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Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review

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Summary

Cytotoxic T lymphocyte antigen 4 (CTLA-4) haploinsufficiency (CHAI) and lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency (LATAIE) are newly identified inborn errors of immunity with shared molecular pathomechanisms and clinical manifestations. In this review, we aimed to provide differential comparisons regarding demographic, clinical, immunological and molecular characteristics between these two similar conditions. A literature search was conducted in PubMed, Web of Science and Scopus databases and included studies were systematically evaluated. Overall, 434 (222 CHAI and 212 LATAIE) patients were found in 101 eligible studies. The CHAI patients were mainly reported from North America and western Europe, while LATAIE patients were predominantly from Asian countries. In CHAI, positive familial history ($P < 0{\cdot}001$) and in LATAIE, consanguineous parents ($P < 0{\cdot}001$) were more common. In CHAI patients the rates of granulomas ($P < 0{\cdot}001$), malignancies ($P = 0{\cdot}001$), atopy ($P = 0{\cdot}001$), cutaneous disorders ($P < 0{\cdot}001$) and neurological ($P = 0{\cdot}002$) disorders were higher, while LATAIE patients were more commonly complicated with life-threatening infections ($P = 0{\cdot}002$), pneumonia ($P = 0{\cdot}006$), ear, nose and throat disorders ($P < 0{\cdot}001$), organomegaly ($P = 0{\cdot}023$), autoimmune enteropathy ($P = 0{\cdot}038$) and growth failure ($P < 0{\cdot}001$). Normal lymphocyte subsets and immunoglobulins except low serum levels of $CD9^+$ B cells (14·0 *versus* 38·4%, $P < 0{\cdot}001$), natural killer (NK) cells (21 *versus* 41·1%, $P < 0{\cdot}001$), immunoglobulin (Ig)G (46·9 *versus* 41·1%, $P = 0{\cdot}291$) and IgA (54·5 *versus* 44·7%, $P = 0{\cdot}076$) were found in the majority of CHAI and LATAIE patients, respectively. The most frequent biological immunosuppressive agents prescribed for CHAI and LATAIE patients were rituximab and abatacept, respectively. Further investigations into the best conditioning and treatment regimens pre- and post-transplantation are required to improve the survival rate of transplanted CHAI and LATAIE patients.

Keywords: CHAI, CTLA-4, inborn errors of immunity, LATAIE, LRBA, primary immunodeficiency disease

Introduction

Inborn errors of immunity (IEIs) are a heterogeneous group of inherited disorders that affect the development and function of the immune system, and predispose patients to chronic susceptibility to recurrent infections, autoimmune disorders, allergy, lymphoproliferation and malignancy. In the last decade, due to the increased availability of genome sequencing, the spectrum of IEIs with immune dysregulation phenotype is rapidly expanding [1].

It has also been shown that the underpinning molecular pathomechanisms of some of these monogenic disorders are greatly overlapping. For instance, disorders of the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) pathway, including autosomal dominant CTLA-4 haploinsufficiency

with autoimmune infiltration (CHAI) and autosomal recessive lipopolysaccharide-responsive beige-like anchor (LRBA) (LATAIE) deficiency with autoantibodies, regulatory T (T_{reg}) cell defects, autoimmune infiltration and enteropathy diseases, often present with similar clinical phenotypes due to their linked biology [2,3].

CTLA-4 is an immune checkpoint molecule, primarily found on the surface of T cells [4]. In addition to direct tolerogenic effects, CTLA-4 outcompetes CD28 for binding to their shared co-stimulatory ligands, CD80 and CD86, and removes them from antigen-presenting cells (APCs) via transendocytosis, thereby preventing continuous activation of T cells [5]. Although CTLA-4 is induced upon T cell receptor (TCR) activation in conventional T cells, it is constitutively expressed on T_{reg} cells and promotes their suppressive function [6]. CTLA-4 is also involved in humoral immunity, as it regulates CD28-dependent follicular helper T cell differentiation [7]. LRBA binds to the cytoplasmic tails of CTLA-4 and prevents the trafficking of CTLA-4 to lysosomes and consequent degradation [8]. CHAI disease is predominantly characterized by lymphoproliferation, autoimmune cytopenia, enteropathy, interstitial lung disease and recurrent infections [9–11]. LATAIE also generally presents with enteropathy, autoimmunity, lymphoproliferation and respiratory infections [12–14]. The immunological phenotype in both disorders includes hypogammaglobulinemia, progressive loss of B cells, an increase in $CD21^{low}$ B cells, and elevated T follicular helper cells [15,16]; however, T_{reg} cell counts are often normal in CHAI, in contrast to its reduced level in LATAIE [17,18].

Despite the fact that several kindreds have been reported in the literature, distinctions between these two groups of patients remain elusive. In this regard, we aimed to provide a systematic review of clinical, immunological and molecular characteristics of patients with CTLA-4 haploinsufficiency and LRBA deficiency and also a differential comparison between these two similar conditions.

Methods

Search strategy, study selection and data extraction

We performed a systematic search of the PubMed, Web of Science and Scopus Library databases for articles published in peer-reviewed journals up to June 2020. The keywords used in our search strategy for patients with CTLA-4 haploinsufficiency were as follows: 'cytotoxic T-lymphocyte-associated protein 4 haploinsufficiency', 'CTLA-4 protein deficiency', 'CTLA-4 haploinsufficiency', 'cytotoxic T-lymphocyte-associated protein 4 deficiency', 'CTLA-4 haploinsufficiency with autoimmune infiltration', 'CHAI', 'CTLA-4 immunodeficiency' or 'CTLA-4 mutation'. In addition, the following search keywords were used for patients with LRBA deficiency: 'lipopolysaccharide-responsive beige-like anchor protein', 'LPS-responsive beige-like anchor protein', 'LRBA', regulatory T cell defects, autoimmune infiltration and enteropathy, 'LATAIE', 'LRBA deficiency', 'LRBA immunodeficiency' or 'LRBA mutation'.

The search strategy is summarized in Supporting information, Fig. S1. Manual screening for references from original articles and major reviews was performed to identify eligible studies. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for performing the systematic review. The methods of screening and selection of eligible articles and extraction of data into an electronic database are described elsewhere in detail [19].

Statistical and genetic analysis

The statistical analyses were performed on a pooled sample of aggregate data derived from related studies. For this purpose, the overall extracted data of two subgroups were combined without weighting. Central and descriptive statistics were used for the interpretation of quantitative data. For variables with abnormal distribution, median and interquartile ranges (IQR) were calculated. For comparisons between two groups of patients, Mann–Whitney *U*, χ^2 or Fisher's exact tests were applied. All statistical tests were two- tailed, and a *P*-value of less than 0·05 was considered statistically significant. The statistical analyses were performed using SPSS version 26.0 software (SPSS, Inc., Chicago, IL, USA).

For the genetic analysis we applied a uniform mutation nomenclature and, in some cases, we changed mutation numberings to conform to the Human Genome Variation Society (HGVS) guidelines. Wherever the mutation's effect on the protein (except for splice site and long InDel mutations) was not reported, the MutationTaster software (http://www.mutationtaster.org) was used to predict amino acid changes.

Ethics approval

The study was approved by the Alborz University of Medical Sciences ethics committee (approval code: IR.ABZUMS.REC.1398.166).

Results

Study characteristics

For CHAI, the literature search identified 562 articles; 258 articles were duplicates and 265 were excluded through the initial title and abstract screening. Overall, 39 articles met the inclusion criteria and were subsequently selected for data extraction. For LATAIE, 37 new articles were found in the literature and 17 articles were eligible. The extracted

data were added to the database prepared for our previous systematic review of patients with LATAIE [12]. A total of 503 patients were reported in these articles, and 434 patients remained for data analysis after the removal of duplicate cases. Further investigations of these 434 patients identified 73 and 148 mutated genes causing CHAI and LATAIE phenotypes in 222 and 212 patients, respectively.

Epidemiological characteristics of CHAI and LATAIE patients

In this review, 434 patients including 222 CHAI patients (101 males, 103 females and 18 of unknown gender) and 212 LATAIE patients (109 males, 96 females and seven of unknown gender) were evaluated.

Figure 1 represents the distribution of patients in different countries. The reported CHAI patients are mainly studied in North America and western Europe, while LATAIE patients have a wider distribution among Asian countries.

Family history of immunodeficiency was reported in 54·7% (210 of 384) of the study population, and patients with CHAI had higher rates of positive family history compared with LATAIE [62·7% (138 of 220) *versus* 43·9% (72 of 164), $P < 0·001$]. All except one of the CHAI patients were born to non-consanguineous parents, while 74·9% (131 of 175) of patients with LATAIE had consanguineous parents ($P < 0·001$) (Table 1).

Among patients with LATAIE, higher rates of death were reported compared with patients with CHAI [21% (42 of 200) *versus* 13·6% (27 of 199), $P = 0·05$]. The reported reasons for death were somewhat variable but mainly consisted of sepsis, lymphoma and organ failure in patients with CHAI and also sepsis, respiratory failure and internal hemorrhage in LATAIE patients (Supporting information, Table S1).

At the time the patients were first reported in the referenced studies, most patients with CHAI were in their third decade of life at a median (IQR) age of 24·5 (17·2–45·0) years, while LATAIE patients were younger with a median (IQR) age of 11·6 (6–18) years. In the same manner, the age at the onset of symptoms in LATAIE patients [median (IQR) = 1·7 (0·6–4·0)] was much lower than that of CHAI patients [median (IQR) = 10·0 (6·0–16·0), $P < 0·001$]. The CHAI patients were diagnosed later in the course of disease, with a median (IQR) diagnostic delay of 11·0 (6·0–19·0) years compared with 5·0 (2·0–9·6) years in LATAIE patients, $P < 0·001$.

In CHAI patients, the median (IQR) age at first autoimmune manifestation was 6·5 (2·0–16·0) years, while in LATAIE patients the first presentations of autoimmunity started at a median (IQR) age of 3·0 (1·3–6·0) years ($P = 0·003$). Furthermore, infectious complications and lymphoproliferative disorders significantly tend to develop earlier in patients with LATAIE, compared with CHAI ($P < 0·001$) (Table 1).

Clinical spectrum of CHAI and LATAIE patients

The schematic comparison of significant clinical differences between CHAI and LATAIE is provided in Fig. 2. A large proportion of patients with CHAI and LATAIE patients initially presented with autoimmune disorders (43·0 *versus* 31·0%, $P = 0·047$), respiratory manifestations (17·0 *versus* 28%, $P = 0·047$) and protracted diarrhea (16·0 *versus* 29%, $P = 0·021$), respectively (Fig. 3).

Among patients with an established primary clinical diagnosis ($n = 259$) (Fig. 4), most patients with CHAI were diagnosed initially with predominantly antibody deficiency (PAD) (34·0%), autoimmunity (28·0%) and enteropathy (18·0%). In LATAIE, the first clinical diagnosis also included predominantly antibody deficiency (40·0%), autoimmunity (21·0%) and autoimmune lymphoproliferative syndrome (16·0%).

Autoimmune disorders were the most common component of both CHAI and LATAIE syndromes, and 66·8% of the patients (290 of 343) had at least one autoimmunity (Table 2). Additionally, 47·7% (207 of 434) of patients suffered from two or more autoimmune disorders. The most common concurrent autoimmune diseases were autoimmune cytopenia and autoimmune enteropathy in both CHAI (18 of 143, 12·5%) and LATAIE (39 of 147, 26·5%) groups, while the second most prevalent overlap was observed between autoimmune cytopenia and autoimmune cutaneous disorders (16 of 143, 11·2%) in CHAI and between autoimmune cytopenia and insulin-dependent diabetes mellitus (IDDM) (23 of 147, 15·6%) in LATAIE patients.

Autoimmune cytopenias, including immune thrombocytopenic purpura, autoimmune hemolytic anemia and autoimmune neutropenia, were the most common autoimmune complications in CHAI [96 (67·6%)] and LATAIE patients [106 (70·2%), $P = 0·408$]. Furthermore, autoimmune gastrointestinal disorders [40 (29·2%) *versus* 61 (40·9%), $P = 0·038$], autoimmune cutaneous disorders (e.g. vitiligo and/or alopecia) [31 (22·8%) *versus* 13 (8·7%), $P = 0·001$] were frequently reported. Among autoimmune endocrinopathies, IDDM [23 (10·8%) *versus* 39 (18·4%), $P = 0·027$], thyroiditis [29 (13·6%) *versus* 19 (9%), $P = 0·130$) and Addison disease [2 (0·9%) *versus* 1 (0·5%), $P = 1·00$] were the most common in CHAI and LATAIE patients, respectively. Other rare autoimmune manifestations, such as autoimmune arthritis, autoimmune hepatitis, vasculitis, autoimmune neurological disorders and autoimmune eye abnormalities in 15 (6.8%) CHAI patients and 17 (8.0%) LATAIE patients were also reported.

Lymphoproliferative disorders were another common complication in both syndromes. The non-malignant

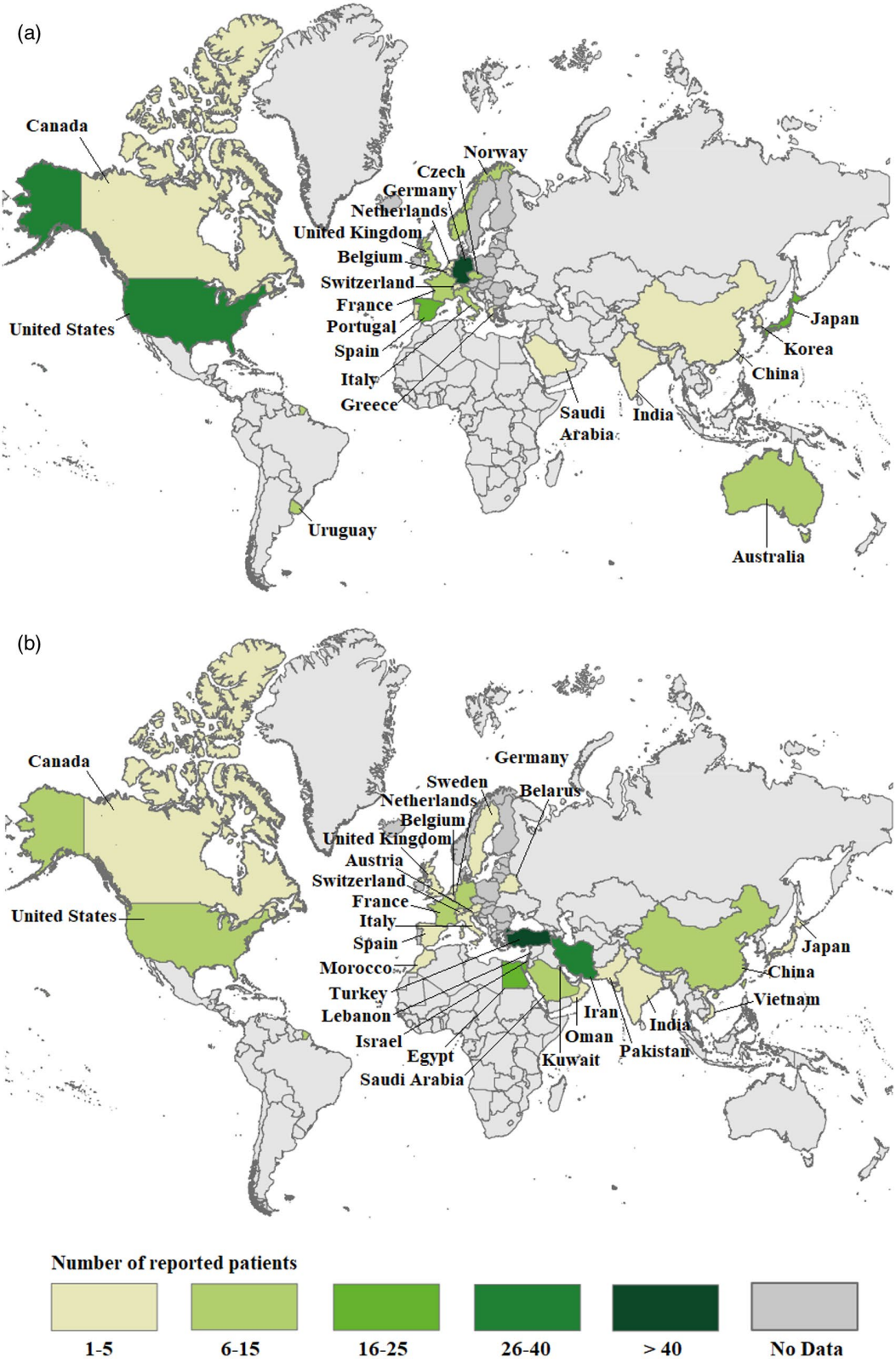

Fig. 1. The geographical distribution of reported cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration (CHAI) (a) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) (b) patients. The reported CHAI patients are mainly studied in North America and western Europe, while LATAIE patients have a wider distribution among Asian countries.

Table 1. Demographic data of patients with CHAI and LATAIE syndrome

Parameters	Total	CHAI	LATAIE	***P*-value**
Number of patients	434	222	212	
Sex ratio, M/F (*n* = 409)	210/199	101/103	109/96	0·459
Family history of PID, % (*n* = 384)	210 (54·7)	138 (62·7)	72 (43·9)	< **0·001***
Consanguinity, % (*n* = 363)	132 (36·4)	1 (0·5)	131 (74·9)	< **0·001***
Dead, % (*n* = 399)	69 (17·3)	27 (13·6)	42 (21)	0·05
Current age, years, median (IQR) (*n* = 382)	18 (10–30)	24·5 (17·2–45)	11·6 (6–18)	< **0·001***
Age at onset, years median (IQR), (*n* = 275)	4 (1–10)	10 (6–16)	1·7 (0·6–4)	< **0·001***
Age at diagnosis, years, median (IQR), (*n* = 220)	15·5 (8–25·5)	23 (17–40)	8 (5–13)	< **0·001***
Delay in diagnosis, years, median (IQR), (*n* = 195)	7 (4–15)	11 (6–19)	5 (2–9·6)	< **0·001***
Age at presentation of first autoimmunity, years, median (IQR) (*n* = 111)	4 (1·8–7)	6·5 (2–16)	3 (1·3–6)	**0·003***
Age at presentation of infection, years, median (IQR) (*n* = 65)	3 (1·25–8)	12·5 (6·5–24)	2 (1–5)	< **0·001***
Age at presentation of allergy, years, median (IQR) (*n* = 12)	4·5 (2–11·5)	12·5 (3–)	4·5 (1·6–8·5)	0·485
Age at presentation of lymphoproliferative disorder, years, median (IQR) (*n* = 45)	6 (3–12)	17 (12–33)	4 (3–7)	< **0·001***
Age at presentation of malignancy, years, median (IQR) (*n* = 23)	28 (17–42)	29 (17–42·7)	2·3	0·087

M = male; F = female; n = count; PID = primary immunodeficiency disorders; IQR = interquartile range; CHAI = cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration; LATAIE = lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy.

The median is shown (with 25th and 75th percentiles).

The statistically significant correlations are indicated in bold.

**P*-value is statistically significant < 0·05.

lymphoproliferation (including lymphadenopathy, splenomegaly and/or hepatomegaly) was more frequently reported in LATAIE (54 *versus* 43·2%, $P = 0·023$) while malignant lymphoproliferation was more common in CHAI (17·4 *versus* 7·1%, $P = 0·001$). Granulomatous changes were reported more commonly in CHAI patients (21·1 *versus* 8·0%, $P < 0·001$) and mainly affected lung and brain.

Enteropathy (41·1 *versus* 28·9%, $P = 0·032$) and failure to thrive (27·8 *versus* 7·5%, $P < 0·001$) were both significantly more prevalent among LATAIE compared with CHAI patients. Ear, nose and throat (ENT) disorders such as otitis media, rhinitis and tonsillitis were more prevalent among LATAIE patients (17 *versus* 4·2%, $P < 0·001$) (Table 3). Skin disorders, including eczema (26·3%), psoriasis (19·0%), atopic dermatitis (20·9%), warts (10·0%), alopecia (10·9%) and vitiligo (11·8%) complicated 81 (38%) CHAI and 29 (13·7%) LATAIE individuals ($P < 0·001$). Neurological manifestations such as seizure, neurodevelopmental delay and demyelinating disorders were more common in CHAI (23·9%) compared with LATAIE (12·3%) patients, $P = 0·002$.

Life-threatening infections including pneumonia, sepsis, meningitis and peritonitis were reported in 156 of all patients [63 (29·6%), CHAI *versus* 93 (43·9%) LATAIE, $P = 0·002$].

The most common viral microorganisms identified in CHAI and LATAIE patients were Epstein–Barr virus (EBV) spp. (13.1 *versus* 5.7%, $P = 0.008$), cytomegalovirus (CMV) (6.1 *versus* 10.8%, $P = 0.079$) and varicella-zoster virus (VZV) spp. (6.6 *versus* 1.9%, $P = 0.016$), respectively. The bacterial infections were mainly caused by *Streptococcus aureus* spp. (7·0 *versus* 2·4%, $P = 0·023$), *Salmonella* (3·8 *versus* 0·9%, $P = 0·105$) and *Mycobacterium tuberculosis* spp. (1·9 *versus* 0·5%, $P = 0·372$) in CHAI and LATAIE patients, respectively. The most common fungal microorganisms were *Candida* spp. (6.6 *versus* 7.5%, $P = 0.695$), and aspergillus (2·8 *versus* 4·2%, $P = 0·425$) in CHAI and LATAIE patients, respectively.

Immunological findings of CHAI and LATAIE patients

Table 4 represents the available quantitative immunological data of patients with CHAI and LATAIE syndrome. Overall, 333 of 434 patients, including 143 CHAI and 190 LATAIE patients, had at least one immunological parameter available in the published data and were included in the analysis described below.

Total lymphocyte counts were lower than the normal range for age in 22 (15·4%) CHAI and 24 (12·6%) LATAIE patients ($P = 0·471$). The median absolute neutrophil count (cells/μl) was significantly lower in CHAI compared with LATAIE patients (1400 *versus* 3861, $P = 0·034$).

Low lymphocyte subsets including $CD3^+$ [12 (8·4%) *versus* 22 (11·6%), $P = 0·342$], $CD4^+$ [19 (13·3%) *versus* 34 (17·9%), $P = 0·255$], $CD8^+$ [14 (9·8%) *versus* 19 (10·0%), $P = 0·949$] and T_{reg} [12 (8·4%) *versus* 23 (12·1%), $P = 0·274$] were reported in a proportion of CHAI and LATAIE patients, respectively. Also, low counts for $CD19^+$ B cells [20 (14·0%) *versus* 73 (38·4%), $P < 0·001$] and natural killer (NK) cells [30 (21%) *versus* 78 (41·1%), $P < 0·001$] were found in the majority of CHAI and LATAIE patients, respectively.

Adjusted to the age-matched normal ranges, low levels of serum IgG [67 (46·9%) *versus* 78 (41·1%), $P = 0·291$], immunoglobulin (Ig)A [78 (54·5%) *versus* 85 (44·7%),

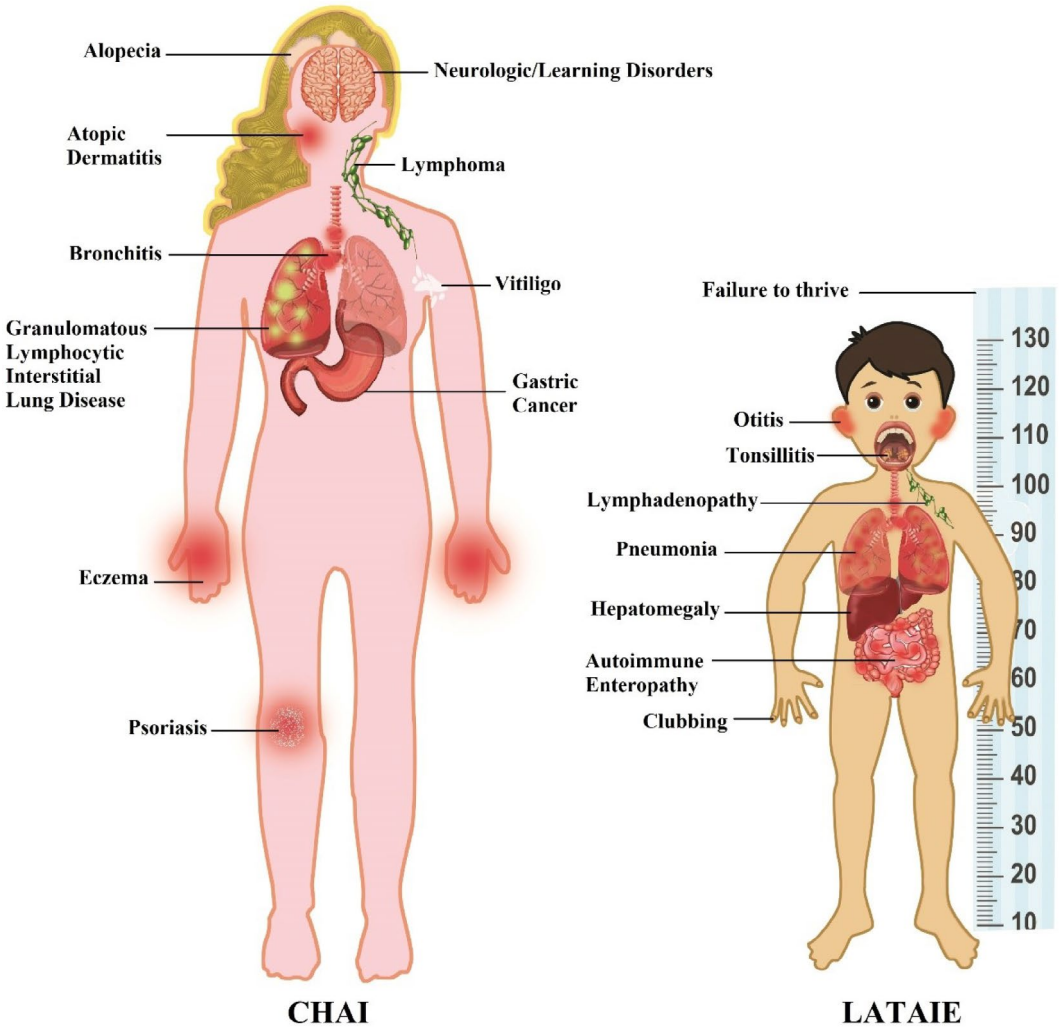

Fig. 2. Significant clinical differences between cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration (CHAI) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) patients. In CHAI patients the rates of granulomas, malignancies, atopy, cutaneous disorders and neurological disorders are higher, while LATAIE patients are more commonly complicated with life-threatening infections, pneumonia, ear, nose and throat disorders, organomegaly, autoimmune enteropathy and growth failure.

P = 0·076], IgM [49 (34·3%) *versus* 53 (27·9%), P = 0·212] and IgE [8 (5·6%) *versus* 5 (2·6%), P = 0·167] were observed in CHAI and LATAIE patients, respectively.

Autoantibodies detected in patients are listed in Table 5. The most frequently detected autoantibodies in CHAI and LATAIE patients tested for autoantibodies were anti-nuclear antibodies (ANA) (39·3%) and anti-erythrocyte antibodies (36·8%), respectively.

Molecular findings of CHAI and LATAIE patients

CHAI and LATAIE disease are caused by loss-of-function mutations in *CTLA-4* and *LRBA* genes, respectively. The human *CTLA-4* gene (OMIM: *123890) is located on the chromosome position 2q33.2. It contains four coding exons that encode a 223-amino acid protein, CTLA-4. There are 73 distinct mutations among 222 patients (124 families) suffering from CHAI, including 37 (50·7%) missense, 14 (19·2%) insertion/deletion frameshift, 10 (13·7%) nonsense, eight (11%) splice-site, three (4·1%) large insertion/deletion and one (1·4%) start codon mutation. Among patients diagnosed with CHAI, the mutation has not been reported for four patients [20–23]. To find a better estimation of penetrance we restricted our assessment to families with available mutation analyses in the proband and family members (at least parents). Among all 160 subjects of 42 unrelated families (88 female and 72 male), 97 affected carriers and 63 unaffected carriers were identified, suggesting a clinical penetrance of at least 60·6%. Interestingly,

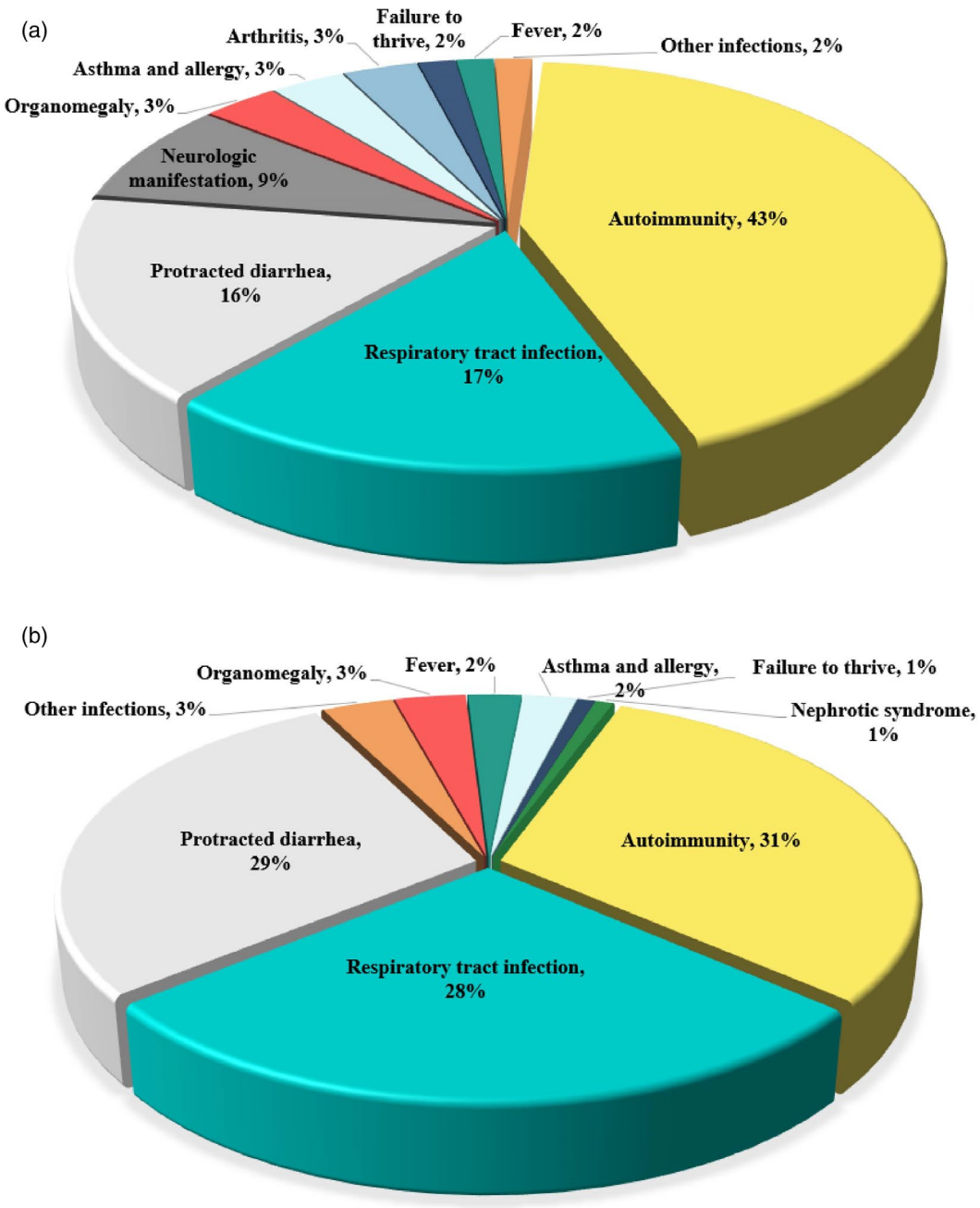

Fig. 3. The first presentations of cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration (CHAI) (a) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) (b). Autoimmunity has been observed as the first presentation in most patients.

the extracellular (Ig) V-like domain had a large proportion (66·9%) of the mutations and the leader (signal peptide) domain and transmembrane domains each had 7·3% of the mutations. So far, no mutation has been identified in the intracellular (cytoplasmic tail, exon 4) domain (Fig. 5). Analysis of the correlation between the type of mutations and clinical and laboratory data demonstrated that enteropathy is more frequent in patients with a missense mutation (84·6%) than patients with nonsense or insertion/deletion frameshift mutations (15·6%, $P = 0{\cdot}028$).

The human *LRBA* gene (OMIM: *606453) is located on the chromosome position 4q31.3. It contains one non-coding and 57 coding exons that encode a large 2863-amino acid protein, LRBA. Among the 212 LATAIE patients

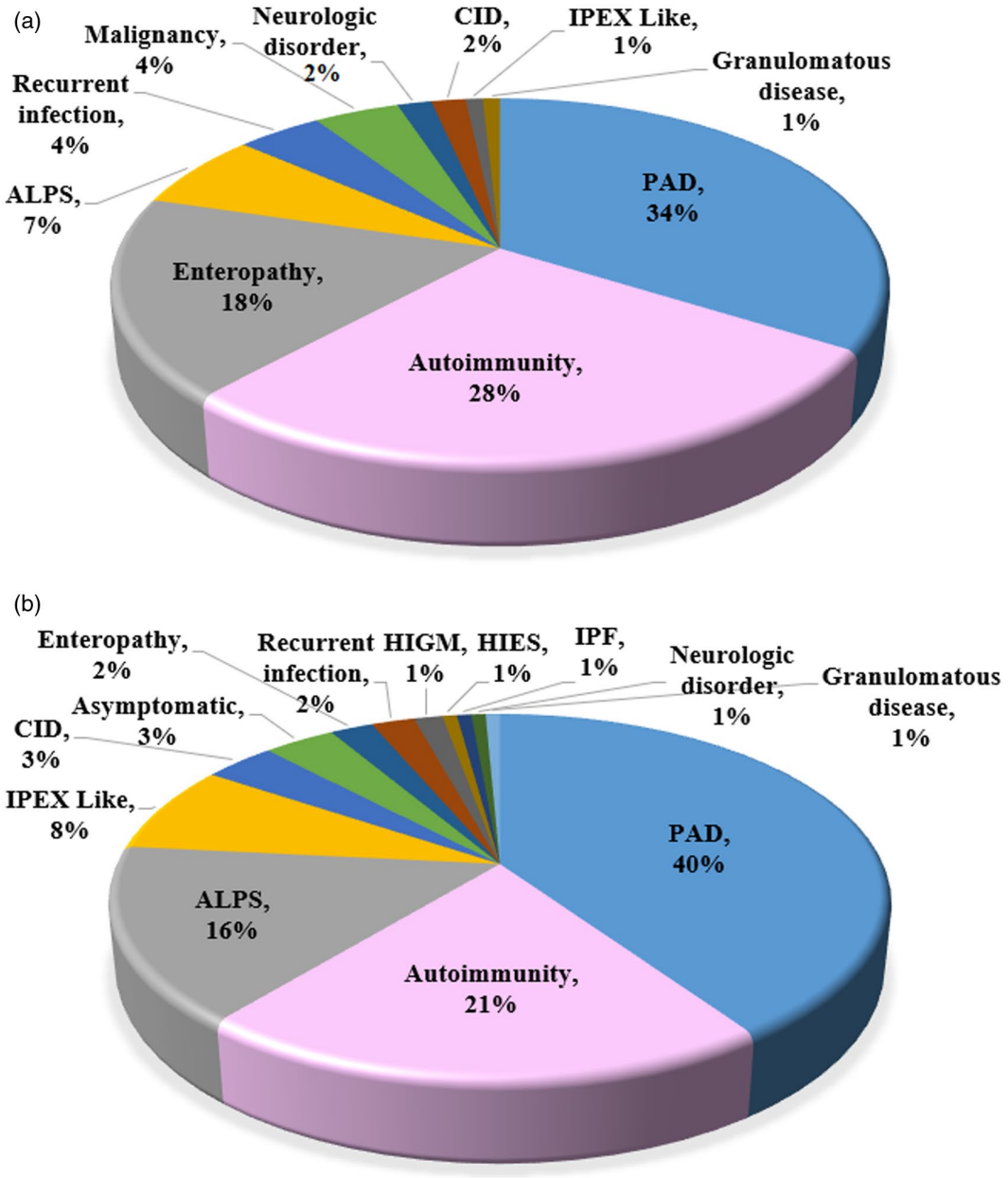

Fig. 4. Distribution of available initial clinical diagnoses given to 259 patients with cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration (CHAI) (a) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) (b) at the presentation. Patients are often diagnosed with predominantly antibody deficiencies. PAD = predominantly antibody deficiency; CVID = common variable immunodeficiency; CID = combined immune deficiency; ALPS = autoimmune lymphoproliferative syndrome; IPEX = immune dysregulation polyendocrinopathy enteropathy X-linked; HIES = hyper IgE syndrome; HIGM = hyper immunoglobulin (Ig)M syndrome; IPF = idiopathic pulmonary fibrosis.

(166 families) identified in our study, 183 (86·3%) patients (in 33 families) had homozygous mutations, 27 (12·7%) patients (in eight families) had compound heterozygous *LRBA* mutations, and for four patients the mutations were not reported [24–27]. Monoallelic (heterozygous) mutations were reported in two patients [28]. Overall, 141 unique mutations were detected. These mutations consisted of 33 missense (23·4%), 36 nonsense (25·5%), 18 splice-site (12·8%), 44 insertion/deletion frameshift (31·2%) and 10 large insertion/deletion (7·1%) mutations. Mutations of the *LRBA* gene were located throughout the gene and no mutational hot-spot was observed (Fig. 5). The correlation analysis of mutation types with clinical and laboratory data showed that polyautoimmunity was more frequent

Table 2. Autoimmune disorders in CHAI and LATAIE syndrome

Autoimmunity	Total (***n*** = 290)	CHAI (***n*** = 141)	LATAIE (***n*** = 149)	***P***-value
Autoimmune endocrinopathy (%)	91 (31·9)	39 (28·9)	62 (41·1)	0·260
Autoimmune enteropathy (%)	101 (35·3)	39 (28·9)	62 (41·1)	**0·038***
Autoimmune cytopenia (%)	202 (68·9)	96 (67·6)	106 (70·2)	0·408
Autoimmune skin disorders (%)	44 (15·4)	30 (22·4)	14 (9·3)	**0·001***
Others (%)	32 (11)	13 (9·2)	19 (12·7)	0·832

The statistically significant correlations are indicated in bold.

CHAI = cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration; LATAIE = lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy.

* *P*-value is statistically significant < 0·05.

Table 3. Clinical manifestations of patients with CHAI and LATAIE syndrome

Parameters	Total (***n*** = 434)	CHAI (***n*** = 222)	LATAIE (***n*** = 212)	***P***-value
Pneumonia (%)	141 (33·2)	56 (26·3)	85 (40·1)	**0·006***
Sinusitis (%)	53 (12·2)	20 (9·4)	33 (15·6)	0·054
Ear, nose and throat disorders (%)	45 (10·6)	9 (4·2)	36 (17)	< **0·001***
Bronchiectasis (%)	56 (13·2)	24 (11·3)	32 (15·1)	0·244
Asthma and allergy (%)	68 (16)	47 (22·1)	21 (9·9)	**0·001***
Interstitial lung disease (%)	84 (19·8)	49 (23)	35 (16·5)	0·093
Granulomas (%)	62 (14·6)	45 (21·1)	17 (8)	< **0·001***
Diarrhea (%)	203 (47·7)	106 (50)	97 (45·3)	0·330
Failure to thrive (%)	75 (17·6)	16 (7·5)	59 (27·8)	< **0·001***
Clubbing (%)	26 (6·1)	1 (0·5)	25 (11·8)	< **0·001***
Hepatobiliary disorders (%)	46 (10·8)	24 (11·3)	22 (10·4)	0·768
Organomegaly (%)	207 (48·7)	92 (43·2)	115 (54·2)	**0·023***
Hematological disorders (%)	219 (50·6)	103 (46·6)	116 (54·7)	0·092
Malignancy (%)	52 (12·2)	37 (17·4)	15 (7·1)	**0·001***
Autoimmunity (%)	290 (66·8)	143 (64·4)	147 (69·3)	0·276
Rheumatological disorders (%)	71 (16·7)	35 (16·4)	36 (17)	0·879
Skin disorders (%)	110 (25·9)	81 (38)	29 (13·7)	< **0·001***
Endocrine disorders (%)	111 (26·1)	52 (24·4)	59 (27·8)	0·423
Neurological/learning disorders (%)	77 (18·1)	51 (23·9)	26 (12·3)	**0·002***
Meningitis (%)	7 (1·6)	2 (0·9)	5 (2·4)	0·284
Cardiovascular disorders (%)	22 (5·2)	16 (7·5)	6 (2·8)	**0·029***
Renal disorders (%)	41 (9·6)	21 (9·9)	20 (9·7)	0·882
Abscess (%)	13 (3·1)	2 (0·9)	11 (5·2)	**0·011***
Osteomyelitis (%)	2 (0·5)	1 (0·5)	1 (0·5)	1·000
Sepsis (%)	31 (7·3)	17 (8)	14 (6·6)	0·585

The statistically significant correlations are indicated in bold.

CHAI = cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration; LATAIE = lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy.

* P-value is statistically significant < 0·05.

in patients with nonsense and insertion/deletion mutations (P = 0·015) in comparison to missense mutations.

The therapeutic approach in CHAI and LATAIE patients

The immunosuppressive treatment for autoimmune and/or inflammatory complications mainly consisted of systemic corticosteroids in combination with biological agents (139 of 298, 46·6%).

Targeted immunosuppressive therapy was applied in 189 of 298 (63.4%) patients [63 (70·8%) CHAI and 126 (60·3%) LATAIE patients]. As illustrated in Fig. 6, CHAI patients were mainly treated with rituximab (n = 24, 38·1%), abatacept (n = 15, 23·8%) and other agents (n = 16, 25·4%), such as cyclophosphamide, adalimumab, etc. LATAIE patients mainly received abatacept (n = 60, 47·6%), sirolimus (n = 35, 27·8%), cyclosporin (n = 35, 27·8%) and mycophenolate mofetil (n = 34, 27·0%). Other immunosuppressive agents, including azathioprine (n = 30, 15·9%), tacrolimus (n = 20, 10·6%), methotrexate (n = 13, 6·9%) and anti-tumor necrosis factor (TNF) alpha (n = 12, 6·3%), were also variably used in both groups.

Table 4. Immunological profile of patients with CHAI and LATAIE syndrome

Parameters	Total (***n*** = 434)	CHAI (***n*** = 222)	LATAIE (***n*** = 212)	***P***-value
WBC × 10^3 (cell/ul), median (IQR) (*n* = 69)	6200 (4500–8715)	5000 (2350–8242)	6200 (4800–8900)	0·121
Absolute lymphocyte count × 10^3 (cells/µl), median (IQR) (*n* = 102)	2275 (1252–3157)	1248 (651·5–1543·5)	2385 (1350–3450)	**0·004***
Absolute neutrophil count × 10^3 (cells/µl), median (IQR) (*n* = 81)	3700 (1554–6000)	1400 (484–3684·5)	3861 (2006·2–6081)	**0·009***
$CD3^+$ T cells × 10^3 (cell/µl), median (IQR) (*n* = 136)	1518 (917–2074)	855·5 (614·5–1326·5)	1696·5 (1142–2187·5)	< **0·001***
$CD4^+$ T cells × 10^3 (cell/µl), median (IQR) (*n* = 125)	672 (397–1113)	450 (278·8–594·7)	732 (440–1150)	**0·016***
$CD8^+$ T cells × 10^3 (cell/µl), median (IQR) (*n* = 127)	625 (314–1032)	219 (112–492)	681 (418–1081)	< **0·001***
$CD4^+/CD8^+$ ratio, (*n* = 131)	1·9 (1·5–3·6)	1·9 (1·5–3·6)	–	-
NK cell, (cell/µl), median (IQR) (*n* = 133)	552 (296–919)	100 (28–376)	570 (323·7–950·7)	**0·001***
$CD19^+$ B cells (cell/µl), median (IQR) (*n* = 142)	165·5 (30–349)	80·5 (11·2–243)	172 (44·7–407·5)	**0·045***
IgG, mg/dl, median (IQR) (*n* = 165)	542 (324·5–943·5)	490 (316–937)	570 (323·7–950·7)	0·427
IgA (mg/dl), median (IQR) (*n* = 155)	40 (10–79·4)	47·5 (23–121)	29·0 (7·0–73·5)	**0·033***
IgM (mg/dl), median (IQR) (*n* = 156)	56 (26·2–121·7)	57·9 (25–99·5)	55·1 (27–135)	0·589
IgE (IU/ml), median (IQR) (*n* = 53)	3 (1–16)	11·9 (3–34·2)	1·9 (0·3–6·3)	**0·016***

The statistically significant correlations are indicated in bold.

Ig = immunoglobulin; WBC = white blood cell; NK = natural killer; IQR = interquartile range; CHAI = cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration; LATAIE = lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy.

* *P*-value is statistically significant < 0·05.

Table 5. Autoantibodies found in patients with CHAI and LATAIE

Autoantibodies	CHAI (%)	LATAIE (%)
Coombs antibody	6 (20)	28 (41·8)
Anti-nuclear antibody	12 (40)	10 (14·9)
Anti-phospholipid antibody	2 (6·7)	5 (7·5)
Anti-smooth muscle antibody	2 (6·7)	1 (1·5)
Anti-neutrophil cytoplasmic antibody	2 (7·1)	3 (4·3)
Anti-thyroid peroxidase antibody	3 (10)	11 (16·4)
Anti-thyroglobulin antibody	1 (3·3)	5 (7·5)
Anti-glutamic acid decarboxylase antibody	5 (16·7)	4 (6)
Anti-insulin/anti-islet cell antibody	2 (6·7)	6 (8·9)

CHAI = cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration; LATAIE = lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy.

Fifty-four (12·7%) patients, including 21 CHAI and 33 LATAIE patients, underwent hematopoietic stem cell transplantation (HSCT). The detailed HSCT characteristics were available in 48 (17 CHAI and 31 LATAIE) patients and summarized in Supporting information, Table S2. Patients with CHAI received transplantation at a median (IQR) age of 17·0 (14·0–22·0) years, while patients with LATAIE were transplanted at a median (IQR) age of 10·0 (7·0–13·0) years ($P < 0·001$). Acute or chronic graft-*versus*-host disease (GvHD) was encountered in 20 of 48 (41·6%) patients. In addition, 26 of 48 (54·1%) patients developed other complications, mainly including CMV reactivation (*n* = 14, 29·1%), adenovirus infection (*n* = 8, 16·6%) and autoimmune flare (*n* = 9, 18·7%). Reduced-intensity or myeloablative conditioning regimen mainly consisted of fludarabine (*n* = 46), busulfan (*n* = 16), treosulfan (*n* = 16), thiotepa (*n* = 13), melphalan (*n* = 11) and alemtuzumab (*n* = 9) in various combinations.

Most patients (83·3%) received human leukocyte antigen (HLA)-identical transplants from a matched unrelated donor (MUD) (*n* = 20, 41·6%), matched sibling donor (MSD) (*n* = 10, 20·8%) or matched family donor (MFD) (*n* = 10, 20·8%). Patients were followed-up at a median (IQR) time-period of 0·9 (0·3–2·6) years, which did not differ between the two groups ($P = 0·659$). One LATAIE patient experienced graft failure before achieving full engraftment, 37 (77·1%) patients showed complete remission at first transplantation and 10 (20·8%) patients died at a median (IQR) age of 12·6 (9·8–17·1). The overall survival rate in LATAIE was lower than in CHAI ($P = 0.031$) patients. The transplantation was associated with lower survival in both groups, although it was not statistically significant ($P = 0·639$) (Supporting information, Fig. S2). Transplanted *versus* non-transplanted patients were reported to have a considerably more complicated pretransplant clinical status (i.e. life-threatening infections, malignancy or polyautoimmunity) ($P = 0·002$).

Discussion

LRBA deficiency and CTLA-4 haploinsufficiency are newly identified inborn errors of immunity with shared clinical presentations. *LRBA* has a crucial role in CTLA-4 regulation and most of the patients with LATAIE reported having defects in CTLA-4 expression; therefore, mutations in these two genes seem to be a phenocopy of each other [29]. In this study, we systematically reviewed and compared the clinical, immunological and molecular characteristics in these two similar conditions.

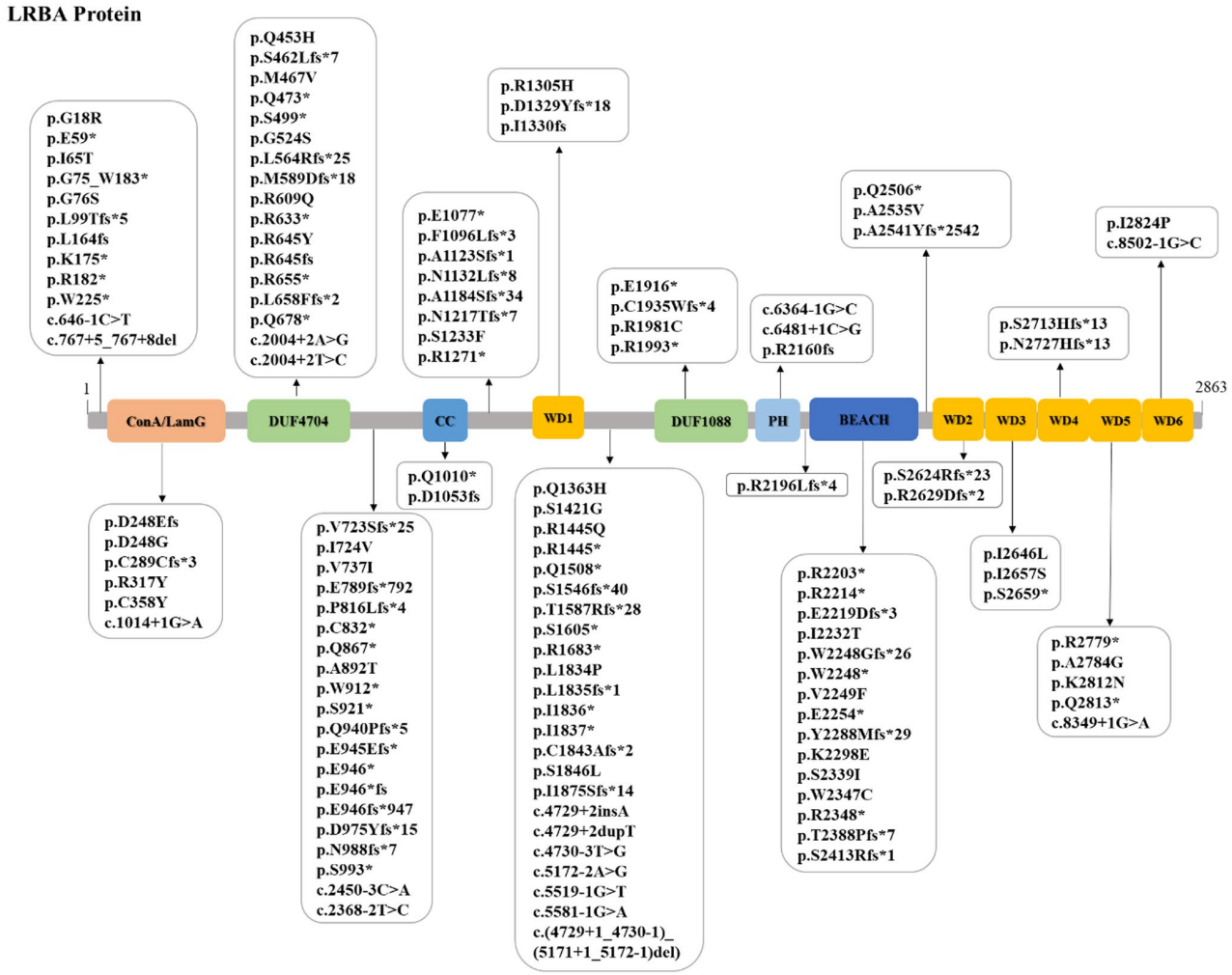

Fig. 5. Graphic illustration of lipopolysaccharide-responsive beige-like anchor (LRBA) and cytotoxic T lymphocyte antigen 4 (CTLA-4) protein domains with locations of published genetic mutations in CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) patients. (a) The 10 reported large deletions/duplications (exons 1–2, 1–22, 1–30, 3–15, 3–37, 18–30, 29–30, 35, 41 and 49–53) are not displayed in the figure. Mutations in *LRBA* occurred throughout the length of the gene, without hot-spots. (b) The three reported large deletions (2q33-2q34del, 2q33.1-2q34del and 2q33.2-2q33.3del) are not displayed in the figure. The disease-causative mutations in *CTLA-4* occur throughout the full-length gene, although the majority of mutations resided within the extracellular domain. Introns that interrupted codons are marked in red. Amino acids are designated by their single letter code. Domain and features positions recruited from UniProt database (https://www.uniprot.org/).

In CHAI patients, positive familial history and in LATAIE consanguineous parents were more common. This may be due in part to the pattern of inheritance and geographical distribution of the two disorders. CHAI is inherited in an autosomal dominant manner, and because of the lower penetrance can be inherited across generations, while LATAIE is an autosomal recessive disorder and most patients (86·3%) are homozygous for the mutation; thus, the two pathogenic alleles often come from two carrier parents from the same family and region.

Despite similarities in clinical manifestations, life-threatening infections are considerably more frequent in LATAIE patients. They are also more prone to lung infections and autoimmune enteropathy with associated failure to thrive. However, in CHAI individuals, granulomas, malignancies, atopies and autoimmune skin disorders are more common. Although the reason for higher rates of granuloma formation and malignancies in CHAI patients is unknown, it is proposed that chronic immune activation in CHAI may favor the occurrence of lymphoma and gastric cancer, and LATAIE patients either die or are cured with HSCT prior to establishing such complications [29]. An alternative hypothesis is that, as CHAI shows incomplete penetrance, disease development may be dependent

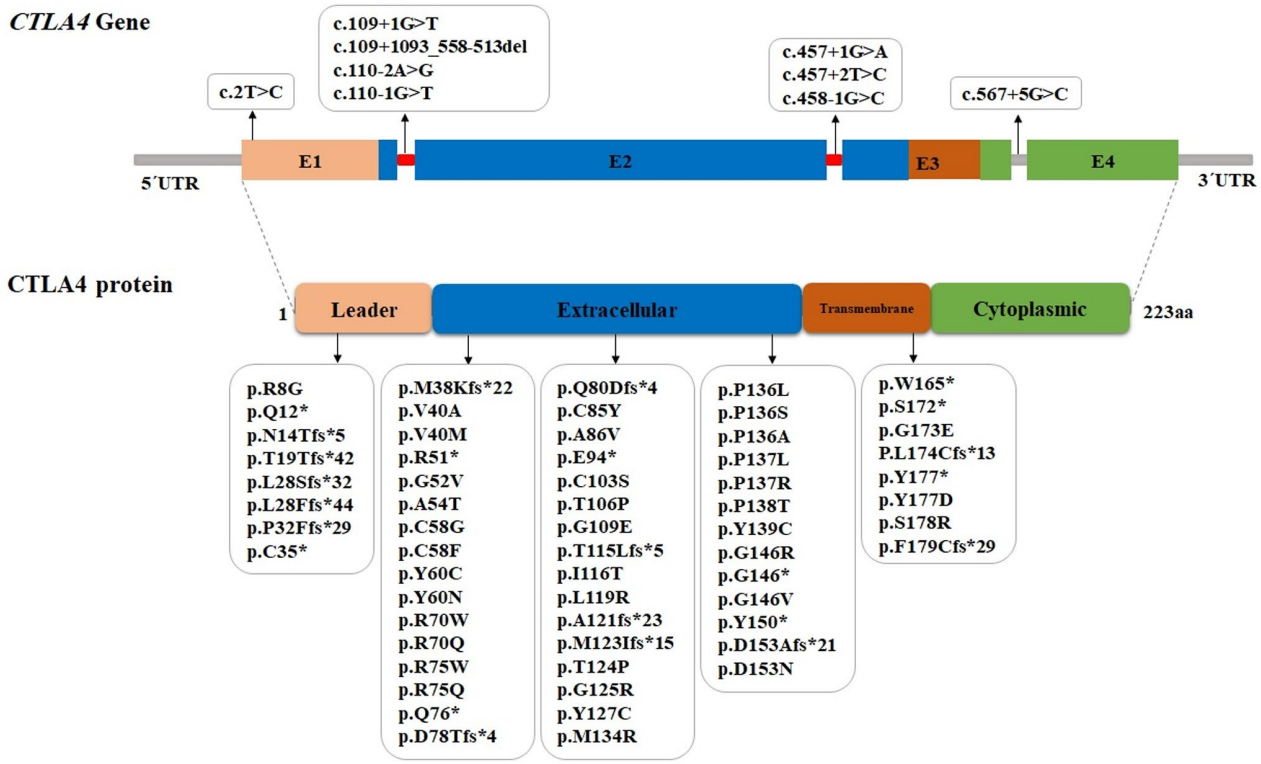

Fig. 5. (Continued)

upon a 'trigger', such as infection with EBV, CMV, human papillomavirus (HPV) or *Helicobacter pylori* that initiates the immune dysregulation and/or lymphoproliferative disease. These pathogens are more likely to cause a chronic infection that would exacerbate immune responses, potentially provoking lymphoproliferative disease as well as the eventual development of malignancy.

Autoimmune disorders, mainly autoimmune cytopenias, were the most common manifestation in both CHAI and LATAIE patients. In this respect, previous studies have introduced *CTLA-4* and *LRBA* as genes to be searched for mutations in pediatric cytopenias [30,31]. However, in the last decade, the spectrum of IEIs with autoimmune features have been expanding, making the diagnosis more complicated. For instance, patients with DEF6 deficiency exhibit early-onset autoimmunity/inflammation mainly in hematological and gastrointestinal systems, lymphoproliferation and susceptibility to EBV infection [32]. In the immunological evaluation, T cell lymphopenia, low class-switched B cells and reduced CTLA-4 expression in memory T_{reg} cells are detected; however, as opposed to CHAI and LATAIE, obvious T cell exhaustion is not usually present [33]. Another example is the presentation of the autoimmune lymphoproliferative syndrome (ALPS)-like phenotype by LATAIE patients [26,34–36]. In this review, 22 (15.6%) LATAIE patients were initially diagnosed with ALPS. Although elevation in double-negative T (DNT) cells classically favors the diagnosis of ALPS, most of these 22 patients had high levels of DNT cells. Therefore, investigation for other validate laboratory-based criteria such as defective lymphocyte apoptosis and elevated plasma sFASL, interleukin (IL)-10, IL-18 or vitamin B12 levels may help to achieve an accurate diagnosis [37].

Currently, there is no clinically available diagnostic laboratory test for distinguishing these two conditions. At the molecular level, higher CTLA-4 expression in stimulated T cells, enhanced sensitivity to lysosomal blocking agents and more efficient ligand uptake in LATAIE compared with CHAI have been proposed [38]. However, LATAIE can generally be determined by the loss of LRBA protein expression. In the genetic evaluation, similar to previous studies [10,39–41] the correlation between phenotype and genotype in CHAI and LATAIE patients was not clear and clinical characteristics were heterogeneous, suggesting the impact of the exposome, modifier genes and epigenetic mechanisms on the phenotype manifestation [12]. Residual expression and function in CHAI and LATAIE patients may, to some extent, explain the clinical heterogeneity between patients with different mutations; however, there is not enough data to verify this claim [17,42]. Mutations in *LRBA* were located throughout the gene; however, in *CTLA4* mutations were mainly

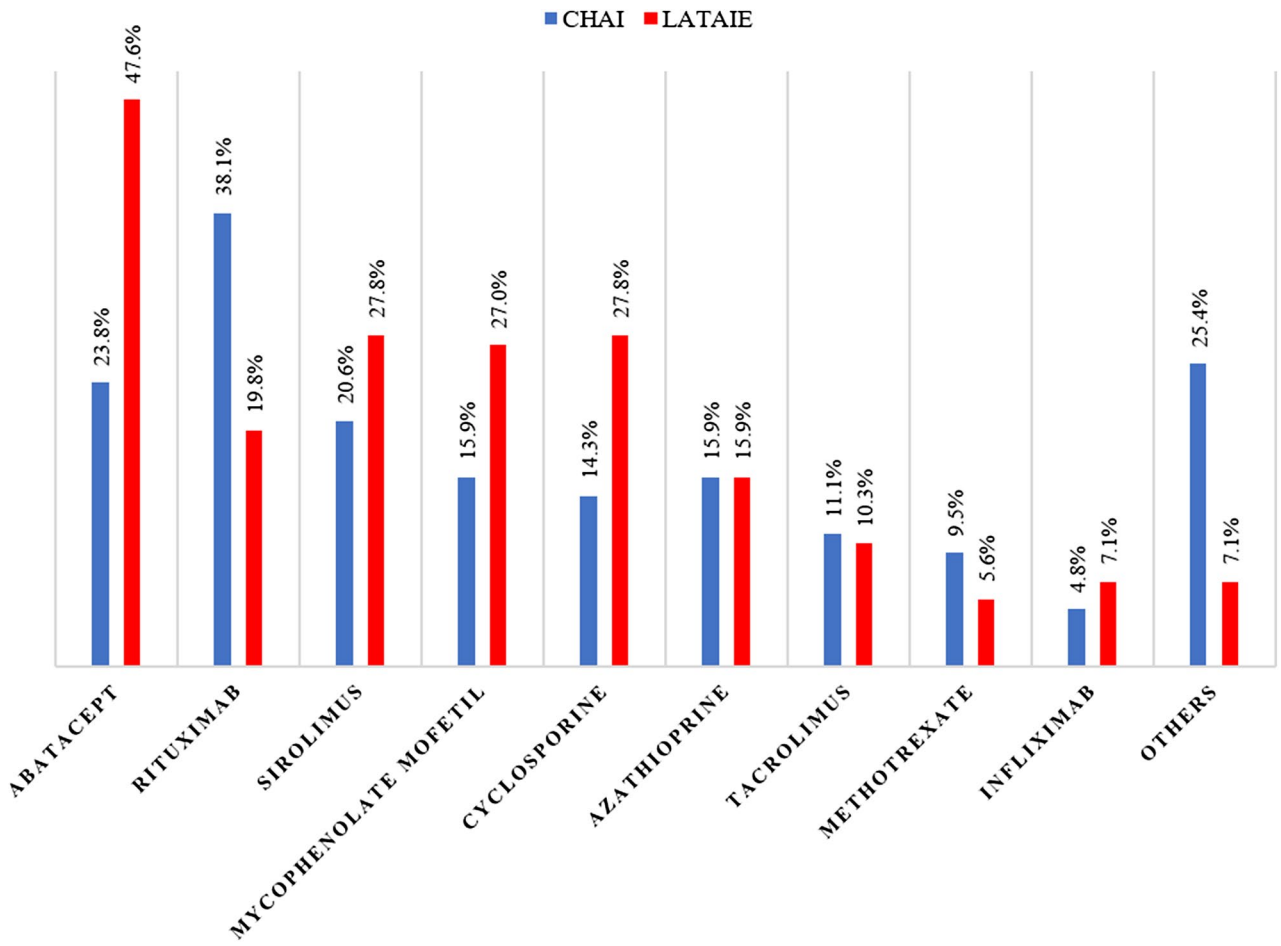

Fig. 6. The application of biologic immunosuppressive agents for the treatment of cytotoxic T lymphocyte antigen 4 haploinsufficiency with autoimmune infiltration (CHAI) and lipopolysaccharide-responsive beige-like anchor deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration and enteropathy (LATAIE) patients. Rituximab for CHAI patients and abatacept for LATAIE patients were the most frequent agents prescribed.

accumulated in the extracellular domain, and no mutation was found in the cytoplasmic domain (exon 4). Despite all, we demonstrated that in patients with LATAIE, insertion/deletion frameshift or nonsense mutations (severe mutations) were associated with polyautoimmunity, and in the CHAI patients the missense mutations were correlated with enteropathy. In this regard, determining the association of clinical and laboratory phenotypes with genetic features would help to prepare an algorithm to ease the diagnosis and management of CHAI and LATAIE [10,26].

LATAIE shows nearly complete penetrance, whereas CHAI has an estimated 60·6% penetrance, which means that more than one-third of individuals with *CTLA-4* mutations are asymptomatic. Accordingly, 39·4% of individuals with *CTLA-4* mutation had no clinical manifestations and were considered unaffected carriers. Recent studies reported a penetrance of around 67–71% in CTLA-4 insufficiency [10,29,43]. The lower estimated penetrance in this review may be due to the assessment of only CTLA-4 insufficiency families with known mutation status in family members (at least in parents) of patients. Furthermore, some individuals with CTLA-4 mutations had no obvious clinical manifestations, referred to as carriers. Despite high rates of penetrance in LATAIE, there are well-documented *LRBA*-mutated individuals, usually siblings of index cases, with no LRBA protein expression and no manifestations of disease. However, it would be reasonable to carefully monitor both asymptomatic LATAIE and CHAI patients, as they may eventually manifest milder or less common features of the disease (e.g. malignancy).

It seems that *CTLA-4* compared with *LRBA* mutations lead to a milder phenotype in humans. At the cellular level, this can partly be explained by the lower CTLA-4 level in memory T_{regs} of LATAIE than those of CHAI patients [38]. Another clue for the higher disease severity

with *LRBA* mutations is provided by the fact that the age of onset and diagnosis of the disease is significantly lower in LATAIE compared to CHAI patients, and the overall survival in LATAIE is lower than CHAI patients. These observations may further emphasize a higher need for timely vigilant management of LATAIE compared to CHAI patients.

Monoclonal antibody-based immunotherapies were widely utilized among CHAI and LATAIE patients. Abatacept, a soluble CTLA-4 fusion protein, has been shown to significantly decrease disease activity in CHAI and LATAIE patients [8,25,35,44] and with other conventional therapies may also be considered as a bridging therapy before HSCT. However, the degree to which CHAI and LATAIE patients are going to benefit from HSCT is obscure. In this study, transplanted *versus* non-transplanted patients had lower survival in both CHAI (P = 0·033) and LATAIE (P = 0·113) groups, which might be attributed to the more complicated pretransplant clinical status (i.e. life-threatening infections, malignancy or polyautoimmunity) (P = 0·002). In the same way, a recent study reported a relatively high mortality rate (29.2%) in transplanted LATAIE patients [25]. For CHAI, there is little information regarding the application of HSCT; however, due to the underlying autoinflammation, they are suggested to receive strict immunosuppression and prophylaxis for GvHD before and after transplantation [45]. These data are somewhat inconclusive for choosing the best therapeutic option, mainly because of the recent application of HSCT in such disorders and the lack of detailed transplantation data available in the literature. To improve HSCT survival, further studies are required to determine which subset of CHAI and LATAIE patients benefit most from transplantation and reach a consensus to candidate eligible patients for HSCT before they become critically ill.

In summary, despite similarities in the clinical picture, the manifestations in patients with LATAIE commence at earlier ages and are more acute and life-threatening in nature, while in patients with CHAI, signs and symptoms take more time to develop and disease has lower penetrance, thus leading to longer survival and greater generational inheritance. Currently, both CHAI and LATAIE patients are responsive to immunosuppression with steroids and biological drugs. HSCT has not been associated with a significant improvement in the survival of CHAI and LATAIE patients. Further prospective investigations into the best conditioning and treatment regimens pre- and post-HSCT may be required to improve the survival rate of transplanted CHAI and LATAIE patients. In order to achieve earlier diagnosis and prevent further complications, it would be appropriate to look for an underlying *CTLA-4* or *LRBA* gene mutation in patients with an initial PAD diagnosis and predominant autoimmune complications.

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Disclosures

The authors declare that they have no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting information of this article.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Fig. S1. Flowchart of the systematic search and study selection process for CTLA4 Haploinsufficiency (A) and LRBA deficiency (B).

Fig. S2. Kaplan Meier's Survival Plots. The overall survival in both groups is evaluated and differences among survival curves are assessed by the log-rank test; A) CHAI patients stratified whether or not they underwent HSCT, $P = 0.033$, B) LATAIE patients stratified whether or not they underwent HSCT, $P = 0.113$, C) The overall survival in CHAI and LATAIE patients is compared, $P = 0.031$, D) Transplanted CHAI vs. LATAIE patients are compared, $P = 0.639$.

Table S1. Causes of death (where stated).

Table S2. Summary of available data on hsct characteristics among patients with chai and lataie syndromes.