REVIEW

Role of the CASZ1 transcription factor in tissue development and disease

Tiantian Liu[1,2*], Tao Li[3] and Shaorui Ke[1,2]

Abstract

The zinc finger transcription factor gene, *CASZ1/Castor* (Castor zinc finger 1), initially identified in *Drosophila*, plays a critical role in neural, cardiac, and cardiovascular development, exerting a complex, multifaceted influence on cell fate and tissue morphogenesis. During neurogenesis, CASZ1 exhibits dynamic expression from early embryonic development to the perinatal period, constituting a key regulator in this process. Additionally, CASZ1 controls the transition between neurogenesis and gliomagenesis. During human cardiovascular system development, CASZ1 is essential for cardiomyocyte differentiation, cardiac morphogenesis, and vascular morphology homeostasis and formation. The deletion or inactivation of CASZ1 mutations can lead to human developmental diseases or tumors, including congenital heart disease, cardiovascular disease, and neuroblastoma. CASZ1 can be used as a biomarker for disease prevention and diagnosis as well as a prognostic indicator for cancer. This review explores the unique functions of CASZ1 in tissue morphogenesis and associated diseases, offering new insights for elucidating the molecular mechanisms underlying diseases and identifying potential therapeutic targets for disease prevention and treatment.

Keywords CASZ1, Development, Biomarker, Cancer

Introduction

The *CASZ1/Castor* (Castor zinc finger 1) gene, initially discovered in *Drosophila*, encodes a zinc finger transcription factor (TF) that regulates neural fate [1]. In humans, CASZ1 is located on chromosome 1p36, acting as a tumor suppressor gene. It encodes two primary isoforms: CASZ1a, spanning 1759 amino acids with 11 TFIIIA-like C2H2 zinc fingers (ZnFs), and CASZ1b, a more evolutionarily conserved isoform containing 1166 amino acids and lacking 6 zinc fingers in the C-terminal region [2].

Highly conserved noncoding DNA elements that are present in the noncoding region of the *CASZ1* gene across species from *Drosophila* to humans [3–5] are strongly associated with developmentally regulated genes [5, 6]. In *Drosophila*, *Casz1* functions as a neuronal fate-determining gene, controlling nervous system development [1, 7, 8], and its loss affects differentiation and alters glial cell numbers and migration [1, 7–9]. In *Xenopus laevis* and humans, CASZ1 plays a critical role in heart development, cardiomyocyte differentiation, vascular assembly, and lumen morphogenesis [10–12].

In addition to its crucial role in both neural and cardiac development, the involvement of CASZ1 in various pathological conditions, including cancer, is being increasingly recognized [13]. In cancer, CASZ1 has emerged as a key player in tumor progression, regulating tumor growth and development. The loss of heterozygosity and/or EZH2-mediated H3K27me3 modification can silence the *CASZ1* gene in tumor samples from patients with a poor prognosis of neuroblastoma (NB) [14]. A clinical case report showed human papillomavirus DNA

*Correspondence:
Tiantian Liu
liutt0768@163.com
[1] Henan Key Laboratory of Chinese Medicine for Respiratory Disease, Henan University of Chinese Medicine, 156 Jinshui East Road, Zhengzhou 450046, Henan, China
[2] Academy of Chinese Medical Sciences, Henan University of Chinese Medicine, Zhengzhou 450046, Henan, China
[3] College of Life Sciences, Henan Agricultural University, Zhengzhou 450002, China

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 2 of 11

integration into the *CASZ1* gene locus in a patient with cervical cancer, which disrupted *CASZ1* gene expression [15]. Furthermore, a CASZ1–MASP2 fusion transcript, detected in colorectal cancer, encodes an N-terminally truncated MASP2 controlled by the CASZ1 promoter [16]. Similarly, CASZ1 exhibits downregulation in esophageal carcinoma, lung adenocarcinoma, and clear cell renal cell carcinoma, where expression levels correlate with patient prognosis [17–19]. However, the expression trend of CASZ1 varies in different solid tumors, exhibiting upregulation in glioma tissues and epithelial ovarian cancer (EOC) cells [20, 21]. Therefore, CASZ1 plays dual biological roles in diverse tumors. Beyond cancer, loss-of-function mutations in CASZ1 have been associated with susceptibility to human heart diseases [22–25], and CASZ1 methylation has been associated with cardiovascular mortality [26]. Additionally, CASZ1 has been implicated in osteoarthritis, immune inflammatory, and regulatory responses [27].

This review provides a comprehensive summary of the role of CASZ1 in both development and disease, offering novel insights into the molecular mechanisms underlying various diseases. Moreover, it highlights the potential of CASZ1 as a prognostic indicator and therapeutic target for diagnosing and treating these diseases, thereby contributing to the advancement of medical research.

Discovery and structural features of CASZ1

In the 1990s, an enhancer detection screen identified a new gene, *Castor*, which is required for the development of the central nervous system in *Drosophila* embryos [1]. The Castor zinc finger protein is expressed in subsets of the Drosophila ventral nerve chord and the procephalic region during embryogenesis. Loss of Castor function leads to precise changes in gene expression in the central nervous system, as well as defects in axonogenesis and embryonic lethality [1, 28–31].

The expression of Castor in *Drosophila* at a developmental stage comparable to later stages of human embryonic neurogenesis [32], led to the identification and cloning of the highly expressed human CASZ1 gene. CASZ1 is expressed in various human tissues, including the heart, lung, skeletal muscle, pancreas, testis, small intestine and stomach, but not in the adult brain [2]. The CASZ1 gene has two mRNA isoforms, hCasz5 (CASZ1b) and hCasz11 (CASZ1a), which are 4.4 kb and 8.0 kb in length, respectively. The hCasz5 isoform encodes a protein of 1166 amino acids (127.7 kDa, p*I* 8.4), containing five TFIIIA class C2H2 ZnF motifs. In addition, the hCasz5 isoform has two nuclear localization signals (NLS) located at 23–29 and 232–248, a nuclear export signal (NES) located at 168–186 [33], a nucleosome remodeling and deacetylase (NuRD) complex binding site located at 21–45, a histone H3 and DNA repair protein binding site located at 640–650 [34], a serine-enriched region located at 743–784, and a congenital heart disease 5 protein (CHD5)-interacting domain (CID) region located at 785–998 [24].

The cDNA sequence of CASZ1a is 7946 bp in length and codes for a protein with 1759 amino acids (190.0 kDa, p*I* 6.64). In addition to the information contained in CASZ1b, CASZ1a has six additional TFIIIA class C2H2 ZnF motifs. Furthermore, CASZ1a has one extra NLS located in 1401–1418, one Glu Asp-rich region located in 1672–1729, and two Ala-rich regions located in 1635–1670 and 1726–1756 [2]. The protein structure of CASZ1 is presented in Fig. 1.

In neural development

Neural progenitor cells undergo identity transitions, generating diverse neurons and glial cells in a precise manner during development. Throughout neurogenesis, the majority of neural stem and progenitor cells alter their output, initially producing neurons followed

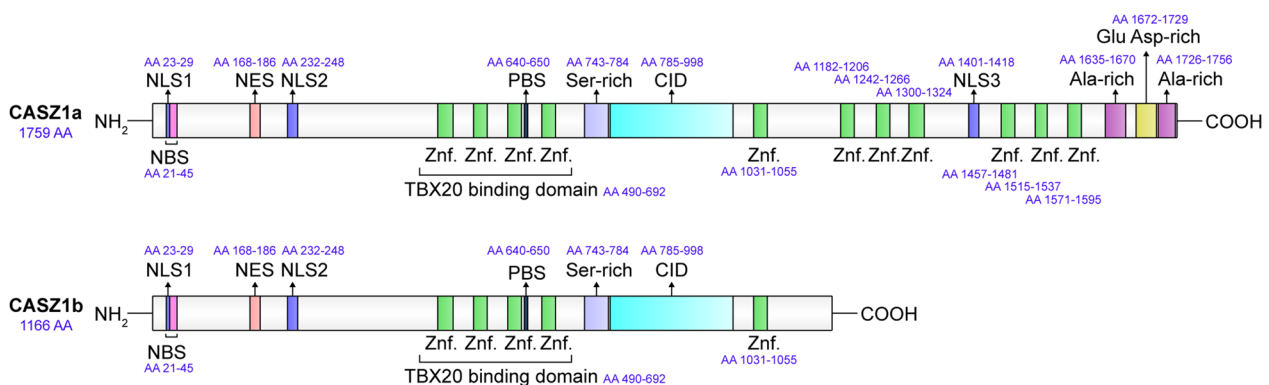

Fig. 1 The protein structure of CASZ1. *Znf.* zinc finger, *NLS* nuclear localization signals, *NES* nuclear export signals, *NBS* NuRD complex binding site, *PBS* histone H3 and DNA repair protein binding site, *CID* CHD5-interacting domain

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 3 of 11

by glial cells [35]. The occurrence of different cortical cell populations is time-separated; in rodents, neurons are produced from embryonic day 12 (E12) to E18, astrocytes appear around E18, and their numbers reach a peak in the neonatal period. Differentiated oligodendrocytes first appear after birth [35]. In vitro primary E10–E12 cortical precursor cells only generate neurons in the first few days, followed by astrocytes and oligodendrocytes [36, 37]. In addition, when the very early cortex is transduced, many precursors only produce neurons, some precursors produce both neurons and glial cells. Surprisingly, some precursors only produce glial cells, which may be because they wait until a later time point to differentiate. Therefore, there are two major conclusions for these studies. First, the capacity of precursor cells changes over time, with a preference for making neurons earlier and glia later. Second, the external environment of the precursor is a key determinant of its differentiation [35]. Certain central nervous system (CNS) regions, such as the neocortex and retina, exhibit additional temporal transitions in progenitor cells at specific developmental stages, generating distinct neuronal subtypes. For instance, during vertebrate retinal development, retinal progenitor cells (RPCs) generate various neuronal subtypes and glia at different pluripotent stages [38–40]. In the *Drosophila* ventral spinal cord, neural stem cells express TFs, including hunchback, Krüppel, nub/pdm2 (collectively pdm), castor, and grainyhead, during development. These temporal recognition factor cascades act as a timing mechanism, coordinating the output of numerous neuroblast lineages within the CNS of *Drosophila* [41].

Casz1 is expressed in the dorsal root ganglia and spinal cord of mice during neurogenesis [11, 42, 43], displaying ubiquitous expression from early embryonic development to the perinatal period. Initially expressed in dorsal interneuron 1 progenitors and their derived neurons in the dorsal spinal cord, Casz1 later extends to a large subset of dorsal late-born excitatory (dILB) neurons. Prrxl1, a key TF for dILB differentiation, positively regulates Casz1 expression in the dorsal embryonic spinal cord. During the perinatal period, Casz1 expression is maintained in a narrow cell layer, predominantly within layer III of the dorsal horn independent of Prrxl1 [44]. Both mouse CASZ1a (mCASZ1a) and CASZ1b (mCASZ1b) exhibit dynamic expression in tested neural tissues, with the expression pattern regulated according to the isoforms ratio [45]. Furthermore, neural differentiation during development is often accompanied by prolonged cell cycles [46, 47], with CASZ1-induced changes potentially extending the cell

doubling time, thereby serving as a potential mechanism for neuronal differentiation regulation.

In retinal development

In mouse retinal progenitors, similar to *Drosophila* neuroblasts, Casz1 regulates temporal progression through a conserved transcriptional cascade. Additionally, Casz1 plays a crucial role in regulating progenitor cell potential and controlling the generation of mid/late-born neurons in the mouse retina. Predominantly observed in middle and late RPCs, conditional Casz1 loss enhances early retinal neuron generation at the expense of late fates [42]. Furthermore, Casz1 interacts with key polycomb repressive complex (PRC) subunits, controlling rod genome organization by silencing laminin a/c [48]. In addition, it epigenetically regulates transcriptional programs by binding to the NuRD complex in retinal cells [34], relying on the NuRD complex and PRC to promote rod fate while suppressing gliogenesis [49].

In heart development

Early heart development is characterized by hyperplastic growth, wherein cardiac cells undergo mitogen-dependent activation during the G1 phase of the cell cycle [50]. During initial heart development stages, cardiomyocytes from the first and second heart fields exhibit high proliferative activity, contributing to substantial embryonic heart growth. As cardiomyocyte terminal differentiation commences, the overall cardiomyocyte proliferation rate gradually diminishes. Subsequently, the vertebrate heart primarily enlarges through hypertrophy, cellular recruitment, and proliferation of the neural crest and epicardium [51], with these processes sustaining heart development and growth.

In humans, CASZ1 exhibits high expression levels in various organs, including the heart, lungs, skeletal muscle, pancreas, testes, small intestine, and stomach. Notably, the highest relative expression level of CASZ1 is observed in the heart [2] where it plays a crucial role in morphogenesis and development [11, 52]. Specifically, during development, Casz1 is vital for the differentiation of distinct cardiomyocytes, exhibiting continuous expression throughout cardiac development. Furthermore, CASZ1 is exclusively expressed in terminally differentiated cardiomyocytes and downregulated in cells re-entering the cell cycle, indicating its association with the terminal differentiation of cardiomyocytes, skeletal muscle cells, and lymphatic cardiac muscle tissue [43]. Moreover, CASZ1 is critical for cardiomyocyte proliferation in two heart regions during the earliest stages of mammalian heart development. CASZ1 loss results in a reduced number of cardiomyocytes, prolonged or arrested S phase, decreased DNA synthesis, increased

phosphorylated RB, and decreased cardiac mitosis [51]. In *Xenopus* embryos, CASZ1 deficiency leads to the failure of ventral midline progenitors to differentiate into cardiomyocytes, resulting in abnormal cardiac morphogenesis and death [10]. Furthermore, the abnormal expression of CASZ1 target genes, such as muscle contractile genes (*TNNI2*, *TNNT1*, and *CKM*), contractile fiber genes (*ACTA1*), and genes encoding arrhythmia-associated ion channels (*ABCC9* and *CACNA1D*) occurs in Casz1-null mouse embryonic hearts, leading to myocardial hypoplasia and congenital ventricular septal defects (VSDs) [11]. Additionally, CASTOR (CASZ1) interacts with congenital heart disease 5 protein (CHD5) or TBX20, a necessary interaction for cardiac morphogenesis and homeostasis [52, 53].

In cardiovascular development

During embryonic development, endothelial cells (ECs) serve as the foundation for functional vasculature formation. The initial phases involve vasculogenesis, where mesodermal cells differentiate into EC progenitors, which subsequently proliferate and migrate, assembling into vascular cords at specific embryo sites. Then, the umbilical cords undergo tubulogenesis or lumen formation and mature through angiogenesis, which involves vessel budding, branching, and remodeling. Finally, pericytes and smooth muscle cells provide structural support by surrounding and stabilizing the vessels [54, 55].

Two genome-wide association studies (GWASs) have revealed a genetic association between the human *Casz1* locus and hypertension [56, 57], suggesting a potential link between CASZ1 and cardiovascular dysfunction. The epidermal growth factor-like domain 7 (*EGFL7*) gene, activated by Castor (CASZ1), is crucial for vessel assembly and luminal morphogenesis [12, 58, 59]. In *Xenopus* and human epithelial cells, CASZ1 directly regulates Egfl7, thereby promoting RhoA-mediated vascular development in vertebrates. CASZ1 deficiency not only impedes the branching and luminal vasculature development of *Xenopus* embryos, but also induces marked changes in human EC adhesion, morphology, and sprouting [12, 59]. The mechanisms of CASZ1 regarding tissue development are summarized in Table 1 and Fig. 2.

In NB

NB is a prevalent solid tumor that affects the pediatric population, predominantly targeting the brain and accounting for ~15% of all pediatric tumor-related deaths, and has a poor prognosis [60]. The CASZ1 TF, a zinc finger protein, plays a critical role in nerve cell development regulation. Abnormal CASZ1 expression has been implicated in the malignant behavior of human NB [61]. Notably, both CASZ1a and CASZ1b isoforms have been identified as inhibitors of NB tumor growth [2, 45, 61, 62]. CASZ1b is expressed in all CASZ1a-expressing NB samples and mouse tissues. Throughout the differentiation of neuroblasts and myoblasts, both the CASZ1 isoforms exhibit coordinated regulation, displaying temporal and region-specific regulation during neurogenesis in vivo. Functionally, CASZ1b and CASZ1a exhibit similar gene-regulatory activities, with their coexpression showing no cross-antagonistic or synergistic effects [45].

The loss of CASZ1 in NB tumors correlates with poor prognosis. An examination of CASZ1 protein expression in a primary NB tissue microarray revealed that tumors from patients with NB and favorable prognoses exhibited higher levels of nuclear CASZ1 protein expression. Conversely, tumors from patients with unfavorable prognosis exhibited cytoplasmic-restricted CASZ1 staining or low nuclear CASZ1 staining [33]. Furthermore, the growth-inhibitory capacity of cytoplasmic-localized CASZ1b is significantly reduced [62]. CASZ1 expression levels increase with the induced differentiation of NB cells and mesenchymal cells [2]. Additionally, low CASZ1 expression exhibits a significant association with increasing patient age, high-risk classification of pediatric tumor group, loss of heterozygosity on chromosome 1p (1p LOH), MYCN amplification, and reduced survival probability. CASZ1 (1p36.22) is located in a common deletion region marked between D1S508 and D1S244 on chr1p. In a study involving 184 primary NB cases with 1p LOH, 180 cases showed CASZ1 deletion. The specific restoration of CASZ1 in NB cells induces cell differentiation, enhances cell adhesion, inhibits migration, and reduces tumorigenicity [61, 62]. No tumor-associated nucleotide mutations have been reported in the CASZ1-coding sequence, suggesting that mechanisms such as epigenetic silencing may be associated with reduced CASZ1

Table 1 Potential role of CASZ1 in tissue development

| Tissue development	Cell types involved	Proposed mechanism	Refs.
Nerve	Dorsal root ganglia and spinal cord	Ratio between casz1a/casz1b isoforms	[45]
Retina	Retinal progenitor cells	Interacts with PRC or NuRD complex	[41–43]
Heart	Cardiomyocytes	Regulates cell cycle or interacts with CHD5/TBX20	[51–53]
Angiography	Endothelial cells	Regulates the Egfl7-RhoA pathway	[12, 59]
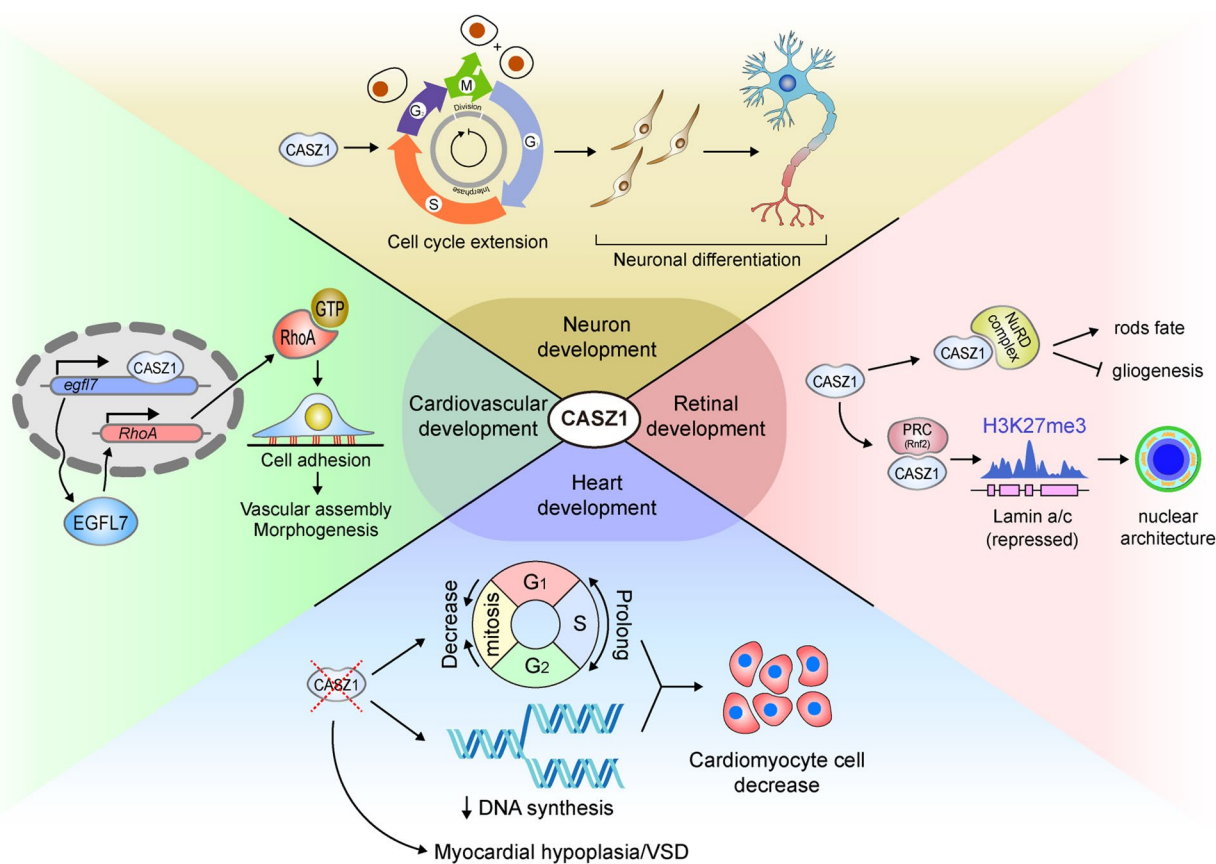
Fig. 2 The role of CASZ1 in tissue development: CASZ1 plays a crucial role in the development of various tissues. It regulates the development of the nervous system and facilitates the production of retinal neurons. Additionally, CASZ1 is essential for the differentiation of myocardial cells and the maintenance of cardiac morphogenesis and homeostasis, as well as the formation of vascular morphology

expression in tumors from patients with poor prognosis [63, 64].

Histone 3 trimethylation at lysine 27 (H3K27me3), a histone modification associated with gene silencing, is catalyzed by the methyltransferase EZH2, an enzymatically active component of the PRC2 [65]. EZH2 is highly expressed in undifferentiated or poorly differentiated stromal NB tumors, and its overexpression correlates with poor prognosis. NB tumor suppressor genes, including *CASZ1*, *CLU*, *NGFR*, and *RUNX3*, are direct targets of EZH2- and H3K27me3-mediated gene silencing [14]. Knocking down EZH2 expression using RNA interference or inhibiting its expression using 3-deazaneplanocin A drugs increases CASZ1 expression, inhibits NB cell growth, and induces neurite extension [14].

Although demethylating agents can induce CASZ1 expression, the methylation status of the 5′ and 3′ CpG-rich regions of the *CASZ1* gene, determined via bisulfite sequencing, appears insufficient to explain the low CASZ1 expression level [61, 63]. HDAC inhibitors, such as depsipeptide, can upregulate the expression of several

genes, with TSA being the sole inducer of CASZ1 expression and three other genes among the 30 genes located in the shortest region of the overlap of Chr1p36 between markers D1S508 and D1S244 [66]. This suggests that only a subset of genes on Chr1p36 is silenced by histone deacetylation. Epigenetic silencing, whether direct or indirect, likely contributes to the low CASZ1 expression level in NB cells.

The dysregulation of the cell cycle mechanism marks cancer progression [67, 68]. Previous microarray analysis has revealed that tumor transcriptomes from patients with poor prognosis are enriched with cell cycle-related genes, whereas those from patients with good prognosis are enriched with differentiation-related genes [69]. Low CASZ1 expression, resulting from the loss of heterozygosity or epigenetic repression, is associated with abnormal regulation of cell cycle genes, including *Cyclin D1* and *Chk1*, leading to an undifferentiated NB phenotype. The increased expression of cyclin D1 and enhanced cyclin D-dependent kinase activity contribute to pRb hyperphosphorylation and E2F release, thereby activating

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 6 of 11

E2F-dependent gene transcription and promoting cell cycle progression in the G1-S phase [70, 71]. CASZ1 restoration activates pRb in the G1 phase, suppressing the expression of G2/M regulators, Cyclin B1, and Chk1, thereby leading to prolonged cell cycle progression and decreased cell proliferation in NB [72]. Furthermore, neural crest lineage-regulated transcription factors constitute a core regulatory circuit (CRC) in NB to specify a noradrenergic tumor phenotype. In NB tumor cells, the CASZ1 tumor suppressor is silenced by the NB CRC component HAND2, whereas CRC components are highly expressed. Restored CASZ1 forms a negative feedback regulatory circuit with the established NB CRC, inducing noradrenergic neuronal differentiation in NB [73].

In other tumors

CASZ1 exhibits distinct expression patterns across various solid tumors, manifesting dual biological functions contingent on tumor type. For instance, Wang et al. reported reduced CASZ1 expression in hepatocellular carcinoma tissues, which hindered abnormal tumor cell proliferation by modulating the MAPK/ERK signaling pathway alongside MMP2 and MMP9 expression in vitro [74]. Similarly, CASZ1 downregulation has been observed in colorectal cancer, esophageal cancer, lung adenocarcinoma, and clear cell renal cell carcinoma, where it has been associated with patient prognosis and could serve as a novel prognostic marker [17–19, 75]. Notably, the loss of CASZ1 activity can impede embryonal rhabdomyosarcoma differentiation through RAS-MEK signaling or genetic mutations, culminating in RMS tumor development [76].

Conversely, contrary to the that reported by several previous studies, high CASZ1 expression has been observed in glioma tissues, where it functions as an oncogene by regulating the transcription of its target gene *p75NTR* [20]. Additionally, CASZ1 is upregulated in EOC cells, promoting their epithelial–mesenchymal transition, whereas CASZ1 knockdown inhibits cancer cell metastasis in vivo [21]. Furthermore, in lung adenocarcinoma and idiopathic pulmonary fibrosis, CASZ1 shows hypermethylation and low expression, which is significantly associated with the prognosis of lung adenocarcinoma [18, 77]. Recent studies have shown that CASZ1 also plays an oncogenic role in lung cancer, with its expression positively correlated with cancer metastasis and poor prognosis. Specifically, CASZ1 regulates ITGAV expression, promoting lung cancer migration, invasion, and epithelial–mesenchymal transition [78]. The complex role of CASZ1 in malignant tumors may be related to tissue and tumor specificity. Hence, investigating the prognostic value of CASZ1 as a biomarker for cancer diagnosis and prognosis is imperative.

In other diseases

In humans, the *CASZ1* gene is located on chromosome 1p36, and 1p36 deletion is the most prevalent telomere deletion. This deletion is causally related to congenital cardiovascular malformations and cardiomyopathy, which are the most common phenotypes of 1p36 deletion syndrome [79]. Specific missense (p.L38P) and nonsense (p.K351X) mutations have been identified in families with congenital VSD [22] and dilated cardiomyopathy (DCM) [23], respectively. Functional studies have revealed that the L38P and K351X mutant CASZ1 proteins lose their transcriptional activity. Additionally, a novel variant of the *CASZ1* gene, c.2443_2459delGTGGGCACCCCC AGCCT (p.Val815Profs*14), was identified in a patient with DCM and left ventricular noncompaction cardiomyopathy (LVNC), highlighting the role of *CASZ1* as a pathogenic gene for human LVNC [24]. In another case of DCM, a de novo frameshift mutation, c.3781del (p.(Trp1261GlyfsTer29)), was identified in the *CASZ1* gene [25]. Associating *CASZ1* loss-of-function mutations with human cardiac disease susceptibility holds potential implications for the personalized prevention and treatment of cardiac diseases.

An epigenome-wide association study, leveraging genome-wide transcriptome data, has revealed that CASZ1 methylation may serve as a regulatory element linked to mortality in patients with cardiovascular disease [26]. GWASs have established significant associations between DNA methylation and the risk of blood pressure (BP) and ischemic stroke, and CASZ1 was reportedly hypomethylated in Chinese patients with hypertensive cerebral infarction [80]. Additionally, CASZ1b, a newly discovered corepressor of the mineralocorticoid receptor (MR), is co-expressed with MR in MR target cells, including renal tubular cells. CASZ1b inhibits MR transcriptional activity, serving as an aldosterone-dependent adapter protein linking MR and the nucleosome remodeling deacetylase (Mi-2/NuRD) complexes, thereby inhibiting epithelial Na$^+$ channel-α and serum/glucocorticoid-regulated kinase 1 expression, which ultimately lowers BP levels [81]. Nevertheless, injecting CASZ1 siRNA into mouse kidneys did not significantly alter BP [82]. In a recent GWAS study on primary aldosteronism, CASZ1 was identified as a gene associated with this condition, and the overexpression of CASZ1 inhibited aldosterone biosynthesis in adrenal cells [83]. These findings suggest that CASZ1 regulates hypertension and primary aldosteronism through dual mechanisms, namely, the modulation of MR transcriptional activity and aldosterone biosynthesis. GWAS on hypertension have reported

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 7 of 11

Table 2 Potential role of CASZ1 in diseases

	Disease types	Gene expression/mutation	Proposed mechanism	Refs.
Cancers	Neuroblastoma	Down		
	Hepatocellular carcinoma	Down	Regulates the MAPK/ERK pathway and MMP2/MMP9 expression, inhibiting abnormal tumor cell proliferation	[74]
	Colorectal cancer Esophageal cancer Lung adenocarcinoma Clear cell renal cell carcinoma	Down	A new prognostic indicator	[17–19, 75]
	Embryonal rhabdomyosarcoma	Down	RAS-MEK signaling or genetic alterations	[76]
	Glioma	Up	Regulates target gene *p75NTR* transcription	[20]
	Epithelial ovarian cancer	Up	Promotes the epithelial–mesenchymal transition of EOC cells	[21]
	Lung adenocarcinoma	Up	Promotes cell migration and invasion by driving ITGAV expression	[78]
Other diseases	Ventricular septal defects (VSD)	Missense mutation p. L38p	–	[22]
	Dilated cardiomyopathy (DCM)	Nonsense mutation p.K351X and c.3781del (p.(Trp1261GlyfsTer29)) frameshift mutation		[23] [25]
	Left ventricular noncompaction cardiomyopathy (LVNC)	p.Val815Profs*14 heterozygous frameshift variant		[24]
	Hypertension	Unknown	Interacts with MR and the Mi-2/NuRD complex to inhibit ENaCα and SGK expression	[81, 83]
	Osteoarthritis	Unknown	Inhibits chondrocyte apoptosis and inflammatory response	[27]
	Immune inflammation	Unknown	Orchestrates T helper (Th) cell differentiation	[87]
	Fasting plasma glucose (FPG)	DNA methylation variants	–	[88]
	Stroke	CASZ1 genetic variants (rs4845941 and rs778228)	–	[90]

that three single-nucleotide polymorphisms (SNPs) in the CASZ1 gene, rs880315 [57, 84, 85], rs284277 [56] and rs12046278 [86], are associated with hypertension.

Osteoarthritis is an age-related condition characterized by articular cartilage degeneration and joint inflammation that has garnered research attention in recent years. Notably, CircANKRD36 has emerged a key player in preventing chondrocyte apoptosis and counteracting inflammatory responses induced by IL-1β treatment. This protective effect is attributed to the ability CircANKRD36 to target miR-599, leading to the upregulation of Casz1 expression [27]. Casz1, a recognized regulator of T helper (Th) cell plasticity, holds major clinical relevance in autoimmune inflammation and mucosal immunity. In both in vitro and in vivo settings, Casz1 plays a vital role in Th differentiation, as evidenced by the reduced susceptibility of CD4$^+$ T cells lacking Casz1 to experimental autoimmune encephalomyelitis. Furthermore, the loss of Casz1 results in the severe impairment of Th17 and Treg responses during mucosal *Candida* infection, rendering

mice deficient in Casz1 less capable of clearing secondary infections [87].

Genome-wide DNA methylation analysis of whole blood from monozygotic twins has revealed that CASZ1 DNA methylation variants are negatively associated with fasting plasma glucose (FPG) levels [88]. Abnormal DNA methylation levels in the promoter region of the placental CASZ1 gene may lead to metabolic diseases including type 2 diabetes mellitus (T2DM) [89]. The association between CASZ1 gene variants and stroke risk in Chinese population studies have shown that CASZ1 genetic variants rs4845941 and rs778228 are significantly associated with an increased risk of stroke. Gender-stratified analysis also shows that CASZ1 rs778228 locus is associated with a higher risk of stroke in females. CASZ1 and its related genes may promote the occurrence of stroke, which is of great significance for the treatment and prevention of stroke [90]. There is a reproducible association between rs11121615 SNP, located within an intron of CASZ1 gene, and chronic venous disease (CVD) [91–93].

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 8 of 11

In addition, the mutation frequency of SNPs rs10511083 of CASZ1 gene was significantly correlated with psoriasis [94]. Table 2 summarizes the mechanisms underlying the effects of CASZ1 on various diseases.

Conclusions

Since its discovery in the early 1990s, the TF CASZ1 has been found to play a crucial role in neural, cardiac, and cardiovascular development. Its utility extends to elucidating the cellular and molecular mechanisms underlying the diversification and subsequent differentiation of neural stem/progenitor cells and cardiomyocytes. In diseases marked by cardiac developmental anomalies, such as DCM, VSD, and LVNC, the loss of CASZ1 expression or genetic mutations can contribute to aberrant cardiac morphogenesis. Notably, the methylation of CASZ1 serves as a regulatory element associated with mortality in patients with cardiovascular disease, and it is reported hypomethylated in Chinese patients with hypertensive cerebral infarction. Furthermore, CASZ1 holds clinical importance in the context of cartilage degeneration and autoimmune inflammation.

CASZ1 plays dual roles in cancer, functioning both as a tumor suppressor and promoter, thereby influencing cancer cell metastasis. The loss of CASZ1 expression or its mutational inactivation is associated with diseases or cancers linked to developmental defects. Moreover, the epigenetic silencing of CASZ1 is linked to poor prognosis in NB. Conversely, CASZ1 is downregulated in hepatocellular carcinoma, colorectal cancer, esophageal cancer, lung adenocarcinoma, and clear cell renal cell carcinoma, and its decreased expression is linked to patient prognosis, with this diminished expression serving as a potential prognostic indicator. Conversely, CASZ1 is highly expressed in glioma and EOC, suggesting a tissue- and tumor-specific expression pattern. The exploration of the potential of CASZ1 as a cancer biomarker for diagnosis and prognosis involves the evaluation of its prognostic value in tumor cells.

In conclusion, as a tumor suppressor gene of neuroblastoma, CASZ1 is involved in the progression of NB through cell cycle regulation and is associated with poor prognosis. Low expression of CASZ1 in hepatocellular carcinoma, colorectal cancer, esophageal cancer, lung adenocarcinoma and clear cell renal cell carcinoma is associated with poor prognosis, while high expression of CASZ1 in glioma, EOC and lung cancer promotes cancer progression. These studies suggest that CASZ1 can be used as a diagnostic and prognostic indicator or as a therapeutic target for cancer. In addition, CASZ1 loss-of-function mutations or mutations at SNPs loci are associated with susceptibility to human diseases, which is of great significance for personalized prevention and treatment of diseases. Therefore, it will be intriguing to investigate the regulatory mechanisms of CASZ1 itself and to identify additional transcriptional targets that could drive development of innovative therapeutic strategies for disease.

Abbreviations

CASZ1	Castor zinc finger 1
NB	Neuroblastoma
EOC	Epithelial ovarian cancer
ZnF	Zinc finger
NLS	Nuclear localization signals
NES	Nuclear export signals
CHD5	Congenital heart disease 5 protein
CID	CHD5-interacting domain
CNS	Central nervous system
RPCs	Retinal progenitor cells
dI1	Dorsal interneuron 1
dILB	Dorsal late-born excitatory
PRC	Polycomb repressive complex
NuRD	Nucleosome remodeling and deacetylase
VSD	Ventricular septal defects
ECs	Endothelial cells
GWAS	Genome-wide association studies
Egfl7	Epidermal growth factor-like domain 7
CRC	Core regulatory circuit
DCM	Dilated cardiomyopathy
LVNC	Left ventricular noncompaction cardiomyopathy
BP	Blood pressure
MR	Mineralocorticoid receptor

Author contributions
All authors wrote, revised, and approved the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

References

1. Mellerick DM, Kassis JA, Zhang SD, Odenwald WF. Castor encodes a novel zinc finger protein required for the development of a subset of CNS neurons in *Drosophila*. Neuron. 1992;9:789–803. https://doi.org/10.1016/0896-6273(92)90234-5.
2. Liu Z, Yang X, Tan F, Cullion K, Thiele CJ. Molecular cloning and characterization of human castor, a novel human gene upregulated during cell differentiation. Biochem Biophys Res Commun. 2006;344:834–44. https://doi.org/10.1016/j.bbrc.2006.03.207.

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 9 of 11

3. Yavatkar AS, Lin Y, Ross J, Fann Y, Brody T, Odenwald WF. Rapid detection and curation of conserved DNA via enhanced-BLAT and Evo-PrinterHD analysis. BMC Genom. 2008;9:106. https://doi.org/10.1186/1471-2164-9-106.

4. Engstrom PG, Fredman D, Lenhard B. Ancora: a web resource for exploring highly conserved noncoding elements and their association with developmental regulatory genes. Genome Biol. 2008;9:R34. https://doi.org/10.1186/gb-2008-9-2-r34.

5. Bejerano G, Pheasant M, Makunin I, Stephen S, Kent WJ, Mattick JS, Haussler D. Ultraconserved elements in the human genome. Science. 2004;304:1321–5. https://doi.org/10.1126/science.1098119.

6. Woolfe A, Goodson M, Goode DK, Snell P, McEwen GK, Vavouri T, Smith SF, North P, Callaway H, Kelly K, et al. Highly conserved non-coding sequences are associated with vertebrate development. PLoS Biol. 2005;3: e7. https://doi.org/10.1371/journal.pbio.0030007.

7. Cui X, Doe CQ. *ming* is expressed in neuroblast sublineages and regulates gene expression in the *Drosophila* central nervous system. Development. 1992;116:943–52. https://doi.org/10.1242/dev.116.4.943.

8. Grosskortenhaus R, Robinson KJ, Doe CQ. Pdm and castor specify late-born motor neuron identity in the NB7-1 lineage. Genes Dev. 2006;20:2618–27. https://doi.org/10.1101/gad.1445306.

9. von Hilchen CM, Beckervordersandforth RM, Rickert C, Technau GM, Altenhein B. Identity, origin, and migration of peripheral glial cells in the *Drosophila* embryo. Mech Dev. 2008;125:337–52. https://doi.org/10.1016/j.mod.2007.10.010.

10. Christine KS, Conlon FL. Vertebrate CASTOR is required for differentiation of cardiac precursor cells at the ventral midline. Dev Cell. 2008;14:616–23. https://doi.org/10.1016/j.devcel.2008.01.009.

11. Liu Z, Li W, Ma X, Ding N, Spallotta F, Southon E, Tessarollo L, Gaetano C, Mukouyama YS, Thiele CJ. Essential role of the zinc finger transcription factor Casz1 for mammalian cardiac morphogenesis and development. J Biol Chem. 2014;289:29801–16. https://doi.org/10.1074/jbc.M114.570416.

12. Charpentier MS, Christine KS, Amin NM, Dorr KM, Kushner EJ, Bautch VL, Taylor JM, Conlon FL. CASZ1 promotes vascular assembly and morphogenesis through the direct regulation of an EGFL7/RhoA-mediated pathway. Dev Cell. 2013;25:132–43. https://doi.org/10.1016/j.devcel.2013.03.003.

13. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci USA. 2005;102:15545–50. https://doi.org/10.1073/pnas.0506580102.

14. Wang C, Liu Z, Woo CW, Li Z, Wang L, Wei JS, Marquez VE, Bates SE, Jin Q, Khan J, et al. EZH2 mediates epigenetic silencing of neuroblastoma suppressor genes CASZ1, CLU, RUNX3, and NGFR. Cancer Res. 2012;72:315–24. https://doi.org/10.1158/0008-5472.CAN-11-0961.

15. Schmitz M, Driesch C, Beer-Grondke K, Jansen L, Runnebaum IB, Durst M. Loss of gene function as a consequence of human papillomavirus DNA integration. Int J Cancer. 2012;131:E593–602. https://doi.org/10.1002/ijc.27433.

16. Hoff AM, Johannessen B, Alagaratnam S, Zhao S, Nome T, Lovf M, Bakken AC, Hektoen M, Sveen A, Lothe RA, et al. Novel RNA variants in colorectal cancers. Oncotarget. 2015;6:36587–602. https://doi.org/10.18632/oncotarget.5500.

17. Wang HQ, Yang CY, Wang SY, Wang T, Han JL, Wei K, Liu FC, Xu JD, Peng XZ, Wang JM. Cell-free plasma hypermethylated CASZ1, CDH13 and ING2 are promising biomarkers of esophageal cancer. J Biomed Res. 2018;32:424–33. https://doi.org/10.7555/JBR.32.20170065.

18. Wang X, Shi D, Zhao D, Hu D. Aberrant methylation and differential expression of SLC2A1, TNS4, GAPDH, ATP8A2, and CASZ1 are associated with the prognosis of lung adenocarcinoma. Biomed Res Int. 2020;2020:1807089. https://doi.org/10.1155/2020/1807089.

19. Kim B, Jung M, Moon KC. The prognostic significance of protein expression of CASZ1 in clear cell renal cell carcinoma. Dis Markers. 2019;2019:1342161. https://doi.org/10.1155/2019/1342161.

20. Mao C, Huang C, Hu Z, Qu S. Transcription factor CASZ1 increases an oncogenic transcriptional process in tumorigenesis and progression of glioma cells. MedComm. 2022;3: e182. https://doi.org/10.1002/mco2.182.

21. Wu YY, Chang CL, Chuang YJ, Wu JE, Tung CH, Chen YC, Chen YL, Hong TM, Hsu KF. CASZ1 is a novel promoter of metastasis in ovarian cancer. Am J Cancer Res. 2016;6:1253–70.

22. Huang RT, Xue S, Wang J, Gu JY, Xu JH, Li YJ, Li N, Yang XX, Liu H, Zhang XD, et al. CASZ1 loss-of-function mutation associated with congenital heart disease. Gene. 2016;595:62–8. https://doi.org/10.1016/j.gene.2016.09.044.

23. Qiu XB, Qu XK, Li RG, Liu H, Xu YJ, Zhang M, Shi HY, Hou XM, Liu X, Yuan F, et al. CASZ1 loss-of-function mutation contributes to familial dilated cardiomyopathy. Clin Chem Lab Med. 2017;55:1417–25. https://doi.org/10.1515/cclm-2016-0612.

24. Guo J, Li Z, Hao C, Guo R, Hu X, Qian S, Zeng J, Gao H, Li W. A novel de novo CASZ1 heterozygous frameshift variant causes dilated cardiomyopathy and left ventricular noncompaction cardiomyopathy. Mol Genet Genomic Med. 2019;7: e828. https://doi.org/10.1002/mgg3.828.

25. Orlova A, Guseva D, Ryzhkova O. Identification of a novel de novo variant in the CASZ1 causing a rare type of dilated cardiomyopathy. Int J Mol Sci. 2022. https://doi.org/10.3390/ijms232012506.

26. Abdulrahim JW, Kwee LC, Grass E, Siegler IC, Williams R, Karra R, Kraus WE, Gregory SG, Shah SH. Epigenome-wide association study for all-cause mortality in a cardiovascular cohort identifies differential methylation in castor zinc finger 1 (CASZ1). J Am Heart Assoc. 2019;8: e013228. https://doi.org/10.1161/JAHA.119.013228.

27. Zhou JL, Deng S, Fang HS, Du XJ, Peng H, Hu QJ. Circular RNA circAN-KRD36 regulates Casz1 by targeting miR-599 to prevent osteoarthritis chondrocyte apoptosis and inflammation. J Cell Mol Med. 2021;25:120–31. https://doi.org/10.1111/jcmm.15884.

28. Kambadur R, Koizumi K, Stivers C, Nagle J, Poole SJ, Odenwald WF. Regulation of POU genes by castor and hunchback establishes layered compartments in the *Drosophila* CNS. Genes Dev. 1998;12:246–60. https://doi.org/10.1101/gad.12.2.246.

29. Odenwald WF. Changing fates on the road to neuronal diversity. Dev Cell. 2005;8:133–4. https://doi.org/10.1016/j.devcel.2005.01.005.

30. Hitier R, Chaminade M, Preat T. The *Drosophila* castor gene is involved in postembryonic brain development. Mech Dev. 2001;103:3–11. https://doi.org/10.1016/s0925-4773(01)00312-4.

31. Grosskortenhaus R, Pearson BJ, Marusich A, Doe CQ. Regulation of temporal identity transitions in *Drosophila* neuroblasts. Dev Cell. 2005;8:193–202. https://doi.org/10.1016/j.devcel.2004.11.019.

32. O'Rahilly R, Muller F. Minireview: summary of the initial development of the human nervous system. Teratology. 1999;60:39–41. https://doi.org/10.1002/(SICI)1096-9926(199907)60:1%3c39::AID-TERA11%3e3.0.CO;2-I.

33. Liu Z, Lam N, Wang E, Virden RA, Pawel B, Attiyeh EF, Maris JM, Thiele CJ. Identification of CASZ1 NES reveals potential mechanisms for loss of CASZ1 tumor suppressor activity in neuroblastoma. Oncogene. 2017;36:97–109. https://doi.org/10.1038/onc.2016.179.

34. Liu Z, Lam N, Thiele CJ. Zinc finger transcription factor CASZ1 interacts with histones, DNA repair proteins and recruits NuRD complex to regulate gene transcription. Oncotarget. 2015;6:27628–40. https://doi.org/10.18632/oncotarget.4733.

35. Miller FD, Gauthier AS. Timing is everything: making neurons versus glia in the developing cortex. Neuron. 2007;54:357–69. https://doi.org/10.1016/j.neuron.2007.04.019.

36. Qian X, Shen Q, Goderie SK, He W, Capela A, Davis AA, Temple S. Timing of CNS cell generation: a programmed sequence of neuron and glial cell production from isolated murine cortical stem cells. Neuron. 2000;28:69–80. https://doi.org/10.1016/s0896-6273(00)00086-6.

37. Shen Q, Wang Y, Dimos JT, Fasano CA, Phoenix TN, Lemischka IR, Ivanova NB, Stifani S, Morrisey EE, Temple S. The timing of cortical neurogenesis is encoded within lineages of individual progenitor cells. Nat Neurosci. 2006;9:743–51. https://doi.org/10.1038/nn1694.

38. Clark BS, Stein-O'Brien GL, Shiau F, Cannon GH, Davis-Marcisak E, Sherman T, Santiago CP, Hoang TV, Rajaii F, James-Esposito RE, et al. Single-cell RNA-seq analysis of retinal development identifies NFI factors as regulating mitotic exit and late-born cell specification. Neuron. 2019;102:1111-1126.e1115. https://doi.org/10.1016/j.neuron.2019.04.010.

39. Rapaport DH, Wong LL, Wood ED, Yasumura D, LaVail MM. Timing and topography of cell genesis in the rat retina. J Comp Neurol. 2004;474:304–24. https://doi.org/10.1002/cne.20134.

40. Carter-Dawson LD, LaVail MM. Rods and cones in the mouse retina. II. Autoradiographic analysis of cell generation using tritiated thymidine. J Comp Neurol. 1979;188:263–72. https://doi.org/10.1002/cne.901880205.

Liu *et al. European Journal of Medical Research*   (2023) 28:562

Page 10 of 11

41. Doe CQ. Temporal patterning in the *Drosophila* CNS. Annu Rev Cell Dev Biol. 2017;33:219–40. https://doi.org/10.1146/annurev-cellbio-111315-125210.

42. Mattar P, Ericson J, Blackshaw S, Cayouette M. A conserved regulatory logic controls temporal identity in mouse neural progenitors. Neuron. 2015;85:497–504. https://doi.org/10.1016/j.neuron.2014.12.052.

43. Amin NM, Gibbs D, Conlon FL. Differential regulation of CASZ1 protein expression during cardiac and skeletal muscle development. Dev Dyn. 2014;243:948–56. https://doi.org/10.1002/dvdy.24126.

44. Monteiro CB, Midao L, Rebelo S, Reguenga C, Lima D, Monteiro FA. Zinc finger transcription factor Casz1 expression is regulated by homeodomain transcription factor Prrxl1 in embryonic spinal dorsal horn late-born excitatory interneurons. Eur J Neurosci. 2016;43:1449–59. https://doi.org/10.1111/ejn.13214.

45. Liu Z, Naranjo A, Thiele CJ. CASZ1b, the short isoform of CASZ1 gene, coexpresses with CASZ1a during neurogenesis and suppresses neuroblastoma cell growth. PLoS ONE. 2011;6: e18557. https://doi.org/10.1371/journal.pone.0018557.

46. McClellan KA, Slack RS. Novel functions for cell cycle genes in nervous system development. Cell Cycle. 2006;5:1506–13. https://doi.org/10.4161/cc.5.14.2980.

47. Fasano CA, Dimos JT, Ivanova NB, Lowry N, Lemischka IR, Temple S. shRNA knockdown of Bmi-1 reveals a critical role for p21-Rb pathway in NSC self-renewal during development. Cell Stem Cell. 2007;1:87–99. https://doi.org/10.1016/j.stem.2007.04.001.

48. Mattar P, Stevanovic M, Nad I, Cayouette M. Casz1 controls higher-order nuclear organization in rod photoreceptors. Proc Natl Acad Sci USA. 2018;115:E7987–96. https://doi.org/10.1073/pnas.1803069115.

49. Mattar P, Jolicoeur C, Dang T, Shah S, Clark BS, Cayouette M. A Casz1-NuRD complex regulates temporal identity transitions in neural progenitors. Sci Rep. 2021;11:3858. https://doi.org/10.1038/s41598-021-83395-7.

50. Ahuja P, Sdek P, MacLellan WR. Cardiac myocyte cell cycle control in development, disease, and regeneration. Physiol Rev. 2007;87:521–44. https://doi.org/10.1152/physrev.00032.2006.

51. Dorr KM, Amin NM, Kuchenbrod LM, Labiner H, Charpentier MS, Pevny LH, Wessels A, Conlon FL. Casz1 is required for cardiomyocyte G1-to-S phase progression during mammalian cardiac development. Development. 2015;142:2037–47. https://doi.org/10.1242/dev.119107.

52. Sojka S, Amin NM, Gibbs D, Christine KS, Charpentier MS, Conlon FL. Congenital heart disease protein 5 associates with CASZ1 to maintain myocardial tissue integrity. Development. 2014;141:3040–9. https://doi.org/10.1242/dev.106518.

53. Kennedy L, Kaltenbrun E, Greco TM, Temple B, Herring LE, Cristea IM, Conlon FL. Formation of a TBX20-CASZ1 protein complex is protective against dilated cardiomyopathy and critical for cardiac homeostasis. PLoS Genet. 2017;13: e1007011. https://doi.org/10.1371/journal.pgen.1007011.

54. De Val S. Key transcriptional regulators of early vascular development. Arterioscler Thromb Vasc Biol. 2011;31:1469–75. https://doi.org/10.1161/ATVBAHA.110.221168.

55. Patan S. Vasculogenesis and angiogenesis as mechanisms of vascular network formation, growth and remodeling. J Neurooncol. 2000;50:1–15. https://doi.org/10.1023/a:1006493130855.

56. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, et al. Genome-wide association study of blood pressure and hypertension. Nat Genet. 2009;41:677–87. https://doi.org/10.1038/ng.384.

57. Takeuchi F, Isono M, Katsuya T, Yamamoto K, Yokota M, Sugiyama T, Nabika T, Fujioka A, Ohnaka K, Asano H, et al. Blood pressure and hypertension are associated with 7 loci in the Japanese population. Circulation. 2010;121:2302–9. https://doi.org/10.1161/CIRCULATIONAHA.109.904664.

58. Charpentier MS, Taylor JM, Conlon FL. The CASZ1/Egfl7 transcriptional pathway is required for RhoA expression in vascular endothelial cells. Small GTPases. 2013;4:231–5. https://doi.org/10.4161/sgtp.26849.

59. Charpentier MS, Dorr KM, Conlon FL. Transcriptional regulation of blood vessel formation: the role of the CASZ1/Egfl7/RhoA pathway. Cell Cycle. 2013;12:2165–6. https://doi.org/10.4161/cc.25539.

60. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. Lancet. 2007;369:2106–20. https://doi.org/10.1016/S0140-6736(07)60983-0.

61. Liu Z, Yang X, Li Z, McMahon C, Sizer C, Barenboim-Stapleton L, Bliskovsky V, Mock B, Ried T, London WB, et al. CASZ1, a candidate tumor-suppressor gene, suppresses neuroblastoma tumor growth through reprogramming

62. Virden RA, Thiele CJ, Liu Z. Characterization of critical domains within the tumor suppressor CASZ1 required for transcriptional regulation and growth suppression. Mol Cell Biol. 2012;32:1518–28. https://doi.org/10.1128/MCB.06039-11.

63. Caren H, Fransson S, Ejeskar K, Kogner P, Martinsson T. Genetic and epigenetic changes in the common 1p36 deletion in neuroblastoma tumours. Br J Cancer. 2007;97:1416–24. https://doi.org/10.1038/sj.bjc.6604032.

64. Caren H, Ejeskar K, Fransson S, Hesson L, Latif F, Sjoberg RM, Krona C, Martinsson T. A cluster of genes located in 1p36 are down-regulated in neuroblastomas with poor prognosis, but not due to CpG island methylation. Mol Cancer. 2005;4:10. https://doi.org/10.1186/1476-4598-4-10.

65. Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P, Jones RS, Zhang Y. Role of histone H3 lysine 27 methylation in polycomb-group silencing. Science. 2002;298:1039–43. https://doi.org/10.1126/science.1076997.

66. Chayka O, Corvetta D, Dews M, Caccamo AE, Piotrowska I, Santilli G, Gibson S, Sebire NJ, Himoudi N, Hogarty MD, et al. Clusterin, a haploinsufficient tumor suppressor gene in neuroblastomas. J Natl Cancer Inst. 2009;101:663–77. https://doi.org/10.1093/jnci/djp063.

67. Montagnoli A, Moll J, Colotta F. Targeting cell division cycle 7 kinase: a new approach for cancer therapy. Clin Cancer Res. 2010;16:4503–8. https://doi.org/10.1158/1078-0432.CCR-10-0185.

68. Matthews HK, Bertoli C, de Bruin RAM. Cell cycle control in cancer. Nat Rev Mol Cell Biol. 2022;23:74–88. https://doi.org/10.1038/s41580-021-00404-3.

69. Krasnoselsky AL, Whiteford CC, Wei JS, Bilke S, Westermann F, Chen QR, Khan J. Altered expression of cell cycle genes distinguishes aggressive neuroblastoma. Oncogene. 2005;24:1533–41. https://doi.org/10.1038/sj.onc.1208341.

70. Molenaar JJ, Ebus ME, Koster J, van Sluis P, van Noesel CJ, Versteeg R, Caron HN. Cyclin D1 and CDK4 activity contribute to the undifferentiated phenotype in neuroblastoma. Cancer Res. 2008;68:2599–609. https://doi.org/10.1158/0008-5472.CAN-07-5032.

71. Muller H, Bracken AP, Vernell R, Moroni MC, Christians F, Grassilli E, Prosperini E, Vigo E, Oliner JD, Helin K. E2Fs regulate the expression of genes involved in differentiation, development, proliferation, and apoptosis. Genes Dev. 2001;15:267–85. https://doi.org/10.1101/gad.864201.

72. Liu Z, Rader J, He S, Phung T, Thiele CJ. CASZ1 inhibits cell cycle progression in neuroblastoma by restoring pRb activity. Cell Cycle. 2013;12:2210–8. https://doi.org/10.4161/cc.25265.

73. Liu Z, Zhang X, Xu M, Lei H, Shern JF, Thiele CJ. Loss of CASZ1 tumor suppressor linked to oncogenic subversion of neuroblastoma core regulatory circuitry. Cell Death Dis. 2022;13:871. https://doi.org/10.1038/s41419-022-05314-6.

74. Wang JL, Yang MY, Xiao S, Sun B, Li YM, Yang LY. Downregulation of castor zinc finger 1 predicts poor prognosis and facilitates hepatocellular carcinoma progression via MAPK/ERK signaling. J Exp Clin Cancer Res. 2018;37:45. https://doi.org/10.1186/s13046-018-0720-8.

75. Sajadi M, Fazilti M, Nazem H, Mahdevar M, Ghaedi K. The expression changes of transcription factors including ANKZF1, LEF1, CASZ1, and ATOH1 as a predictor of survival rate in colorectal cancer: a large-scale analysis. Cancer Cell Int. 2022;22:339. https://doi.org/10.1186/s12935-022-02751-3.

76. Liu Z, Zhang X, Lei H, Lam N, Carter S, Yockey O, Xu M, Mendoza A, Hernandez ER, Wei JS, et al. CASZ1 induces skeletal muscle and rhabdomyosarcoma differentiation through a feed-forward loop with MYOD and MYOG. Nat Commun. 2020;11:911. https://doi.org/10.1038/s41467-020-14684-4.

77. Yang IV, Pedersen BS, Rabinovich E, Hennessy CE, Davidson EJ, Murphy E, Guardela BJ, Tedrow JR, Zhang Y, Singh MK, et al. Relationship of DNA methylation and gene expression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190:1263–72. https://doi.org/10.1164/rccm.201408-1452OC.

78. Taheri Baghmisheh S, Wu YY, Wu JE, Hsu KF, Chen YL, Hong TM. CASZ1 promotes migration, invasion, and metastasis of lung cancer cells by controlling expression of ITGAV. Am J Cancer Res. 2023;13:176–89.

79. Zaveri HP, Beck TF, Hernandez-Garcia A, Shelly KE, Montgomery T, van Haeringen A, Anderlid BM, Patel C, Goel H, Houge G, et al. Identification of critical regions and candidate genes for cardiovascular malformations

and cardiomyopathy associated with deletions of chromosome 1p36. PLoS ONE. 2014;9: e85600. https://doi.org/10.1371/journal.pone.0085600.

80. Mo XB, Zhang H, Wang AL, Xu T, Zhang YH. Integrative analysis identifies the association between CASZ1 methylation and ischemic stroke. Neurol Genet. 2020;6: e509. https://doi.org/10.1212/NXG.0000000000000509.

81. Yokota K, Shibata H, Kurihara I, Kobayashi S, Murai-Takeda A, Itoh H. CASZ1b is a novel transcriptional corepressor of mineralocorticoid receptor. Hypertens Res. 2021;44:407–16. https://doi.org/10.1038/s41440-020-00562-5.

82. Ji SM, Shin YB, Park SY, Lee HJ, Oh B. Decreases in Casz1 mRNA by an siRNA complex do not alter blood pressure in mice. Genom Inform. 2012;10:40–3. https://doi.org/10.5808/GI.2012.10.1.40.

83. Yokota K, Shibata H, Kurihara I, Itoh H, Sone M. CASZ1: a promising factor modulating aldosterone biosynthesis and mineralocorticoid receptor activity. Hypertens Res. 2023;46:417–20. https://doi.org/10.1038/s41440-022-01131-8.

84. Lu X, Wang L, Lin X, Huang J, Charles GuC, He M, Shen H, He J, Zhu J, Li H, et al. Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. Hum Mol Genet. 2015;24:865–74. https://doi.org/10.1093/hmg/ddu478.

85. Simino J, Shi G, Bis JC, Chasman DI, Ehret GB, Gu X, Guo X, Hwang SJ, Sijbrands E, Smith AV, et al. Gene–age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia. Am J Hum Genet. 2014;95:24–38. https://doi.org/10.1016/j.ajhg.2014.05.010.

86. Irvin MR, Sitlani CM, Floyd JS, Psaty BM, Bis JC, Wiggins KL, Whitsel EA, Sturmer T, Stewart J, Raffield L, et al. Genome-wide association study of apparent treatment-resistant hypertension in the CHARGE Consortium: the CHARGE pharmacogenetics working group. Am J Hypertens. 2019;32:1146–53. https://doi.org/10.1093/ajh/hpz150.

87. Bhaskaran N, Liu Z, Saravanamuthu SS, Yan C, Hu Y, Dong L, Zelenka P, Zheng L, Bletsos V, Harris R, et al. Identification of Casz1 as a regulatory protein controlling T helper cell differentiation, inflammation, and immunity. Front Immunol. 2018;9:184. https://doi.org/10.3389/fimmu.2018.00184.

88. Wang W, Yao W, Tan Q, Li S, Duan H, Tian X, Xu C, Zhang D. Identification of key DNA methylation changes on fasting plasma glucose: a genome-wide DNA methylation analysis in Chinese monozygotic twins. Diabetol Metab Syndr. 2023;15:159. https://doi.org/10.1186/s13098-023-01136-4.

89. Chen PY, Chu A, Liao WW, Rubbi L, Janzen C, Hsu FM, Thamotharan S, Ganguly A, Lam L, Montoya D, et al. Prenatal growth patterns and birthweight are associated with differential DNA methylation and gene expression of cardiometabolic risk genes in human placentas: a discovery-based approach. Reprod Sci. 2018;25:523–39. https://doi.org/10.1177/1933719117716779.

90. Zhang F, Fu C, Deng Y, Zhang M, Peng H, Li W, Zhong J, Zhou Q, Huang L, Xiao S, et al. Association of CASZ1 genetic variants with stroke risk in the Chinese population. J Stroke Cerebrovasc Dis. 2023;32: 107169. https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.107169.

91. Jones GT, Marsman J, Pardo LM, Nijsten T, De Maeseneer M, Phillips V, Lynch-Sutherland C, Horsfield J, Krysa J, van Rij AM. A variant of the castor zinc finger 1 (CASZ1) gene is differentially associated with the clinical classification of chronic venous disease. Sci Rep. 2019;9:14011. https://doi.org/10.1038/s41598-019-50586-2.

92. He R, Cai H, Jiang Y, Liu R, Zhou Y, Qin Y, Yao C, Wang S, Hu Z. Integrative analysis prioritizes the relevant genes and risk factors for chronic venous disease. J Vasc Surg Venous Lymphat Disord. 2022;10:738-748.e735. https://doi.org/10.1016/j.jvsv.2022.02.006.

93. Shadrina AS, Sharapov SZ, Shashkova TI, Tsepilov YA. Varicose veins of lower extremities: insights from the first large-scale genetic study. PLoS Genet. 2019;15: e1008110. https://doi.org/10.1371/journal.pgen.1008110.

94. Xing J, Zhao X, Li X, Wang Y, Li J, Hou R, Niu X, Yin G, Li X, Zhang K. Variation at ACOT12 and CT62 locus represents susceptibility to psoriasis in Han population. Mol Genet Genomic Med. 2020;8: e1098. https://doi.org/10.1002/mgg3.1098.

Publisher's Note