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Mutations in *CHD7* in patients with CHARGE syndrome cause T–B + natural killer cell + severe combined immune deficiency and may cause Omenn-like syndrome

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Summary

More than 11 genetic causes of severe combined immunodeficiency (SCID) have been identified, affecting development and/or function of T lymphocytes, and sometimes B lymphocytes and natural killer (NK) cells. Deletion of 22q11.2 is associated with immunodeficiency, although less than 1% of cases are associated with T–B + NK + SCID phenotype. Severe immunodeficiency with CHARGE syndrome has been noted only rarely Omenn syndrome is a rare autosomal recessive form of SCID with erythroderma, hepatosplenomegaly, lymphadenopathy and alopecia. Hypomorphic recombination activating genes 1 and 2 mutations were first described in patients with Omenn syndrome. More recently, defects in *Artemis*, *RMRP*, *IL7Rα* and common gamma chain genes have been described. We describe four patients with mutations in *CHD7,* who had clinical features of CHARGE syndrome and who had T–B + NK + SCID (two patients) or clinical features consistent with Omenn syndrome (two patients). Immunodeficiency in patients with DiGeorge syndrome is well recognized – CHARGE syndrome should now be added to the causes of T–B + NK + SCID, and mutations in the *CHD7* gene may be associated with Omenn-like syndrome.

Keywords: CHARGE syndrome, CHD7, DiGeorge syndrome, graft *versus* host disease, microdeletion 22q11, Omenn syndrome, severe combined immunodeficiency, thymic aplasia

Introduction

More than 11 genetic causes of severe combined immunodeficiency (SCID) have been identified to date [1] affecting development and/or function of T lymphocytes, and sometimes B lymphocytes and natural killer (NK) cells. Patients present within the first few months of life, with persistent infection, usually viral, affecting the gastrointestinal and respiratory tract, leading to malabsorption, growth failure and chronic lung disease. In addition, infection with protozoa such as *Pneumocystis jiroveci* may be found. Omenn syndrome is a rare autosomal recessive disease characterized by symptoms of SCID associated with erythroderma, hepatosplenomegaly, lymphadenopathy and alopecia [2]. Without definitive treatment with haematopoietic stem cell transplantation (HSCT), or in some cases gene therapy, SCID is fatal by 1 year of age.

DiGeorge syndrome (DGS) because of 22q11.2 deletion is associated with immunodeficiency [3] and in < 1% of cases has been associated with T–B + NK + SCID phenotype [4]. Absence of T lymphocytes in DGS is due to thymic aplasia, rather than an intrinsic haematopoietic stem cell defect. Some characteristics of DGS overlap with those of CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome [5], described first in 1979 [6,7]. Other

anomalies include cleft lip and/or palate and tracheo-oesophageal fistula. Mutations in the gene *CHD7* were identified recently as a cause of CHARGE syndrome [8,9]. CHARGE syndrome is thought to result from haploinsufficiency of CHD7, because there is no phenotypic difference between gene deletions and point mutations.

The recognition of CHARGE syndrome with immunodeficiency is not appreciated widely. One child had immunoglobulin G2 (IgG2) subclass deficiency and recurrent respiratory infection, a second had diphtheria and pneumococcal antibody deficiency with impaired T lymphocyte proliferation associated with frequent upper respiratory tract infection and pneumonia and a third had T lymphopenia with subnormal antigen stimulation studies associated with chronic sinusitis and otitis media [10]. In addition, a 6-month-old girl with CD4 lymphopenia associated with malakoplakia of the colon has been described previously [11]. More recently, 14 patients with features of CHARGE syndrome were reported in a series of patients undergoing thymic transplantation for complete DGS [12]. A new report details two patients with a T–B + NK + SCID phenotype in whom mutations in CHD7 were identified [13]. We report a further two cases of T–B + NK + SCID patients and two Omenn-like syndrome patients with features consistent with CHARGE syndrome in whom mutations in the *CHD7* gene have been identified, and highlight the importance of considering immunodeficiency in these patients.

Methods

Patients were referred to the Northern Supra Regional Haematopoietic Stem Cell Transplant Unit for SCID and Related Disorders for assessment and treatment. Lymphocyte phenotype analysis was measured by flow cytometry, as described previously [14]. Lymphocyte surface marker studies were performed on fresh whole blood collected in ethylenediamine tetraacetic acid using appropriate markers [CD3 fluorescein isothiocyanate, CD4 allophycocyanin (APC), CD8 phycoerythrin (PE), CD45 peridinin chlorophyll CD19 APC, CD16 CD56 PE; Becton Dickinson UK Ltd, Oxford]. Data acquisition was performed using a fluorescence activated cell sorter Calibur four-colour flow cytometer and Cellquest software (BD Biosciences, Oxford, UK). T and B lymphocyte numbers were defined as normal or low using age-specific reference ranges [15]. The markers $CD4^+$/$CD45RA^+$/$CD27^+$ and $CD4^-$/$CD45RA^+$/$CD27^+$ were used as surrogates for recent thymic emigrant (RTE) T lymphocytes. The CD3 subset was gated and $CD4^+$/$CD45RA^+$/$CD27^+$ cells identified. It was assumed that the majority of $CD4^-$ lymphocytes in this population were $CD8^+$. By identifying $CD4^-$ $CD45RA^+$ $CD27^+$ lymphocytes, effector cells (which are $CD45RA^+$ $CD27^-$) were excluded. Cells were described as present or absent. T cell receptor β chain (TCRVB) analysis was performed as described previously [16]. The incidence of perturbations in TCRVB families was analysed using the arbitrary definition of an expansion or dropout as outwith 3 standard deviations, as suggested previously [17,18]. Ig concentrations were measured by rate nephrometry. Lymphocyte responses to stimulation with phytohaemagglutinin (PHA) were performed using standard tritiated thymidine uptake methods and measured as a percentage of the response of a healthy adult control [19].

Materno–fetal engraftment and transfusion-associated graft-*versus*-host-disease (GVHD) were investigated using standard XY-FISH techniques and polymerase chain reaction (PCR) of informative short tandem repeat loci, as described previously [20].

DNA was obtained using standard laboratory protocols. The *CHD7* gene PCR was performed to amplify the 37 coding exons (2–38) in 39 fragments (exons 2, 31 and 38 were covered using overlapping fragments); sequencing was performed and then analysed on ABI 3100 using POP6 polymer and 50 cm capillary array. Resulting electropherograms were compared against a reference trace derived from the National Center for Biotechnology Information GenBank (NT_008183) and (NM_017780·2) reference sequences using Mutation Surveyor version 3·10. Parental consent was obtained prior to genetic testing.

Results

Four patients with features suggestive of DGS/CHARGE were referred. Two had features consistent with SCID (Table 1). Patient 1 was referred aged 7 weeks. Dysmorphic features were noted shortly after birth. Absence of the thymus was noted on a chest radiograph. Immunological and genetic features are listed (Table 1); 22q11.2 deletion was excluded by the demonstrating the presence of F9130, F5429, DNA probes within the 22q11.2 region in both copies of chromosome 22.

The patient received a replete marrow infusion from a matched unrelated donor without previous cytoreductive chemotherapy, and never developed GVHD. At 12 years post-transplant she has normal numbers of T, B and NK lymphocytes, but has never had $CD4^+$ $CD45RA^+$ $CD27^+$ or $CD4^-$ $CD45RA^+$ $CD27^+$ naive T lymphocytes or T lymphocyte receptor excision circle-containing T lymphocytes (data not shown), indicating absence of thymic function. Only T lymphocytes are donor in origin. Serum Ig levels and vaccine antigen responses to tetanus, haemophilus B and pneumococcal polysaccharide are normal. She has global developmental delay of uncertain aetiology, related probably to her genetic disorder. Sequence analysis of *CHD7* identified the novel heterozygous sequence change c.4527delT p.F1509LfsX37, which introduces a frameshift mutation predicted to lead to premature termination of the CHD7 protein.

Patient 2 was referred at age 4 months. He was born at 34 weeks' gestation. Features of CHARGE syndrome were noted (Table 1). He developed chronic lung disease.

Table 1. Clinical and laboratory features of two patients with T–B + natural killer cell + severe combined immunodeficiency and two patients with Omenn-like syndrome and CHARGE syndrome.

Patient	Eosinophil $\times 10^9$/l (0·04–0·8)	CD3 (2300–6900)	CD16/56 (100–1400)	CD19 (600–3000)	CD8 (400–2200)	CD4 (1400–5300)	DR+ %	RTE (120–460)	IgG (2·4–8·8)	IgA (0·1–0·5)	IgM (0·2–1·0)	IgE	PHA cpm	CHD7
1. Presentation 7/52 Choroidal coloboma, microphthalmia, micrognathia, abnormal ear pinnae, PDA,ASD, hypocalcaemia	0·2	0	790	760	0	0	0	0	3·18	<0·07	0·3	n.d.	Absent	c.4527delT p.F1509LfsX37
2. Presentation 4/12 Bilateral iris coloboma, bilateral choanal atresia, tracheo-oesophageal fistula, oesophageal atresia, micropenis, PDA, hypocalcaemia	0·07	0	243	1008	0	0	0	0	1·7	<0·06	0·35	n.d.	Absent	c.2505T > G p.Y835X
3. Presentation 2·5/12 Unilateral cleft lip and palate, facial asymmetry, poorly formed ears, absent left tibia, bilateral talipes, right pre-axial polydactyly, left microphtalmia, disc and choroidal coloboma, hypocalcaemia, bilateral cryptorchidism, micropenis PDA, absent thymus	1·3	142	801	1162	0	128	93	0	3·16	<0·07	0·35	63 KU/l (0–11)	Absent	c.689C > G p.S230X
4. Presentation at birth Truncus arteriosus, low set anteverted ears with primitive helical pattern, small mouth, retrognathia, pre-auricular tags, sacral dimple, VSD, ASD, bilateral optic disc hypoplasia, hypocalcaemia, absent thymus	0·09	0	807	1133	0	0	0	0	2·39	<0·07	0·43	n.d.	Absent	c.6292C > T p.R2098X
4. 3·5 months	0·4	11 368	737	1736	6981	3156	98	0	4·16	0·22	0·59	n.d.		
4. 5 months	4·1	19 291	2190	1710	1 2061	4823	97	0	4·16	<0·25	0·59	n.d.		

PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventriculoseptal defect; RTE, recent thymic emigrant ($CD4^+/CD45RA^+/CD27^+$ and $CD4^-/CD45RA^+/CD27^+$); n.d., not done; PHA, phytohaemagglutinin; cpm, counts per minute; Ig, immunoglobulin.

Lymphopenia with hypogammaglobulinaemia was noted. Immunological and genetic features are listed (Table 1); 22q11.2 deletion was excluded by the demonstrating the presence of TUPLE 1, a DNA probe within the 22q11.2 region, in both copies of chromosome 22. The child received a T lymphocyte-depleted infusion of human leucocyte antigen haploidentical paternal haematopoietic stem cells but failed to develop any T lymphocytes. He died of lung disease on day +87. Necroscopy was not performed. Sequence analysis of *CHD7* revealed a heterozygous non-sense mutation c.2505T > G, p.Y835X, predicted to lead to premature termination of the *CHD7* protein.

Two patients developed symptoms consistent with Omenn syndrome. Patient 3 was transferred at age 2 months, with clinical features of CHARGE syndrome (Table 1). He had a macular rash on the upper trunk, with hepatomegaly but no associated splenomegaly or lymphadenopathy. Serial immunophenotyping of peripheral blood lymphocytes is listed (Table 1). The $CD4^+$ T lymphocytes were highly activated and there were no recent thymic emigrant T lymphocytes. A few $CD4^+$ $CD25^{BRIGHT+}$ T lymphocytes were present; forkhead box $P3^+$ lymphocytes were not examined. No thymus was identified by ultrasonography. Analysis of the TCRVB region showed an abnormal pattern with overexpansion of VB3, 13·6, 17 and 21·3 and dropout of VB8, 11, 13·1, 18, 22 and 23. He was hypogammaglobulinaemic apart from a raised IgE with associated eosinophilia. Cytogenetic interphase fluorescent *in situ* hybridization studies of chromosome region 22q11.2 were normal. There was no evidence of materno–fetal or third-party engraftment on cytogenetic or molecular genetic studies. Skin biopsy showed a moderate subacute spongiotic reaction with necrotic keratinocytes compatible with GVHD; only occasional eosinophils were noted in the infiltrate. Subsequent analysis of genomic DNA showed a *de novo* heterozygous frameshift/non-sense sequence change c.689C > G, p.S230X, predicted to lead to premature termination of the CHD7 protein, likely to be pathogenic. He received unrelated umbilical cord haematopoietic stem cell infusion without previous chemotherapy, but died of acquired parainfluenza viral pneumonitis associated with lung disease secondary to recurrent gastro-oesophageal reflux.

The fourth patient, born at 36 weeks' gestation, was diagnosed with truncus arteriosus shortly after birth. Dysmorphic features were noted, consistent with possible CHARGE syndrome (Table 1). No thymus was identified at sternotomy. Genetic studies to investigate 22q11.2 deletion failed on three occasions because lymphocytes failed to proliferate when stimulated with PHA; 22q11.2 studies on buccal cells and investigation of interphase nuclei on blood were normal. Subsequent lymphocyte phenotype analysis is listed (Table 1). Skin was normal; there was no evidence of lymphoid tissue, with no palpable lymph nodes or tonsillar tissue visible. At 3·5 months of age she developed a widespread florid, scaly and icthyotic maculopapular rash, with marked axillary and inguinal lymphadenopathy, but no hepatosplenomegaly. A lymphocytosis with a marked increase in activated $CD3^+$ T lymphocytes was noted. TCRVB studies demonstrated marked oligoclonality of $CD4^+$ and $CD8^+$ populations, with overexpansion of VB14, 16 and 18 and dropout of VB1, 2, 4, 5·1, 5·2, 7·1, 8, 9, 11, 12, 13·1, 13·2, 13·6, 17, 21·3 and 22. The presence of $CD4^+CD25^{BRIGHT+}$ T lymphocytes was unreportable because of autofluorescence. There were no recent thymic emigrant T lymphocytes. There was no evidence of materno–fetal or third-party engraftment on cyto- or molecular genetic studies. No infective trigger was identified. Subsequent analysis of genomic DNA showed a *de novo* non-sense heterozygous sequence change c.6292C > T p.R2098X, predicted to lead to premature termination of the CHD7 protein and likely to be pathogenic. An unrelated donor whole-marrow infusion was planned, but the patient died from cardiorespiratory insufficiency shortly before the procedure. Necroscopy was not performed.

Discussion

The two patients reported here with T–B + NK + SCID, with absent T lymphocytes, absent lymphocyte stimulation to PHA, consistent with absence of T lymphocytes, absent thymus and hypogammaglobulinaemia, confirm the link of *CHD7* mutations in CHARGE syndrome with SCID. Published mutations in *CHD7* are scattered throughout the gene and include missense, non-sense and splicing mutations. The mutation in our second patient has been reported previously, but our first patient has a novel mutation. No significant distinct phenotype/genotype correlations have been identified for *CHD7* mutations [21].

Additionally, this is the first report confirming *CHD7* mutations in patients with clinical features consistent with Omenn-like syndrome. Patient 4 had no T lymphocytes initially, but developed lymphocytosis in conjunction with other clinical features and eosinophilia. The evolution of SCID to Omenn syndrome has been described in a recombination activating genes 2-deficient patient [22], subsequent to parainfluenza 3 virus infection, which may have acted as the trigger to expand the few clones of autoreactive T lymphocytes. Our patient 4 had no evidence of bacterial, fungal or viral infection, despite extensive screening. She did have gastro-oesophageal reflux with aspiration; inflammation secondary to this may have acted as the trigger to cause lymphocyte expansion.

Omenn syndrome was considered initially a disorder of recombination activating genes gene missense mutations, allowing limited VDJ recombination in a few TCR [23]. More recently, the clinical phenotype has been linked with mutations in *Artemis*, *IL7Rα*, *RMRP* and *CγC* genes [24–27]. Not all classical features of Omenn syndrome are present in these disorders, with presence of B lymphocytes and normal

Ig levels described [25,26]. Descriptions of patients with Omenn syndrome-like features and the clinical phenotype of DGS or CHARGE syndrome have been published [28,29], but until now none have been shown to have mutations in *CHD7*.

CHD7 is a member of the chromodomain helicase DNA binding domain family of adenosine-5′-triphosphate-dependent chromatin remodelling enzymes. The related CHD1, CHD3 and CHD4 proteins contribute to nucleosome remodelling and histone deacetylation, which regulates dynamic changes in chromatin structure during transcription, recombination, repair and replication [30,31], and is important in regulating early embryonic development and cell cycle control. These proteins lead to transcriptional activation or repression of a gene or region. It is likely that CHD7 has a similar function [32]. CHD7 is expressed throughout the neural crest containing mesenchyme of the pharyngeal arches [32,33]. Seven of 10 CHARGE fetuses were found to have thymic hypoplasia or agenesis [33]. The clinical overlap of CHARGE and DGS reported previously [5,12] suggests a common neural crest defect. In DGS, defects in thymus, parathyroid and conotruncal regions of the heart are caused by impaired migration of neural crest cells into pouch exoderm (reviewed in [34]). A number of genes in the 22q11 deletion domain have been identified, including TBX1, a transcription factor that contains a DNA binding domain, which may be a functional target for *CHD7*, explaining some of the overlapping features in CHARGE syndrome and DGS. In this respect it is interesting to speculate that humoral immune deficiency, including impaired polysaccharide antibody function, as well as autoimmunity, may be more common than recognized previously in patients with CHARGE syndrome, as also found in patients with DGS, and indeed have already been reported in one CHARGE patient [10].

The incidence of immunodeficiency in patients with CHARGE syndrome is unknown, but should be looked for. It may be, as in DGS, that severe T cell immunodeficiency is rare.

Finally, optimal treatment for T lymphocyte absence in CHARGE syndrome has yet to be established. One of our patients has good T lymphocyte immunity following infusion of replete bone marrow, but has no evidence of thymic function, which may be important for long-term immune reconstitution [35]. Failure of T lymphocyte development in patient 2 is perhaps unsurprising, given thymic aplasia, although T lymphocytes normally take 140 days to appear after T lymphocyte-depleted HSCT. Thymic transplant may be an alternative treatment, leading to long-term thymic function [12].

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