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研究成果の刊行物・別冊

Congenital Anomalies
THE JAPANESE TERATOLOGY SOCIETY
12 *Congenital Anomalies* 2011; **51**, 12–15 doi:10.1111/j.1741-4520.2010.00309.x

INVITED REVIEW ARTICLE

Role of rare cases in deciphering the mechanisms of congenital anomalies: CHARGE syndrome research

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ABSTRACT **In this review, our work on CHARGE syndrome will be used to exemplify the role of rare cases in birth defects research. The analysis of 29 cases with mutations of *CHD7*, the causative gene for CHARGE syndrome, clarified the relative importance of the cardinal features, including facial nerve palsy and facial asymmetry. Concurrently, *in situ* hybridization using chick embryos studies were performed to delineate the expression pattern of *Chd7*. The *Chd7*-positive regions in the chick embryos and the anatomical defects commonly seen in patients with CHARGE syndrome were well correlated: expression in the optic placode corresponded with defects such as coloboma, neural tube with mental retardation, and otic placode with ear abnormalities. The correlation between expression in the branchial arches and nasal placode with the clinical symptoms of CHARGE syndrome, however, became apparent when we encountered two unique CHARGE syndrome patients: one with a DiGeorge syndrome phenotype and the other with a Kallman syndrome phenotype. A unifying hypothesis that could explain both the DiGeorge syndrome phenotype and the Kallman syndrome phenotype in patients with CHARGE syndrome may be that the mutation in *CHD7* is likely to exert its effect in the common branch of the two pathways of neural crest cells. As exemplified in CHARGE syndrome research, rare cases play a critical role in deciphering the mechanisms of human development. Close collaboration among animal researchers, epidemiologists and clinicians hopefully will enhance and maximize the scientific value of rare cases.**

Key Words: CHARGE syndrome, *CHD7*, dysmorphology, London Dysmorphology Database, methimazole embryopathy

The key components of birth defects research include animal experiments, epidemiological studies, and detailed case studies. Animal studies involve experimental procedures, including prenatal exposure to potential teratogens or gene targeting; in human studies, on the other hand, experimental approaches are not feasible and observational studies must instead be undertaken. Collectively, birth defects are relatively common in humans. Nevertheless, individual disorders are relatively uncommon, and information obtained through detailed analyses of individual cases, including genetic analyses, are thus invaluable. This notion constitutes the basis for dysmorphology. In this review, our work on CHARGE syndrome will be used to exemplify the role of rare cases in birth defects research.

CHARGE syndrome is one of the most common multiple malformation syndromes. Its characteristic features include C – coloboma, H – heart defects, A – choanal atresia/stenosis, R – retardation of growth, G – genital hypoplasia, and E – external ear abnormalities (Pagon *et al.* 1981). Vissers *et al.* identified *CHD7* at chromosome 8q12.1 as the causative gene for CHARGE syndrome in 2004 (Vissers *et al.* 2004). The causative gene was identified through physical mapping; thus, the biological function of *CHD7* was unknown at the time of its discovery.

EPIDEMIOLOGICAL STUDY

In 2006, 24 cases were identified in Japan (Aramaki *et al.* 2006). Seventeen of these 24 cases had mutations in the *CHD7* gene. The frequency of the cardinal features of CHARGE syndrome among 17 mutation-positive cases is shown in Table 1.

In a nationwide study of CHARGE syndrome that was performed recently, we sent a questionnaire regarding CHARGE syndrome to 179 hospitals in which members of the Japan Society of Pediatric Genetics belonged at the time of study. Eighteen hospitals responded that at least one patient with CHARGE syndrome had been managed at the hospital; among these 18 hospitals, 132 patients with CHARGE syndrome were being followed. Among these 132 patients, at least 29 patients had tested positive for the *CHD7* mutation. The questionnaire contained items regarding the presence or absence of 50 characteristic features of CHARGE syndrome, including those used in the original criteria defined by Blake *et al.* (Blake and Prasad 2006).

The results of the questionnaire are summarized in Table 2. The first column contains the names of the features that were relatively common among the 29 mutation-positive cases, the second column (parameter a) contains the number of patients with that particular feature, and the third column (parameter b) contains the frequency

Table 1 Frequency of cardinal features of CHARGE syndrome (Aramaki *et al.* 2006)

C – coloboma: 15/17
H – heart defects: 13/17
A – choanal atresia/stenosis: 5/17
R – retardation of growth: 14/17 and development: 14/14
G – genital hypoplasia: 8/8 (male), 5/9 (female)
E – external ear abnormalities and hearing loss: 17/17
Cleft lip and palate: 8/17
Tracheoesophageal fistula: 3/17

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Received November 11, 2010; revised and accepted December 6, 2010.
Presented at the 50th Anniversary Meeting of the Japanese Teratology Society, Awaji Island, July, 2010.

Table 2 Delineation of specific features of CHARGE syndrome

Features	**a**: Number of patients among 29 mutation-positive cases	**b**: Frequency a/29	**c**: Number of syndromes in London Dysmorphology Database	**d**: b/c × 100
Choanal atresia or stenosis	8	0.28	74	0.37
Coloboma (iris, optic nerve, retina/choroid)	24	0.83	178	0.46
Characteristic external ears	29	1.00	202	0.50
Cleft palate	15	0.52	466	0.11
Congenital heart defects	20	0.69	817	0.08
Undescended testes or micropenis	13	0.45	427	0.10
Esophago-tracheal anomalies	7	0.24	104	0.23
Facial nerve palsy or asymmetric face	26	0.90	103	0.87
Developmental delay	29	1.0	1137	0.088
Short stature	29	1.0	1392	0.072

of the feature. To evaluate the specificity of each cardinal feature, we searched the London Dysmorphology Database (Winter and Baraitser 1987), which contains more than 3000 syndromes with 700 query features. The fourth column (parameter c) contains the number of syndromes with that particular feature as registered in the London Dysmorphology Database. Thus, smaller numbers indicate more specific features. Finally, to define the relative importance of the features in supporting the diagnosis of CHARGE syndrome, we divided the number in the third column (parameter b) by the number in the fourth column (parameter c). The resulting parameter is shown in the fifth column (parameter d).

An analysis of these parameters revealed the following observations: first, developmental delay and short stature had high values (i.e. 100%) for parameter b. Nevertheless, the values of parameter c were also high, resulting in a low parameter d-values for developmental delay and short stature. Second, the value of parameter d for facial nerve palsy and/or an asymmetric face was very high and thus may be considered as a useful feature. In the Blake criteria (Blake and Prasad 2006), both facial nerve palsy and swallowing function were included in the cranial nerve palsy. However, swallowing dysfunction had a very high value for parameter c and thus could be excluded from the criteria. Based on the relative importance of these cardinal features, as outlined above, the author suggests that the existing clinical criteria for CHARGE syndrome could be revised (Table 3). The validity of this proposed revision of the diagnostic criteria needs to be evaluated in a separate group of *CHD7* mutation-positive CHARGE syndrome patients.

Table 3 Proposed revision of the clinical criteria for CHARGE syndrome

Essential features
Bilateral hearing loss with external ear anomalies
Short stature
Developmental delay of variable degree
Major criteria
Ocular coloboma of any kind
Choanal atresia or cleft palate
Facial nerve palsy or facial asymmetry
Minor criteria
Congenital heart defects
Tracheoesophageal anomalies
Micropenis or undescended testes (male)

Clinical diagnosis of CHARGE syndrome can be made when the patient fulfils the essential features and has two or more major features or has one major feature with two or more minor features.

CHICK *IN SITU* HYBRIDIZATION STUDY

As the clinical spectrum of CHARGE syndrome has now been clarified, we wished to know whether the anatomical distribution of defects was correlated with the expression pattern of CHD7 in early embryos. We performed *in situ* hybridization using chick embryos to delineate the expression pattern of *Chd7* (Aramaki *et al.* 2007). First, we identified partial fragments of chicken *Chd7* sequences using a bioinformatics analysis and determined the missing portion of the transcript using reverse transcriptase polymerase chain reaction (RT-PCR). The presumable chicken *Chd7* mapped to chicken chromosome 2. The order of genes surrounding the *Chd7* gene was conserved between humans and chickens. Based on this finding, we concluded that a true homolog or ortholog of human *Chd7* was identified in the chicken genome. Using a probe that is complementary to the putative chicken *Chd7* cDNA sequence, the expression pattern of the *Chd7* gene was delineated.

At Hamburger and Hamilton stage 8, *Chd7* expression was detected along the entire rostrocaudal axis of the neuroectoderm. At stages 12 and 13, *Chd7* expression was seen in the neural ectoderm and was uniformly expressed at high levels. Two paraxial crescent signals representing the dorsal halves of the otic placodes were identified at the hindbrain level. At stage 14, *Chd7* was expressed at the optic vesicles. At stage 20, *Chd7* was expressed in the brain and the optic placode, including the lens vesicle. *Chd7* expression was also observed in the branchial arches and olfactory placodes. The *Chd7*-positive regions in the chick embryos and the anatomical defects commonly seen in patients with CHARGE syndrome were well correlated: expression in the optic placode corresponded with defects such as coloboma, neural tube with mental retardation, and otic placode with ear abnormalities. The correlation between

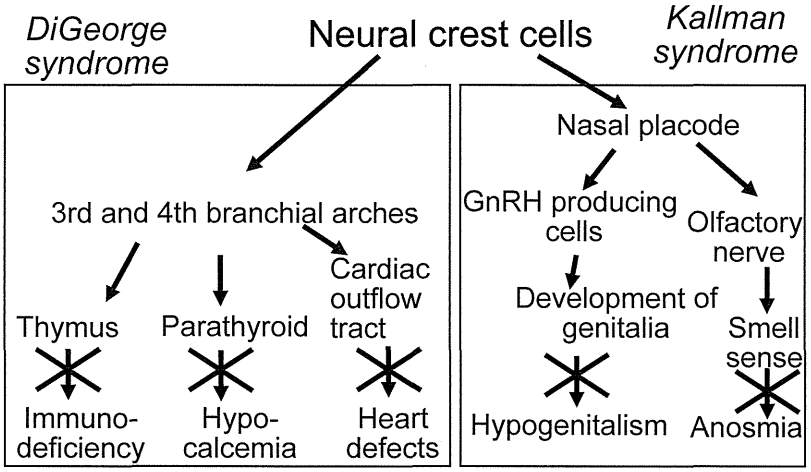

Fig. 1 Two developmental pathways affected in DiGeorge syndrome phenotype and Kallman syndrome phenotype are depicted. The two pathways share a common feature: the involvement of the neural crest.

expression in the branchial arches and nasal placode with the clinical symptoms of CHARGE syndrome, however, was not obvious until we encountered two unique cases (Ogata *et al.* 2006; Inoue *et al.* 2010).

SIGNIFICANT CASES

Interestingly, we had the opportunity to analyze a patient with CHARGE syndrome and a *CHD7* mutation who exhibited a DiGeorge syndrome phenotype (Inoue *et al.* 2010). DiGeorge syndrome is characterized by cellular immunodeficiency as a result of thymus hypoplasia, hypocalcemia arising from parathyroid hypoplasia, and heart defects. Similar cases have been reported from other groups recently (Hoover-Fong *et al.* 2009). Hence, the association between the *CHD7* mutation and DiGeorge syndrome is unlikely to have occurred by chance. The developmental abnormality leading to DiGeorge syndrome is accounted for by defects in the formation of the neural crest that contributes to the third and fourth branchial arch derivatives including the thymus, parathyroid, and thyroid glands. The observation that patients with CHARGE syndrome phenotype and *CHD7* mutation exhibited a DiGeorge syndrome phenotype does not prove but strongly suggests that *CHD7* contributes to either the formation or the maintenance of neural crest cells of the third and fourth branchial arches.

We also encountered a patient with CHARGE syndrome who also exhibited a Kallman syndrome phenotype, a combination of central hypogonadism accompanied by anosmia, or a lack of the sense of smell (Ogata *et al.* 2006). Furthermore, our collaborators have shown that a defect in the olfactory bulb is a common finding among patients with CHARGE syndrome (Asakura *et al.* 2008). This finding was subsequently confirmed by other groups as well. The formation of these two apparently different defects in a patient (CHARGE syndrome and Kallman syndrome) is accounted for by a defect in a common developmental pathway: the nasal placode contributes to both gonadotropin releasing hormone-producing cells in the hypothalamus and olfactory nerve cells. Defects in the origin of both cell lineages, the nasal placode or its upstream structures neural crest cells, may lead to the Kallman syndrome phenotype. The observation that patients with the CHARGE syndrome phenotype and *CHD7* mutation exhibited Kallman syndrome phenotype suggests that *CHD7* contributes to either the formation or maintenance of the neural nasal placode. So, based on observations of rare cases, we suggested that expression in the branchial arches (Aramaki *et al.* 2007) may be correlated with the DiGeorge syndrome phenotype (Inoue *et al.* 2010) and that expression in the nasal placode (Aramaki *et al.* 2007) may be correlated with the Kallman syndrome phenotype (Ogata *et al.* 2006).

A unifying hypothesis that could explain both the DiGeorge syndrome phenotype and the Kallman syndrome phenotype in patients with CHARGE syndrome may be that the mutation in *CHD7* is likely to exert its effect in the common branch of the two pathways of neural crest cells (Fig. 1). Indeed, the notion that *CHD7* plays a critical role in neural crest formation was recently demonstrated by Dr Wysocka's group (Bajpai *et al.* 2010). They induced neural crest cells from human embryonic stem cells (ES) cells and abolished the function of the *CHD7* gene using small interfering RNA (SiRNA), documenting the subsequent defects in the migration of multipotent neural crest cells. In other words, *CHD7* plays a critical role in the formation of multipotent migratory neural crest cells. Hence, what was strongly suggested by clinical observation was documented using *in vitro* studies.

Overall, animal (i.e. chicken) experiments have provided insight that was later proven to be relevant in humans. More specifically, expression in the branchial arch or expressions in the nasal placode (Aramaki *et al.* 2007) may account for the DiGeorge syndrome phenotype (Inoue *et al.* 2010) or the Kallman syndrome phenotype (Ogata *et al.* 2006) that can appear in patients with CHARGE syndrome who have a *CHD7* mutation.

METHIMAZOLE EMBRYOPATHY AS PHENOCOPY OF CHARGE SYNDROME

Here, the author wishes to illustrate how detailed case studies can contribute to epidemiological studies, using methimazole embryopathy as an example (Aramaki *et al.* 2005). Whether methimazole, an antithyroid drug, represents a teratogen has been the subject of debate. The vast majority of infants prenatally exposed to methimazole are normal. Nevertheless, several reports have suggested a possible causal relationship between methimazole exposure and birth defects, including aplasia cutis, esophageal malformations, and persistent vitelline duct (Johnsson *et al.* 1997; Clementi *et al.* 1999). Interestingly, choanal atresia, one of the cardinal features of

CHARGE syndrome, has been reported several times. Greenberg reported a case of prenatal exposure to methimazole resulting in choanal atresia and hypoplastic nipples (Greenberg 1987). Subsequently, Wilson *et al.* reported another patient prenatally exposed to methimazole who exhibited choanal atresia (Wilson *et al.* 1998). Barbero *et al.* recently reported three cases of prenatal exposure to methimazole resulting in choanal atresia (Barbero *et al.* 2004).

Choanal atresia is a congenital failure of the communication of the nasal cavity and nasopharynx and is a highly specific feature for CHARGE syndrome. So, the natural question to ask would be whether methimazole may be associated with another very specific feature of CHARGE syndrome, coloboma of the eyes. Indeed, the author recently evaluated a newborn female who had been prenatally exposed to methimazole (Aramaki *et al.* 2005). The patient exhibited multiple anomalies, including vitelline duct anomalies and nipple hypoplasia. In place of choanal atresia, however, the baby exhibited ocular coloboma. Because choanal atresia and coloboma occur together more frequently than otherwise expected and are features of CHARGE syndrome, we suspected that this case may expand the phenotypic spectrum of prenatal methimazole exposure. Furthermore, we suggested that the pathogenesis of methimazole embryopathy and the CHARGE syndrome phenotype may be causally associated. The molecular mechanism leading to methimazole embryopathy is completely unknown at present, and our case may provide a new clue. It would be important to test whether *CHD7* expression is affected after prenatal methimazole exposure using animal models.

FUTURE DIRECTIONS

What can we do to better exploit the scientific value of rare cases among specialists in various fields of teratology? First of all, descriptive terms for congenital malformations should be standardized to enable better interdisciplinary communication. Fortunately, an international working group has proposed a standard terminology for human teratology, and a consensus has been published together with hundreds of pictures in the *American Journal of Medical Genetics* (Allanson *et al.* 2009). The Japanese Teratology Society finalized similar standard terminology for mice, and hopefully comparisons between humans and mice will be easier to perform with the help of such standard terminology (Makris *et al.* 2009). Second, I would propose that a detailed postnatal physical examination be performed when epidemiological studies on prenatal exposure to teratogens are performed. The use of standard terminology will be extremely helpful for precise communication and documentation. Again, collaboration between epidemiologists and dysmorphologists would be invaluable and essential. The standardization of phenotypic information should also help to establish national or international registries for rare conditions. Such registries would be even more valuable if biological samples were available for *in vitro* research.

In summary, rare cases play a critical role in deciphering the mechanisms of human development. Close collaboration among animal researchers, epidemiologists and clinicians hopefully will enhance and maximize the scientific value of rare cases.

ACKNOWLEDGMENTS

This research was partially supported by a Grant-in-Aid from the Ministry of Health, Labour, and Welfare, Japan.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Ophthalmic Features of CHARGE Syndrome With CHD7 Mutations

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Received 26 December 2010; Accepted 25 October 2011

Coloboma and various ocular abnormalities have been described in CHARGE syndrome, although the severity of visual impairment varies from case to case. We conducted a multicenter study to clarify the ophthalmic features of patients with molecularly confirmed CHARGE syndrome. Thirty-eight eyes in 19 patients with CHARGE syndrome and confirmed CHD7 mutations treated at four centers were retrospectively studied. Colobomata affected the posterior segment of 35 eyes in 18 patients. Both retinochoroidal and optic disk colobomata were bilaterally observed in 15 patients and unilaterally observed in 3 patients. The coloboma involved the macula totally or partially in 21 eyes of 13 patients. We confirmed that bilateral large retinochoroidal colobomata represents a typical ophthalmic feature of CHARGE syndrome in patients with confirmed CHD7 mutations; however, even eyes with large colobomata can form maculas. The anatomical severity of the eye defect was graded according to the presence of colobomata, macula defect, and microphthalmos. A comparison of the severity in one eye with that in the other eye revealed a low-to-moderate degree of agreement between the two eyes, reflecting the general facial asymmetry of patients with CHARGE syndrome. The location of protein truncation and the anatomical severity of the eyes were significantly correlated. We suggested that the early diagnosis of retinal morphology and function may be beneficial to patients, since such attention may determine whether treatment for amblyopia, such as optical correction and patching, will be effective in facilitating the visual potential or whether care for poor vision will be needed.

Key words: CHARGE syndrome; *CHD7*; coloboma; ophthalmic features

How to Cite this Article:
Nishina S, Kosaki R, Yagihashi T, Azuma N, Okamoto N, Hatsukawa Y, Kurosawa K, Yamane T, Mizuno S, Tsuzuki K, Kosaki K. 2012. Ophthalmic features of CHARGE syndrome with CHD7 mutations.
Am J Med Genet Part A 158A:514–518.

INTRODUCTION

CHARGE syndrome is a multiple malformation syndrome named from the acronym of its major features: coloboma, heart defects, atresia of the choanae, retarded growth and/or development, genital anomalies, and ear abnormalities [Pagon et al., 1981; Zentner et al., 2010]. The major ocular feature of CHARGE syndrome is coloboma, and a previous investigation by ophthalmologists revealed an incidence of up to 86%, although the severity

Grant sponsor: Ministry of Health, Labour and Welfare, Tokyo, Japan.
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Published online 2 February 2012 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.34400