



## Congenital arch vessel anomalies in CHARGE syndrome: A frequent feature with risk for co-morbidity☆☆☆



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### ABSTRACT

**Background:** CHARGE syndrome is a complex multiple congenital malformation disorder with variable expression that is caused by mutations in the *CHD7* gene. Variable heart defects occur in 74% of patients with a *CHD7* mutation, with an overrepresentation of atrioventricular septal defects and conotruncal defects – including arch vessel anomalies.

**Methods and results:** We report an index patient with an arch vessel anomaly underlying serious feeding problems that resolved after arch vessel surgery. This led us to examine the incidence of arch vessel anomalies in our previously studied cohort of 299 patients with a *CHD7* mutation. Forty-two patients (14%) had an aortic arch anomaly, mostly aberrant subclavian artery or right aortic arch, which usually occurred in combination with other congenital heart defects (81%). The majority of these patients also had feeding problems that may be linked to their arch anomaly, but insufficient information was available to exclude other causes.

**Conclusions:** Arch vessel anomalies occur in a significant proportion of patients with a *CHD7* mutation, and these anomalies may cause morbidity due to compression of the esophagus or trachea. Since symptoms of vascular compression can mimic those caused by other abnormalities in CHARGE syndrome, it is important to be aware of arch vessel anomalies in this complex patient category. Whether a solitary arch vessel anomaly is an indicator for CHARGE syndrome still needs to be studied, but doctors should look out for other CHARGE syndrome features in patients with arch vessel anomalies.

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## 1. Introduction

CHARGE syndrome (MIM 214800, Coloboma, Heart disease, Choanal atresia, Retardation of growth and/or development, Genital hypoplasia and Ear abnormalities with or without deafness) is a multiple congenital malformation disorder with variable expression and an incidence of 5.8–6.7 per 100,000 newborns [1]. CHARGE syndrome is usually a sporadic condition that is caused, in particular, by *de novo* loss-of function mutations in the *CHD7* gene (MIM 608892) [2].

Congenital heart defects occur in 74% of patients who have CHARGE syndrome due to a *CHD7* mutation, and in 80% of patients with a truncating *CHD7* mutation [3]. Our previous study showed that while

the types of heart defects found in CHARGE syndrome patients are variable, atrioventricular septal defects and conotruncal defects are overrepresented compared to typically non-syndromic heart defects [3]. Congenital arch vessel anomalies such as aberrant right subclavian artery (ARSA) were highly overrepresented within our group of patients with CHARGE syndrome [3].

The aortic arch and its vessels are formed after the fourth week of embryogenesis by remodeling and re-arrangement of the aortic sac, the branchial arch arteries and the dorsal root aorta's. An embryo developing normally initially has one aortic sac which communicates with the heart via the truncus arteriosus and is connected to two dorsal root aortas via paired branchial arch arteries. The eventual left sided aortic arch derives from the aortic sac, left 4th branchial arch artery and left dorsal root aorta. The first origin, the brachiocephalic trunk, arises from the aortic sac. The right and left common carotid arteries develop from the 3rd branchial arch arteries. The root and first part of the right subclavian artery is formed by the right 4th branchial arch artery and right dorsal root aorta. The rest of the right subclavian artery and the complete left subclavian artery derive from an intersegmental artery that originates directly from the dorsal root aorta. The molecular control

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of this complex process is not well understood, but defective remodeling results in congenital arch vessel anomalies [4–6].

A common congenital arch vessel anomaly is an aberrant subclavian artery in which the right or left subclavian artery has an abnormal anatomical position. An aberrant right subclavian artery, which is also called *arteria lusoria*, passes posterior to the esophagus and left aortic arch. It occurs when the right fourth branchial arch artery and proximal portion of the right dorsal root aorta disappears, while the distal right dorsal root aorta persists [6]. Aberrant subclavian arteries have been found in 1–2% of pediatric patients who had echocardiograms and in cardiac autopsy specimens [7,8]. Another frequent arch vessel abnormality is a right-sided aortic arch (RAA) which is caused by the persistence of the right dorsal root aorta and disappearance of the left fourth branchial arch artery and left dorsal root aorta [6]. A RAA is usually associated with a congenital heart malformation [8,9].

Arch vessel anomalies are usually asymptomatic, but problems may occur when a complete or incomplete vascular ring causes compression of the esophagus and the trachea. A double aortic arch in which both left- and right-sided aortic arches surround the trachea and esophagus is the most common cause of vascular compression in children [10]. Presenting symptoms of vascular compression vary, but include recurrent respiratory infections, stridor, wheezing, cough, dyspnea, respiratory distress, dysphagia, feeding difficulties and vomiting [5,10].

In this study we describe CHARGE patients with congenital arch vessel anomalies and focus on the health problems that might be caused by arch vessel anomalies in these patients.

## 2. Patients and methods

### 2.1. Case report

We report a clinically diagnosed CHARGE patient with dysphagia due to an arch vessel anomaly. Clinical information was obtained from the extensive medical correspondence concerning this patient. The patient's parents have given consent for the publication of this data.

### 2.2. Cohort of patients with an arch anomaly and a *CHD7* mutation

We previously studied heart defects in 299 patients with a proven *CHD7* mutation, of whom 220 had a congenital heart defect [3]. This cohort consisted of patients tested for a *CHD7* mutation because of a clinical suspicion of CHARGE syndrome. The *CHD7* analysis was performed on a diagnostic basis at the DNA laboratory in Nijmegen, The Netherlands, between 2004 and 2009. Patients lived in The Netherlands (34%) and other European countries (54%), but also on other continents (12%). The accredited Medical Ethics Review Committee of the University Medical Center Groningen waived full ethical evaluation because, according to Dutch guidelines, no ethical approval is necessary if medical information that was already available is used anonymously and no extra tests have to be performed.

We selected patients from this previous study who had a vascular ring of any type, a RAA, an interrupted aortic arch, an aberrant left or right subclavian artery, or an aberrant origin of an aortic arch vessel. We studied cardiac phenotype and extra-cardiovascular symptoms in these patients. The patient described in the case report was not part of this cohort.

### 2.3. Control cohort to compare extra-cardiovascular features

The data collected about our study cohort were compared descriptively to a previously published group of 280 CHARGE patients with a known *CHD7* mutation [2]. Because there is some overlap between this group and our present study group, statistical comparisons were not possible. However, excluding these overlapping patients described here might bias the control group.

## 3. Results

### 3.1. Case report

We report new findings on a twenty-year-old male with CHARGE syndrome. He was born after an uneventful full-term pregnancy and with a birth weight of 8 lb (about 3500 g). He was evaluated directly after birth because of congenital anomalies and respiratory distress. He was diagnosed with laryngomalacia and had a tracheostoma until he was 8.5 years old. A diagnosis of CHARGE syndrome (which was then still an association) was made based on the combination of following anomalies: colobomata of the optic nerve and fundus, choanal stenosis, pulmonary valve dysplasia, genital hypoplasia with unilateral cryptorchism, small kidneys with subcortical cysts, a grade IV vesicoureteral reflux, velopharyngeal incompetence (due to 9<sup>th</sup> and 10<sup>th</sup> cranial nerve dysfunction), right sided facial nerve palsy and external ear anomalies with absent response to BAER. Further evaluation during the years showed profound sensorineural deafness with absent auditory nerves, absent semicircular canals, dysplastic cochlea, anosmia, hypogonadotropic hypogonadism and significant short stature with growth hormone deficiency. He had a normal conventional karyotype, but *CHD7* analysis had never been done. He does fulfill the current diagnostic criteria for CHARGE syndrome [11,12].

The boy experienced feeding problems from birth, for which he received tube feeding until the age of 9 years. Even after decannulation and removal of the feeding tube, his feeding problems persisted; he aspirated water and could only eat soft foods. He had several swallowing studies done through the years that showed a constriction of the esophagus. From the age of 10 years his esophagus was dilated several times, but his feeding problems did not improve. He had several periods of choking, which warranted further evaluation. At the age of 18 years, he had a gastroscopy, which indicated a vessel compressing the esophagus. An angiogram confirmed an aberrant right subclavian artery as the cause. After surgical re-implantation of the aberrant subclavian artery, the boy was finally able to eat normally, and no new feeding problems or periods of choking have occurred since that time.

### 3.2. Arch vessel anomalies in a cohort of patients with a *CHD7* mutation

Of the 299 patients with a *CHD7* mutation, 42 had a congenital arch vessel anomaly (14%). This group consists of 23 males and 19 females (see Table 1). Most patients had a truncating *CHD7* mutation (33/42, 79%). Fourteen patients were deceased (33%), ten of the twelve patients for whom the age of death was known died in the first year of life (see Table 1).

Right sided aortic arch (20 patients) and aberrant subclavian arteries (19 patients) were most frequently identified (see Table 1). A vascular ring was identified in five patients. An abnormal origin of an arch vessel was diagnosed in four patients, two concerning the subclavian artery (patient 1 and 37) and two the carotid arteries (patient 17 and 20). In patient 1, who had an interrupted aortic arch type B and a malalignment ventricular septal defect, the subclavian artery derived from the descending aorta. In patient 37, who had a right-sided aortic arch and a bicuspid aortic valve, the left subclavian artery derived from the pulmonary artery. Patient 17 had a persistent ductus arteriosus (PDA) and ARSA in combination with a right internal carotid artery that was inserted higher than usual. Patient 20 had a PDA and ARSA with a truncus bicaroticus, which means both carotid arteries originated from one common origin of the aortic arch.

Most patients had other heart defects in addition to their arch vessel anomaly (34/42, 81%), and one patient had a congenital conduction disorder. Interestingly, seven patients (17%) had an arch vessel anomaly as an isolated cardiovascular feature (see Table 1). The accompanying heart defects were variable, but often included septal defects (atrial as well as ventricular), PDA and tetralogy of Fallot or double outlet right ventricle.

**Table 1**  
Overview of 42 patients with a *CHD7* mutation and an arch vessel anomaly.

	Mutation type	Arch vessel anomaly	Other heart defect
1 <sup>a</sup>	f Fs	Aberrant origin SA, IAA	VSD
2	m Fs	ASA	PS
3 <sup>a</sup>	f Fs	ASA, IAA	AVSD, DORV
4	f Fs	ASA	ASD
5	f Fs	ASA	SAS
6	f Mis	ASA	VSD
7	m Non	ASA	Truncus
8	m Non	ASA	AVSD
9	m Non	ASA	ASD, BAV, VSD
10 <sup>a</sup>	f Non	ASA	ASD, coarctation, VSD
11	m Non	ASA	Fallot
12 <sup>a</sup>	f Non	ASA, IAA	Absent left AV valve, DORV
13 <sup>a</sup>	m Splice	ASA	Fallot, TAPVR
14	f Splice	ASA	PDA
15 <sup>a</sup>	f Splice	ASA	HLHS, coarctation
16	m Transl	ASA	ASD, PDA
17 <sup>a</sup>	m Non	ASA, aberrant origin RCA	PDA
18	m Mis	ASA, RAA	Peripheral PS
19	m Non	ASA, RAA	Coarctation
20	f Fs	ASA, truncus bicaroticus	PDA
21	m Fs	RAA	Fallot
22	f Fs	RAA	
23	f Fs	RAA	PDA
24 <sup>a</sup>	m Fs	RAA	Fallot
25	f Fs	RAA	
26	f Non	RAA	Coarctation, VSD
27	m Non	RAA	Coarctation, SAS, VSD
28	f Non	RAA	Fallot
29 <sup>a</sup>	f Non	RAA	
30 <sup>a</sup>	m Non	RAA	ASD, VSD
31	f Non	RAA	Fallot
32 <sup>a</sup>	m Non	RAA	
33	m Non	RAA	ASD, PDA
34 <sup>a</sup>	m Splice	RAA	DORV, VSD
35 <sup>a</sup>	m Splice	RAA	AVSD
36	m Splice	RAA	PDA
37 <sup>a</sup>	m Fs	RAA, aberrant origin LSA	BAV
38	m Fs	Vasc. ring	ASD, VSD
39	m Fs	Vasc. ring	
40	m Non	Vasc. ring	
41	f Splice	Vasc. ring	
42	f Non	Vasc. ring, RAA	

Sex: f, female; m, male.

Mutation type: Fs, frameshift; Mis, missense; Non, nonsense; Splice, splice site or intronic variant; Transl, translocation t(2;8) (q11.2; q11.2).

Arch vessel anomalies: ASA, aberrant subclavian artery; LSA, left subclavian artery; RAA, right aortic arch; RCA, right coronary artery; SA, subclavian artery; Vasc. ring, vascular ring. Other heart defects: ASD, atrial septal defect; AVSD, atrioventricular septal defect; AV valve, atrioventricular valve; BAV, bicuspid aortic valve; coarctation, coarctation aorta; DORV, double outlet right ventricle; Fallot, tetralogy of Fallot; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; SAS, subvalvular aortic stenosis; TAPVR, total anomalous pulmonary venous return; Truncus, truncus arteriosus; VSD, ventricular septal defect.

<sup>a</sup> Deceased.

The most common extracardiovascular features were external ear anomaly (36/36), hearing loss (34/34) and semicircular canal abnormalities (23/24), which were present in almost all patients for whom the information was known (see Table 2). Developmental delay, genital hypoplasia (e.g. micropenis or hypogonadotropic hypogonadism) and cranial nerve dysfunction were present in the majority of patients (>80%). These extracardiovascular features did not clearly differ between our study cohort and the control cohort (see Table 2).

Information on feeding or swallowing history was known for 26 of 37 patients who were alive at the age of 1 month. Only one out of these 26 patients was recorded not to have feeding or swallowing problems. Thus, these problems were present in 96% of patients (range 25/37–36/37 = 68–97%). Remarkably, at least twenty patients (77%, range 20/37–36/37 = 54–97%) had feeding problems that necessitated tube feeding. Information on feeding was known for 110 patients in our control cohort, and tube feeding was necessary in 90

patients (82%, range 90/280–260/280 = 32–93%). We have no information on recurrent respiratory infections, stridor, wheezing, cough or dyspnea in both our study and control group.

#### 4. Discussion

In our study cohort, arch vessel anomalies were present in 14% (42/299) of patients with a *CHD7* mutation and in 19% (42/220) of patients with a *CHD7* mutation and a cardiovascular defect. We might have missed patients with an arch vessel anomaly in our retrospective study because it can be missed with echocardiography, and because we know the collected data are not complete. We also did not have enough information to classify heart defects in 18 patients (8%), and in approximately 60% we had to base our classification on the information from the medical doctor who requested the *CHD7* analysis.

Several previous studies on smaller populations (between 47 and 83 patients) also documented arch vessel anomalies in 4 to 23% of the patients with CHARGE syndrome, or in 5 to 36% of the patients with CHARGE syndrome and a heart defect [13–16]. However the data from our study and the previous studies cannot easily be compared for a number of reasons. First, not every study used the same definition for arch vessel anomalies, while the type of heart defects that are categorized as arch vessel anomaly are not clear in others. For example, we did not include hypoplastic aortic arch as an arch vessel anomaly based on the classification system we used to classify heart defects [17,18], while a previous study did [16]. Second, we included patients with arch vessel anomalies and other cardiac anomalies in our percentages while, in at least one other study, patients with an arch vessel anomaly and another heart defect were partly categorized in a different group [16]. Finally, the populations differ because patients in all previous studies had a clinically based diagnosis of CHARGE syndrome, while we included only patients with a definite molecular diagnosis. Nonetheless, both our study and all previous studies show that arch vessel anomalies do occur more frequently in CHARGE syndrome than in the general population.

We primarily identified patients with aberrant subclavian arteries and right-sided aortic arch in our cohort, but rarer arch vessel anomalies can also occur in patients with CHARGE syndrome. For example, we identified an abnormal origin of an arch vessel in four of our patients (see Table 1). An aberrant origin has also been described previously in CHARGE patients for the left brachiocephalic trunk and left subclavian artery out of the pulmonary artery, respectively [19,20]. In our study cohort, the arch vessel anomalies usually occurred in combination with other heart defects. However, it is important to note that arch vessel anomalies such as right aortic arch and aberrant subclavian artery were solitary in 17% of our patient cohort.

Based on these clinical observations, *CHD7* probably has an effect on the embryonic development of the branchial arch arteries. This hypothesis is supported by animal studies in which knockdown of *CHD7* has been shown to have an effect on pharyngeal arch development [21,22]. We did not find an indication that truncating mutations in *CHD7* are more likely to be the cause of arch vessel anomalies, as they were present in comparable percentages in our study and control cohort (79% vs. 71%), while they are known to be present significantly more often in CHARGE patients with a congenital heart defect [3].

CHARGE syndrome is a complex multiple congenital malformation disorder. Children with CHARGE syndrome face significant problems. Feeding problems, chronic aspiration and swallowing dysfunction are often present and can result in recurrent respiratory infections [23,24]. Identifying the cause of feeding problems in CHARGE syndrome is complex, because they can be associated with structural problems of the oral cavity, the nasal cavity, the pharynx or larynx; cranial nerve defects; congenital heart defects; or a combination of factors. Since respiratory aspiration is a risk factor for early death in CHARGE syndrome, it is important to carefully evaluate feeding problems [25]. A vascular ring, caused by an arch vessel anomaly, may present as feeding problems

**Table 2**  
Other features of CHARGE syndrome in patients with arch vessel anomalies.

Patient		C	A	DD	GR	G	E	HL	SCC	CLP	F	CN
1 <sup>a</sup>	f	y	y	?	?	?	y	?	y	?	?	?
2	m	n	n	y	n	y	y	y	y	n	y	y
3 <sup>a</sup>	f	y	y	?	?	?	y	y	y	n	n	?
4	f	n	?	?	?	?	y	y	?	y	?	?
5	f	y	y	y	y	?	?	y	?	?	y	?
6	f	n	n	?	y	?	?	?	n	n	y	?
7	m	n	n	y	?	y	y	?	y	?	y <sup>c</sup>	y
8	m	y	n	y	y	?	y	y	y	?	y	?
9	m	y	?	?	?	y	y	y	y	y	y <sup>b</sup>	y
10 <sup>a</sup>	f	?	?	?	?	?	y	y	?	y	?	?
11	m	?	?	y	?	y	?	y	?	?	?	?
12 <sup>a</sup>	f	n	y	?	?	?	?	?	?	?	?	?
13 <sup>a</sup>	m	y	n	?	n	?	y	?	?	y	?	?
14	f	y	n	y	y	y	y	y	?	n	?	y
15 <sup>a</sup>	f	y	n	?	?	?	y	?	?	y	?	?
16	m	n	y	?	y	y	y	y	?	y	y	y
17 <sup>a</sup>	m	y	n	?	y	y	y	y	?	?	y <sup>b,c</sup>	y
18	m	y	?	?	?	y	y	?	?	?	?	y
19	m	n	y	?	n	y	y	y	y	n	y	?
20	f	y	n	y	n	?	y	y	y	?	?	?
21	m	y	n	y	n	y	y	y	y	n	?	y
22	f	n	?	y	?	?	y	y	y	y	y	n
23	f	y	?	?	?	?	y	y	?	?	?	y
24 <sup>a</sup>	m	n	y	?	n	y	y	y	y	n	?	?
25	f	?	y	y	?	?	?	y	?	?	?	?
26	f	y	n	n	y	n	y	y	y	n	y	y
27	m	y	y	?	n	n	y	y	y	n	y	y
28	f	y	n	n	y	?	y	y	y	n	y	y
29 <sup>a</sup>	f	y	y	y	y	n	y	y	y	n	y	y
30 <sup>a</sup>	m	y	y	?	?	?	y	y	?	?	y <sup>b</sup>	?
31	f	y	?	y	y	?	y	y	?	?	y <sup>c</sup>	y
32 <sup>a</sup>	m	y	n	y	?	?	y	y	y	y	y	n
33	m	n	n	y	y	y	y	y	?	n	y	?
34 <sup>a</sup>	m	y	n	?	y	y	y	y	y	?	y <sup>c</sup>	?
35 <sup>a</sup>	m	n	n	y	y	y	y	y	?	n	?	y
36	m	y	n	?	y	y	y	y	y	y	?	n
37 <sup>a</sup>	m	y	y	?	?	y	y	?	y	n	?	y
38	m	n	n	y	y	n	y	y	?	y	y	y
39	m	y	y	n	n	y	y	y	y	n	y	?
40	m	y	n	?	n	y	y	y	y	n	y	?
41	f	n	n	y	y	?	?	y	y	y	?	?
42	f	n	y	y	n	?	y	y	y	n	y	y
Total		25/39	14/34	18/21	16/26	18/22	36/36	34/34	23/24	11/28	20/24	19/22
%		64	41	86	62	82	100	100	96	39	83	86
Range%		60–67	33–52	43–93	38–76	43–90	86–100	81–100	55–98	26–60	48–90	45–93
Control %		81	55	99	37	81	97	?	94	48	82	99
Control Range%		68–84	35–71	53–99	13–79	42–90	80–98	?	39–98	28–70	32–93	62–100

m, male; f, female; y, feature present; n, feature absent; ?, unknown/no information.

C, Coloboma or microphthalmia; A, Choanal atresia or stenosis; DD, Developmental delay; GR, growth retardation; G, genital hypoplasia, e.g. micropenis, hypogonadotropic hypogonadism; E, external ear anomaly; HL, hearing loss; SCC, semicircular canal anomaly, CLP, cleft lip and/or palate; F, feeding problems, needing tube feeding.

Total, patients in whom feature was present/all patients of whom information was known; %, percentage of patients of whom information was known who had this feature; Range%, shows the minimum–maximum frequency of a feature in this cohort as calculated by  $(\text{positive}/\text{total}) \times 100\% - (\text{positive} + \text{unknown}/\text{total}) \times 100\%$ ; Control, numbers based on a previously studied cohort of 280 patients with a pathogenic *CHD7* mutation [2].

<sup>a</sup> Deceased.

<sup>b</sup> No information on tube feeding, not included in total number of patients.

<sup>c</sup> Swallowing problems are mentioned.

and respiratory problems. Our study indicates that arch vessel anomalies are often present in patients with molecularly diagnosed CHARGE syndrome, but we could not identify predictive factors for the existence of an arch vessel anomaly, e.g. *CHD7* mutation type or other CHARGE-related congenital malformations (see Table 2). Furthermore feeding problems for which tube feeding was needed doesn't occur more often in patients with arch vessel anomalies (83% range 48–90%) compared to the control population of patients with a *CHD7* mutation (82%, range 32–93%, see Table 2). However, the medical history described in our case report clearly illustrates that vascular compression due to an arch vessel anomaly should be taken into account in patients with CHARGE syndrome who also have respiratory and/or feeding problems, especially when choking occurs. The exact prevalence of

symptomatic vascular compression of the trachea and/or esophagus in CHARGE syndrome needs to be established.

Since 74% of the patients with molecularly proven CHARGE syndrome have a heart defect, an echocardiography is usually performed in CHARGE patients [3]. However, a normal transthoracic echocardiography does not exclude an arch vessel anomaly since its sensitivity for detecting arch vessel anomalies is low [26]. To indicate the presence of a vascular ring, a regular chest X-ray for tracheal compression, and barium contrast esophagography for esophageal compression, respectively, have a higher sensitivity [9,26]. For identifying the exact morphology of an arch vessel anomaly, non invasive imaging techniques like magnetic resonance imaging and computed tomography are warranted, and they can be used with the same efficiency as invasive

angiographic techniques, which has been the gold standard for decades [9,27]. The identification of abnormal aortic arch arteries can also be important for asymptomatic CHARGE syndrome patients who need interventional or surgical procedures because routine procedures may be complicated in patients with arch vessel anomalies, e.g., when associated with anomalies of the laryngeal nerve.

Given the high prevalence of arch vessel anomalies in CHARGE syndrome, it remains interesting to study how often patients with arch vessel anomalies have a *CHD7* mutation. Our recent study in 46 patients with syndromic conotruncal heart defects or AVSD, including eight with an arch vessel anomaly, did not identify any pathogenic *CHD7* mutations [28]. In a previous study that focused on the prevalence of bicarotid trunk in patients who underwent cardiac catheterization, genetic syndromes were also assessed; CHARGE syndrome was present in three of the 310 patients (1%) with a bicarotid trunk [29]. A study of 257 patients with a tetralogy of Fallot with pulmonary stenosis showed that the incidence of chromosomal or genetic abnormalities, including CHARGE syndrome, increased significantly in patients who had an aberrant subclavian artery with either a left or right aortic arch [30]. While we don't yet have enough support to advise *CHD7* analysis in all patients with arch vessel anomalies, current studies suggest arch vessel anomalies might be an indicator of CHARGE syndrome. We therefore do advise health care professionals to look carefully for other features of CHARGE syndrome (e.g. external ear anomalies, balance problems, deafness and coloboma) in patients with arch vessel anomalies.

In conclusion, arch vessel anomalies are present in a significant portion of patients with a *CHD7* mutation. They may cause problems due to compression of the esophagus and/or trachea. Therefore, doctors caring for patients with CHARGE syndrome should be aware of this underlying and treatable cause of swallowing and respiratory problems. Future studies are warranted to identify more precisely the frequency of symptomatic arch vessel anomalies in CHARGE syndrome. More evidence is needed to support that an arch vessel anomaly is an indicator of CHARGE syndrome, but doctors should be aware of other features of this complex entity in patients with an arch vessel anomaly.

### Conflicts of interest

None.

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