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Clinical spectrum of immunodeficiency, centromeric instability and facial dysmorphism (ICF syndrome)

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ABSTRACT

Background: Immunodeficiency, centromeric instability and facial dysmorphism (ICF syndrome) is a rare autosomal recessive disease characterised by facial dysmorphism, immunoglobulin deficiency and branching of chromosomes 1, 9 and 16 after PHA stimulation of lymphocytes. Hypomethylation of DNA of a small fraction of the genome is an unusual feature of ICF patients which is explained by mutations in the DNA methyltransferase gene *DNMT3B* in some, but not all, ICF patients.

Objective: To obtain a comprehensive description of the clinical features of this syndrome as well as genotype–phenotype correlations in ICF patients.

Methods: Data on ICF patients were obtained by literature search and additional information by means of questionnaires to corresponding authors.

Results and conclusions: 45 patients all with proven centromeric instability were included in this study. Facial dysmorphism was found to be a common characteristic (n = 41/42), especially epicanthic folds, hypertelorism, flat nasal bridge and low set ears. Hypo- or agammaglobulinaemia was demonstrated in nearly all patients (n = 39/44). Opportunistic infections were seen in several patients, pointing to a T cell dysfunction. Haematological malignancy was documented in two patients. Life expectancy of ICF patients is poor, especially those with severe infections in infancy or chronic gastrointestinal problems and failure to thrive. Early diagnosis of ICF is important since early introduction of immunoglobulin supplementation can improve the course of the disease. Allogeneic stem cell transplantation should be considered as a therapeutic option in patients with severe infections or failure to thrive. Only 19 of 34 patients showed mutations in *DNMT3B*, suggesting genetic heterogeneity. No genotype–phenotype correlation was found between patients with and without *DNMT3B* mutations.

In 1978 two patients were reported independently who shared specific facial characteristics, immunodeficiency and instability of pericentromeric regions of chromosomes 1, 9 and 16 upon cytogenetic testing (ICF syndrome).[1 2] So far some 30 patients have been reported,[3–28] most of them at very young age. In most patients reduced serum immunoglobulin levels as well as severe recurrent, and often fatal, infections were documented. Mild facial anomalies are a common characteristic of which epicanthic folds, hypertelorism and a flat nasal bridge are most frequently reported. Centromeric instability is the hallmark of the disease with ICF patients. In only a small percentage of the genome, most notably on the sat 2 and 3 repeats on chromosome 1, 9 and 16, DNA methylation is strongly reduced.[29 30] Decondensation of these regions leads to the characteristic cytogenetic abnormalities which are prone to breakage and rejoining, leading to the formation of multiradiate chromosomes in mitogen-stimulated lymphocytes.[15] In 1998 a locus associated with ICF syndrome was mapped to the proximal long arm of chromosome 20.[31] This region contains a de novo DNA methyltransferase gene, *DNMT3B*, and mutations in this gene were identified in ICF patients.[32 33] However, mutations were not demonstrated in all patients investigated, suggesting involvement of other genes in ICF syndrome.[34]

The aim of the present study was to obtain a comprehensive description of the clinical features of ICF syndrome, the natural history as well as possible genotype–phenotype correlations in such patients.

PATIENTS AND METHODS

A computer assisted literature search using Pubmed and EMBASE was conducted to identify and obtain data on patients with ICF syndrome. Only patients showing the cytogenetic hallmark of the diagnosis—that is, instability of the pericentromeric heterochromatin of chromosomes 1, 9 and 16 upon PHA stimulation—were included in the study. Supplementary information was obtained from questionnaires completed by their attending physicians. Data of patients previously reported in the literature (n = 32) were updated and new patients (n = 13) have been included. Ethical approval was obtained for the publication of these data.

Questions focused on age at diagnosis, facial anomalies, psychomotor development, hypotonia and gastrointestinal problems. The diagnosis of immunodeficiency was made by reductions of serum IgG, IgG subclasses, IgA and/or IgM according to age standardised reference ranges. Agammaglobulinaemia was defined as a decrease of IgG below 2.5 g/l. Special attention was given to frequency and type of infections and laboratory results reflecting immunological status. These included complete blood count, level of serum immunoglobulins G, A, M, E and IgG subclasses

and number of T and B lymphocyte subpopulations.

RESULTS

A total of 45 ICF patients were included in this study (table 1).

Sociodemographic features

The 45 patients include 25 males and 20 females, originating from 39 families, with consanguinity confirmed in 18 patients (table 1). There were six sibling pairs. In two children with a positive family history the diagnosis of ICF was confirmed shortly after birth through genetic analysis on cord blood (patient 16, 33).

Seventeen patients (40.5%) died, with cause of death being predominantly severe respiratory tract infections, sepsis and failure to thrive. Median age at death was 8 years (range 6 months–42 years).

Facial anomalies

In most evaluable patients (41/42) typical distinctive facial appearances were found (fig 1, table 2). Hypertelorism, flat nasal bridge, epicanthic folds and low set ears were most frequent. The combination of epicanthic folds, hypertelorism, flat nasal bridge and low set ears was observed in 11 cases. Among those patients who were followed into adulthood only one had no facial anomalies (patient 25). Patient 30 had complaints of chronic fatigue at the age of 17, due to a sleep/apnoea syndrome caused by anatomic anomalies of the tongue.

Congenital defects

The most common malformations found were inguinal hernia and hypospadia (4/42), cleft palate (3/42) and syndactyly (2/42). Cardiac anomalies were reported in two patients and included a ventricular septal defect and an atrial septal defect (patients 31 and 39, respectively). Congenital hypothyroidism was found in one patient (patient 42).

Cerebral malformations were reported in individual patients and include focal cortical heterotopy, corpus callosum hypoplasia and hydrocephalus (patients 40, 8 and 5, respectively).

Immunodeficiency and infections

With the exception of one (patient 14), all remaining patients had documented signs of immunodeficiency (table 1). Patient 5 died at 6 months; follow up was too short in order to draw conclusions regarding the immune status. In 27 patients the immunoglobulin levels were consistent with a diagnosis agammaglobulinaemia; they all had B cells. Twelve patients had decreased levels of all immunoglobulins and four patients were reported with selective IgA (patient 2), IgM (patients 13 and 21) and IgG2 subclass deficiency (patient 19). The diagnosis of hypo/agammaglobulinaemia was made in early childhood in all patients (median age 3 years). Data for T cell subpopulations were available for 38 patients (table 2). Normal percentages of T cells were observed in all but two patients (patients 5 and 9), and CD4 positive cells were decreased (<p10) in five of 38 patients (13.1%). A limited number of patients underwent T cell function testing in vitro. Of the 28 tested, three patients showed decreased or absent proliferation when stimulated with the mitogen PHA.

At the time of data collection, 29 patients were receiving intravenous immunoglobulin (IVIG) replacement.

Infections were a prominent clinical feature for 43 patients with available data (table 2) and were the leading cause of death (table 1) for 12 patients (26.6%). The most common were respiratory tract infections in 35 patients (81.4%). Three patients were reported with *Pneumocystis jiroveci* pneumonia (patients 11, 29 and 43). Sepsis was reported in 10 patients. In six patients, positive blood cultures were reported including *Staphylococcus aureus* (patients 3 and 13), *Pseudomonas* (patients 17 and 45) and *Klebsiella* species (patients 15 and 29). *Streptococcus pneumoniae* meningitis was documented in one patient (patient 39) and persistent *Candida stomatitis* in six (patients 5, 8, 9, 10, 44 and 45). Patient 13, with known selective IgM deficiency, developed a progressive multifocal leucoencephalopathy, due to JC virus[14] at the age of 35 years; at that moment she had an agammaglobulinaemia. Infections with JC virus, *Pneumocystis jiroveci* and *Candida* suggest that a subtle defect of T cell function must be present, apart from the hypogammaglobulinaemia.

Gastrointestinal problems were reported in 27 patients (65.8%) (table 2) and included multiple episodes of acute diarrhoea in 18 patients (43.9%). Seven had chronic diarrhoea, two with persistent bacterial enteritis (salmonella in patient 6; campylobacter in patient 33). For three patients (patients 8, 15 and 29) diarrhoea was severe enough to warrant the administration of total parenteral nutrition for several months.

In four patients allogeneic stem cell transplantation (alloSCT) has been performed (patient 24 because of MDS; patients 33, 34 and 43 for infections and failure to thrive).

Malignancies and haematological abnormalities

Haematological malignancies were reported in two patients and included one patient who developed a classical Hodgkin lymphoma (patient 37),[25] and a second patient who developed myelodysplastic syndrome (patient 24). Patient 45 developed aplastic anaemia. An adrenocortical adenoma was described in one patient (patient 39). Acquired leucopenia and thrombocytopenia of unknown origin were documented in patients 16, 30 and 41. In two of them (patients 16 and 41) cortical atrophy evolved at the same time without evidence of an infectious origin.

Growth, development and neurological problems

The average gestational age was 38 weeks (range 30–42 weeks). Eight patients (18.6%) were born preterm. Among the 35 patients with adequate growth records, 20 (57.1%) had a birth weight below the 10th centile (table 2) according to the World Health Organization Child Growth Standard. Data regarding sexual maturation were available in 10 cases: all entered puberty normally.

Developmental milestones were delayed in 28 of 41 patients (68.3%). Of these, 18 (43.9%) were delayed in speech development and 21 (51.2%) did not start walking until 18 months of age. Nine patients with a delayed motor development were reported with hypotonia. Intelligence quotients were available from 44 patients, with 17 (38.6%) showing a normal intelligence, 17 (38.6%) a mild retardation and 10 (22.7%) moderate retardation.

Five patients (patients 2, 12, 16, 18 and 41) had cortical atrophy. Two of them (patients 12 and 18) developed generalised tonic–clonic seizures within their first 2 years of life. Two other patients (patients 2 and 16) had a progressive deterioration of cognitive functions at the age of 10 years.

Genetics

A total of 35 individuals with the syndrome were screened for mutations of the gene *DNMT3B* (table 1). Mutations were

Table 1 Epidemiologic features and results of DNA and immunological analyses of ICF patients in this study

	Sex	Origin	Ref	Born	Con†	Sibling pairs	Gene mutation‡	Age§ (years, months, weeks)	IgG¶	IgA	IgM	Age at death (years)	Cause of death
1	M	UK	1	1972	−		V718G/G655S	1	0.17	Und	0.07	14	Unknown
2	M	Italian	2	1966	−		H814R/V818M	11 y 6 m	16.70	0.03	3.86	12	Respiratory failure
3	F	Belgian	3	1979	−		Neg	1	0.63	Und	Und	1.5	Sepsis
4	M	UK	4	1978	−		NT	1	0.14	Und	0.18		
5	F	Bulgarian	5	1984	−		NT	4 m	4.00*	0.20	0.30	0.5	Enterocolitis
6	F	Italian	6	1981	−		Neg	5	3.73	0.10	0.40		
7	F	American	7	?	−		A603T/STP807ins	6 m	1.19	Und	0.11		
8	M	French	8	1985	−		Ins1bp/D737het	11	3.9	Und	0.98	16	Respiratory failure
9	M	Algerian	9	1985	+	Sib of 10	NT	5 m	0.10	Und	Und	0.5	Pneumonia
10	F	Algerian	9	1987	+	Sib of 9	NT	6 m	Und	Und	Und	1	Pneumonia
11	F	UK	10	1987	+		Neg	8	11.1*	Und	Und	13	Pneumonia
12	M	German	12	1989	−		NT	?	Decreased	Decreased	Decreased		
13	F	Italian	13	1960	−	Sib of 14	Neg	29	12.19*	1.43	0.15	42	Sepsis
14	M	Italian	13	1959	−	Sib of 13	Neg	30	Normal	Normal	0.46		
15	M	Dutch	15	1992	+	Sib of 16	V726G/V726G	1	Und	Und	Und	8	Sepsis
16	M	Dutch		1994	+	Sib of 15	V726G/V726G	5 wks	Cord blood	Und	Und		
17	F	Dutch/Turkish		1983	+		Neg	5	4.25	0.00	0.00	11	Sepsis
18	M	Africa/American	16	?	−		Neg	1 y 7 m	0.29	0.00	0.12	3	Unknown
19	M	Italian	17	?	−		NT	1	5.01	Normal	0.27		
20	M	Italian	17	?	−		NT	6	4.25	1.47	0.27		
21	F	Danish	18	1969	−		NT	?	Normal	Normal	Decreased		
22	M	Danish	19	1973	+	Sib of 23	V818M/V818M	9	3.4	1.4	0.09		
23	F	Danish	19	1976	+	Sib of 22	L656T/L656T	6	4.0	0.09	0.2		
24	F	German	20	1988	−		V606A/Q204X	6	Decreased	Decreased	Decreased	18	RSV infection
25	M	UK		1982	−		A766P/A766P	5	0.6	Und	1.4		
26	M	Belgian	21	1995	−		Neg	4 m	2.08	0.03	0.19		
27	M	Italian	22	1981	−		Neg	13 y 6 m	3.80	0.20	1.24		
28	M	Italian		1990	+		NT	?	Und	Und	Und	3.5	Pneumonia
29	F	Dutch/Turkish		1996	+	Sib of 33	STP807ins/STP807ins	11 m	Und	Und	Und	3	Pneumonia
30	M	Dutch/Antillian		1988	−		Q42X/V699G	3	Und	Und	0.13		
31	M	Japanese	23	1981	−		Q42term/R832Q	3	Und	Und	Und		
32	F	Lebanese	24	1995	+		A585V/A585V	?	6.28*	<0.32	<0.20		
33	M	Dutch/Turkish		2000	+	Sib of 29	STP807ins/STP807ins	5 wks	Cord blood	Und	Und		
34	F	UK		2000	−		Neg	10 m	Und	Und	0.10		
35	F	Japanese	23	1997	+		S282P/S282P	1	1.55	0.07	0.06		
36	M	Japanese	23	2001	+		S282P/S282P	?	1.75	Und	0.04		
37	M	German	25	1998	−	Sib of 38	Neg	3	3.9	2.89	0.09	8	Malignancy
38	F	German	25	2001	−	Sib of 37	Neg	7 m	3.0	0.81	0.23		
39	F	Japanese	26	2001	−		Neg	3	6.54	0.71	0.8		
40	M	Swiss/Turkish	27	2001	+		Neg	4	1.70	Und	0.1		
41	M	Swiss/Turkish	27	1986	+		Neg	5	1.50	Und	0.15		

Continued

Table 1 Continued

	Sex	Origin	Ref	Born	Con†	Sibling pairs	Gene mutation‡	Age§ (years, months, weeks)	IgG¶	IgA	IgM	Age at death (years)	Cause of death
42	M	Jordan		2004	+		R826C/R826C	5 wks	3.05*	Und	Und		
43	F	UK		2004			D809G/V605A	8 m	0.8	<0.6	<0.04		
44	F	Turkish	28	1996	+		NT	5.5 y	3.47	0.23	0.69	5.5	Rubella-pneumonia
45	F	Austrian		1989	–		R756S/I773KfsX23	16 y	6.86*	0.01	Und		

All children were tested positively for centromeric instability
*IgG due to intravenous immunoglobulin (IVIG) or maternal IgG; †Con, consanguine; ‡NT, not tested; §Age at diagnosis of immunodeficiency; ¶Und, undetectable; ?, Unknown.

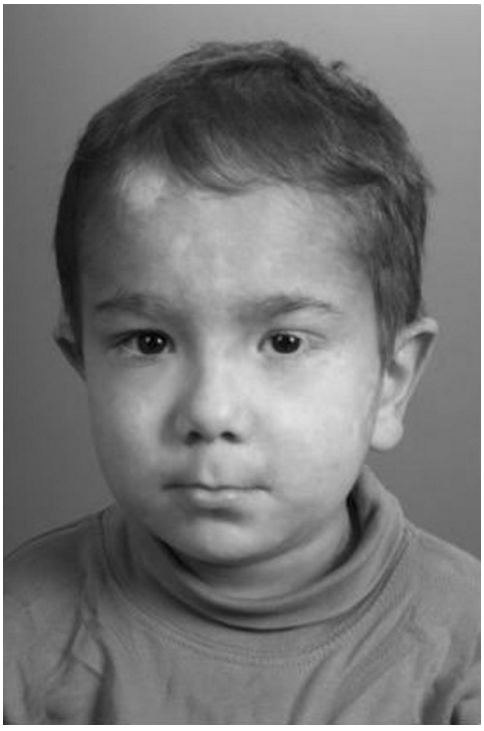

Figure 1 Patient with typical ICF features: hypertelorism, epicanthic folds, flat nasal bridge and up turned nose. Parental/guardian informed consent was obtained for publication of this figure.

detected in 20 (57.1%) cases. Ten patients showed a homozygous mutation, the remainder were compound heterozygous. The homozygous patients were all of proven consanguineous descent. One patient (patient 25) born from non-consanguineous parents had a single mutation. The majority of mutations are missense mutations (table 1). Other mutations included nonsense mutations and splice-site mutations.

In order to study a possible genotype–phenotype correlation the cases in this report were divided into two groups based on mutation data. Group 1 entailed those with *DNMT3B* mutation (n = 20), and group 2 included those without mutation after DNA analysis (n = 15). As shown in table 2, no relevant differences were noted concerning immunology, facial findings and development. The number and severity of infections was similar in both groups.

DISCUSSION

The diagnosis of ICF is based on the triad of immunodeficiency, centromeric region instability and facial dysmorphism.[1 2] The clinical spectrum in this study group, however, was very broad. In this study of cytogenetically proven ICF patients it became clear that these hallmarks are not equally present in all patients. While centromeric region instability was by definition present in all patients, facial dysmorphism was lacking in some and the immune defect varied from a severe combined immunodeficiency to nearly normal immunity.

In most patients facial dysmorphism was present and included hypertelorism, flat nasal bridge, epicanthic folds, low set ears, micrognathia or upturned nose. One patient developed a nocturnal sleep apnoea syndrome due to abnormalities of the tongue and motor problems of the mouth (patient 30). Obvious facial dysmorphism at birth without other symptoms at that time was the reason for cytogenetic studies in one patient (patient 42), leading to the diagnosis of ICF syndrome. Another patient (patient 25) did not have dysmorphism at all, while

Table 2 Clinical data and results of immunological analyses in relation to presence or absence of DNMT3B mutation

	Total*	DNMT3B mutation	No mutation
Demographic features	Total 45	Total 20†	Total 15†
Consanguine	18/45	10/20	4/15
Died	17/42	5/18	3/15
Growth and development			
Gestational age <37 weeks	8/43	2/18	4/15
Birth weight ⩽p10	20/35	6/17	6/8
Failure to thrive	21/41	6/16	8/15
Delays in motor development	21/41	10/17	9/15
Delays in speech and language development	18/41	7/14	7/15
Intelligence			
Normal intelligence	17/44	11/20	4/15
Mild retardation	17/44	4/20	8/15
Moderate retardation	10/44	5/20	3/15
Craniofacial features			
Hypertelorism	27/42	10/18	10/15
Flat nasal bridge	25/42	13/18	9/15
Epicanthus	25/42	13/18	7/15
Low set ears	20/42	8/18	7/15
Micrognathia	12/42	5/18	4/15
Up-turned nose	14/42	6/18	6/15
Round face	11/42	7/18	3/15
Macroglossia	8/42	4/18	3/15
Telecanthus	9/42	4/18	2/15
High forehead	10/42	3/18	3/15
Tongue protrusion	7/42	2/18	3/15
Congenital malformation	17/42	3/18	4/15
Gastrointestinal problems			
Diarrhoea	18/41	7/16	6/15
Malabsorption	4/41	2/16	1/15
Infections			
Bronchopneumonia	35/43	15/18	11/15
Otitis	13/43	8/18	3/15
Sepsis	8/43	2/18	6/15
Candida infection	6/33	2/18	0/15
Pneumocystis jerovici	3/33	2/18	1/15
Neurology			
Cerebral atrophy	5/45	2/20	2/15
Seizures	3/45	0/20	2/15
Immunology			
Agammaglobulinaemia	26/45	14/20	8/15
Hypogammaglobulinaemia	12/45	5/20	4/15
IgM deficiency	2/45	0/20	1/15
IgA deficiency	1/45	1/20	0/15
IgG2 subclass deficiency	1/45	0/20	0/15
T cells			
CD 4 decreased	7/38	2/17	2/15

*All cytogenetically proven ICF patients.
†10 patients who were not screened for DNMT3B mutation are not listed.

patient 16 had normal features at birth and developed dysmorphism during childhood. Therefore, absent dysmorphism in patients with agammaglobulinaemia, in whom B cells are present, does not preclude ICF syndrome and cytogenetic analysis should be considered. In addition a variety of congenital malformations were seen suggesting that *DNMT3B* plays an important broad role during embryogenesis. Further evidence for the role of *DNMT3B* in embryogenesis/morphogenesis was recently provided in transgenic mice models.[35]

The most prominent clinical feature in the study group was respiratory tract infections, with at least one episode of bronchopneumonia occurring in nearly all of the cases. Severe pulmonary infections were also the most common cause of death, indicative of the severity of immunodeficiency in these patients. By an unknown mechanism it is possible that *DNMT3B* mutations—probably as a result of DNA hypomethylation—are involved in lymphogenesis dysregulation causing this immunodeficiency.[36]

Two patients with a positive family history of ICF were treated from birth with IVIG and did not have pulmonary infections in infancy. This has also been described in patients with X-linked agammaglobulinaemia (XLA), who are now surviving into adulthood with fewer pulmonary problems due to earlier treatment with IVIG.[37]

Normally, infections in patients with agammaglobulinaemia are mostly caused by pyogenic encapsulated bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae*. These microorganisms were observed in only a minority of the ICF patients. Opportunistic infections such as *Pneumocystis jiroveci* or severe candida stomatitis occurred in several ICF patients with apparently only a B cell defect and normal T cell numbers and function.

This suggests that a subtle defect of T cell function or a defect in antigen presenting cells (dendritic cells or monocytes) must be present. Studies in murine ICF models have demonstrated an effect on postnatal thymocyte survival.[35] Further studies are required to determine the impact on peripheral T cell populations and their function in these mice and ICF patients. In practical terms this means that prophylaxis with co-trimoxazole should be employed.

A high proportion of the children died at a young age from respiratory infections or failure to thrive. In particular, children with gastrointestinal problems in combination with failure to thrive had a poor prognosis, leading to a worsening of the disease. Because the prognosis is poor in the patients with severe infections or failure to thrive, alloSCT should be considered in those patients. Recent experience indicates that alloSCT can be safely performed in ICF patients with improvement in immune function and clinical outcome.[38]

This study shows that growth retardation is a frequent problem in ICF patients. It is possible that initial growth problems were related to low birth weight. Furthermore, a number of children (43.9%) suffered diarrhoea secondary to infections or other gastrointestinal problems, and half the children failed to thrive (51.2%). In the case of two brothers with ICF, the elder with intestinal problems had poor growth, but his younger brother who was treated from birth with immunoglobulin substitution did not suffer from chronic diarrhoea, and had normal growth. This suggests that the poor growth is not directly related to the genetic defect.

One of the first reported patients with ICF suffered from severe mental retardation.[2] We here demonstrate that, although the majority of children with ICF syndrome do have some degree of mental retardation (27/44, 61%), more than one third (16/41, 39%) have normal intelligence. One child was reported as doing exceptionally well in high school showing that the disorder can exist without retardation. Children with ICF in this cohort frequently have difficulty with speech and gross motor skills. Physiotherapeutic support and speech therapy often has positive influence on their development. Neurological problems may develop over time. In three ICF patients (patients 2, 16 and 41) non-infectious encephalopathy was seen. Progressive deterioration and/or thrombocytopenia and leucopenia in combination with cerebral atrophy is similar to the pathology of neurological manifestations in systemic lupus erythematosus which is linked to DNA hypomethylation.[39] Development of haematological abnormalities—for example, aplastic anaemia in patient 45, or thrombocytopenia and

leucocytopenia seen in patient 30, who also developed hepatosplenomegaly and gonarthritis—may be caused by autoimmune mechanisms. Autoimmunity in the absence of antibodies suggests activation of autoreactive T cells by T cell receptor or innate activating receptors directly.

A predisposition to cancer is frequently associated with immunodeficiency. Various types of cancer such as breast adenocarcinomas,[40] ovarian epithelial carcinomas[41] and Wilms tumours[42] share with ICF syndrome cells the characteristic of hypomethylated satellite 2 DNA. It has been proposed that hypomethylation of this area affects chromatin structure leading to chromosomal instability as well as possibly altered gene expression.[43] It is unclear whether the malignancy seen in patients 24 and 37 was a chance association or linked to the ICF syndrome.

Only 20 of the 35 patients tested showed mutations in *DNMT3B*, suggesting genetic heterogeneity. No genotype–phenotype correlation was found. Thus patients with mutations in the *DNMT3B* gene have the same phenotype as patients without this mutation (table 2). In those with a demonstrable mutation, the phenotype differed widely. Two factors influenced our ability to demonstrate a genotype–phenotype correlation in this study: (1) the number of proven ICF patients was small; and (2) most patients were compound heterozygotes and most mutations occurred only once.[34] It is likely that a complex interaction of factors leads to the broad variation in phenotypic characteristics as seen in ICF syndrome.

In conclusion, ICF syndrome should be considered in all patients with agammaglobulinaemia with B cells or common variable immunodeficiency, where other features such as a history of delayed milestones raise the possibility of ICF. Early diagnosis is important since early treatment with IVIG can improve the natural history of the disease. AlloSCT should be considered as a therapeutic option in patients with severe infections or failure to thrive.

This review of the spectrum of ICF features should contribute to a better recognition of ICF patients. Close follow up and central registration of patients will allow the prevalence and the natural history of the syndrome to become clearer.

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Ethics approval: Ethical approval was obtained for the publication of the data in this study.

Parental/guardian informed consent was obtained for publication of fig 1.

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