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

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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.

1. 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 **C**oloboma, **H**eart malformations, **A**tresia of the choanae, **R**etardation of growth and/or development, **G**enital anomalies, and **E**ar 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.

2. 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.

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Table 1
CHD7 pathogenic variants and clinical features among individuals with CHARGE syndrome.

Patient	Age (y)	Sex	*CHD7* 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/ plate	Growth deficiency
1[H]	5	M	c.4164G > A, p. Trp1388*	+	–	NA	+	+	+	+	+	+	+	+	+	+	NA	+	+
2[H]	16	M	c.4164G > A, p.Trp1388*	+	+	+	+	+	+	–	+	+	NA	NA	NA	+	+	–	+
3[H]	13	F	–	+	+	+	–	+	+	–	+	–	+	NA	NA	+	NA	–	+
4[H]	13	M	–	+	–	+	+	+	+	–	+	+	+	NA	–	+	+	+	–
5[H]	14	F	–	NA	–	+	+	–	–	+	+	–	+	+	+	+	NA	–	+
6[H]	13	F	–	NA	–	+	–	+	–	+	+	–	NA	NA	NA	+	NA	+	+
7[H]	10	M	–	+	–	+	+	+	+	–	+	+	–	NA	NA	+	NA	–	+
8[H]	6	F	–	+	–	+	+	+	+	–	+	–	–	+	–	+	NA	–	+
9[H]	9	F	–	+	–	+	+	+	+	–	+	–	+	+	+	+	+	–	–
10[H]	19	M	–	NA	+	NA	+	+	+	+	+	+	–	NA	–	–	+	–	–
11[H,G]	15	M	1774C > T, p.Gln592*	+	–	+	+	+	–	–	+	+	–	NA	–	–	NA	+	–
12[H]	6	M	c.6322G > A, p.Gly2108Arg	+	–	+	+	+	–	–	+	+	–	+	–	–	NA	–	–
13[H,G]	14	F	2254A > T, P.Arg752*	+	+	NA	+	+	–	–	+	+	+	+	–	+	+	+	+
14 [H,G]	23	M	c.3881T > C, p.Leu1294Pro	+	+	NA	+	+	+	–	+	NA	+	NA	+	NA	+	–	+
15[H]	14	F	c.2839C > T, p.Arg947*	–	–	+	+	+	+	+	+	–	NA	+	–	+	+	+	+
16[H,G]	22	M	c.5458C > T, p.Arg1820*	+	–	+	+	+	+	–	+	+	–	+	–	+	+	–	+
17[H]	16	M	c.729delC, p.Pro243fs	+	–	+	+	+	+	–	+	+	+	+	NA	+	–	–	+
18[H]	33	F	2724G > A, p.Trp908*	–	+	NA	+	+	+	–	+	–	–	+	+	+	+	–	+
19[H]	14	M	c.7282C > T, p.Arg2428*	–	–	+	+	+	–	–	+	+	–	+	+	–	+	–	+
20[H]	4	F	c.7447G > T, p.Glu2483*	+	+	+	+	+	+	–	+	–	–	+	+	+	NA	–	–
21[H]	3	F	c.1925dupA, p.Lys643Glufs	–	–	+	+	+	+	–	+	–	+	+	–	+	+	–	+
22[H]	3	F	c.2689dupC, p.Arg897Profs	+	+	+	+	+	+	+	+	–	+	NA	–	+	–	–	+
23[H,G]	4	M	c.2839C > T, p.Arg947*	+	+	+	+	–	+	–	+	+	–	+	+	+	NA	+	–
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; *, truncation. Variants are provided according to CHD7 transcript NM_017780.3 and protein NP_060250.2.