Published in final edited form as:

Eur J Med Genet. 2018 April ; 61(4): 225–229. doi:10.1016/j.ejmg.2017.11.019.

Atopic disorders in CHARGE syndrome: a retrospective study and literature review

Fang Kong^a and Donna M. Martin^{b,c,*}

^aDepartment of Rheumatology and Allergy, Xuanwu Hospital, Capital Medical University, Beijing, China

^bDepartments of Pediatrics and Communicable Diseases, The University of Michigan Medical School, Ann Arbor, Michigan, USA

^cDepartment of Human Genetics, The University of Michigan Medical School, Ann Arbor, Michigan, USA

Abstract

Background—Atopic disorders have been reported in CHARGE syndrome, but the prevalence and underlying mechanisms are not known.

Methods—We performed a retrospective study of atopic disorders in 23 individuals with CHARGE syndrome, and reviewed other published reports of atopic disorders in CHARGE syndrome. We assayed for enrichment of atopic disorders in CHARGE syndrome based on gender and presence of a *CHD7* pathogenic variant.

Results—In our cohort, 65% (15/23) of individuals with CHARGE syndrome were found to have a pathogenic *CHD7* variant. Overall, 65% (15/23) of individuals with CHARGE had atopic disorders. Among the 23 individuals with CHARGE, 22% (5/23) had food allergy, 26% (6/23) exhibited drug allergy, 22% (5/23) had contact allergy, 9% (2/23) had allergic rhinitis, and 22% (5/23) had asthma. In our cohort, the proportion of males to females with CHARGE and atopic disorders was 11:4 ($P < 0.01$), and there was no significant difference between atopic disorders in individuals with *CHD7* pathogenic variants and those without *CHD7* pathogenic variants ($P > 0.05$).

Conclusion—In our cohort of 23 individuals with CHARGE syndrome, 15 (65%) exhibited atopic disorders, with a slight male predominance.

Keywords

allergy; atopic disorders; CHARGE syndrome; *CHD7*

*Corresponding author: Donna M. Martin, M.D., Ph.D., 8220C Medical Science Research Building III, 1150 W. Medical Center Dr., The University of Michigan Medical Center, Ann Arbor, MI 48109-5646, USA, donnamm@umich.edu, Tel: (734) 647-4859, Fax: (734) 763-9512.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

CHARGE syndrome is a rare, multiple congenital anomaly disorder caused by heterozygous pathogenic variants in the *CHD7* gene (Vissers et al., 2004). The birth prevalence of CHARGE syndrome is estimated at one in 15,000 to 17,000 newborns (Janssen et al., 2012). *CHD7* encodes a member of the Chromodomain Helicase DNA (CHD) binding protein family that regulates gene expression during embryonic development (Woodage et al., 1997). The main characteristics of CHARGE are ocular Coloboma, Hear malformations, Atresia of the choanae, Retardation of growth and/or development, Genital anomalies, and Ear malformations including hearing loss and vestibular dysfunction. Individuals with CHARGE syndrome also have other symptoms, some of which occur at an incidence higher than the general population. For example, Hsu et al. reported that 65% of individuals with CHARGE syndrome had at least one atopic disorder (Hsu et al., 2016). However, detailed reports of atopic disorders in CHARGE syndrome have not yet been published.

Here, we present a retrospective study of atopic disorders in CHARGE syndrome from our cohort of 23 individuals. We also discuss the various types of atopic disorders reported in individuals with CHARGE syndrome and review other published studies.

MATERIALS AND METHODS

All individuals included in the study were diagnosed and evaluated at The University of Michigan Pediatric Genetics clinic between 2003 and 2016. All individuals fulfilled clinical diagnostic criteria for CHARGE syndrome (Blake et al., 1998; Hale et al., 2016; Verloes, 2005). *CHD7* pathogenic variant screening had been previously performed in all individuals as part of their medical evaluations. All clinical symptoms, allergy histories, feeding histories, laboratory results and treatment histories were collected through the electronic medical record (EMR). Food/drug/contact allergy histories were obtained through physician observation, parental report and/or allergy testing. Comparisons were carried out relative to gender and *CHD7* pathogenic variant status.

ANOVA was used to compare differences in continuous variables between groups by Fisher's exact tests. $P < 0.05$ was considered significant.

RESULTS

A total of 23 individuals with CHARGE syndrome were included in our study. The clinical features and *CHD7* pathogenic variants of the individuals are listed in Table 1. The clinical features of the 23 individuals with CHARGE syndrome have been published previously (Green et al., 2014; Hale et al., 2016); where relevant, updated clinical information was provided. The median age of individuals in our cohort was 13 years (range, three to 33 years), with 12 males and 11 females. Fifteen of the 23 individuals (65%) were found to carry a pathogenic *CHD7* variant, including two missense, three frameshift, and 10 nonsense pathogenic variants.

In our cohort, 48% (11/23) of individuals with CHARGE syndrome were allergic to various allergens. Details are shown in Table 2. Five individuals (5/23, 22%) were diagnosed with

food allergy: three were diagnosed through physician observation, one was diagnosed via parental report, and one was diagnosed by allergy testing and physician observation. The ratio of males to females for these five individuals with food allergy was 4:1 ($P > 0.05$). The most common allergen was nuts, and others included egg, gluten protein, and milk. The allergic phenomena described included nausea, vomiting, abdominal pain, gastrointestinal distress, loose stools, bloody stools, and respiratory difficulty. Seven individuals (6/23, 26%) were diagnosed with drug allergy, all via physician observation. The most common drug allergen was antibiotics, and the most common symptom was rash. One individual experienced serum sickness and another individual exhibited cough. No episodes of anaphylaxis were reported. Five individuals (5/23, 22%) were diagnosed with contact allergy: one was diagnosed through allergy testing and four were diagnosed via parental report. These five individuals with contact allergy were allergic to lanolin, latex, adhesive tape, ethyl alcohol or natural rubber, mild to severe rashes reported. Two individuals (2/23, 9%) were reported to have allergic rhinitis and five (5/23, 22%) had asthma. Twelve individuals (12/23, 52%) had a history of tube feeding and 17 (17/23, 74%) were reported to have a history of parenteral nutrition. One individual had IgE levels measured, and were normal. Eosinophils were measured in 15/23 (65%) of individuals as part of a complete blood cell (CBC) analysis; among these, only two individuals demonstrated eosinophilia, on one occasion each.

We asked whether, for our cohort, food allergy was correlated with histories of tube feeding or parenteral nutrition (see Table 3). Three of five individuals with CHARGE and food allergy had a history of tube feeding, whereas nine of 18 individuals with CHARGE but no food allergies had no history of tube feeding. Based on Fisher's exact test, this was not statistically significant ($P > 0.05$). All five (5/5, 100%) individuals with food allergies had a history of parenteral nutrition, whereas six of 18 (33%) of individuals without food allergies had no history of parenteral nutrition. This was also not statistically significant ($P > 0.05$).

In our cohort, six of 23 individuals had 1,25-dihydroxyvitamin D (vitamin D) levels measured. Using the consensus classification system for vitamin D levels (Munns et al., 2016), four exhibited vitamin D deficiency (less than 25 ng/ml), and the other two had vitamin D levels in the insufficiency range (25–50 ng/ml). Five of the six (83.3%) individuals with vitamin D levels also exhibited atopic disorders.

We observed a male predominance of atopic disorders in our cohort (see Table 4). Among 12 males, 11 exhibited atopic disorders, compared to four of 11 females. The proportion of males and females with atopic disorders was 11:4 ($P < 0.01$). Among individuals with atopic disorders, there was no significant difference between the number of individuals with a *CHD7* pathogenic variant and those without ($P > 0.05$).

Among individuals with CHARGE syndrome, atopic disorders, and a history of tube feeding, the proportion males to females was 6:3 ($P > 0.05$) (see Table 5). There was no significant difference between the proportion of males vs females with atopic disorders and history of parenteral feeding ($P > 0.05$).

DISCUSSION

Here, we found that 65% (15/23) of individuals with CHARGE syndrome in our cohort exhibited atopic disorders. In previous studies, Hsu et al. reported atopic disorders among 65% of individuals with CHARGE (Hsu et al., 2016), whereas Wong et al. and Theodoropoulos reported a prevalence estimate of ~30% (Theodoropoulos, 2003; Wong et al., 2015). These differences in prevalence across studies may be related to sample size or methods of collecting medical information about the individual participants in each study. Further studies of larger cohorts should help clarify whether the prevalence of atopic disorders is higher in CHARGE syndrome than in the general population, which is estimated to be 10–40% (WAO, 2013).

Individuals with CHARGE syndrome in our cohort experienced several types of atopic disorders, including food allergy, drug allergy, contact allergy, atopic dermatitis, allergic rhinitis and asthma. We found that almost half (48%) of the individuals with CHARGE syndrome exhibited food/drug/contact allergy, among which 22% had food allergy. In the study by Wong (Wong et al., 2015), the most common atopic disorder was food allergy (25%), and the study by Theodoropoulos (Theodoropoulos, 2003) reported food allergy in one of three individuals (see Table 6). Together with our data, these studies suggest that food allergies may be an important type of atopic disorder among individuals with CHARGE syndrome. Since 2007, the incidence of food allergy has increased in the general population to 10% of children and 6% of adults (Lee, 2017). Interestingly, food allergy has also been proposed as the first step in the allergic march, a phenomenon whereby food allergy may precede and trigger advancement or development of additional allergies (Allen and Dharmage, 2010). For example, individuals with food allergies may progress to exhibit early-onset eczema, later-onset allergic rhinitis, and asthma in childhood or adulthood (Burgess et al., 2008; Lowe et al., 2008).

Many individuals with CHARGE syndrome experience failure to thrive in childhood and require feeding support. In a retrospective study of 302 children in feeding programs, Yeung and colleagues found a higher proportion of food allergy compared to the general population (Yeung et al., 2015). It seems possible that tube feeding or parenteral nutrition could increase allergic sensitivity, potentially by reducing exposure to oral foods and/or lowering the varieties of food types exposed, although we are unaware of studies that have specifically addressed this. In our cohort, 25% (3/12) of individuals with a history of tube feeding had food allergy, and 29% (5/17) of individuals with a history of parenteral nutrition had food allergy, but neither group was significantly over-represented compared to individuals without tube feeding or parenteral nutrition histories.

It has been suggested that Vitamin D deficiency in early life may play a role in the acquisition of food allergies, due to its modulatory functions in the innate and acquired immune systems (Suaini et al., 2015). In our cohort, five of six (83%) of individuals with low Vitamin D levels had atopic disorders. The etiology of vitamin D deficiency among individuals in our cohort is unclear, and may be associated with hypoparathyroidism (Abate and Clarke, 2016; Jain et al., 2011), although this was not explicitly tested.

Drug allergy was also relatively common among individuals in our cohort (26%), at a frequency similar to that of the general population. We found a slight male predominance of atopic disorders among individuals with CHARGE syndrome. Males were more likely than females to have food allergy (4:1), history of tube feeding (6:3), and history of parenteral nutrition (8:2), but these observations were not statistically significant. Other studies have attributed differences in immunity between males and females to sex chromosome and/or sex hormone differences (Chen et al., 2008; Schieck et al., 2016). Given that *CHD7* regulates gene expression, it is possible that immune-related gene expression could be affected by heterozygous loss of *CHD7* function. However, we found no correlation between pathogenic *CHD7* variant status and presence of atopic disorders.

The prevalence of pathogenic *CHD7* variants in our population (65%) was lower than previous large studies in which up to 90% of individuals with a clinical diagnosis of CHARGE were found to have pathogenic variants in *CHD7* (Janssen et al., 2012). The relatively lower prevalence of individuals with pathogenic variants in *CHD7* in our cohort may reflect ascertainment bias of study recruitment or higher motivation by parents whose children lack *CHD7* variants to participate in research.

There are several limitations of our study. First, the retrospective design could have led to omission and underestimation of the types and/or frequencies of atopic disorders. Second, we did not obtain longitudinal or natural history data, and some disorders may be transient or resolved. Third, we did not employ a targeted comprehensive survey of atopic disorders, relying instead on earlier parental reports obtained by general questionnaire, physician observation, or in-person discussions. Finally, the small size of our cohort may not reflect larger population frequencies or prevalence. However, despite these limitations, we found a high prevalence (65%) of atopic disorders among our 23 individuals with CHARGE syndrome. Among the atopic disorders, food allergy was most common. While ours is a small study, these observations raise the possibility that atopic disorders may be more common in CHARGE syndrome than in the general population, and warrant further analysis to clarify the prevalence, type, and pathogenesis of atopic disorders in CHARGE syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

D.M.M. is supported by NIH R01 DC009410, R01 DC014456, and by the Donita B. Sullivan, MD Research Professorship in Pediatrics and Communicable Diseases.

References

- Abate EG, Clarke BL. Review of Hypoparathyroidism. *Front Endocrinol (Lausanne)*. 2016; 7:172. [PubMed: 28138323]
- Allen KJ, Dharmage SC. The role of food allergy in the atopic march. *Clin Exp Allergy*. 2010; 40(10): 1439–1441. [PubMed: 20937060]

- Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM Jr. CHARGE association: an update and review for the primary pediatrician. *Clinical pediatrics*. 1998; 37(3):159–173. [PubMed: 9545604]
- Burgess JA, Dharmage SC, Byrnes GB, Matheson MC, Gurrin LC, Wharton CL, Johns DP, Abramson MJ, Hopper JL, Walters EH. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *The Journal of allergy and clinical immunology*. 2008; 122(2): 280–285. [PubMed: 18572229]
- Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy*. 2008; 63(11):1418–1427. [PubMed: 18925878]
- Green GE, Huq FS, Emery SB, Mukherji SK, Martin DM. CHD7 Mutations and CHARGE Syndrome in Semicircular Canal Dysplasia. *Otol Neurotol*. 2014; 35(8):1466–1470. [PubMed: 24979395]
- Hale CL, Niederriter AN, Green GE, Martin DM. Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. *Am J Med Genet A*. 2016; 170A(2):344–354. [PubMed: 26590800]
- Hsu P, Ma A, Barnes EH, Wilson M, Hoefsloot LH, Rinne T, Munns C, Williams G, Wong M, Mehr S. The Immune Phenotype of Patients with CHARGE Syndrome. *J Allergy Clin Immunol Pract*. 2016; 4(1):96–103. e102. [PubMed: 26563674]
- Jain S, Kim HG, Lachawan F, Meliciani I, Wenzel W, Kurth I, Sharma J, Schoeneman M, Ten S, Layman LC, Jacobson-Dickman E. Unique phenotype in a patient with CHARGE syndrome. *International journal of pediatric endocrinology*. 2011; 2011:11. [PubMed: 21995344]
- Janssen N, Bergman JE, Swertz MA, Tranebjaerg L, Lodahl M, Schoots J, Hofstra RM, van Ravenswaaij-Arts CM, Hoefsloot LH. Mutation update on the CHD7 gene involved in CHARGE syndrome. *Hum Mutat*. 2012; 33(8):1149–1160. [PubMed: 22461308]
- Lee S. IgE-mediated food allergies in children: prevalence, triggers, and management. *Korean J Pediatr*. 2017; 60(4):99–105. [PubMed: 28461822]
- Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ, Dharmage SC. Do boys do the atopic march while girls dawdle? *The Journal of allergy and clinical immunology*. 2008; 121(5): 1190–1195. [PubMed: 18313134]
- Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Makitie O, Ramos-Abad L, Ward L, DiMeglio LA, Atapattu N, Cassinelli H, Braegger C, Pettifor JM, Seth A, Idris HW, Bhatia V, Fu J, Goldberg G, Savendahl L, Khadgawat R, Pludowski P, Maddock J, Hyponen E, Oduwole A, Frew E, Aguiar M, Tulchinsky T, Butler G, Hogler W. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. *J Clin Endocrinol Metab*. 2016; 101(2):394–415. [PubMed: 26745253]
- Schieck M, Schouten JP, Michel S, Suttner K, Toncheva AA, Gaertner VD, Illig T, Lipinski S, Franke A, Klintschar M, Kalayci O, Sahiner UM, Birben E, Melen E, Pershagen G, Freidin MB, Ogorodova LM, Granell R, Henderson J, Brunekreef B, Smit HA, Vogelberg C, von Berg A, Bufe A, Heinzmann A, Laub O, Rietschel E, Simma B, Genuneit J, Jonigk D, Postma DS, Koppelman GH, Vonk JM, Timens W, Boezen HM, Kabesch M. Doublesex and mab-3 related transcription factor 1 (DMRT1) is a sex-specific genetic determinant of childhood-onset asthma and is expressed in testis and macrophages. *The Journal of allergy and clinical immunology*. 2016; 138(2):421–431. [PubMed: 26906082]
- Suaini NH, Zhang Y, Vuillermin PJ, Allen KJ, Harrison LC. Immune Modulation by Vitamin D and Its Relevance to Food Allergy. *Nutrients*. 2015; 7(8):6088–6108. [PubMed: 26225992]
- Theodoropoulos DS. Immune deficiency in CHARGE association. *Clin Med Res*. 2003; 1(1):43–48. [PubMed: 15931284]
- Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A*. 2005; 133(3):306–308.
- Visser 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. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet*. 2004; 36(9):955–957. [PubMed: 15300250]
- WAO. [Accessed October 14 2017] WAO White Book on Allergy 2013 Update. 2013. <http://www.worldallergy.org/wao-white-book-on-allergy>

- Wong MT, Lambeck AJ, van der Burg M, la Bastide-van Gemert S, Hogendorf LA, van Ravenswaaij-Arts CM, Scholvinck EH. Immune Dysfunction in Children with CHARGE Syndrome: A Cross-Sectional Study. *PLoS One*. 2015; 10(11):e0142350. [PubMed: 26544072]
- Woodage T, Basrai MA, Baxevanis AD, Hieter P, Collins FS. Characterization of the CHD family of proteins. *Proc Natl Acad Sci U S A*. 1997; 94(21):11472–11477. [PubMed: 9326634]
- Yeung KA, Taylor T, Scheimann A, Carvalho R, Reinhardt E, Girolami P, Wood R. The Prevalence of Food Allergies in Children Referred to a Multidisciplinary Feeding Program. *Clinical pediatrics*. 2015; 54(11):1081–1086. [PubMed: 26130398]

Table 1

CHD7 pathogenic variants and clinical features among individuals with CHARGE syndrome

Patient	Age (y)	Sex	<i>CHD7</i> pathogenic variant (cDNA, Protein change)	Coloboma	Choanal atresia	Inner ear anomalies	External ear anomalies	Hearing loss	Heart defect	TEF	DD	Genital anomalies	Renal anomalies	CN dysfunction	Brain anomalies	Feeding difficulties	Skeleton anomalies	Cleft lip/pate	Growth deficiency
<i>1^H</i>	5	M	c.4164G>A, p. Trp1388*	+	–	NA	+	+	+	+	+	+	+	+	+	+	NA	+	+
<i>2^H</i>	16	M	c.4164G>A, p. Trp1388*	+	+	+	+	+	+	–	+	+	NA	NA	NA	+	+	–	+
<i>3^H</i>	13	F	–	+	+	+	–	+	+	–	+	–	+	NA	NA	+	NA	–	+
<i>4^H</i>	13	M	–	+	–	+	+	+	+	–	+	+	+	NA	–	+	+	+	–
<i>5^H</i>	14	F	–	NA	–	+	+	–	–	+	+	–	+	+	+	+	NA	–	+
<i>6^H</i>	13	F	–	NA	–	+	–	+	–	+	+	–	NA	NA	NA	+	NA	+	+
<i>7^H</i>	10	M	–	+	–	+	+	+	+	–	+	+	–	NA	NA	+	NA	–	+
<i>8^H</i>	6	F	–	+	–	+	+	+	+	–	+	–	–	+	–	+	NA	–	+
<i>9^H</i>	9	F	–	+	–	+	+	+	+	–	+	–	+	+	+	+	+	–	–
<i>10^H</i>	19	M	–	NA	+	NA	+	+	+	+	+	+	–	NA	–	–	+	–	–
<i>11^{H,G}</i>	15	M	1774C>T, p. Gln592*	+	–	+	+	+	–	–	+	+	–	NA	–	–	NA	+	–
<i>12^H</i>	6	M	c.6322G>A, p. Gly2108Arg	+	–	+	+	+	–	–	+	+	–	+	–	–	NA	–	–
<i>13^{H,G}</i>	14	F	2254A>T, P.Arg752*	+	+	NA	+	+	–	–	+	+	+	+	–	+	+	+	+
<i>14^{H,G}</i>	23	M	c.3881T>C, p. Leu1294Pro	+	+	NA	+	+	+	–	+	NA	+	NA	+	NA	+	–	+
<i>15^H</i>	14	F	c.2839C>T, p. Arg947*	–	–	+	+	+	+	+	+	–	NA	+	–	+	+	+	+
<i>16^{H,G}</i>	22	M	c.5458C>T, p. Arg1820*	+	–	+	+	+	+	–	+	+	–	+	–	+	+	–	+
<i>17^H</i>	16	M	c.7294bC, p. Pro243fs	+	–	+	+	+	+	–	+	+	+	+	NA	+	–	–	+
<i>18^H</i>	33	F	2724G>A, p. Trp908*	–	+	NA	+	+	+	–	+	–	–	+	+	+	+	–	+
<i>19^H</i>	14	M	c.7282C>T, p. Arg2428*	–	–	+	+	+	–	–	+	+	–	+	+	–	+	–	+
<i>20^H</i>	4	F	c.7447G>T, p. Gln2483*	+	+	+	+	+	+	–	+	–	–	+	+	+	NA	–	–
<i>21^H</i>	3	F	c.1925dupA, p. Lys643Glnfs	–	–	+	+	+	+	–	+	–	+	+	–	+	+	–	+
<i>22^H</i>	3	F	c.2689dupC, p. Arg897Profs	+	+	+	+	+	+	+	+	–	+	NA	–	+	–	–	+
<i>23^{H,G}</i>	4	M	c.2839C>T, p. Arg947*	+	+	+	+	–	+	–	+	+	–	+	+	+	NA	+	–

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patient	Age (y)	Sex	<i>CHD7</i> pathogenic variant (cDNA, Protein change)	Coloboma	Choanal atresia	Inner ear anomalies	External ear anomalies	Hearing loss	Heart defect	TEF	DD	Genital anomalies	Renal anomalies	CN dysfunction	Brain anomalies	Feeding difficulties	Skeleton anomalies	Cleft lip/palate	Growth deficiency
number, percent affected			15, 65%	16, 70%	9, 39%	18, 78%	21, 91%	21, 91%	17, 74%	6, 26%	23, 100%	12, 52%	10, 44%	14, 61%	8, 35%	18, 78%	11, 48%	7, 30%	16, 70%

H published previously in Hale et al., 2016;

G published previously in Green et al., 2014;

–, absent; +, present; NA, not available; TEF, tracheoesophageal fistula; DD, developmental delay; CN, cranial nerve. Variants are provided according to CHD7 transcript NM_017780.3 and protein NP_060250.2.

Table 2

Atopic features and feeding characteristics of individuals with CHARGE syndrome

Patient	Sex	<i>CHD7</i> pathogenic variant	Food allergy	Drug allergy	Contact allergy	Allergic rhinitis	Asthma	Atopic disorders	Tube feeding	Parenteral nutrition	IgE levels (0–150 kU/L)	Eosinophils (0–5%)
1	M	+	–	–	+	–	–	+	GJ	+	NA	1.6–2.5
2	M	+	–	–	+	–	–	+	G	–	23	1.7–8.5
3	F	–	–	–	–	–	+	+	–	–	NA	NA
4	M	–	–	–	–	–	+	+	G	–	NA	0.3–1.3
5	F	–	–	–	–	–	+	+	G	–	NA	NA
6	F	–	–	–	–	–	–	–	–	–	NA	NA
7	M	–	–	+	–	–	+	+	–	–	NA	NA
8	F	–	+	–	+	–	–	+	G	+	NA	0–0.6
9	F	–	–	–	–	–	–	–	–	+	NA	0.1–1.1
10	M	–	–	+	–	–	–	+	–	+	NA	NA
11	M	+	+	–	–	–	–	+	–	+	NA	NA
12	M	+	–	–	–	–	–	–	–	+	NA	NA
13	F	+	–	–	–	–	+	+	G	+	NA	1.1
14	M	+	–	+	–	–	–	+	–	+	NA	1.6–4.7
15	F	+	–	–	–	–	–	–	–	+	NA	NA
16	M	+	+	+	–	+	–	+	G	+	NA	0
17	M	+	–	+	–	+	–	+	G	+	NA	0–1.2
18	F	+	–	–	–	–	–	–	–	+	NA	0.1–3.20
19	M	+	+	–	–	–	–	+	–	+	NA	0
20	F	+	–	–	–	–	–	–	G	+	NA	0.7–5.7
21	F	+	–	–	–	–	–	–	G	+	NA	0–0.3
22	F	+	–	–	–	–	–	–	G, GJ	+	NA	0
23	M	+	+	+	+	–	–	+	G	+	NA	0.2–3.0
#affected, percent		15, 65%	5, 22%	6, 26%	5, 22%	2, 9%	5, 22%	15, 65%	12, 52%	17, 74%		

–, absent; +, present; NA-no data available; GJ, gastrojejunal tube; G, gastric tube; normal ranges are given for IgE levels and eosinophil percentages.

Table 3

Tube feeding and parenteral nutrition histories in individuals with CHARGE syndrome with or without food allergy

	Tube feeding#	Without tube feeding (oral feeding)	Parenteral nutrition	Without parenteral nutrition
With food allergy	3	2	5	0
Without food allergy	9	9	12	6
P*		1.0		0.2827

includes gastrojejunal and gastric tubes.

P*: Fisher's exact test

Table 4

Individuals with CHARGE syndrome by gender and *CHD7* pathogenic variant

	Male	Female	<i>CHD7</i> pathogenic variant positive	<i>CHD7</i> pathogenic variant negative
With atopic disorders	11	4	9	6
Without atopic disorders	1	7	6	2
<i>P</i> *	0.009		0.775	

*P**: Fisher's exact test

Table 5

Individuals with CHARGE and atopic disorders by type of feeding support

	History of tube feeding	No history of tube feeding	History of parenteral nutrition	No history of parenteral nutrition
Male with atopic disorders	6	5	8	3
Female with atopic disorders	3	1	2	2
<i>P</i> *	0.604		0.560	

*P**: Fisher's exact test

Table 6

Prevalence of atopic disorders in individuals with CHARGE syndrome

	Patients (N)	Atopic disorders (N, %)	Allergy (N, %)	Atopic dermatitis (N, %)	Allergic rhinitis (N, %)	Asthma (N, %)
Our cohort	23	15, 65	11, 48	-	2, 9	5, 22
Hsu P	20	13, 65	3, 15	4, 20	4, 20	9, 45
Theodoropoulos DS	3	1, 33	1, 33	-	-	-
Wong MT	24	8, 33	6, 25	2, 8	-	1, 4
Range (%)		33 – 65	15 – 48	8 – 20	9 – 20	4 – 45