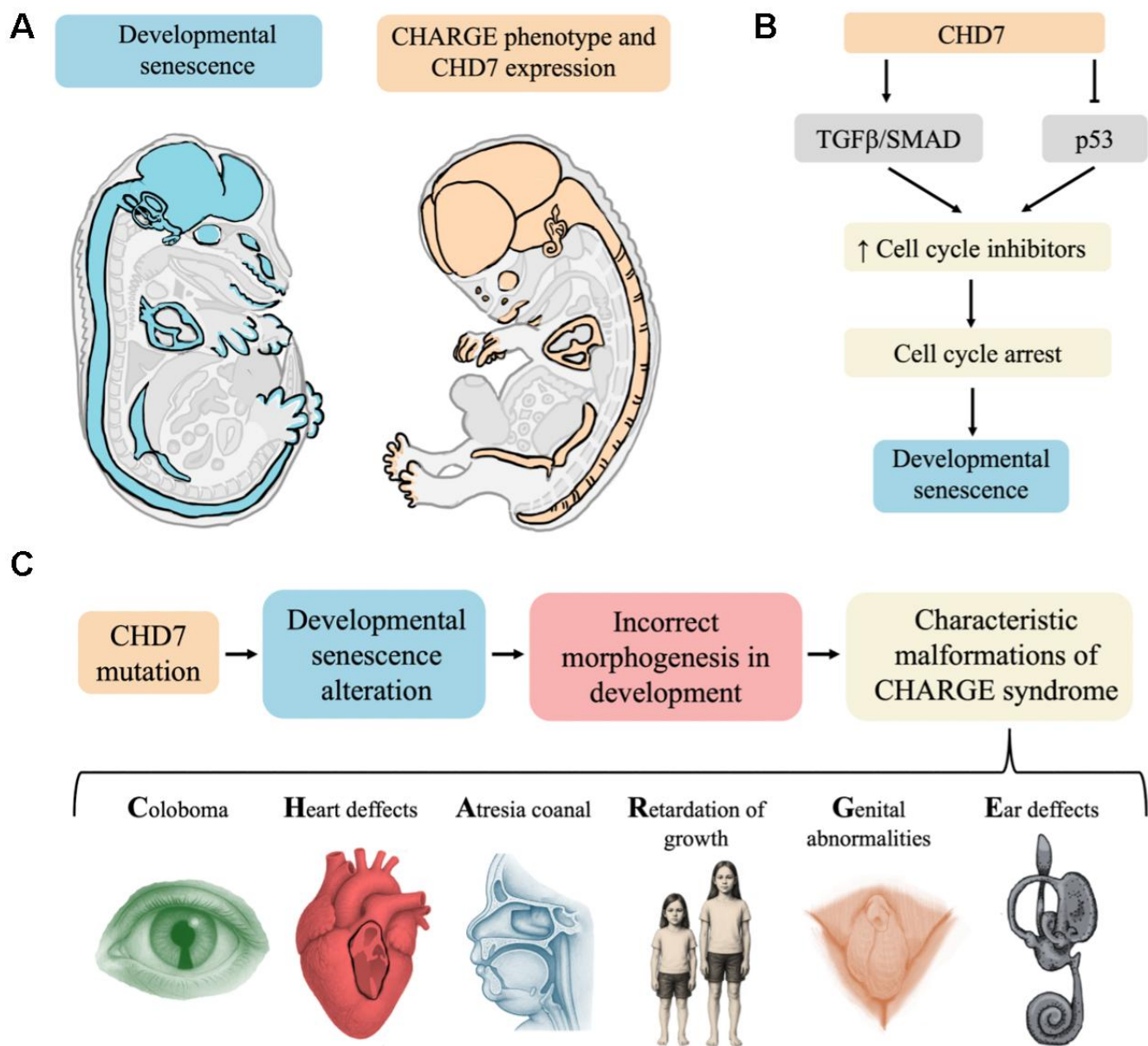


Figure 1. Anatomical and molecular framework for a possible contribution of developmental senescence to CHARGE syndrome. (A) Comparative map of CHARGE-associated anatomical domains and embryonic regions in which developmental senescence has been reported. (B) Simplified molecular scheme showing how CHD7-dependent chromatin regulation may intersect with p53, p21, and related cell-cycle control pathways linked to senescence-associated programs. (C) Conceptual developmental model in which altered CHD7 function may disturb senescence-related regulation, thereby affecting progenitor behaviour, tissue remodeling, and congenital morphogenesis in selected embryonic territories.

Recent studies have begun to clarify how perturbations of developmental senescence can give rise to congenital disorders [16]. One of the clearest demonstrations comes from *Six1*-deficient mice, a model for Branchio-Oto-Renal (BOR) syndrome [17]. In the developing inner ear, where physiological senescence is reported in the dorsal endolymphatic region [2, 18], *Six1* loss causes a dramatic expansion of senescence into dorsal territories, accompanied by reduced proliferation in regions that will give rise to the endolymphatic sac and the vestibular system. The phenotype is mechanistically linked to an imbalance in TGF β /BMP signaling, with reduced expression of TGF β ligands and ectopic activation of BMP circuits. Pharmacological manipulations further support causality: senolytics mitigate the aberrant expansion of senescence and normalize *BMP* expression, whereas senogenic agents phenocopy the defects in wild-type tissue. This provides the first *in vivo* evidence that abnormal senescence can directly generate the morphological hallmarks of a human developmental genetic syndrome [17].

In human spinal cord organoids, valproic acid triggers a senescence-associated program in SOX10-positive neural crest cells, with increased SA- β -gal activity, higher p21 protein levels, and a larger proportion of p21-positive cells, together with induction of senescence-related markers including *CDKN2A* (*p16INK4A*), *MYC* and *TGF β 1*. This is associated with marked SOX10 loss, depletion of neural crest markers and aberrant differentiation toward mesenchymal lineages at the expense of neuronal specification. Notably, the bulk RNA-seq heatmap in the same study also includes *CHD7* among the neural crest-associated transcripts altered after VPA exposure, although this observation is not discussed explicitly by the authors. The data further implicate an Akt-mTOR-p53-p21 pathway together with AP1-related regulators such as *EGR1*, *EGR2*, *EGR3*, *FOS*, *FOSB* and *JUNB*, whereas rapamycin suppresses senescence and partially restores neural crest identity and developmental trajectory [19]. In maternal diabetes, premature senescence is detected in the embryonic neuroepithelium during neurulation, as shown by increased SA- β -gal activity, early p21 induction, SASP-associated gene expression and macrophage infiltration in affected regions. In this model, rapamycin attenuates senescence-associated changes and decreases the frequency of neural tube defects, consistent with a pathogenic contribution of ectopic senescence to failed neural tube closure [20]. A similar senescence-associated phenotype has also been described in trisomy 21, where iPSC-derived neural progenitor cells display transcriptional and cellular abnormalities, including reduced proliferative and migratory capacity, that are partially ameliorated by senolytic treatment with dasatinib and quercetin [21].

Together, these models suggest that excessive, ectopic, or misallocated senescence can disrupt development across diverse etiologies.

These observations also support the view that developmental senescence does not operate in isolation, but rather within a broader morphogenetic context involving apoptosis and tissue remodeling. In developmental settings, senescence-associated programs have been shown to coexist with or complement apoptotic and remodeling events, indicating that embryonic defects may arise not only from the presence or absence of senescence, but also from its imbalance relative to other cell fate responses [8]. In this framework, oxidative or metabolic stress and autophagy-related adaptive responses may be relevant modulators of whether senescence-associated programs are triggered, maintained, or resolved in embryonic tissues, although their precise contribution is likely to be highly context dependent and remains insufficiently defined in most developmental systems. This broader perspective is particularly relevant for neural crest-related defects, since neural crest cells depend on a tightly coordinated balance between proliferation, lineage specification, migration, and selective elimination, and may therefore be especially vulnerable to stress-response misregulation, as illustrated by the valproic acid model discussed above [19].

More generally, these findings indicate that developmental senescence may be perturbed not only by primary genetic lesions, but also by adverse maternal or environmental conditions. Maternal diabetes provides a clear example, as it induces premature senescence in the embryonic neuroepithelium and promotes neural tube defects that are alleviated by rapamycin treatment [20]. Likewise, teratogenic exposure to valproic acid induces a senescence-associated program in SOX10-positive neural crest cells and disrupts their developmental trajectory [19]. Together, these observations reinforce the idea that congenital anomalies may result from abnormal spatiotemporal deployment of senescence in response not only to mutations, but also to altered embryonic environments.

A common pattern emerging from these findings is that developmental systems may fail not simply because senescence is absent, but because developmental senescence appears in the wrong place, at the wrong time, or in the wrong quantity. Developmental senescence acts as a morphogenetic regulator whose activity must be tightly integrated with proliferative cues, differentiation programs, and tissue-specific signaling networks. When this integration is perturbed through genetic mutations affecting transcriptional control, altered growth factor signaling, metabolic stress, or

chromosomal imbalance, the resulting mispatterning of senescence can impair progenitor proliferation, disrupt tissue architecture and developmental patterning, and ultimately lead to congenital anomalies.

Taken together, these findings suggest that some human developmental disorders could be re-examined in terms of senescence misregulation. Among them, CHARGE syndrome provides a particularly relevant case.

Anatomical convergence between charge defects, *CHD7* expression, and developmental senescence

CHARGE syndrome is a rare developmental disorder (ORPHA:138; incidence around 1 in 10,000) characterized by coloboma, heart defects, choanal atresia, growth and developmental delay, genitourinary anomalies, and ear abnormalities, including semi-circular canal malformations [22]. Most patients with CHARGE syndrome carry pathogenic variants in *CHD7* [4, 23]. These mutations account for most CHARGE cases, and the spectrum of defects they produce maps onto a broad set of embryonic tissues in which developmental senescence has been described in vertebrate models. A comparative analysis of CHARGE-associated malformations reveals a notable anatomical convergence between tissues affected in the syndrome, domains of *CHD7* expression, and embryonic regions in which developmental senescence has been reported (Figure 1A and Table 1). This overlap is particularly evident in craniofacial and sensory structures. *CHD7* is expressed in the optic and otic placodes, in branchial arches, and in the olfactory placode or pit during vertebrate development, including chick, mouse, and human embryos, precisely in territories that give rise to structures commonly affected in CHARGE, such as the eye, inner ear, choanal and palatal regions, and olfactory system [24–27]. Several of these same domains, or closely related morphogenetic territories, have also been identified as sites of developmental senescence, including the optic region, pharyngeal and oral derivatives, the neural tube, and especially the otic vesicle and dorsal endolymphatic apparatus [2, 3, 18, 28]. The correspondence is particularly compelling in the inner ear, where developmental senescence has been described first around the otic pore and later in the endolymphatic duct and sac, while *CHD7* expression has been documented in the otic vesicle and related sensory territories during embryogenesis [18, 26]. In the nervous system, *CHD7* is broadly expressed in neuroepithelial and cranial sensory regions, which partially overlap with embryonic domains in which senescence has also been observed [3, 24, 26].

Although these correspondences are not identical in every case and derive from different vertebrate models, the overall pattern supports the view that CHARGE preferentially affects embryonic territories in which *CHD7*-dependent regulatory programs intersect with regions sensitive to developmental senescence. This anatomical convergence does not in itself demonstrate mechanism, but it provides a strong comparative framework for proposing that *CHD7* deficiency may disrupt the timing, localization, or intensity of senescence in specific embryonic structures, thereby contributing to the multisystem phenotype of CHARGE.

In the urogenital domain, the evidence is more uneven and should be interpreted more cautiously. Renal anomalies are a recognized component of the CHARGE spectrum, and *Chd7* expression has been reported in the developing kidney in mouse embryos, while developmental senescence has been documented in nephric territories, including the mesonephros in mammals and pronephric or Wolffian-duct-related structures in anamniotes [2, 28, 29]. By contrast, the genital component of CHARGE is much better established phenotypically than anatomically at the level of local *CHD7* expression. Evidence from human embryonic material suggests that at least part of the genital phenotype in CHARGE reflects altered hypothalamic-pituitary-GnRH development rather than a primary defect of the embryonic gonad itself [24, 30]. The cardiac phenotype of CHARGE can also be viewed within this comparative framework. Congenital heart defects are a frequent component of the syndrome, with an overrepresentation of atrioventricular septal and conotruncal defects [31, 32]. Consistent with this, *Chd7* is expressed in embryonic cardiac territories, including the outflow tract, cardiac neural crest-associated domains, and mesodermal heart fields, where it contributes to normal cardiovascular morphogenesis [29, 33, 34]. Developmental senescence has also been described during heart morphogenesis, particularly in transient remodeling regions of the embryonic outflow tract and conotruncal area, although the available evidence is currently stronger in avian models than in the classic mammalian maps of developmental senescence [8]. Together, these observations raise the possibility that part of the cardiac phenotype of CHARGE arises in developmental territories shaped by both *CHD7* function and senescence-associated remodeling processes.

These parallel patterns of *CHD7* expression, developmental senescence, and phenotypic involvement suggest that *CHD7* may contribute to the spatiotemporal regulation of senescence during organogenesis. This interpretation is strengthened by experimental evidence

Table 1. CHARGE alterations occur in regions expressing *Chd7* and showing developmental senescence.

CHARGE phenotype	Affected organ	CHD7 expression	Cellular senescence
Coloboma	Eye	Optic cup (h, m)	Optic cup (ck), lens vesicle (ck)
Heart malformations: septal defects, abnormal branching	Heart	Pharyngeal arches (h, m), heart (m)	Pharyngeal arches (m, ck), heart (m, ck)
Atresia choanal	Nasal cavity, Choanae	Pharyngeal arches (h, m)	Pharyngeal arches (m, ck)
Retardation of growth, hypoplasia of several brain structures, mental retardation	Nervous system, pituitary	Neural tube (h, m, ck), midbrain (h, m, ck, xn), forebrain (m), olfactory bulb (m)	Neural tube (m, ck), hindbrain (m, xn), midbrain (ck, xn)
Genital alterations	Urogenital system	Metanephros (m), renal tubule (m), gonads (m)	Pronephros (ax, xn), metanephros (m, h, q, ck), wolffian duct* (m)
Ear defects: semicircular canal dysplasia, hearing and vestibular affected responses	Outer and middle ear	Pharyngeal arches (h, m)	Pharyngeal arches (m, ck)
	Inner Ear	Otic vesicle (h, m, ck), semicircular canals (m), crista (m), macula (h, m), cochlea (m)	Otic vesicle (m, ck), endolymphatic duct (h, m, ck) **, semicircular canals (m, ck), crista (ck), basilar papilla (ck)***
Anosmia	Olfactory epithelium	Olfactory epithelium (h, m)	Olfactory placode (ck, ax)
Cleft lip/palate	Oral regions	Pharyngeal arches (h, m)	Pharyngeal arches (m, ck), cement gland (xn)****
Polydactyly, J-shaped 'hockey stick'	Limb	Limb bud mesenchyme (h, m)	Limb apical ectodermal ridge (m, ck), interdigit tissue (m, ck)

ax, axolotl; ck, chicken; h, human; m, mouse; q, quail; xn, *Xenopus*.

Chd7* and *p21* mutant mouse show vaginal malformations; *Chd7* and *p21* mutant mouse show endolymphatic defects;

Our unpublished results; * Local inhibition of senescence alters *xenopus* oral cavity.

showing that developmental senescence is not merely correlative but functionally required in several embryonic contexts. In the mammalian embryo, loss of senescence in the absence of p21 leads to developmental abnormalities, despite partial compensation by apoptosis, indicating that normal morphogenesis depends on the proper execution of senescence programs [2]. Likewise, studies of developmental senescence in embryonic signaling centers have shown that these programs depend on TGF β - and ERK-associated regulatory networks that contribute to growth and patterning [2, 3]. In the developing inner ear, this functional link has been demonstrated particularly clearly: elimination of senescent cells with senolytic treatment blocks formation of the endolymphatic sac primordium, whereas experimental enhancement of senescence promotes dorsal epithelial morphogenesis [18]. More broadly, other developmental disease models support a causal role for senescence misregulation, since pharmacological or genetic attenuation of senescence ameliorates malformations in *Six1*-deficient embryos, valproic acid-treated spinal cord organoids, diabetic embryopathy, and trisomy 21-derived neural progenitors [17, 19–21]. Together, these observations do

not demonstrate that CHD7 directly governs senescence in every affected tissue, but they make it biologically plausible that senescence misregulation represents one component of CHARGE pathogenesis. Among the tissues discussed, the inner ear currently provides the strongest combination of anatomical overlap, experimental tractability, and direct developmental evidence.

The inner ear as a particularly informative developmental context

Among the affected organs, the inner ear provides a particularly informative, though not exclusive, example of how CHD7-dependent programs may intersect with developmental senescence. The vestibular apparatus, including the three semicircular canals, forms through a tightly coordinated series of morphogenetic events initiated by otic placode invagination and otic vesicle formation. During canal development, dorsal and lateral epithelial pouches extend and fuse, generating transient fusion plates that must be resolved to produce the hollow ducts of the mature canals [35]. CHARGE patients frequently display semicircular canal hypoplasia or aplasia, one of the most penetrant

diagnostic features of the syndrome, and *Chd7* mutant mice reproduce major vestibular abnormalities [36]. Several *Chd7* mutant lines show impaired elimination of fusion plate cells, altered proliferation in the canal epithelium, and abnormal expression of key regulators of canal morphogenesis, including *Bmp2*, *Bmp4*, *Sox2*, and *Fgf10*. Additionally, *Chd7* is expressed in the canal-forming pouches and associated sensory epithelia [26, 29]. Independent work has shown that developmental senescence contributes to dorsal otic morphogenesis and to formation of the endolymphatic duct and sac [2, 18], and our unpublished results further identify senescence in the fusion plates of the developing semicircular canals, supporting the idea that senescence participates directly in the transient remodeling events required for normal vestibular morphogenesis. These observations provide a plausible developmental framework for understanding why CHD7-dependent defects disproportionately affect vestibular structures in CHARGE. If this hypothesis is correct, *Chd7*-deficient otic epithelia should show not only altered proliferation but also a spatial redistribution, persistence, or quantitative expansion of p21/SA- β -gal-positive domains relative to normal transient remodeling territories.

Molecular links between CHD7 and senescence-related pathways

The relation between CHARGE-associated malformations and developmental senescence is not only anatomical but also mechanistic at the level of chromatin and transcriptional control (Figure 1B). This possibility is also consistent with the relevance of TGF β -responsive developmental programs in tissues affected in CHARGE, linking CHD7-dependent morphogenesis to signaling environments implicated in senescence regulation and tissue remodeling [2, 18, 37]. Consistent with its established roles in enhancer accessibility and transcriptional competence, CHD7 is well positioned to influence pathways that regulate cell-cycle arrest and senescence-associated responses [38, 39]. In primary human cells, CHD7 acts as a transcriptional coactivator required for oncogenic Ras-induced *CDKN2A* expression and senescence and can be recruited to the *CDKN2A* promoter through MZF1, indicating that CHD7 can directly participate in senescence-regulatory circuitry, although this evidence derives from tumor-suppressive senescence rather than embryonic development [39, 40]. In zebrafish embryos, *chd7* knockdown causes cell-cycle arrest together with upregulation of *cdkn1a*, *cdkn2ab*, and *cdkn1bb* [11]. The *chd7* zebrafish phenotype is partially rescued by co-deletion of *kdm2bb/fbxl10*, an H3K36 histone demethylase implicated in the regulation of proliferation and senescence-associated cell-cycle inhibitors, supporting a functional inter-

action between CHD7-dependent chromatin regulation and cell-cycle restraint [41]. CHD7 is also linked to senescence-related pathways through its cooperation with the transcription factor SIX1. In human inner ear organoid models, *CHD7* deficiency reduces *SIX1* and other downstream otic regulators, and chimeric organoids show partial rescue of *SIX1* expression [42]. Given that loss of *Six1* alters TGF β /BMP-mediated control of proliferation and expands domains of developmental senescence [17], the CHD7–SIX1 module represents an additional molecular axis through which CHD7 can influence senescence-sensitive patterning programs.

A particularly relevant mechanistic link is provided by p53. Elevated p53 levels have been reported in CHARGE fetal tissues, and mouse models with inappropriate p53 activation recapitulate major CHARGE-like anomalies. *Chd7* binds the *Trp53* promoter and negatively regulates *Trp53* expression, and partial reduction of *Trp53* dosage rescues several developmental defects caused by *Chd7* deficiency [9]. Given the central role of p53 in stress-induced and developmental cell-cycle arrest, these observations support the idea that loss of CHD7 may lower the threshold for pathological activation of senescence-associated programs in sensitive embryonic territories.

In this framework, CHD7 would not act simply as a regulator of proliferation or differentiation in isolation, but as a chromatin-level modulator of the transcriptional context that determines where and when cell-cycle arrest programs are engaged. This model does not yet demonstrate that CHD7 directly contributes to developmental senescence in all affected organs, but it provides a plausible molecular basis for proposing that *CHD7* deficiency predisposes selected tissues to ectopic, prolonged, or mistimed senescence-like responses during organogenesis.

Beyond charge: developmental syndromes in which senescence-related mechanisms may contribute

The idea that developmental senescence contributes to congenital pathology is not restricted to CHARGE. Several developmental syndromes display molecular and anatomical features consistent with alterations in senescence-related programs. Although the available evidence varies in strength, collectively these conditions outline a broader landscape in which mis-timed cell-cycle arrest, stress-responsive transcriptional states or aberrant secretory activities may perturb developmental patterning.

Below we describe a series of syndromes in which senescence during development has not been studied, but all of them share characteristics related to defects in senescence programs. The idea that senescence-related mechanisms may contribute to congenital pathology is not restricted to CHARGE but may extend to a broader group of developmental disorders with different genetic origins (Table 2).

The first group of examples involves disorders of epigenetic regulation in which early neural lineages appear particularly vulnerable. Rett syndrome is a rare X-linked neurodevelopmental disorder (ORPHA:778), caused in most classic cases by mutations in *MECP2* [43], that is characterized by an initial period of apparently normal development followed by regression with loss of acquired hand use and spoken language, stereotypic hand movements, gait abnormalities, and frequent seizures [44]. In this context, several studies have reported p53 activation and p21 upregulation together with stress-related and senescence-associated transcriptional changes in neural cells. In *MECP2*-deficient patient-derived neurons, these alterations include induction of p53 target genes and a senescence-associated secretory program, while pharmacological inhibition of p53 partially rescues neuronal defects, supporting a functional contribution of this pathway rather than a purely correlative stress response [45]. Consistent with this, neural stem cells from a mouse model of Rett syndrome are prone to senescence, show reduced capacity to cope with genotoxic stress, and display impaired differentiation [46]. Together, these findings suggest that epigenetic disruption caused by *MECP2* deficiency can favor aberrant p53-p21-dependent arrest and senescence-like states during neurodevelopment.

Treacher-Collins syndrome is a rare craniofacial developmental disorder (ORPHA:861), most commonly caused by haploinsufficiency of *TCOF1*, and characterized by bilateral hypoplasia of the zygomatic complex and mandible, downward-slanting palpebral fissures, lower eyelid abnormalities, external and middle ear malformations, and conductive hearing loss [47]. Reduced *Tcof1* impairs ribosome biogenesis, triggers nucleolar stress, and is associated with elevated p53 signaling in the embryonic neuroepithelium, leading predominantly to apoptosis together with deficient production and proliferation of cranial neural crest cells [48, 49]. Pharmacological or genetic inhibition of p53 markedly ameliorates the craniofacial phenotype in experimental models, indicating that inappropriate p53 activity is a major driver of pathogenesis in this context [49]. The combination of nucleolar stress, strong p53 signaling, cell-cycle restraint, and impaired neural crest output places this

disorder within the conceptual range of developmental conditions in which senescence-related mechanisms may be worth considering.

22q11.2 deletion syndrome, which includes the clinical spectrum historically referred to as DiGeorge syndrome, is a rare developmental disorder (ORPHA:567) characterized by conotruncal cardiac defects, palatal anomalies, and thymic or parathyroid hypoplasia [50]. Reduced dosage of *TBX1* is a major contributor to the syndrome and is required for normal development of the pharyngeal apparatus and cardiac outflow tract [51]. Developmental senescence has been described in pharyngeal territories, including branchial arches and pharyngeal pouches, and senescence-associated remodeling has also been reported during morphogenesis of the embryonic cardiac outflow tract [8, 52]. In parallel, partial suppression of p53 ameliorates cardiovascular defects in *Tbx1*-deficient mouse models, indicating inappropriate engagement of p53-dependent developmental checkpoints, while *Tbx1* has also been shown to modulate progenitor proliferation in dental epithelium by modulating *Pitx2* activation of p21 [51, 53].

A further point of comparison comes from *SOX10*-associated neurocristopathies. Waardenburg syndrome is a rare disorder (ORPHA:3440) characterized mainly by congenital sensorineural hearing loss and pigmentary abnormalities of the iris, hair, and skin, whereas related severe presentations include the PCWH phenotype, which combines peripheral dysmyelinating neuropathy, central demyelinating leukodystrophy, Waardenburg features, and Hirschsprung disease (ORPHA:163746) [54, 55]. Variants in *SOX10*, and in some subtypes in the melanocyte regulator *MITF*, disrupt neural crest-derived lineages involved in pigment cell specification, enteric nervous system development, and glial maturation, including melanocyte-dependent function of the stria vascularis in the cochlea [55]. Experimental work outside the congenital setting shows that *SOX10* loss can induce durable cell-cycle arrest and senescence-associated programs linked to p21 and p27 [56]. In that sense, Waardenburg syndrome and related *SOX10*-associated phenotypes can be viewed as candidate neurocristopathies in which senescence-related mechanisms may be worth exploring.

A final and more exploratory point of comparison comes from disorders of developmental guidance rather than tissue patterning itself. Kallmann syndrome is a rare developmental disorder (ORPHA:478) characterized by congenital hypogonadotropic hypogonadism associated with hyposmia, reflecting abnormal olfactory development and defective migration or survival of GnRH neurons from the nasal placode to the

Table 2. Developmental disorders potentially compatible with senescence-related mechanisms.

Disorder	Main gene(s) / pathway	Rare disease code	Main developmental system affected	Evidence compatible with senescence involvement
CHARGE syndrome	<i>CHD7</i>	ORPHA:138	Craniofacial, otic, neural, cardiac, urogenital	Anatomical overlap with embryonic senescence territories; links with chromatin regulation, p53, p21, and otic senescence-associated remodeling p53 activation, p21 upregulation, senescence-associated transcriptional and secretory changes; neural stem cells prone to senescence
Rett syndrome	<i>MECP2</i>	ORPHA:778	Neural	Nucleolar stress, p53 activation, apoptosis with growth restraint, rescue after p53 suppression p53-sensitive defects, Pitx2-p21-related proliferation control, overlap with senescent pharyngeal and outflow tract territories
Treacher-Collins syndrome	<i>TCOF1</i>	ORPHA:861	Craniofacial / neural crest	SOX10 loss can induce durable cell-cycle arrest and senescence-associated programs outside the congenital setting
22q11.2 deletion syndrome / DiGeorge spectrum	<i>TBX1</i> dosage	ORPHA:567	Pharyngeal apparatus, cardiac outflow tract	Guidance depends on matrix and local signaling environments potentially compatible with senescence-associated remodeling
Waardenburg syndrome and related SOX10-associated phenotypes	<i>SOX10, MITF</i>	ORPHA:3440; PCWH ORPHA:163746	Neural crest derivatives, pigment cells, enteric nervous system, glia	
Kallmann syndrome	<i>ANOS1, FGFR1, SEMA3A, SEMA3E</i>	ORPHA:478	Olfactory system / GnRH neuron guidance	

PCWH, peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease.

forebrain [57]. Pathogenic variants affect genes involved in extracellular matrix interactions and axonal guidance, including *ANOS1*, *FGFR1*, *SEMA3A*, and *SEMA3E*, all of which contribute to the embryonic environment through which GnRH neurons and olfactory axons navigate [57–59]. Kallmann syndrome is conceptually relevant because senescent cells can influence local tissue environments through secreted and matrix-remodeling factors. It is therefore plausible that abnormal senescence in placodal, olfactory, or forebrain territories could alter the migratory landscape encountered by GnRH neurons.

All this evidence suggests that senescence-related mechanisms may be relevant beyond CHARGE across a broader spectrum of developmental disorders with diverse genetic origins. Although these disorders do not define a single mechanistic class, they repeatedly involve stress-responsive checkpoints, activation of CDK inhibitors, abnormal proliferative restraint, or altered secretory states in progenitor populations that depend on tight temporal regulation. Whether such

alterations correspond to authentic developmental senescence or to related senescence-like arrest states remains unresolved. Nevertheless, the overall picture supports the view that developmental senescence may constitute a sensitive regulatory system whose mistiming, ectopic activation, abnormal persistence, or insufficient induction can influence congenital pathology across multiple embryonic tissues. Within this broader framework, *CHD7* deficiency and CHARGE syndrome emerge as a particularly compelling candidate in which altered senescence responses may contribute to pathogenesis. A graphical summary of the proposed conceptual framework is provided in the Graphical Abstract (Figure 2).

Working hypothesis and future directions

The evidence reviewed here supports a working hypothesis in which developmental senescence acts as a transient regulatory process during morphogenesis, and *CHD7* contributes to defining when and where this program can be engaged in tissues that are normally

sensitive to it. Under this view, reduced *CHD7* dosage or altered *CHD7*-dependent chromatin regulation could disturb the normal timing, intensity, localization, or resolution of senescence-like responses in selected embryonic territories (including the otic epithelium, pharyngeal arches, neural domains, and urogenital primordia). Such a model remains to be tested directly, but it is compatible with the anatomical distribution and developmental logic of CHARGE syndrome (Figure 1C).

Future work should determine more precisely when and where *CHD7* shapes competence for senescence during development. This will require temporal and spatial mapping of canonical markers such as p21, SA- β -gal, and secretory or matrix-remodeling readouts associated with senescence, together with lineage-restricted perturbations of *CHD7* and its regulatory partners, and functional analyses in complementary embryonic systems including mouse, chick, and zebrafish. Particular attention should be given to three questions: first, whether *CHD7* regulates chromatin accessibility at loci encoding p21 and related cell-cycle inhibitors; second, whether *CHD7* influences the composition,

intensity, or duration of embryonic secretory programs associated with senescence; and third, how senescent cells interact with epithelial-mesenchymal signaling and developmental guidance cues during organogenesis.

Although senotherapeutic approaches, including senolytics and senomorphics, have shown partial benefit in other models in which senescence misregulation contributes to developmental defects, any extension of such strategies to *CHD7*-related contexts requires caution. Developmental senescence is part of normal morphogenesis, and both excessive elimination and artificial induction of senescence can perturb embryonic development. For this reason, organoid, explant, and *ex vivo* systems will be especially valuable as controlled platforms in which to test senescence-modulating interventions before drawing conclusions about their relevance *in vivo*.

Concluding remarks

The available anatomical, developmental, and molecular evidence does not yet demonstrate that

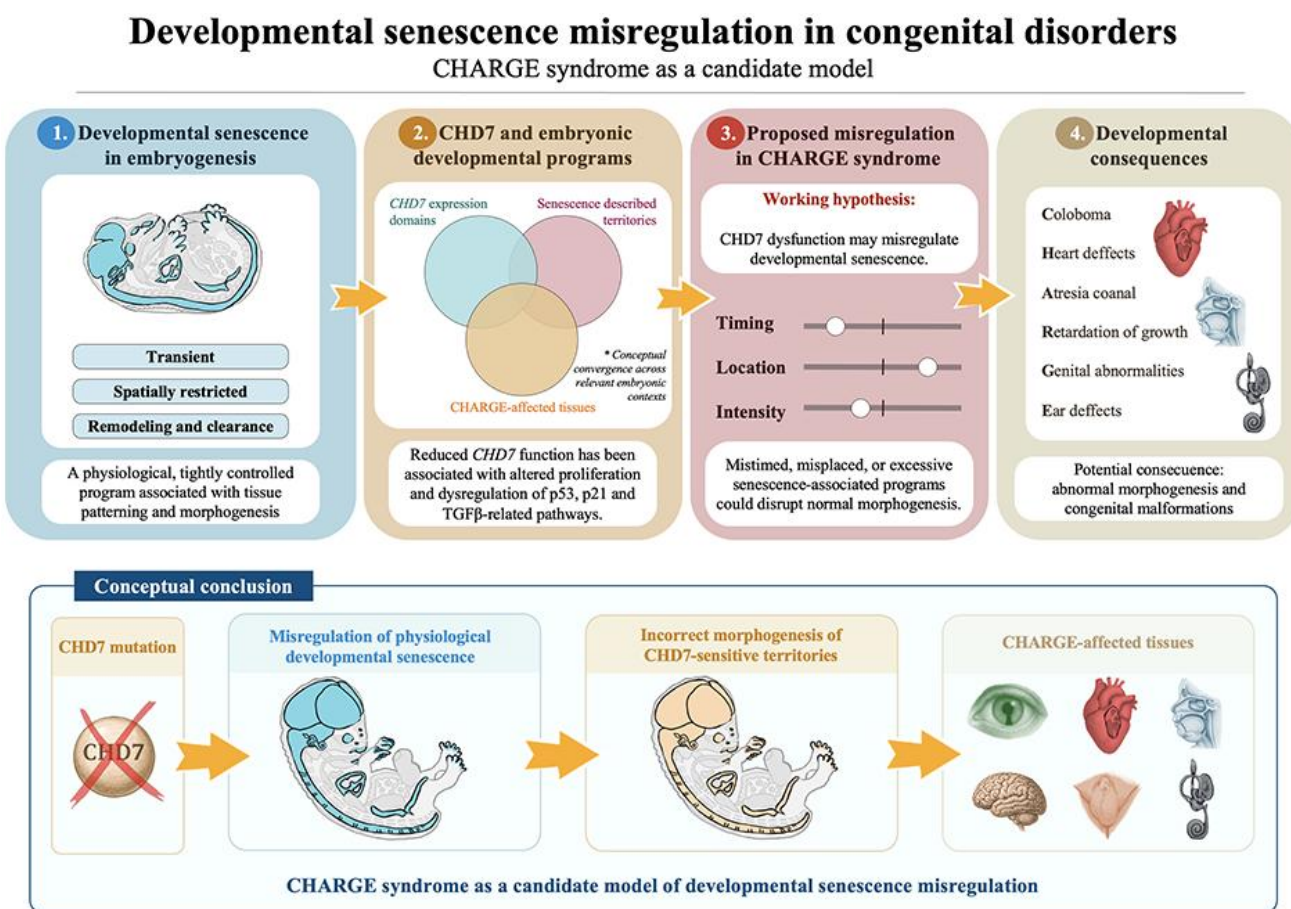


Figure 2. Graphical Abstract.

CHARGE syndrome is a disorder of senescence misregulation. It does, however, support the idea that developmental senescence provides a biologically coherent and experimentally testable framework through which diverse features of the syndrome can be re-examined. More broadly, this perspective places CHARGE within an emerging landscape of developmental disorders in which abnormal activation, persistence, reduction, or mislocalization of senescence-related programs may contribute to congenital pathology. Defining the extent to which this is true will require moving from anatomical overlap and mechanistic plausibility to direct embryological and functional evidence in defined CHD7-sensitive territories, especially in the inner ear. At the same time, the currently available literature remains heterogeneous and, in many cases, indirect, with relatively limited direct evidence linking CHD7 dysfunction to developmental senescence across affected embryonic territories. Accordingly, the framework proposed here should be interpreted as a biologically grounded and experimentally testable model rather than as direct proof of causality.

Abbreviations

ANOS1: anosmin 1; AP-1: activator protein 1; ax: axolotl; BMP: bone morphogenetic protein; BOR: Branchio-Oto-Renal; CDKN2A: cyclin dependent kinase inhibitor 2A; CHARGE: coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital abnormalities, and ear anomalies; CHD7: chromodomain helicase DNA-binding protein 7; ck: chick; DNA: deoxyribonucleic acid; ERK: extracellular signal-regulated kinase; FGFR1: fibroblast growth factor receptor 1; FOXO: forkhead box O; GnRH: gonadotropin-releasing hormone; h: human; MECP2: methyl-CpG binding protein 2; m: mouse; MITF: microphthalmia-associated transcription factor; mTOR: mechanistic target of rapamycin; NCCs: neural crest cells; ORPHA: Orphanet rare disease identifier; p15: cyclin dependent kinase inhibitor 2B; p16: cyclin dependent kinase inhibitor 2A; p16INK4A: cyclin dependent kinase inhibitor 2A isoform INK4A; p21: cyclin dependent kinase inhibitor 1A; p27: cyclin dependent kinase inhibitor 1B; p53: tumor protein p53; PCWH: peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease; PI3K: phosphoinositide 3-kinase; q: quail; SA- β -gal: senescence-associated beta-galactosidase; SASP: senescence-associated secretory phenotype; SEMA3A: semaphorin 3A; SEMA3E: semaphorin 3E; SIX1: sine oculis homeobox homolog 1; SMAD: SMAD family transcription factors; SOX10: SRY-box transcription

factor 10; TBX1: T-box transcription factor 1; TCOF1: Treacher Collins-Franceschetti syndrome 1; TGF β : transforming growth factor beta; VPA: valproic acid; xn: *Xenopus*.

AUTHOR CONTRIBUTIONS

Conceptualization: Álvaro J. Arana, Laura Sánchez, Marta Magariños. Writing – original draft preparation: Álvaro J. Arana. Writing – review and editing: all authors. Visualization: Pablo Palau-Irisarri, Álvaro J. Arana. Supervision: Laura Sánchez, Manuel Collado, Marta Magariños. Funding acquisition: Laura Sánchez, Manuel Collado, and Marta Magariños. Unpublished experimental observations discussed in the manuscript were generated by Marta Magariños, Pablo Palau-Irisarri, and Yolanda León. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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