間で経験したガラス片による眼外傷. 第328回岩手眼科集談会, 盛岡, 2011.4.

93. 町田繁樹、後藤謙元、高橋公美、長谷川豊、藤原貴光、吉村長久、黒坂大次郎：ポリープ状脈絡膜血管症（PCV）の双子例の臨床経過および遺伝子型. 第328回岩手眼科集談会, 盛岡, 2011.4.
94. 川原温、五十嵐羊羽、黒坂大次郎、吉田晃敏：白内障手術での一手法、二手法による惹起乱視. 第155回日本眼科学会総会, 東京, 2011.5.
95. 東範行、不二門尚、石橋達朗、佐藤美保、近藤峰生、大鹿哲郎、黒坂大次郎、永本敏之：先天白内障の手術に関する全国調査. 第65回日本臨床眼科学会, 東京, 2011.10.
96. 田中三知子、黒坂大次郎、永本敏之、不二門尚、近藤峰生、佐藤美保、石橋達朗、大鹿哲郎、東範行：先天白内障における眼内レンズ二次挿入に関する多施設アンケート調査. 第65回日本臨床眼科学会, 東京, 2011.10.
97. 永本敏之、東範行、不二門尚、石橋達朗、佐藤美保、近藤峰生、大鹿哲郎、黒坂大次郎：全国調査結果による先天白内障に対するIOL挿入眼と非挿入例の比較. 第65回日本臨床眼科学会, 東京, 2011.10.
98. 大鹿哲郎、永本敏之、黒坂大次郎、江口秀一郎、稲村幹夫：難症例の白内障手術. 第65回日本臨床眼科学会, 東京, 2011.10.
99. 石川清乃、大関尚行、及川誠、後藤恭孝、木村桂、黒坂大次郎：東日本大震災における岩手県での眼科被災地診療初期の実態　緑内障について. 第65回日本臨床眼科学会, 東京, 2011.10.
100. 及川誠、大関尚行、石川清乃、後藤恭孝、木村桂、黒坂大次郎：東日本大震災における岩手県での眼科被災地診療初期の実態. 第65回日本臨床眼科学会, 東京, 2011.10.
101. 西村智治、町田繁樹、玉田邦房、黒坂大次郎：加齢黄斑変性におけるラニビズマブ投与による網膜神経節細胞機能への影響. 第65回日本臨床眼科学会, 東京, 2011.10.
102. 町田繁樹、玉田邦房、西村智治、横山大輔、原田朋美、黒坂大次郎：ポリープ状脈絡膜血管症に対するReduced fluence PDT後の黄斑機能. 第65回日本臨床眼科学会, 東京, 2011.10.
103. 藤原貴光、今村裕、西田泰典、Luiz H.Lima、Richard F. Spaide、黒坂大次郎：強度近視眼における脈絡膜厚と視力. 第65回日本臨床眼科学会, 東京, 2011.10.
104. 原田朋美、町田繁樹、藤原貴光、西田泰典、黒坂大次郎：Uveal effusion syndromeの脈絡膜所見. 第65回日本臨床眼科学会, 東京, 2011.10.
105. 横山大輔、橋爪公平、藤原貴光、小林貴樹、黒坂大次郎：非結核性坑酸菌症治療中に生じたリファブチン関連ぶどう膜炎の1例. 第65回日本臨床眼科学会, 東京, 2011.10.
106. 黒坂大次郎：進化したワンピースレンズについて考えてみよう. 第65回日本臨床眼科学会, 東京, 2011.10.
107. 黒坂大次郎：白内障手術における fluidics. 第229回鹿児島眼科集談会, 鹿児島, 2011.5.
108. 石川清乃、黒坂大次郎：虹彩離断を伴った外傷性白内障4症例の手術成績. 第50回日本白内障学会総会・第26回日本白内障屈折矯正手術学会総会, 福岡, 2011.6.
109. 橋爪公平、石川陽平、西郡秀夫、眞島行彦、黒坂大次郎：ステロイド誘発鶏胚白内障モデルでのSSAO阻害剤の効果. 第50回日本白内障学会総会・第26回日本白内障屈折矯正手術学会総会, 福岡, 2011.6.
110. 黒坂大次郎：一段上のQOVを目指す白内障症例. 第50回日本白内障学会総会・第26回日本白内障屈折矯正手術学会総会, 福岡, 2011.6.
111. 黒坂大次郎：極小切開白内障手術の魅力. 第50回日本白内障学会総会・第26回日本白内障屈折矯正手術学会総会, 福岡, 2011.6.
112. 鳥羽良陽、木村桂、石澤裕見子、及川誠、村井憲一、黒坂大次郎：トーリック眼内レンズの術後眼内回旋量の検討. 第50回日本白内障学会総会・第26回日本白内障屈折矯正手術学会総会, 福岡, 2011.6.
113. 黒坂大次郎：小児白内障の病態と治療. 第67回日本弱視斜視学会総会・第36回日本小児眼科学会総会, 京都, 2011.7.
114. 西田泰典、藤原貴光、黒坂大次郎：若年者の強度近視眼における脈絡膜厚. 第623回岩手医学会例会, 盛岡, 2011.7.
115. 伊藤愉一胤、村井憲一、鳴海新平、黒坂大次郎：特発性黄斑円孔手術後のうつむき姿勢に関する検討. 第329回岩手眼科集談会, 盛岡, 2011.7.
116. 黒坂大次郎：白内障ケーススタディ2011. 第6回東北6大学眼科STEP UPセミナー, 青森, 2011.7.
117. 黒坂大次郎：最近の白内障手術の話題. 函館眼科医会学術講演会, 函館, 2011.9.
118. 木村桂、工藤利子、江川勲、石川陽平、横山大輔、黒坂大次郎：角膜移植抜糸前後の角膜後面屈折力の変化. 第11回東北屈折矯正研究会, 盛岡, 2011.9.

119. 西村智治、町田繁樹、玉田邦房、黒坂大次郎：加齢黄斑変性におけるラニビズマブの網膜神経節細胞機能への影響. 第 330 回岩手眼科集談会, 盛岡, 2011.11.

120. 黒坂大次郎：極小切開眼内レンズ. 第 50 回日本白内障学会・第 26 回日本白内障屈折矯正手術学会　合同学術総会　ウィンターセミナー, 東京, 2011.12.

121. 鎌田有紀、木澤純也、黒坂大次郎. 水晶体乳化吸引術における創口およびサイドポートからの灌流液の漏れの影響. 第 25 回日本眼内レンズ屈折手術学会総会, 大阪, 2010.6

G. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得（予定）

細野克博、堀田喜裕・EYS 遺伝子の変異を検出するためのプライマー、プローブ、マイクロアレイ、及び、これらを備える検出キット、並びに網膜色素変性症原因遺伝子変異の検査方法、網膜色素変性症への遺伝的感受性の検査方法・特願 2010-294236・2010

2. 実用新案登録

なし

3. その他

なし

研究成果の刊行に関する一覧表

書　籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
仁科幸子	角膜の先天・周産期異常、網膜の先天・周産期異常	大鹿哲郎	眼科学 第2版	文光堂	東京	2011	98-99, 388-400
仁科幸子	風疹	村田敏規	眼科診療クオリファイ 5 全身疾患と眼	中山書店	東京	2011	140-141
仁科幸子	視覚障害	本田真美ほか	小児リハビリテーションポケットマニュアル	診断と治療社	東京	2011	165-172
仁科幸子	家族性滲出性硝子体網膜症	白神史雄	眼科診療クオリファイ 8 網膜血管障害	中山書店	東京	2011	226-233
仁科幸子	先天白内障による形態覚遮断弱視、小眼球・ぶどう膜欠損、母斑症	仁科幸子	眼科診療クオリファイ 9 子どもの眼と疾患	中山書店	東京	2011	114-115, 155-157, 220-226
近藤寛之	小児網膜硝子体手術	門之園一明	Eye Surgery Now 6. きれいな小児眼科手術これであなたも悩まない！	メジカルビュー社	東京	2011	132-137
近藤寛之	家族性滲出性硝子体網膜症へのレーザー光凝固の適応と方法	白神史雄	眼科臨床クオリファイ 8 網膜血管障害	中山書店	東京	2011	234-236
近藤寛之	第一次硝子体過形成遺残、家族性滲出性硝子体網膜症、Coats病	仁科幸子	眼科臨床クオリファイ 9 子どもの眼と疾患	中山書店	東京	2012	141-143, 150-152, 153-154
西田保裕	斜視・外眼筋手術 基本的手技（直筋の前後転）	山本哲也	新 Eye Surgery Now（きれいな小児眼科手術）	メジカルビュー社	東京	2011	64-71

西田保裕	眼位・眼球運動・両眼視機能	仁科幸子	眼科診療クオリファイ 9 子どもの眼と疾患	中山書店	東京	2012	19-24
黒坂大次郎	眼科疾患 白内障	山口徹ほか	今日の治療指針 私はこう治療している.	医学書院	東京	2011	246
黒坂大次郎	超音波水晶体乳化吸引術、術式	大鹿哲郎	眼科学 第2版	文光堂	東京	2011	1337-1342
黒坂大次郎	眼内レンズ縫着術	下村嘉一ほか	「超入門」眼科手術基本術式50	メディカ出版	東京	2011	124-128
仁科幸子	乳児の眼鏡処方	所 敬、梶田雅義	眼鏡処方の実際	金原出版	東京	2010	2-9
仁科幸子	Coats 病、乳児内斜視、人形の眼現象、Bergmeister 乳頭、Bell 現象	山本 節	視能矯正学用語解説辞典	メデイカル葵出版	東京	2010	73-74, 177-178, 213-214
小林百合、仁科幸子	眼科領域の特徴	奥山眞紀子ほか	医療従事者のための子ども虐待防止サポートブック	クインテッセンス出版	東京	2010	148-149
近藤寛之	色覚異常、網膜色素変性、網膜剥離	円藤吟史、堀江正知、萩原聡	臨床病理レビュー、特集病気をもちながらどこまで働けるか—疾病と就労の臨床診断—	臨床病理刊行会	東京	2010	214, 220-221, 224
西田保裕	検影法	大鹿哲郎	眼科診療クオリファイ（屈折異常と眼鏡矯正）	中山書店	東京	2010	12-16
西田保裕	乳幼児の検影法のコツを教えてください	大鹿哲郎	眼科診療クオリファイ（屈折異常と眼鏡矯正）	中山書店	東京	2010	17-19
黒坂大次郎	白内障	金澤一郎、永井良三	今日の診断指針	医学書院	東京	2010	1611-1612
黒坂大次郎	白内障術者の乱視への関心度	ビッセン宮島弘子	トーリック眼内レンズ	南山堂	東京	2010	48-49

黒坂大次郎	白内障	泉　孝英	今日の診療のために、ガイドライン外来診療2010	日経メディカル開発	東京	2010	484-487
黒坂大次郎	眼軸長が測定しにくい患者の検査法：片眼手術患者や強度近視患者の術後度数を検査で決めるには	山下英俊、谷原秀信	眼科検査のグノーティ・セアウント、この検査では、ここが見えない	シナジー	東京	2010	119-121
黒坂大次郎	眼疾患　白内障	門脇　孝、小室一成、宮地良樹	診療ガイドライン　UP-to-date 2010-2011	メディカルレビュー社	東京	2010	46-48

雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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
Nishina S, Kosaki R, Yagihashi T, Azuma N, Okamoto N, Hatsukawa Y, Kurosawa K, Yamane T, Mizuno S, Tsuzuki K, Kosaki K	Ophthalmic Features of CHARGE Syndrome with CHD7 Mutations.	Am J Med Genet A		Epub ahead of print	2012, Feb 2
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
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

Kondo H, Kusaka S, Yoshinaga A, Uchio E, et al.	Mutations in TSPAN12 gene in Japanese patients with familial exudative vitreoretinopathy.	Am J Ophthalmol	151	1095-1100	2011
Miyamoto N, Izumi H, Miyamoto R, Kondo H. et al.	Quercetin induces the expression of peroxiredoxin 3 and 5 through Nrf2/NRF1 transcription pathway.	Invest Ophthalmol Vis Sci	52	1055-1063	2011
Miyamoto N, Izumi H, Miyamoto R, Bin H, Kondo H, et al.	Transcriptional regulation of activating transcription factor 4 (ATF4) under oxidative stress in retinal pigment epithelial ARPE-19 cells.	Invest Ophthalmol Vis Sci	52	1266-1234	2011
近藤寛之	家族性滲出性硝子体網膜症	あたらしい眼科	28	963-968	2011
渡辺晃久、近藤寛之、松下五佳、森田啓文、田原昭彦	未熟児網膜症に対する抗ＶＥＧＦ療法の効果の検討	眼科手術	25	115-117	2012
有田直子、林 英之、内尾英一、近藤寛之	重症未熟児網膜症に対しベバシズマブ硝子体内投与を行った症例の検討	臨眼	65	1225-1229	2011
尾崎弘明、ファンジェーン、井上浩利、小沢昌彦、近藤寛之、内尾英一	急性網膜壊死の治療成績	臨眼	65	1819-1825	2011
Nakanishi H, Ohtsubo M, Iwasaki S, Hotta Y, Usami S, Mizuta K, Mineta H, Minoshima S	Novel *USH2A* mutations in Japanese Usher syndrome type 2 patients: marked differences in the mutation spectrum between the Japanese and other populations.	J.Hum.Genet	56(7)	484-990	2011
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
Higashiyama T, Nishida Y, Ugi S, Ishida M, Nishio Y, Ohji M	A case of extraocular muscle swelling due to IgG4-related sclerosing disease.	Jpn J Ophthalmol	55(3)	315-317	2011

伊藤友香、西田保裕、村木早苗、柿木雅志、大路正人	上転障害以外に眼所見が乏しかった甲状腺眼症の２例	臨床眼科	65 (9)	1425-1429	2011
Ishikawa Y, Hashizume K, Kishimoto S, Tezuka Y, Nishigori H, Yamamoto N, Kondo Y, Maruyama N, Ishigami A, Kurosaka D	Effect of vitamin C depletion on UVR-B induced cataract in SMP30/GNL knockout mice.	Exp Eye Res	94 (1)	85-89	2012
田中三知子、黒坂大次郎	眼内レンズにまつわるトラブル．小児の場合	眼科	53 (5)	667-671	2011
黒坂大次郎	特集 若年者の白内障手術のポイント．アトピー白内障手術のポイント	IOL&RS	25 (3)	328-331	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
Ito M, Yokoi T, Sugita S, Shinohara N, Nishina S, Azuma N	Endogenous candida chorioretinitis in a healthy infant.	Jpn J Ophthalmol	54	629-631	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
Shoji K, Ito N, Ito Y, Inoue N, Adachi S, Fujimaru T, Nakamura T, Nishina S, Azuma N, Saitoh A	Is a 6-week course of ganciclovir therapy effective for chorioretinitis in infants with congenital cytomegalovirus infection?	J Pediatr	157	331-333	2010
Wu J, Kubota J, Hirayama J, Nagai Y, Nishina S, Yokoi T, Asaoka Y, Seo J, Shimizu N, Kajiho H, Watanabe T, Azuma N, Katada T, Nishina H	p38 mitogen-activated protein kinase controls a switch between cardiomyocyte and neuronal commitment of murine embryonic stem cells by activating MEF2C-dependent BMP2 transcription.	Stem Cells Dev	19	1723-1734	2010
伊藤―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―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
Poulter J, Ali M, Gilmour DF, Rice A, Kondo H, et al.	Mutations in TSPAN12 cause autosomal-dominant familial exudative vitreoretinopathy.	Am J Hum Genet	86	248-253	2010
Kondo H, Saito K, Urano M, Sagara Y, Uchio E, Kondo M	A case of Fukuyama congenital muscular dystrophy associated with negative electroretinograms.	Jpn J Ophthalmol	54	622-624	2010
小山田剛、近藤寛之、林英之、内尾英一	成人と小児における増殖硝子体網膜症の手術成績	臨眼	64	543-546	2010
Ohtsubo M, Sato M, Hikoya A, Hosono K, Minoshima S, Hotta Y	A Japanese Case of X-linked Ocular Albinism Associated with *GPR143* Gene Mutation.	Jpn J Ophthalmol	56	624-626	2010
Nakanishi H, Ohtsubo M, Iwasaki S, Hotta Y, Takizawa Y, Hosono K, Mizuta K, Mineta H, Minoshima S	Mutation analysis of the *MYO7A* and *CDH23* genes in Japanese patients with Usher syndrome type 1.	J Hum Genet	55	796-800	2010
Nakanishi H, Ohtsubo M, Iwasaki S, Hotta Y, Mizuta K, Mineta H, Minoshima S	Hair roots as an mRNA source for mutation analysis of Usher syndrome-causing genes.	J Hum Genet	55	701-703	2010
Sawada M, Sato M, Hikoya A, Wang C, Minoshima S, Azuma N, Hotta Y	A case of aniridia with unilateral Peters anomaly.	J AAPOS		in press	2011

西川亜希子、西田保裕村木早苗、柿木雅志、大路正人	外傷性下直筋断裂に用いた水平筋全幅移動術	眼科臨床紀要	3	145-148	2010
西田保裕	複視の画像診断	あたらしい眼科	27	869-874	2010
西田保裕	固定名斜視の MRI による評価について教えてください	あたらしい眼科	27	249-251	2010
西田保裕	外転神経麻痺に対する眼筋移動術	眼科	52	1877-1882	2010
Tamada K, Machida S, Oikawa T, Miyamoto H, Nishimura T, Kurosaka D	Correlation between Photopic Negative Response of Focal Electroretinograms and Local Loss of Retinal Neurons in Glaucoma.	Current Eye Reseach	35	155-164	2010
Hamabata K, Hashizume K, Ishikawa Y, Fujiwara T, Machida S, Kurosaka D	Mutton Fat-like Subretinal Precipitates Associated with Vogt-Koyanagi-Harada Disease.	Ocular Immunology & Inflammation	18	44-45	2010
Machida S, Tamada K, Yokoyama D, Kaneko M, Kurosaka D.	Sensitivity and specificity of photopic negative response of focal electororetinogram to detect glaucomatous eyes.	Br J Ophthalmol	94	202-208	2010
Yokoyama D, Machida S, Kondo M, Terasaki H, Nishimura T, Kurosaka D.	Pharamacologicak Dissection of Multifocal Electroretiongrams of Rabbits with Pro347Leu Rhodopsin Mutation.	Jpn J Ophthalmol	54	458-466	2010
黒坂大次郎	特集：内科医のための眼疾患の診かたと治療 4.高齢者に多い眼疾患の診断と治療 2) 加齢白内障	Progress in Medicine	30	1277-1279	2010
黒坂大次郎	小児の度数決定	臨床眼科	64	137	2010
木村　桂、工藤利子、江川　勲、浦上千佳子鎌田有紀、黒坂大次郎	岩手県におけるマイクロケラトロンでの直接採取強角膜片の細菌学的ならびに角膜内皮細胞密度の検討	あたらしい眼科	27	1445-1448	2010
早川真奈、木村　桂、濱端久仁子、黒坂大次郎	TECHNIS　1－Piece (ZCB00)の術後早期成績の検討	IOL&RS	24	113-117	2010
黒坂大次郎、鎌田有紀	白内障・屈折手術の論点、コアキシャル　フェイコ	IOL&RS	24	72-74	2010

黒坂大次郎、浦上千佳子	特集 眼のかすみ　眼のかすみを起こす疾患（2）白内障	あたらしい眼科	27	158-164	2010

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CLINICAL INVESTIGATION

Survey of microphthalmia in Japan

Sachiko Nishina · Daijiro Kurosaka · Yasuhiro Nishida · Hiroyuki Kondo · Yuri Kobayashi · Noriyuki Azuma

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Abstract
Purpose To report the current status of patients with microphthalmia based on a cross-sectional survey of patient hospital visits.
Methods A questionnaire was sent to the departments of ophthalmology in 1,151 major Japanese hospitals to survey the following: the number of patients with microphthalmia who visited the outpatient clinics between January 2008 and December 2009; gender; age; family history; associated ocular anomalies; complications and systemic diseases; surgical treatment; vision and management. A retrospective quantitative registry of 1,254 microphthalmic eyes (851 patients) from 454 hospitals (39.4%) was compiled.
Results Of the patients for whom data were available, 50% ranged in age from 0 to 9 years. The major ocular findings were nanophthalmos, coloboma, and vitreoretinal malformations. Ocular complications frequently developed, including cataracts, glaucoma, and retinal detachment. Surgery was performed in 21.4% of all cases, and systemic diseases were present in 31% of all cases. The vision associated with microphthalmia exceeded 0.1 in about 30% of the eyes. Glasses and low vision aids were used by 21.6% of patients.
Conclusions Patients with microphthalmia often have ocular and systemic anomalies. Early assessment and preservation of vision and long-term complication management are needed.

Keywords Microphthalmos · Epidemiology · Survey · Intractable disease

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Introduction

Microphthalmos is defined as the arrested development of all global dimensions and is often is associated with other ocular and systemic anomalies [1]. Chromosomal disorders, genetic syndromes, and environmental factors, such as maternal infection and exposure to X-rays or drugs, are reported as causes [2]. However, in most cases the precise pathogenesis is unknown although some causative genes (*SOX2* and *PAX6*) have been identified [2–4].

Previous studies conducted in the UK report that the prevalence rates of microphthalmia, anophthalmia, and typical coloboma are 10–19 per 100,000 births [4–7]. Microphthalmia is rare, and only a few disease, genetic, and epidemiologic studies and a few reports on the practical patient status have been published. The condition generally causes substantial visual impairment, but standard management and treatments have not been established.

We conducted a cross-sectional national survey to investigate the current status of patients with microphthalmia, focusing especially on ocular associations,

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complications, surgery, and vision examinations performed by ophthalmologists.

Materials and methods

A questionnaire was sent to the departments of ophthalmology in 1,151 major hospitals nationwide, all of which are authorized by the Japanese Ophthalmological Society as training institutions for physicians specializing in ophthalmology, to survey the number of patients with microphthalmia who visited their outpatient clinics between January 2008 and December 2009. Patients referred to other hospitals during this period were excluded.

The diagnostic criterion for pure microphthalmos is the presence of an eye with two-thirds the normal ocular volume, i.e., 0.87 below the normal axial length [1]. The Japanese criteria were established by Majima [8], based on the average axial length for each age group of Japanese patients. The clinical definition can be determined by a substantial size difference between the two eyes. Axial lengths of <21 mm in adults and <19 mm in 1-year-old children, i.e., two standard deviations below normal, are used. Corneal diameters of <10 mm in adults and <9 mm in infants are used for a simple diagnosis [9]. In our survey, either Majima's criteria for pure microphthalmos or the clinical definition for complicated microphthalmos was applied.

The questionnaire asked for either the numbers of patients or the number of eyes and was divided into two sheets. The first sheet comprised questions on the number of cases, the number of cases operated on, whether the condition was unilateral or bilateral, gender, age, family history; the second sheet consisted of questions about the number of associated ocular anomalies and complications, surgical treatment, associated systemic diseases, vision and management with glasses, low vision aid, and the use of a prosthetic shell.

A retrospective quantitative registry of microphthalmia was compiled from the responses from 454 hospitals (39.4%). The data from 1,254 microphthalmic eyes of 851 cases in total were collected from the first sheet, but as some hospitals did not complete the second sheet, only data from 1,069 eyes of 722 cases were collected from the second sheet. Of the data collected for these 1,069 eyes, data on the vision of 56 eyes (5.2%) were incomplete. Thus, data from 1,013 eyes were analyzed for vision.

We surveyed the number of patients managed in Japanese hospitals and analyzed the associated ocular anomalies and complications, surgical treatment, systemic diseases, vision and ophthalmic management.

Results

Of the 851 cases [396 (46.5%) male, 455 (53.5%) female] of microphthalmia reported on the first sheet, 444 (52%) were unilateral and 405 (48%) were bilateral (for two cases no information on unilateralism or bilateralism was reported). In terms of age distribution, 50% of the patients were 0–9 years and 16% were 10–19 years; between ages 20 and 79 years, the prevalence remained relatively constant, ranging between 4.3 and 6.8% (Fig. 1). Family histories were positive in 61 cases (7.2%), of which 25 cases (41%) of autosomal dominant inheritance, three cases of X-linked recessive inheritance, and one case of autosomal recessive inheritance were identified; the other 32 cases were undetermined.

The data from the 1,069 microphthalmic eyes of 722 cases retrieved from the second sheet were compiled and analyzed for associated ocular anomalies and complications, surgical treatment, associated systemic diseases, and management with glasses, low vision aids, and prosthetic shells. The ocular abnormalities and complications associated with microphthalmia are shown in Fig. 2. The identified ocular findings were nanophthalmos, coloboma (choroid, retina, lens, iris), vitreoretinal malformation (retinal dysplasia, retinal fold, persistent fetal vasculature, etc.), anophthalmos/extreme microphthalmos, anterior segment dysgenesis (Peters' anomaly, aniridia), and optic

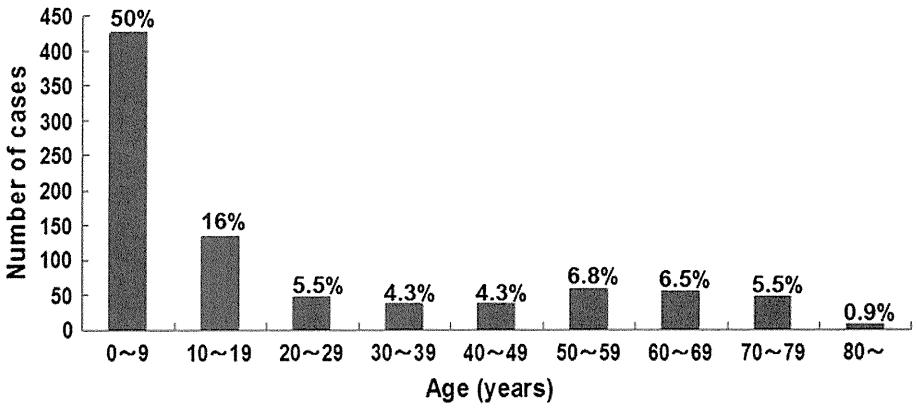

Fig. 1 Ages of patients with microphthalmia managed in the surveyed hospitals. The rate is given for each age group ($N = 851$ cases)

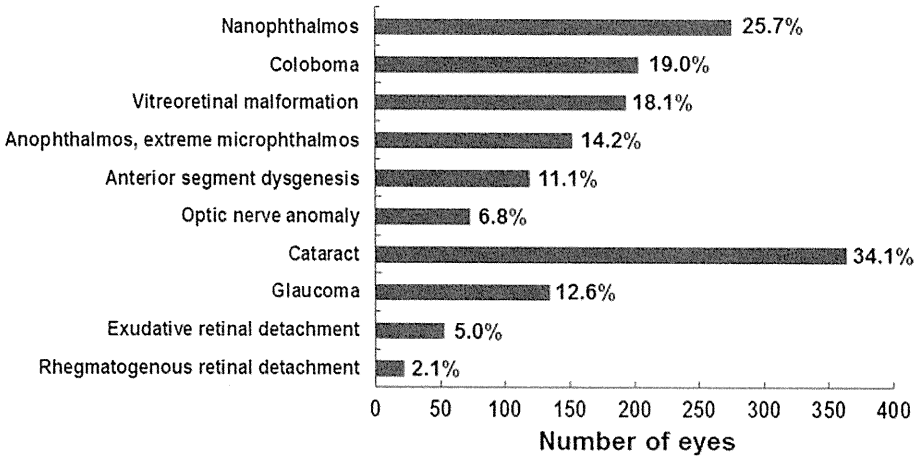

Fig. 2 Ocular abnormalities and complications associated with microphthalmia. The rate of each associated anomaly or complication is given ($N = 1{,}069$ eyes)

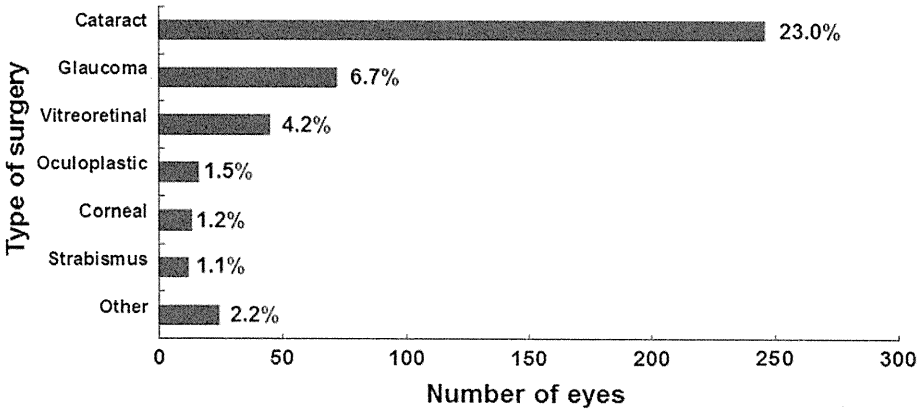

Fig. 3 Surgical treatments for ocular complications in microphthalmia. The rate of each surgical procedure is given ($N = 1{,}069$ eyes)

nerve anomaly (disc anomaly, optic nerve hypoplasia). The most frequent ocular complications were cataracts in 34.1%, followed by glaucoma and exudative or rhegmatogenous retinal detachment.

Surgery had been performed in 182 (21.4%) of the 851 cases; the surgical procedures for ocular complications are shown in Fig. 3. The procedures performed the most often were cataract extraction in 246 eyes (23.0%) of 1,069 eyes, followed by glaucoma surgery and vitreoretinal surgery.

Systemic diseases were present in 224 patients (31%) of 722 cases of microphthalmia, with 92 cases (12.7%) of developmental cerebral anomalies and mental deficiency, 68 cases (9.4%) of multiple anomalies and genetic syndromes, 26 cases (3.6%) of chromosomal disorders, and 38 cases (5.3%) of others.

The distribution of vision in microphthalmia is shown in Fig. 4. The data from 1,013 microphthalmic eyes were analyzed for vision. The visual acuity (VA) in microphthalmos was <0.02 in 348 eyes (34.4%), <0.1 but not <0.02 in 116 eyes (11.4%), <0.3 but not <0.1 in 93 eyes (9.2%), not <0.3 in 157 eyes (15.5%), unmeasurable with poor visual performance in 241 eyes (23.8%), and good visual performance in 58 eyes (5.7%).

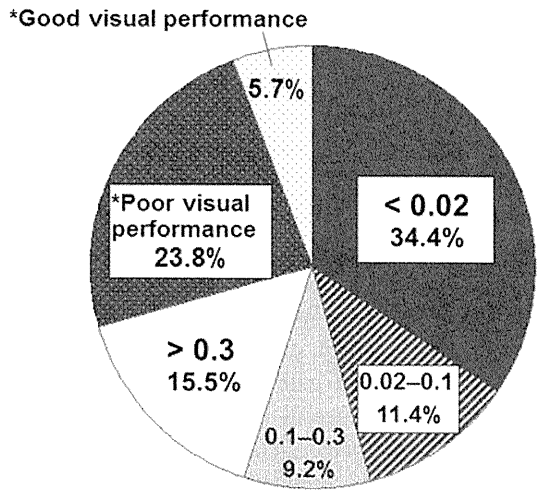

Fig. 4 Visual acuity (VA) in microphthalmos. *Asterisk* VA not measured due to young age or mental retardation. The rate of each VA group is given ($N = 1{,}013$ eyes)

Glasses and low vision aids were used in 156 cases (21.6%) of 722 cases, while prosthetic shells were applied in 211 eyes (19.7%) of 1,069 eyes.

Discussion

This is the first national survey that reports the epidemiologic aspects and current status of patients with microphthalmia in Japan. It is also the largest survey conducted by ophthalmologists of patients with microphthalmia who present at a hospital. The results based on cross-sectional surveys of patients' hospital visits may be considerably biased and may not be comparable with those of previous epidemiologic studies in other countries. However, the results of this survey showing the precise ocular associations, complications, types of surgeries, and vision, may be useful for future ocular management and investigation.

Approximately one-half of the patients in this survey who presented to a hospital were children under the age of 10 years, indicating that diagnosis and treatment of microphthalmia during the period of visual development are both needed and common practice in Japan. In addition, continuous management of low vision and ocular complications is required in order to maintain proper vision throughout life. Among the responders in this study, the distribution of microphthalmia was evenly divided between men and women and between unilateral cases and bilateral cases. Previous studies also report no biased association between microphthalmia and gender; however, those on laterality are mixed, with bilateral being more common in some studies and unilateral cases being more common in others [10]. Kallen et al. [11] reported that among their patient population, >70% of microphthalmia cases were bilateral and associated with chromosomal disorders, 53–60% were either associated or not associated with other malformations, but only 27% were cases of isolated microphthalmia. Microphthalmos associated with systemic diseases, nanophthalmos, colobomatous microphthalmos, and some cases of complicated microphthalmos often develop bilaterally and need more medical management for low vision and periodic follow-up. However, the current survey indicated that unilateral cases also require ophthalmic treatment and management.

The family histories were positive in 7.2% of cases; however, most cases have not been investigated for genetic etiology. To clarify the pathogenesis of various microphthalmia and develop useful treatments, effective genetic screening should be performed.

The current patient population had varying kinds and degrees of ocular-associated anomalies; among these, posterior segment dysgenesis, including coloboma and vitreoretinal malformations, was seen frequently. Thus, early morphologic and electrophysiologic evaluation of the posterior segment may be required to assess the visual potential and indications for surgical, optical, and amblyopia treatment or for a cosmetic shell.

The rates of developing cataracts, glaucoma, and retinal detachments were extremely high among the young patients. These ocular complications were major indications for surgical intervention, although the prognoses were generally poor [12]. Patients with microphthalmia require lifelong management for early prevention and detection of these complications. A less invasive surgical procedure for microphthalmia should be developed [13–19].

Various systemic anomalies are frequently associated with microphthalmia, indicating that initial assessment and continuous management by pediatricians are essential. Although 31% of the cases in our survey were microphthalmia associated with systemic disease, analysis of a population-based birth defects registry in Hawaii from 1986 to 2001 revealed that only 5% of the 96 cases had either isolated anophthalmia or microphthalmia, whereas 25% had confirmed chromosomal abnormalities, such as trisomy 18 and 13, and others had malformation syndromes, limb and musculoskeletal system defects, and cardiac and circulatory system defects [10]. Our survey included more unilaterally isolated cases, probably because ophthalmologists conducted the survey and provided detailed descriptions of the ocular status of the patients who presented to the hospitals.

Overall useful vision and good visual performance >0.1 were obtained in about 30% of microphthalmia cases, whereas about 34% of microphthalmia patients were blind (VA <0.02). However, glasses and low vision aids were used in around 22% of the cases, while prosthetic shells were used in about 20% of eyes. The visual prognosis of microphthalmos depends largely on the difference between the two eyes. The chances of obtaining good VA are limited in cases of severe unilateral microphthalmos, where orbital growth may be retarded and facial deformity may develop. Early socket expansion and wearing of a prosthetic shell are important for cosmetic treatment in anophthalmos and extreme microphthalmos [20]. However, microphthalmos with visual potential should be assessed early and glasses prescribed to maximize the VA.

In summary, our analysis of the survey data revealed that patients with microphthalmia have various ocular and systemic anomalies and that the rates of ocular complications are high in young patients. Early assessment, preservation of vision, and long-term management of complications are needed for these patients.

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References

1. Duke-Elder S. Microphthalmos. In: Duke-Elder S, editor. System of ophthalmology, vol III. Normal and abnormal development,

part 2. Congenital deformities. London: Henry Kimpton; 1964. p. 488–95.
2. Verma AS, Fitzpatrick DR. Anophthalmia and microphthalmia. Orphanet J Rare Dis. 2007;2:47.
3. Hever AM, Williamson KA, van Heyningen V. Developmental malformations of the eye: the role of *PAX6, SOX2* and *OTX2*. Clin Genet. 2006;69:459–70.
4. Morrison D, FitzPatrick D, Hanson I, Williamson K, van Heyningen V, Fleck B, et al. National study of microphthalmia, anophthalmia, and coloboma (MAC) in Scotland: investigation of genetic aetiology. J Med Genet. 2002;39:16–22.
5. Dolk H, Busby A, Armstrong BG, Walls PH. Geographical variation in anophthalmia and microphthalmia in England, 1988–94. Br Med J. 1998;317:905–9.
6. Busby A, Dolk H, Collin R, Jones RB, Winter R. Compiling a national register of babies born with anophthalmia/microphthalmia in England 1988–94. Arch Dis Child Fetal Neonatal Ed. 1998;79:F168–73.
7. Shah SP, Taylor AE, Sowden JC, Ragge NK, Russell-Eggitt I, Rahi JS, et al. Anophthalmos, microphthalmos and typical coloboma in the UK: a prospective study of incidence and risk. Invest Ophthalmol Vis Sci. 2011;52:558–64.
8. Majima A. Microphthalmos and its pathogenic classification (in Japanese with English abstract). Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc). 1994;98:1180–200.
9. Weiss AH, Kousseff BG, Ross EA, Longbottom J. Complex microphthalmos. Arch Ophthalmol. 1989;107:1619–24.
10. Forrester MB, Merz RD. Descriptive epidemiology of anophthalmia and microphthalmia, Hawaii, 1986–2001. Birth Defect Res A Clin Mol Teratol. 2006;76:187–92.
11. Kallen B, Robert E, Harris J. The descriptive epidemiology of anophthalmia and microphthalmia. Int J Epidemiol. 1996;25:1009–16.
12. Singh OS, Simmons RJ, Brockhurst RJ, Trempe CL. Nanophthalmos: a perspective on identification and therapy. Ophthalmology. 1982;89:1006–12.
13. Yu SY, Lee JH, Chang BL. Surgical management of congenital cataract associated with severe microphthalmos. J Cataract Refract Surg. 2000;26:1219–24.
14. Nishina S, Noda E, Azuma N. Outcome of early surgery for bilateral congenital cataracts in eyes with microcornea. Am J Ophthalmol. 2007;144:276–80.
15. Vasavada VA, Dixit NV, Ravat FA, Praveen MR, Shah SK, Vasavada V, et al. Intraoperative performance and postoperative outcome of cataract surgery in infant eyes with microphthalmos. J Cataract Refract Surg. 2009;35:519–28.
16. Brockhurst RJ. Cataract surgery in nanophthalmic eyes. Arch Ophthalmol. 1990;108:965–7.
17. Wu W, Dawson DG, Sugar A, Elner SG, Meyer KA, McKey JB, et al. Cataract surgery in patients with nanophthalmos: results and complications. J Cataract Refract Surg. 2004;30:584–90.
18. Wladis EJ, Gewirtz MB, Guo S. Cataract surgery in the small adult eye. Surv Ophthalmol. 2006;51:153–61.
19. Kocak I, Altintas AG, Yalvac IS, Nurozler A, Kasim R, Duman S. Treatment of glaucoma in young nanophthalmic patients. Int Ophthalmol. 1997;20:107–11.
20. Ragge NK, Subak-Sharpe ID, Collin JRO. A practical guide to the management of anophthalmia and microphthalmia. Eye. 2007;21:1290–300.

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

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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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

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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

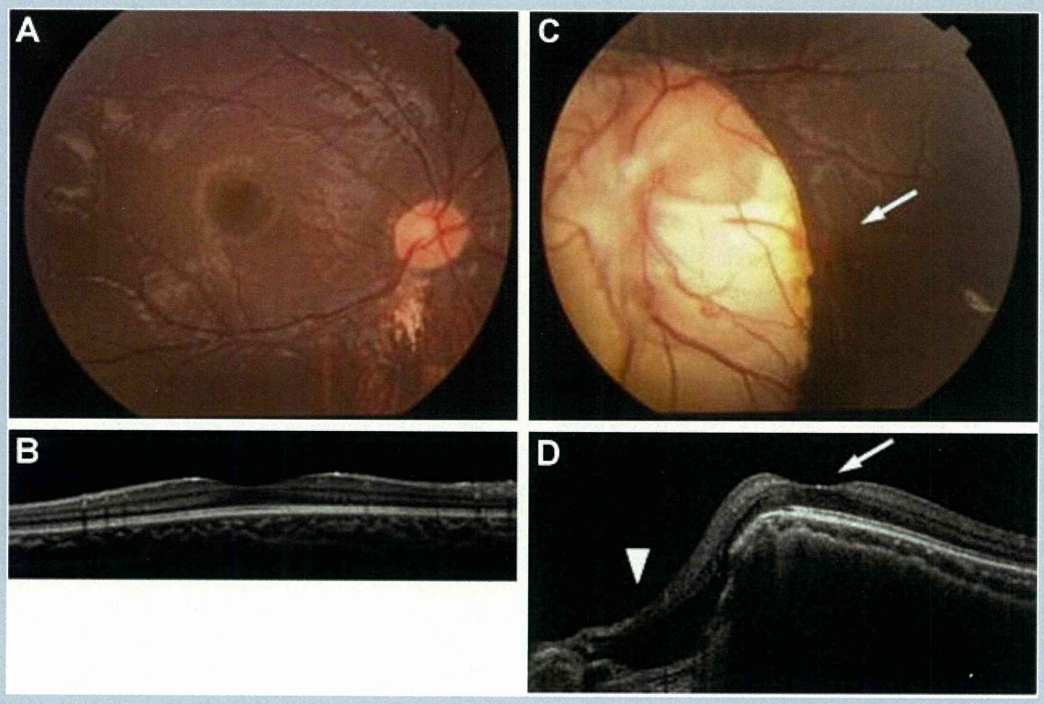

FIG. 1. Fundus photographs and spectral domain optical coherence tomography (SD-OCT) scan of the retina in the right eye (A,B) and the left eye (C,D) in a 6-year-old girl. A: Retinochoroidal colobomata inferior to the optic disk is visible in the right eye. B: The SD-OCT shows a good macular formation 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 amblyopia treatment.

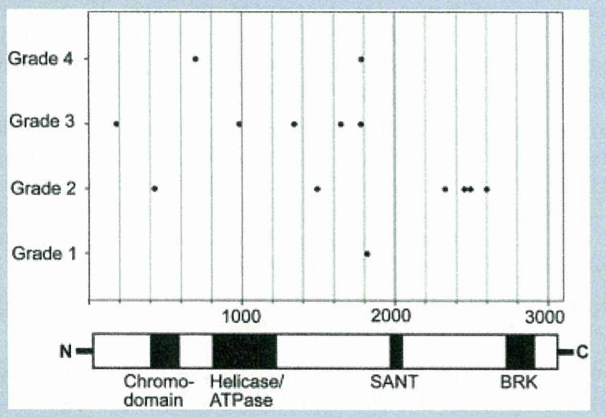

FIG. 2. The correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the CHD7 protein occurred in the same individual. Horizontal axis indicates amino acid position of the CHD7 protein together with the domains of the protein. Vertical 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.