Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, Makita Y, Seishima M, Wakamatsu N.	MBTPS2 mutation causes BRESEK/BRESHECK syndrome	Am J Med Genet A		Epub ahead of print	2011
Seiji Mizuno, Daisuke Fukushi, Reiko Kimura, Kenichiro Yamada, Yasukazu Yamada, Toshiyuki Kumagai, Nobuaki Wakamatsu	Clinical and genomic characterization of siblings with a distal duplication of chromosome 9q (9q34.1-qter)	Am J Med Genet A,	155 (9)	224-2280	2011
Hayashi S, Imoto I, Aizu Y, Okamoto N, Mizuno S, Kurosawa K, Okamoto N, Honda S, Araki S, Mizutani S, Numabe H, Saitoh S, Kosho T, Fukushima Y, Mitsubuchi H, Endo F, Chinen Y, Kosaki R, Okuyama T, Ohki H, Yoshihashi H, Ono M, Takada F, Ono H, Yagi M, Matsumoto H, Makita Y, Hata A, Inazawa J.	Clinical application of array-based comparative genomic hybridization by two-stage screening for 536 patients with mental retardation and multiple congenital anomalies	J Hum Genet.	56(2):	110-24	2011
Nishina S, Kurosaka D, Nishida Y, Kondo H, Kobayashi Y, Azuma N	Survey of microphthalmia in Japan.	Jpn J Ophthalmol		Epub ahead of print	2012, Feb 23
Hosono K, Ishigami C, Takahashi M, Park DH, Hirami Y, Nakanishi H, Ueno S, Yokoi T, Hikoya A, Fujita T, Zhao Y, Nishina S, Shin JP, Kim IT, Yamamoto S, Azuma N, Terasaki H, Sato M, Kondo M, Minoshima S, Hotta Y.	Two Novel Mutations in the *EYS* Gene are Possible Major Causes of Autosomal Recessive Retinitis Pigmentosa in the Japanese Population.	PLoS ONE	7(2)	E31036	2012
Shigeyasu C, Yamada M, Mizuno Y, Yokoi T, Nishina S, Azuma N	Clinical features of anterior segment dysgenesis associated with congenital corneal opacities.	Cornea	31 (3)	293-298	2012
Nishina S, Suzuki Y, Yokoi T, Kobayashi Y, Noda E, Azuma N	Clinical features of congenital retinal folds.	Am J Ophthalmol	153 (1)	81-87	2012
Nishina S, Tanaka M, Yokoi T, Kobayashi Y, Azuma N	Stereopsis after early surgery for bilateral congenital cataracts.	Transaction book of XIth ISA meeting		in press	

Yamasaki T, Kawasaki H, Arakawa S, Shimizu K, Shimizu S, Reiner O, Okano H, Nishina S, Azuma N, Penninger JM, Katada T, Nishina H	Stress-activated protein kinase MKK7 regulates axon elongation in the developing cerebral cortex.	J Neurosci	31(46)	16872-16883	2011
Suzuki S, Kim O-H, Makita Y, Saito T, Lim G-Y, Cho T-J, Al-Swaid A, Alrashees S, Sadoon E, Miyazaki O, Nishina S, Superti-Furga A, Unger S, Fujieda K, Ikegawa S, Nishimura G	Axial Spondylometaphyseal Dysplasia: Additional Reports.	Am J Med Genet A	155A (10)	2521-2528	2011
Tanaka M, Nishina S, Ogonuki S, Akaike S, Azuma N	Nishida's procedure combined with medial rectus recession for large-angle esotropia in Duane syndrome.	Jpn J Ophthalmol	55(3)	264-267	2011
Kobayashi Y, Yokoi T, Yokoi T, Hiraoka H, Nishina S, Azuma N	Fluorescein staining of the vitreous during vitrectomy for retinopathy of prematurity.	Retina	31(8)	1717-1719	2011
Hiraki Y, Nishimura A, Hayashidani M, Terada Y, Nishimura G, Okamoto N, Nishina S, Tsurusaki Y, Doi H, Saitsu H, Miyake N, Matsumoto N	A de novo deletion of 20q11.2-q12 in a boy presenting with abnormal hands and feet, retinal dysplasia, and intractable feeding difficulty.	Am J Med Genet A	155	409-414	2011
Yokoi T, Yokoi T, Kobayashi Y, Nishina S, Azuma N	Risk factors for recurrent fibrovascular proliferation in aggressive posterior retinopathy of prematurity after early vitreous surgery.	Am J Ophthalmol	150	10-15	2010
Fujinami K, Yokoi T, Hiraoka M, Nishina S, Azuma N.	Choroidal neovascularization in child following laser pointer-induced macular injury.	Jpn J Ophthalmol	54	631-633	2010
仁科幸子、中山百合、横井匡、東範行、近藤寛之、西田保裕	小眼球症に伴う眼窩発育異常の画像評価.	眼科臨床紀要	4	印刷中	2012
仁科幸子、東 範行	小児の緑内障治療.	あたらしい眼科	29	7-12	2012
伊藤牧子、仁科幸子	視力障害、斜視、弱視.	小児科診療	75	189-194	2012
仁科幸子	乳児の眼鏡.	あたらしい眼科	28	38-40	2011
仁科幸子	視力障害のフォローアップ.	周産期医学	41	1396-1398	2011
初川嘉一、仁科幸子、菅澤 淳、木村亜紀子、矢ヶ崎悌司、不二門 尚、平野慎也	小児の間欠性外斜視に対する後転短縮術の治療成績：多施設共同研究.	日本眼科学会雑誌	115	440-446	2011

伊藤一清水里美、 赤池祥子、越後貫滋子仁科幸子、東 範行	液晶視力表システムチャートSC-2000 によるロービジョン児のコントラスト視力測定と遮光レンズの効果.	眼科臨床紀要	3	70-73	2010
仁科幸子、横井 匡、 横井多恵、小林百合、野田英一郎、東 範行	乳幼児眼疾患の発見・受診経路と初診時期.	眼科臨床紀要	3	172-177	2010
仁科幸子	視神経無形成.	眼科	52	205-209	2010
伊藤一清水里美、 赤池祥子、越後貫滋子仁科幸子、東 範行	国立成育医療センターにおける小児ロービジョンケアの特徴.	眼科臨床紀要	3	346-352	2010
田中三知子、仁科幸子	小児の眼筋麻痺	あたらしい眼科	27	909-915	2010
福島梨沙、重安千花、水野嘉信、横井 匡、 中川温子、仁科幸子、東範行、山田昌和	セントラルデルモイドの１例	臨眼	64	1337-1340	2010
Matsui T, Takano M, Yoshida K, Soichiro Ono, Fujisaki C, Matsuzaki Y, Toyama Y, Nakamura M, Okano H, Akamatsu W.	Neural stem cells directly differentiated from partially reprogrammed fibroblasts rapidly acquire gliogenic competency	Stem Cells		In press	2012
Komoike, Y., Inamura, H., Matsuoka, M.	Effects of salubrinal on cadmium-induced apoptosis in HK-2 human renal proximal tubular cells	Archives of Toxicology	86	37-44	2012

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研究成果の刊行物・別冊

RESEARCH ARTICLE

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Ophthalmic Features of CHARGE Syndrome With CHD7 Mutations

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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

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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

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of coloboma and visual impairment varied from case to case [Russell-Eggitt et al., 1990].

Recently, the gene *Chromodomain helicase DNA-binding protein-7* (*CHD7*) at chromosome 8q12.1 was identified as a causative gene of CHARGE syndrome [Vissers et al., 2004]. Up to 70% of patients clinically diagnosed as having CHARGE syndrome exhibit mutations in the *CHD7* gene [Aramaki et al., 2006a; Jongmans et al., 2006; Lalani et al., 2006]. Although the exact function of this gene product remains unknown, it may have an important effect on an early stage of ocular morphogenesis.

We conducted the present multicenter study to clarify the ophthalmic features of patients with molecularly confirmed CHARGE syndrome and to explore the role of *CHD7* in ocular development.

PATIENTS AND METHODS

Thirty-eight eyes in 19 patients clinically diagnosed as having CHARGE syndrome at the National Center for Child Health and Development, the Osaka Medical Center and Research Institute for Maternal and Child Health, the Kanagawa Children's Medical Center, or the Institute for Developmental Research, Aichi Human Service Center were retrospectively studied. All the patients had been molecularly confirmed to carry *CHD7* mutations at the Keio University School of Medicine [Aramaki et al., 2006a]. The clinical diagnosis of CHARGE syndrome was made based on the Blake criteria [Blake et al., 1998]. Molecular screening for mutations in the *CHD7* gene was conducted as reported previously [Aramaki et al., 2006b]. Ophthalmic features were examined using slit-lamp biomicroscopy and binocular indirect ophthalmoscopy. Two patients were also examined using a spectral domain optical coherence tomography (SD-OCT). The SD-OCT images were obtained with RS-3000 (NIDEK Co., Ltd., Gamagori, Japan). The best-corrected visual acuity (BCVA) was measured with a standard Japanese VA chart using Landolt rings or pictures at 5 m, then converted to Snellen VA.

The anatomical severity of the eye defect was classified as follows: Grade 1, Normal; Grade 2, colobomata with macular formation; Grade 3, colobomata including the macula; and Grade 4, colobomata, macular defect, and microphthalmos. Then, Cohen's kappa coefficient [Cohen, 1960] was used to measure the agreement of the severity in the two eyes among 19 CHD7-mutation positive patients. The potential correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the *CHD7* protein occurred in the same individual was evaluated among 14 patients with protein-truncating mutations.

This study was approved by the institutional ethics committee; the patients or the parents of the patients provided informed consent prior to enrollment in the study.

RESULTS

The characteristics of the 38 eyes of the 19 patients with CHARGE syndrome carrying *CHD7* mutations are summarized in Table I. Ten patients (53%) were male and 9 (47%) were female. The age of the patients at the time of the examination ranged from 1 to 21 years (mean 7.9 ± 5.0 years). Ocular abnormalities were found in 18 patients (94.7%), bilateral abnormalities were observed in 17 patients (89.4%), and unilateral abnormalities were observed in 1 patient (5.3%). Among these 18 patients, all 35 abnormal eyes had varying severities of colobomata.

TABLE I. Characteristics of Patients of CHARGE Syndrome With CHD7 Mutations (n = 9)

Variable	Number
Gender	
Male	10 (53%)
Female	9 (47%)
Age at examination	1–21 years
Mean	7.9 ± 5.0 years
Ocular abnormalities (colobomata)	
Bilateral	17 (89.4%)
Unilateral	1 (5.3%)
None	1 (5.3%)
BCVA	
<20/400	4 (21.1%)
20/400 to <20/60	7 (36.8%)
20/60 to 20/20	6 (31.6%)
Not measured	2 (10.5%)

BCVA, best-corrected visual acuity.

The ocular features of the individual patients are summarized in Table II. Colobomata affected the posterior segment in 35/38 eyes (92.1%), retinochoroidal coloboma was present in 33 eyes (86.8%), and optic disk coloboma was present in 33 eyes (86.8%). Both retinochoroidal coloboma and optic disk coloboma were bilaterally present in 15 patients (78.9%) and unilaterally present in 3 patients (15.8%). The coloboma involved the macula totally or partially in 21 eyes (55.3%) of the 13 patients (68.4%): bilaterally in 8 patients

TABLE II. Ocular Features of the Patients (n = 19 patients, 38 eyes)

	Number of patients (%)			
Findings	Bilateral	Unilateral	Total	Number of eyes (%)
Colobomata	17 (89.5)	1 (5.3)	18 (94.7)	35 (92.1)
Retinochoroidal	15 (78.9)	3 (15.8)	18 (94.7)	33 (86.8)
Optic disk	15 (78.9)	3 (15.8)	18 (94.7)	33 (86.8)
Macula	8 (42.1)	5 (26.3)	13 (68.4)	21 (55.3)
Iris	1 (5.3)	0 (0.0)	1 (5.3)	2 (5.3)
Lens	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
Microphthalmos	3 (15.8)	2 (10.5)	5 (26.3)	8 (21.1)
Microcornea	3 (15.8)	1 (5.3)	4 (21.1)	7 (18.4)
Ptosis	1 (5.3)	1 (5.3)	2 (10.5)	3 (7.9)
PFV	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
Cataract	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
High myopia (>6.0 D)	2 (10.5)	1 (5.3)	3 (15.8)	5 (13.2)

PFV, persistent fetal vasculature.

(42.1%) and unilaterally in 5 patients (26.3%). The SD-OCT demonstrated a partially formed macula and cystic changes in the colobomatous area in 1 case (Fig. 1).

Only 2 eyes of 1 patient (5.3%) were identified as having iris colobomata, and 1 eye (2.6%) of another patient was revealed by examination under general anesthesia to have a dislocated and colobomatous lens. No cases of eyelid colobomata were seen, but congenital ptosis was present in 3 eyes (7.9%) of 2 patients who had undergone surgical treatment. All the cases of ptosis were not pseudoptosis associated with microphthalmos and/or cranial nerve palsy, but were true congenital ptosis associated with poor levator function. We evaluated the levator muscle function in each case. None of the patients had a history of acquired causes or signs of oculomotor palsy, such as paralytic strabismus and limited ocular movement.

Microphthalmos was found in 8 eyes (21.1%) of 5 patients (26.3%): bilaterally in 3 patients (15.8%) and unilaterally in 2 patients (10.5%). Microcornea was also present in 7 eyes (18.4%) of 4 patients (21.1%): bilaterally in 3 patients (15.8%) and unilaterally in 1 patient (5.3%). Persistent fetal vasculature was identified in 1 eye (2.6%). Cataracts had developed in 1 eye (2.6%), but neither glaucoma nor retinal detachment was observed in this series.

The refraction could be estimated in 23 eyes of 12 patients (63.2%). Of these eyes, 10 were myopic, 7 were emmetropic, and 6 were hypermetropic. High myopia (−6.00 diopters or more) was found in 5 eyes (13.2%) of 3 patients (15.8%).

The BCVA are shown in Table I. The measurement of VA was possible in 17 patients (89.5%) older than 3 years of age. The remaining 2 patients were infants or mentally retarded. The binocular BCVA or BCVA in the better eye was less than 20/400 in 4 patients (21.1%), less than 20/60 but no less than 20/400 in 7 patients (36.8%), and 20/60 to 20/20 in 6 patients (31.6%) with macular formation (Fig. 1). The overall prevalence of blindness and visual impairment (less than 20/60) [World Health Organization, 1992] among the 17 patients was 65%.

The agreement of anatomical severity between the 2 eyes in each of the 19 patients was evaluated using Cohen's Kappa statistics. The κ statistic of 0.41 suggested a moderate degree of agreement, per the guidelines by Landis and Koch [1977]. Because there was a moderate, if not a substantial, agreement between the severity of the 2 eyes, the severity grading of the more severely affected eye was used as the representative grade for the severity of the eyes in an individual. The correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the CHD7 protein occurred in the same individual is illustrated in Figure 2. Patients with truncated protein devoid of the SANT domain tended to have severer anatomical defects of the eyes. Subcategorization of the patients according to the presence or absence of the SANT domain (4 cases with intact SANT domain and 10 other cases), and the subcategorization of the anatomical severity of the eyes in an individual (7 cases classified as Grade 1 or 2 vs. 7 cases classified as Grade 3 or 4) revealed a statistically

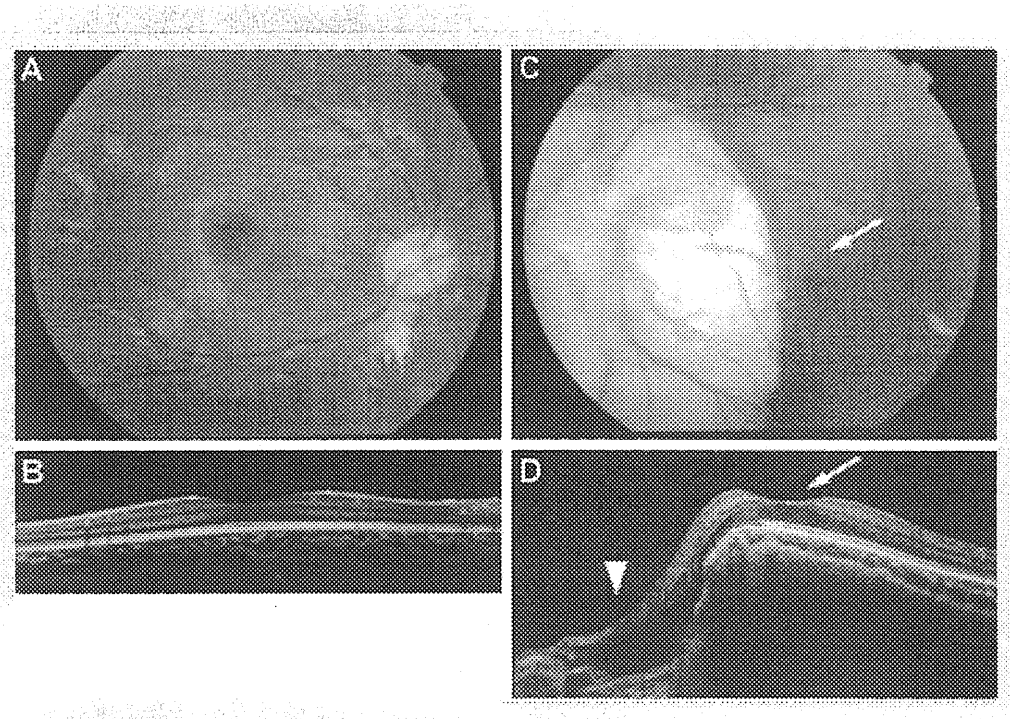

FIG. 1. Fundus photographs and spectral domain optical coherence tomography (SD-OCT) scan of the retina in the right eye (A,B) and the left eye (C,D) in a 6-year-old girl. A: Retinochoroidal colobomata inferior to the optic disk is visible in the right eye. B: The SD-OCT shows a good macular formation in the right eye, resulting in a BCVA of 20/20. C: Retinochoroidal and optic disk coloboma are seen in the left eye. The colobomata partially involved the macula (arrow). D: The SD-OCT shows a partially formed macula (arrow) and cystic changes in the colobomatous area (arrow head) in the left eye, resulting in a BCVA of 20/50 after ambiyopia treatment.

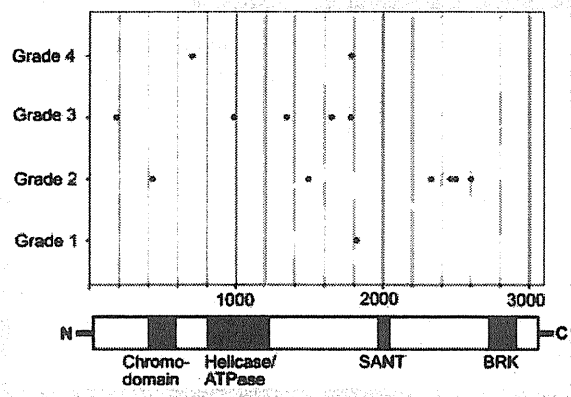

FIG. 2. The correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the CHD7 protein occurred in the same individual. Horizontal axis indicates amino acid position of the CHD7 protein together with the domains of the protein. Vertical axis indicates the anatomical severity of the eye defect classified as follows: Grade 1, Normal; Grade 2, colobomata with macular formation; Grade 3, colobomata including the macula; and Grade 4, colobomata, macular defect, and microphthalmos.

significant correlation between the location of protein truncation and the anatomical severity of the eyes ($P = 0.02$, chi-squared test).

DISCUSSION

In the current series, the incidence of coloboma, the major ocular feature of CHARGE syndrome, was 94.7% (18/19), which was much higher than the previously reported incidence. Since most of the authors were ophthalmologists, the number of cases without eye defects might have been underrepresented. Hence, this high incidence should be viewed with caution. Nevertheless, attending clinical geneticists were on duty at all the participating children's hospitals, and thus the bias from such underrepresentation may be relatively small. The finding that there was one mutation-positive patient who did not have abnormal eye findings confirms that no finding in CHARGE syndrome has a 100% penetrance as is sometimes surmised.

Both retinochoroidal and optic disk coloboma occurred in 94.7% of the cases, mostly bilaterally, while the incidence of iris coloboma was only 5.3% (1/19). Coloboma also affected the macula in 68.4% of the cases. We confirmed that bilateral large retinochoroidal colobomata represent a typical ophthalmic feature of CHARGE syndrome with *CHD7* mutations.

The incidence of anomalies in the anterior segment was lower than that in the posterior segment, although microphthalmos, microcornea, PFV, and cataracts were present in some cases bilaterally or unilaterally. The presence of characteristic large retinochoroidal coloboma indicates the essential role of *CHD7* in the closure of the fetal fissure posteriorly between 5 and 6 weeks of gestation, and the malfunction of *CHD7* may have an effect so severe as to influence the entire ocular morphogenesis to some degree. Although most cases had bilateral colobomata in the posterior segment, the severity and associated features often differed between the two eyes. Other associated features in this series were ptosis in 10.5% and high myopia in 15.8%. Subtle-associated anomalies and refractive errors may have been underestimated in examinations that were not performed under general anesthesia.

The anatomical severity grading of the eye defect was evaluated in two ways: a comparison between the severity in one eye in comparison with that in the other eye and the correlation between the severity and the genotype. The low-to-moderate degree of agreement between the two eyes (i.e., left and right) reflects the general facial asymmetry in patients with CHARGE syndrome [Zentner et al., 2010]. In other words, the lack of substantial or perfect agreement between the anatomical severity of the right and the left eyes indicates a variable phenotypic effect of the same mutation. Yet, the location of protein truncation and the anatomical severity of the eyes were significantly correlated: if the chromodomain, helicase/ATP domain, and SANT domains are intact, the severity of the eyes tends to be milder. Interestingly, all four cases in which those domains were intact had less severe eye defects with intact macula. Further studies are warranted to verify this potential genotype–phenotype correlation.

The visual acuities of the eyes ranged between no light perception and 20/20, and the prevalence of blindness and visual impairment (less than 20/60) was 65% among 17 patients. A poor visual prognosis depended on the presence of a large coloboma involving the macula in the posterior segment and associated microphthalmos or microcornea, as reported previously [Russell-Eggitt et al., 1990; Hornby et al., 2000]. On the other hand, even eyes with large colobomata as a result of *CHD7* mutations were capable of forming maculas, resulting in good central visual acuity with superior visual field defects. As shown in the case illustrated in Figure 1, even a partially formed macula will enable useful vision following the adequate treatment of amblyopia as optical correction and patching during the earlier age of visual development. A recent report of a case examined using OCT revealed additional morphologic characteristics of eyes in patients with CHARGE syndrome carrying *CHD7* mutations [Holak et al., 2008]. Further investigation of retinal morphology and function using OCT and electroretinograms (ERG) may help to clarify the function of *CHD7* in ocular morphogenesis, including macular formation.

We suggested that the early diagnosis of retinal morphology and function, especially of macular lesions by way of OCT and ERG, 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. An infant's visual acuity rapidly develops during its first 2–3 years and continues up until 7–8 years of age, but plasticity decreases progressively thereafter. Thus, a better visual prognosis can be obtained with the earlier treatment of amblyopia during the critical period of visual development.

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REFERENCES

Aramaki M, Udaka T, Kosaki R, Makita Y, Okamoto N, Yoshihashi H, Oki H, Nanao K, Moriyama N, Oku S, Hasegawa T, Takahashi T, Fukushima Y, Kawame H, Kosaki K. 2006a. Phenotypic spectrum of CHARGE syndrome with CDH7 mutations. J Pediatr 148:410–414.

Aramaki M, Udaka T, Torii C, Samejima H, Kosaki R, Takahashi T, Kosaki K. 2006b. Screening for CHARGE syndrome mutations in the CDH7 gene using denaturing high-performance liquid chromatography. Genet Test 10:244–251.

Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM Jr. 1998. CHARGE association: An update and review for the primary pediatrician. Clin Pediatr (Phila) 37:159–173.

Cohen J. 1960. A coefficient of agreement for nominal scales. Educ Psychol Meat 20:37–46.

Holak HM, Kohlhase J, Holak SA, Holak NH. 2008. New recognized ophthalmic morphologic anomalies in CHARGE syndrome caused by the R2319C mutation in the CHD7 gene. Ophthalmic Genet 29:79–84.

Hornby SJ, Adolph S, Girbert CE, Dandona L, Foster A. 2000. Visual acuity in children with coloboma. Clinical features and a new phenotypic classification system. Ophthalmology 107:511–520.

Jongmans MC, Admiraal RJ, van der Donk KP, Vissers LE, Baas AF, Kapusta L, van Hagen JM, Donnai D, de Ravel TJ, Veltman JA, van Kessel AG, De Vries BB, Brunnaer HG, Hoefsloot LH, van Ravenswaaj CM. 2006. CHARGE syndrome: The phenotypic spectrum of mutations in the CHD7 gene. J Med Genet 43:306–314.

Lalani SR, Saliullah AM, Fernbach SD, Harutyunyan KG, Thaller C, Peterson LE, McPherson JD, Gibbs RA, White LD, Hefner M, Davenport SLH, Graham JM Jr, Bacino CA, Glass NL, Towbin JA, Craigen WJ, Neish SR, Lin AE, Belmont JW. 2006. Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype–phenotype correlation. Am J Hum Genet 78:303–314.

Landis JR, Koch GG. 1977. The measurement of observer agreement for categorical data. Biometrics 33:159–174.

Pagon RA, Graham JM Jr, Zonana J, Yong SL. 1981. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 99:223–227.

Russell-Eggitt IM, Blake KD, Taylor DSI, Wyse RKH. 1990. The eye in the CHARGE association. Br J Ophthalmol 74:421–426.

Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG. 2004. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957.

World Health Oraganization. 1992. International statistical classification of diseases and related problems. 10th revision. Vol. 1. Geneva, Switzerland: World Health Organization.

Zentner GE, Layman WS, Martin DM, Scacheri PC. 2010. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. Am J Med Genet Part A 152A:674–686.

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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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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

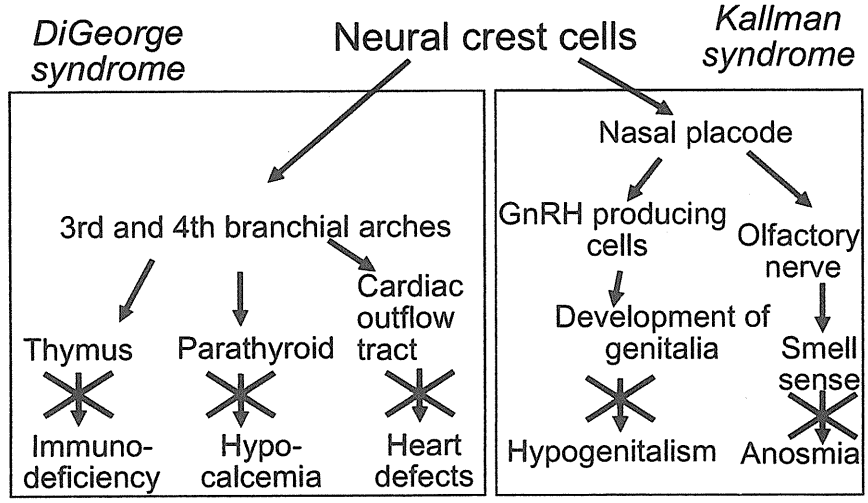

Fig. 1 Two developmental pathways affected in DiGeorge syndrome phenotype and Kallman syndrome phenotype are depicted. The two pathways share a common feature: the involvement of the neural crest.

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

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REFERENCES

Allanson JE, Biesecker LG, Carey JC, Hennekam RC (2009) Elements of morphology: introduction. *Am J Med Genet A* **149A**: 2–5.

Aramaki M, Hokuto I, Matsumoto T *et al.* (2005) Iridic and retinal coloboma associated with prenatal methimazole exposure. *Am J Med Genet A* **139A**: 156–158.

Aramaki M, Udaka T, Kosaki R *et al.* (2006) Phenotypic spectrum of CHARGE syndrome with CHD7 mutations. *J Pediatr* **148**: 410–414.

Aramaki M, Kimura T, Udaka T *et al.* (2007) Embryonic expression profile of chicken CHD7, the ortholog of the causative gene for CHARGE syndrome. *Birth Defects Res A Clin Mol Teratol* **79**: 50–57.

Asakura Y, Toyota Y, Muroya K *et al.* (2008) Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. *J Clin Endocrinol Metab* **93**: 920–924.

Bajpai R, Chen DA, Rada-Iglesias A *et al.* (2010) CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature* **463**: 958–962.

Barbero P, Ricagni C, Mercado G, Bronberg R, Torrado M (2004) Choanal atresia associated with prenatal methimazole exposure: three new patients. *Am J Med Genet* **129A**: 83–86.

Blake KD, Prasad C (2006) CHARGE syndrome. *Orphanet J Rare Dis* **1**: 34.

Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R (1999) Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet* **83**: 43–46.

Greenberg F (1987) Choanal atresia and athelia: methimazole teratogenicity or a new syndrome? *Am J Med Genet* **28**: 931–934.

Hoover-Fong J, Savage WJ, Lisi E *et al.* (2009) Congenital T cell deficiency in a patient with CHARGE syndrome. *J Pediatr* **154**: 140–142.

Inoue H, Takada H, Kusuda T *et al.* (2010) Successful cord blood transplantation for a CHARGE syndrome with CHD7 mutation showing DiGeorge sequence including hypoparathyroidism. *Eur J Pediatr* **169**: 839–844.

Johnsson E, Larsson G, Ljunggren M (1997) Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* **350**: 1520.

Makris SL, Solomon HM, Clark R *et al.* (2009) Terminology of developmental abnormalities in common laboratory mammals (version 2). *Congenit Anom* **49**: 123–246.

Ogata T, Fujiwara I, Ogawa E, Sato N, Udaka T, Kosaki K (2006) Kallmann syndrome phenotype in a female patient with CHARGE syndrome and CHD7 mutation. *Endocr J* **53**: 741–743.

Pagon RA, Graham JMJ, Zonana J, Yong SL (1981) Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* **99**: 223–227.

Vissers LE, van Ravenswaaij CM, Admiraal R *et al.* (2004) Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet* **36**: 955–957.

Wilson LC, Kerr BA, Wilkinson R, Fossard C, Donnai D (1998) Choanal atresia and hypothelia following methimazole exposure in utero: a second report. *Am J Med Genet* **75**: 220–222.

Winter RM, Baraitser M (1987) The London Dysmorphology Database. *J Med Genet* **24**: 509–510.

重度難聴に対する人工内耳手術と聴覚脳幹インプラント

加我君孝

1．人工内耳とは

人工内耳は、先天性あるいは後天性高度あるいは重度の感音難聴に対して、人工内耳電極を蝸牛へ埋込む手術を行い、聴覚を人工的に獲得させることを目的としたデバイスである。現在使われている多チャンネル人工内耳は1980年代に海外で開発されたもので、わが国ではオーストラリアのCochlear社製、オーストリアのMED-EL社製、米国のBionics社製の製品が健康保険に採用されている。人工内耳は、体外部のスピーチプロセッサー（マイク、増幅器、プロセッサー、ボタン電池）と体内部のレシーバー、電極部分からなる（図1)。スピーチプロセッサーとレシーバー間では電磁誘導で電力を起こし、音声情報を同時に神経信号に変換して伝達する。蝸牛の鼓室階に挿入された電極が蝸牛軸の中の蝸牛神経を刺激する。蝸牛軸の中を走る基底回転から頂回転に起源をもつすべての蝸牛神経を刺激する。人工内耳は健康保険の適用となっているが、外部装置が約100万円、内部装置が約150万円もする高価なものである。手術と入院費用は約100万円相当である。

2．人工内耳の適応疾患

a．幼小児の難聴

高度あるいは重度の①先天性感音難聴（i.遺伝子異常、ii.内耳奇形)、②先天性Auditory Neuropathy、③周産期の難聴（i.サイトメガロウィルス感染、ii.横隔膜ヘルニアに対するECMO使用)、④後天性の高度あるいは重度の感音難聴（i.髄膜炎、ii.流行性耳下腺炎、iii.進行性感音難聴（原因不明））[1)]

b．成人の難聴

①髄膜炎や②特発性進行性の難聴、③両側突発難聴、④両側メニエール病、⑤両側音響外傷（補聴器を含む)、⑥Pendred症候群（前庭水管拡大症）

c．老人の難聴

高齢者の手術に年齢制限は特にない。70～80代の高齢者も人工内耳で聴覚が回復する。

3．人工内耳手術の禁忌

かつて難聴以外に発達障害や脳神経障害を伴う場合は禁忌とされていたが、言葉の獲得が困難でも、音が聞こえていれば交通事故から避け得るようであれば手術の価値がある。幼児の場合の手術年齢は1歳半以上としているが、髄膜炎で蝸牛の内部の骨化を予防するためにはそれ以下の年齢でも行う。

4．人工内耳機器の構造と構成(図1)

22チャンネル人工内耳は、蝸牛内に挿入した電極に電気刺激パルスを出力する音声受信－刺激ユニットと、患者が接着するマイクロ

PROFILE

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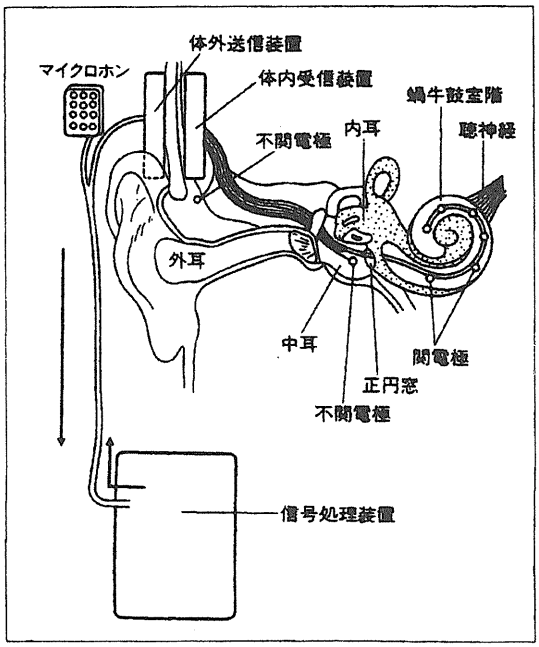
ホン・ヘッドセットからなる受信－刺激ユニットに音声と情報を伝送するスピーチプロセッサーとで構成されている。さらに手術後のリハビリテーションに用いる特性テスト・プログラム作成システム(マッピング装置)が必要である。

1）音声の受信と刺激電極―埋込まれる部分

手術で埋込む部分である。現在、わが国では最も多く使用されているコクレア社製の場合、蝸牛内に埋込む電極はシリコン製の支持体に支えられた22個の白金のリングでできており、先端より17mmの範囲に等間隔で配置されている。銀ボール電極がアースとして皮下に埋没させる。蝸牛の基底回転は高い周波数、頂回転は低周波数を担当している。頭皮下に埋設させるレシーバーである受信－刺激ユニットは発信回路と集積回路からなる電子装置であり、体外コイルからの電磁誘導により2相性電気パルスがあらかじめ設定した1対の電極の間に出力する双極刺激とアースとの間の単極刺激を選ぶことができる。電極が長いと頂回転に届くが、短いと基底回転のみとなる。レシーバーの厚さは各社で異なり、そのためレシーバーが厚いと頭皮が少しだけ盛り上がって見える。

図1　人工内耳システム―外部装置と内部装置の図解
信号処理装置は箱型から耳掛型に移行しつつある. 矢印は信号の流れ



b. スピーチプロセッサー（体外部）

患者が体外に持つもので、箱型と耳掛型がある。最近では耳掛型が開発され、小児でも使われるようになっている。マイクロホンから入ってくる音声入力信号の情報を分析し、電気パルス刺激の頻度、強さの設定および電極の選択を行い、これらの情報を高周波電気信号として頭部の体外コイルから電磁誘導で頭皮下の体内コイル、すなわち受信－刺激ユニットへ伝送する。スピーチプロセッサーにはバッテリーが入っており、体内コイルへ電磁誘導により電源の供給も行う。

5．人工内耳埋込み術

耳の後ろ（耳介部）を5～6cm切開し内耳に埋込まれる電極を含めた内部装置を設置する手術である。手術は全身麻酔をかけて行う。頭蓋骨の一部を削り受信機を固定し、さらに内耳への進路を作成、蝸牛基底回転に約1mmの穴を開け、刺激電極を蝸牛の1～2回転に挿入して埋込む。熟練した技術を必要とする手術である。

6．人工内耳のフォローアップ.

a. スピーチプロセッサーのプログラム作成（マッピング）

人工内耳術後2～4週間後に、人工内耳の各電極のカバーする周波数帯ごとに流す電流量の範囲を決める。これを“マッピング”と呼んでいる。本人が聞きやすく、かつ顔面痙攣、めまい、痛みなどが生じないように調整する。マッピングは定期的に行い、常に聞きやすくする。患者固有の情報をスピーチプロセッサー内のメモリーに書き込む。言葉の未発達の小児では頻回に行うが、既に言語を獲得している成人に対しては、小児ほど必要はないが少なくとも2年は必要である。

b. 機器の管理とメンテナンス

人工内耳の内部装置と電極は一体となっているが、電子部品で出来ており何等誘因なく故障することが稀にある。その故障は装用者が聞こえなくなったことを訴えるのでわかる。一方頭部外傷のあと断線が生じることがある。いずれも再手術して新しい内部装置と電極を取り換える。

体外装置のスピーチプロセッサーも自然に故障が生じる場合と外傷で故障することがある。いずれも修理するか新品と交換する。スピーチプロセッサーが修理不能の場合、健康保険の特定保健医療材料費の援助制度を使い、装用者の負担を少なくしている。以上の問題を除き特別なことはない。

c. 脳のCTとMRI

手術で頭皮下と蝸牛内に移植されたインプラント部分は金属製である。そのために脳のCTを撮影した時はインプラント部分からまるで放射するようなアーチファクトが生じる。脳のMRIは埋込まれている磁石をとりはずしても、低信号の大きなアーチファクトの影響を受ける。

d. 消耗品

ケーブルの断線、空気亜鉛電池、マイクカバーなどの消耗品のうち、自己負担するものと公的援助がされるものがある。

7．その他特記すべき点

新しい人工内耳として、聴力の低音部が残存している患者のために補聴器と人工内耳のハイブリッドさせたEAS（ElectoroAuditory Stimulation）が開発されている。わが国では海

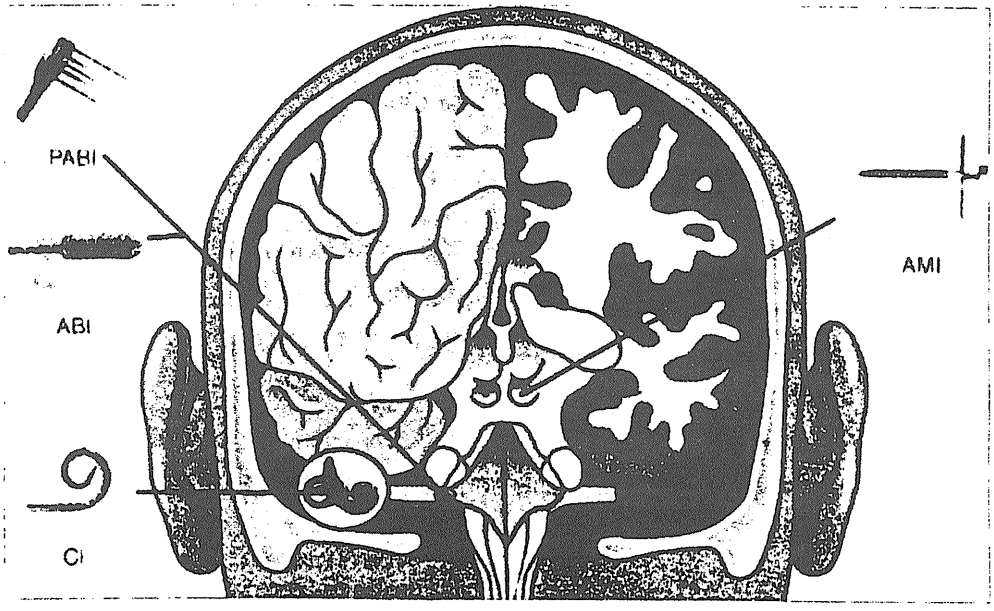
外の医療機器の認可が遅いことが問題である。人工内耳は約270万円という高額の医療機器であり、国産の製品がないのが今後も課題である。小児の人工内耳手術は、教育は①厚生労働省管轄の難聴児通園施設、②市立あるいは県立の身障センターあるいは療育センター、③文部科学省管轄のろう学校がある。ろう学校の教師の中には手話中心主義の者がおり、いかに聴力が重度でも人工内耳をすすめることをしないため難聴児の未来に影響を与えている。

8．聴覚脳幹インプラント

両側の聴神経に腫瘍が発達するレックリングハウゼン病のうちNeurofibromatosis type Ⅱ（NF Ⅱ）の患者は、腫瘍の増大あるいは腫瘍の摘出によって聴力が廃絶する。この場合、補聴器も人工内耳も聴覚の改善のためには効果がない。それであっても聴覚を取り戻すために考え出された手術が聴覚脳幹インプラント（ABI: Auditory Brainstem Implant）である。

聴神経が延髄に投射する部位は蝸牛神経核背側核と腹側核である。脳外科的アプローチによって延髄の背側核が存在する部位が見えるようにし、レシーバーと電極からなるインプラントを移植する。レシーバーは人工内耳と同様に側頭部の頭蓋骨に移植し、電極は白金イリジウムのボール状電極が12個並べた電極のシー

図2　ABI（脳幹インプラント）　PABI（脳幹刺入型インプラント）
AMI（中脳インプラント）　CI（人工内耳）



トを蝸牛神経背側核に近い延髄の表面に置き、フィブリン糊で接着させ固定する。電極を置く適切な部位はその周辺をあらかじめ電気刺激によるABRを記録して探索し、反応のあるところを確認してから選ぶ。この点がABI手術特有である。その他は人工内耳と同じで、スピーチプロセッサーも人工内耳と同じものを使う(図2)。

ABIの手術はまだ保険には認可されていないため、研究費あるいは自己負担で行われている。わが国ではまだ10例程度にすぎないが、筆者が経験した3例はいずれも成人で、聴力廃絶状態であった。しかし3例とも聴覚を再獲得し、そのうち1例はABIを使い始めた当日、筆者ともある程度の会話が可能な状態までになった。NF Ⅱのために聴力が廃絶したままの患者は全国に1,000人以上存在すると見込まれ、デバイスと手術が健康保険でカバーされるように期待したい。

イタリア、トルコ、ドイツでは幼小児の先天性難聴で蝸牛神経低形成あるいは無形成のために人工内耳が効果がないと診断されるとABIを行うようになりつつある。その成果は人工内耳よりは不十分であるが、聴覚を獲得するという。ABIも不適応である場合、中脳下丘に電極を移植する中脳インプラントの報告もある(図2)。[2]

文献

1. 加我君孝他. 幼小児の人口内耳手術. BIO INDUSTRY 26, 92-98, 2009
2. Lenarz T. et al., The Auditory Midbrain Implant: A New Auditory Prosthesis for Neural Deafness-Concept and Device Description. Otol Neurotol. 27:838-843, 2006

障害を持つ子どもたちが通う病院と施設

聴覚障害

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はじめに

筆者は幼小児の難聴と言語障害の外来を東京医療センターをはじめとして埼玉，東京，川崎市にある病院や療育センターで行なっています。東京医療センターの「幼小児難聴・言語障害クリニック」（http://www.ntmc.go.jp/nancho/index.htm）は，開いてわずか2年半でインターネットのヒット数がGoogle, Goo, Yahoo！のいずれでも第1位となっております。私の外来には聴覚障害のお子さんを持つ保護者が，新生児聴覚スクリーニングで難聴を疑われると，インターネットで調べて受診，今井絵理子さんの本「ココロノウタ」（祥伝社）（この本の中で私と今井絵理子さんの対談が掲載されております）を読んで受診します。同時に，日本聾話学校，難聴児通園施設の富士見台聴こえとことばの教室，神奈川県のろう学校や療育センターなどから紹介されて受診されます。難聴は検査をしないと診断できません。私がこの問題に本格的に取り組んで20年以上になりますが，今もなお耳鼻科や小児科の先生方の知識が乏しいために発見が遅れたり，間違ったお話しを両親にするために混乱が生じています。検査データの判定を正しくできない耳鼻科や新生児科や産科の先生が多いという「不都合な現実」があります。ここでは正しい受診の仕方をわかりやすく解説します。

新生児聴覚スクリーニングとはなんですか？

コンピューターを使った聴力検査に聴性脳幹反応（Auditory Brainstem Response：ABR）があります。これは専門家の操作によって行なわれ正確に難聴の重さや脳幹の発達を評価できるのですが，1例につき約1時間かかります。これを短時間（約10分程度）でだれでも簡単に操作できる難聴のスクリーニング検査の代表的なものが自動ABR（Automatic ABR：AABR）です。ただし結果は詳細には表れず，pass（合格），refer（要精密聴力検査）として表示されます。もう一つの検査法は耳音響放射（Otoacoustic emission：OAE）といい，過渡的耳音響放射（Transient OAE）と歪成分耳音響放射（Distortion Product OAE：DPOAE）の二つがあります。ここで注意が必要なのはスクリーニングでの正常と異常を二分する音圧レベルです。AABRは35 dBに設定され，TOAEもDPOAEも20～30 dB以上の難聴があると無反応になるような小さな値であるため，少しでも中耳や内耳に異常があると「要精密聴力検査」と出てしまうことです。

わが国では2000年より厚生省

著者プロフィール　1971年東京大学医学部卒業。帝京大学耳鼻咽喉科助教授，東京大学耳鼻咽喉科教授などを経て，現在は国立病院機構東京医療センター・臨床研究（感覚器）センター長。ほかに，東京大学名誉教授，獨協医科大学特任教授，目白大学客員教授。専門は耳科学，聴覚医学，めまい・平衡医学，小児耳鼻咽喉科学。関連著書・文献に，「加我君孝，編：新生児聴覚スクリーニング 早期発見・早期教育のすべて．金原出版，2005」「Kaga K：Central Auditory Pathway Disorders. Springer Verlag 2009」などがある。

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(現・厚生労働省) の主導で 2007 年まで検査に援助がありましたが，現在は地方自治体の責任となっています。

難聴が疑われたときの受診の経路

先天性難聴を想定すると三つの経路があります。

1) 耳鼻咽喉科の受診

大きな病院の耳鼻咽喉科の受診を勧めます。耳鼻咽喉科の先生は開業医や病院医師，大学の教室の先生などですが，専門が耳や聴覚とは限りません。鼻や頭頸部の癌や音声を専門とする場合，必ずしも難聴について詳しくないことが多いのです。とくに幼小児の難聴について詳しい先生は極めて少ないのです。そのため，「しばらく様子をみましょう」と言われ発見が遅れることが少なくありません。大きい病院の耳鼻科には，コンピューターを利用した聴力検査装置の ABR や耳音響放射装置などが備えられており，難聴の有無を判定できます。日本耳鼻咽喉科学会では，全国精密聴力検査機関として 164 の数の病院をホームページに紹介しています。近くにこのリストに掲載されている病院があれば受診を勧めます。

2) 小児科の受診

小児科の先生は，難聴による言語の発達の遅れについては詳しいとはいえません。「この年齢では聴こえは検査できないし，喃語があるので難聴はないでしょうから，半年後に来るように」と言われたりすることがありますが，これは正しくはありません。

3) 保健所

保健所では小児科医が 3〜4 か月から 3 歳に至るまで定期健診をしますが，面接あるいはアンケートのみで検査をすることがない難聴の発見は困難です。そのため保健所でも様子をみることを勧めるか，耳鼻科受診を勧めます。

耳鼻咽喉科ではどのようにして難聴の診断をするのですか？

小児の聴覚障害を専門とする病院では，次のような検査で最終診断をします。

1) 行動反応聴力検査

音に対する身体の反応を，音の大きさを変えて調べ，その反応するもっとも小さな反応を“閾値”といい目安とします。検査方法には Behavioral Observation Audiometry (BOA) と Conditioned orientation Reflex Audiometry (COR) があります。

2) 他覚的聴力検査

聴性脳幹反応 (ABR)，耳音響放射聴力検査 (TOAE, DPOAE)，聴性定常反応聴力検査 (Auditory Steady-State Response：ASSR)，Tympanometry があります。

以上のどの検査も長所と欠点があります。それを考慮しながら総合的に診断します。成長とともに改善したり，逆に悪化することがあるので注意深くフォローアップして確定診断をします。

難聴が診断されたあとはどのような経路をたどるのでしょうか？(就学前教育)

難聴が診断されると，資格のある耳鼻科の先生によって身体障害者診断書 (聴覚) を発行します。難聴の重症度別に 6 級から 2 級の認定をし，最後に役所に届けて身体障害者手帳が発行されます。そのあと補聴器意見交付書によって，ベビー型や耳掛型か箱型などの補聴器の種類を決めて役所に申請します。難聴児は

表 1 修学前の教育施設

	1．聴覚口話法	2．日本語対応手話＋聴覚口話法
先天性難聴児 中途失聴児	難聴児通園施設 (25) 公立療育センター (多数，ただし不明) 私立ろう学校 (1) 国立ろう学校 (1)	公立ろう学校 (100) 私立明晴学園 (1) 日本手話
難聴に他障害合併	同上	同上
盲ろう児 (2 重障害)	盲ろう児施設 (全国にあるが数は少ない)	

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