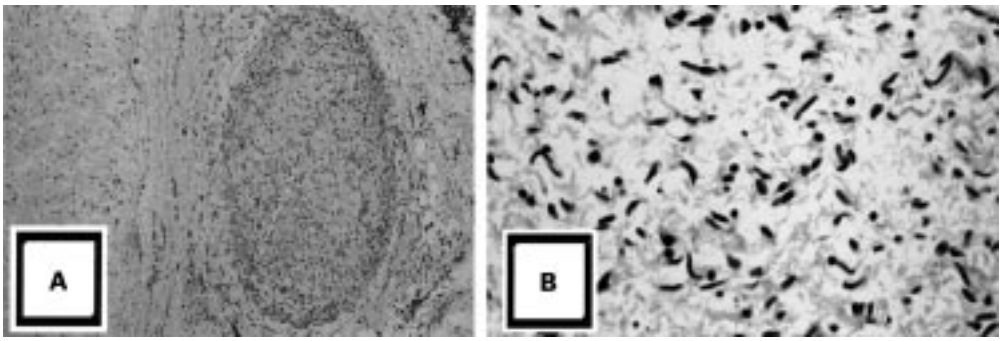

Figure 5 (A) Low power photomicrograph of plexiform neurofibroma from patient BNF3. The left half of the figure shows one ill defined nodule of neurofibroma, with a second, well defined fascicle in the right side of the figure. (B) High power photomicrograph of neurofibroma from patient BNF2. Note the wavy nuclei and myxoid background.

phenotype that at times was familial. Other patients may represent a mosaic form of NF1 with either localised manifestations or a generalised but attenuated form of the disease. Our current work is focused on identifying additional patients, clarifying the natural history of this phenotype, and studying patients' blood and tumour specimens in an effort to determine its molecular genetic aetiology.

We thank the patients and families for their participation in this work, and Dr Kevin Ruggles for his help with the evaluation of patient BNF4. This work was supported by National Institutes of Health grants R01 NS35878-02 (MM) and R01 NS24279 (DNL) and was presented in part at the 49th Annual Meeting of the American Society of Human Genetics, San Francisco, California, October 1999.

1 Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis. *Brain* 1988;**111**:1355-81.
2 Creange A, Zeller J, Rostaing-Rigattieri S, Brugieres P, Degos JD, Revuz J, Wolkenstein P. Neurological complications of neurofibromatosis type 1 in adulthood. *Brain* 1999;**122**(pt 3):473-81.
3 Goldgar DE, Green P, Parry DM, Mulvihill JJ. Multipoint linkage analysis in neurofibromatosis type I: an international collaboration. *Am J Hum Genet* 1989;**44**:6-1.
4 Halliday AL, Sobel RA, Martuza RL. Benign spinal nerve sheath tumors: their occurrence sporadically and in neurofibromatosis types 1 and 2. *J Neurosurg* 1991;**74**:248-53.
5 Mautner VF, Lindenau M, Baser M, Kluwe L, Gottschalk J. Skin abnormalities in neurofibromatosis 2. *Arch Dermatol* 1997;**133**:1539-43.
6 Kluwe L, Mautner V, Parry D, Jacoby L, Baser M, Gusella J, Davis K, Stavrou D, MacCollin M. The parental origin of new mutations in neurofibromatosis 2. *Neurogenetics* 2000; **3**:17-24.
7 Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann Intern Med* 1990;**113**: 39-52.
8 Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;**278**: 51-7.
9 Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. *Brain* 1988;**111**(pt 6):1355-81.
10 Tinschert S, Naumann I, Stegmann E, Buske A, Kaufmann D, Thiel G, Jenne DE. Segmental neurofibromatosis is caused by somatic mutation of the neurofibromatosis type 1 (*NF1*) gene. *Eur J Hum Genet* 2000;**8**:455-9.
11 Betti R, Cerri A, Gualandri L, Moneghini L, Crosti C. Regional eruptive neurofibromas. *J Dermatol* 1997;**24**:198-201.
12 Hager CM, Cohen PR, Tschen JA. Segmental neurofibromatosis: case reports and review. *J Am Acad Dermatol* 1997;**37**:864-9.
13 Pulst SM, Riccardi VM, Fain P, Korenberg JR. Familial spinal neurofibromatosis: clinical and DNA linkage analysis. *Neurology* 1991;**41**:1923-7.
14 Poyhonen M, Leisti EL, Kytola S, Leisti J. Hereditary spinal neurofibromatosis: a rare form of NF1? *J Med Genet* 1997; **34**:184-7.
15 Ars E, Kruyer H, Gaona A, Casquero P, Rosell J, Volpini V, Serra E, Lazaro C, Estivill X. A clinical variant of neurofibromatosis type 1: familial spinal neurofibromatosis with a frameshift mutation in the *NF1* gene. *Am J Hum Genet* 1998;**62**:834-41.
16 Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. *Neurordiology* 1999;**41**:625-9.
17 Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. *Am J Med Genet* 1999; **89**:23-30.
18 MacCollin M, Woodfin W, Kronn D, Short MP. Schwannomatosis: a clinical and pathologic study. *Neurology* 1996;**46**:1072-9.

B cell immunodeficiency, distal limb abnormalities, and urogenital malformations in a three generation family: a novel autosomal dominant syndrome?

Patrick Edery, Françoise Le Deist, Marie-Louise Briard, Marianne Debré, Arnold Munnich, Claude Griscelli, Alain Fischer, Stanislas Lyonnet

J Med Genet 2001;**38**:488–492

We report on a three generation family with four affected members presenting with a combination of B cell immunodeficiency, distal limbs abnormalities, genitourinary malformations, and mild dysmorphic features. All affected patients had normal intelligence and growth. No chromosomal abnormalities were observed using both standard and high resolution banding methods on the patients' lymphocytes. The observation of affected subjects of both sexes along with the occurrence of one male to male transmission suggests autosomal dominant inheritance of the trait with marked intrafamilial variable expression of the disease. While several multiple congenital anomalies (MCA) syndromes include both skeletal dysplasia and immune deficiency, the striking combination of congenital anomalies presented here, for which we propose the acronym BILU (B cell Immunodeficiency, Limb anomalies,

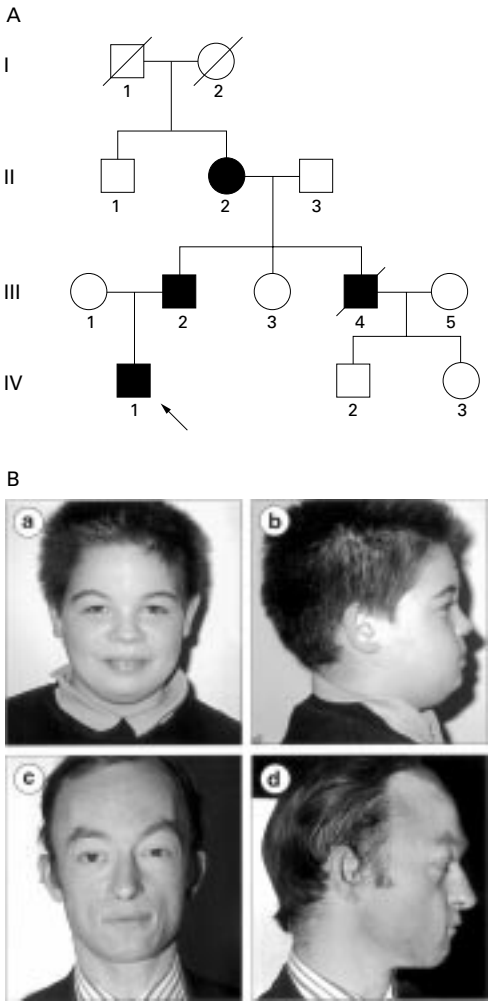

Figure 1 (A) Three generation pedigree including four affected members. The arrow indicates the proband. (B) (a, b) Face of the proband (IV.1). (c, d) Face of proband's father (III.2).

Service de Génétique Médicale, Hôpital Necker Enfants-Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France
P Edery
M-L Briard
A Munnich
S Lyonnet

Service de Génétique, Hospices Civils de Lyon, Hôpital Hôtel-Dieu, 1 place de l'Hôpital, 69288 Lyon Cedex 02, France
P Edery

Unité d'Immunologie et d'Hématologie, and INSERM U429 Hôpital Necker Enfants-Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France
F Le Deist
M Debré
C Griscelli
A Fischer

Correspondence to:
Dr Lyonnet,
lyonnet@necker.fr

and Urogenital malformations), is likely to represent a novel MCA syndrome.

Case reports

The proband (case 1, IV.1, fig 1) is an only child, born to unrelated parents. He was born at term by caesarian section with normal measurements (weight 3620 g, length 50 cm, and OFC 37 cm). Genital anomalies noted at birth included micropenis, scrotal hypospadias, and bilateral cryptorchidism, which required multiple surgical corrections. Despite testosterone substitution therapy, the size of the testes and penis only increased during puberty. Endocrine investigations including basal state testosterone, dihydrotestosterone, adrenal hormones, gonadotrophin plasma levels, gonadotrophin response to LHRH, and testosterone response to HCG were normal. Ultrasonography of the urinary system showed bilateral hydronephrosis.

Urography (IV) showed right hydronephrosis with atresia of the upper segment of the right ureter, right vesicoureteral reflux, and absence of secretion in the left kidney (fig 2). A left ureteronephrectomy was performed at 2½ months. Histological examination of the left urinary apparatus showed a dysplastic kidney

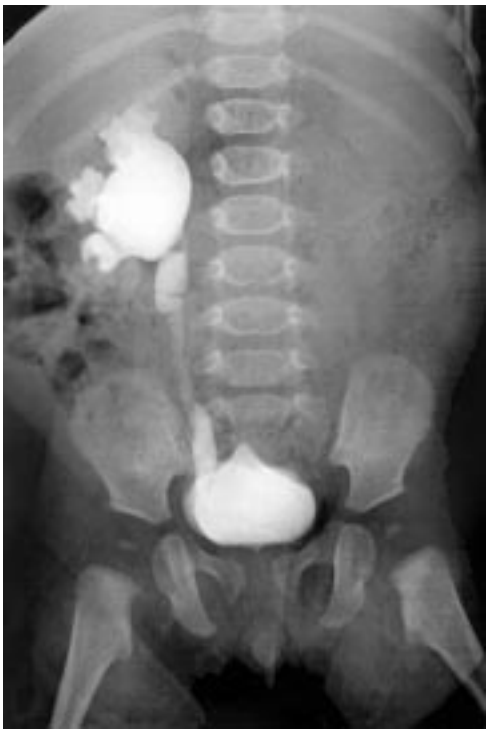

Figure 2 Urography of the proband (case 1). Note the absence of secretion of the left kidney and right hydronephrosis, ureteral stenosis, and vesicoureteral reflux.

with segmental cortical agenesis and localised ureteral atresia with a very thin underlying ureter. Atresia of the right ureter also required surgical correction.

As shown in fig 3, the proband also had bilateral distal limb abnormalities including short digits, thenar hypoplasia, bilateral palmar creases, brachymesophalangism of both fifth fingers, congenital flexion contractures of the interphalangeal joints of both thumbs and both big toes, skin syndactyly of toes 3-4, and clinodactyly of the fourth toes. *X* rays showed bilateral brachymesophalangism of toes 3-5 and short articular distances between phalanges P1 and P2 of the fourth toes. Mild dysmorphic features were noted including mild hypertelorism and fullness of the periorbital regions (fig 1).

A history of respiratory infections led us to investigate the haematological and immunological status of the proband. He had marked hypogammaglobulinaemia involving at least IgG and IgA (table 1). Anti-polio virus antibodies I, II, and III and anti-B allohaemagglutinins were undetectable in the plasma. No CD19 and no surface IgM could be detected in blood, indicating the absence of B cells. In contrast, other blood cell counts were repeatedly normal, as were T cell numbers when expressed as absolute values or ratios (CD3=85%, CD4=45%, CD8=35% (proband aged 13 months)) and T cell functions (PHA, candidin, and tetanus toxoid proliferation assays, mixed leucocyte reaction, natural killer (NK) activity, and cell mediated cytotoxicity). There has been no significant immunological change in the course of the proband's life. He still has marked hypogammaglobulinaemia involving IgG, IgA, IgM, and IgG 1-3

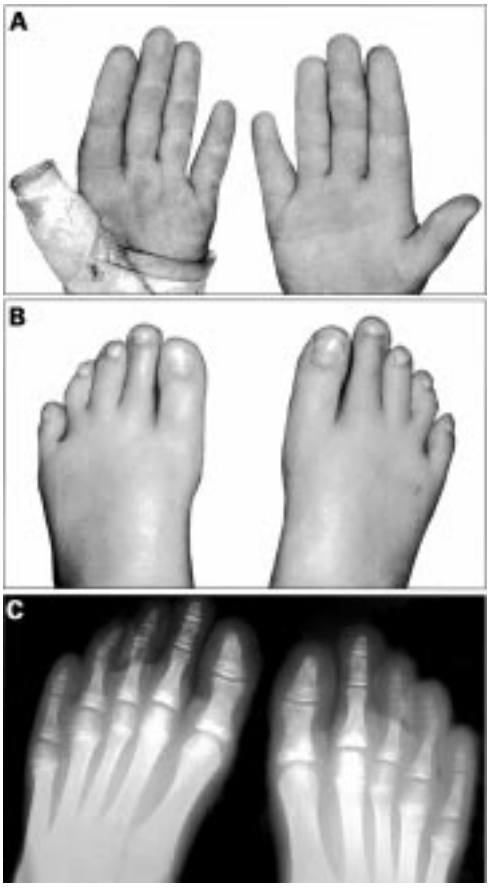

Figure 3 Proband (case 1). (A) Note short fingers, thenar hypoplasia, absence of flexion crease of the right thumb (left thumb not seen), and brachymesophalangism of the fifth fingers. (B) Note skin syndactyly of toes 3-4. (C) Brachymesophalangism of toes 3-5.

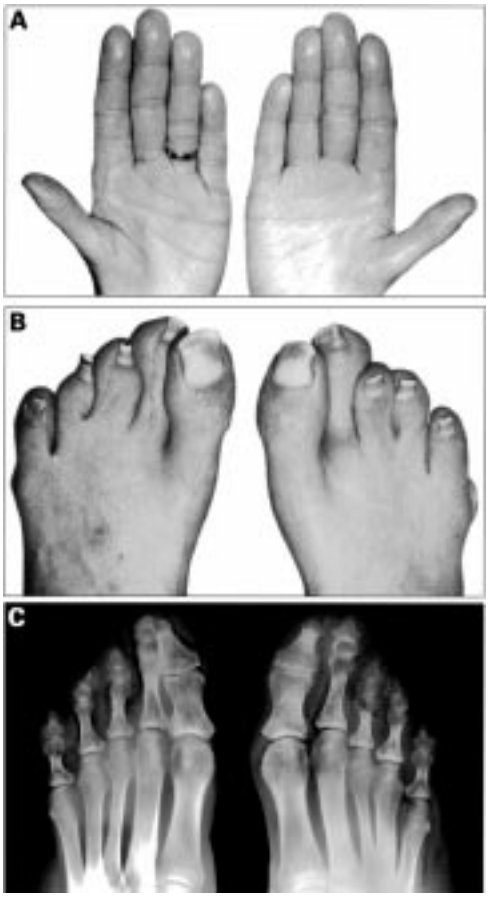

Figure 4 Father of the proband (case 2). (A) Hypoplasia of the thumbs and absence of flexion creases of the thumbs. (B) Overlapping first and second toes and skin syndactyly of toes 3-4. (C) Brachymesophalangism of toes 2-5 and absence of the third phalanx of the fifth toes.

subclasses (data not shown). Immunoglobulin perfusions were required every three weeks with a very good effect on respiratory infections. Unfortunately, we have not been able to perform a bone marrow biopsy as the proband has refused it so far, thus preventing the study of B lymphocyte precursors.

The proband had normal intelligence and growth until the age of 6 years when increased weight gain led to obesity (weight 113 kg, height 166 cm aged 15 years) and triggered or worsened psychological problems. Standard and high resolution banding karyotypes showed normal lymphocyte chromosomes.

Table 1 Results of significant haematological and immunological investigations in affected subjects

	Affected subjects				*Control ranges in adults*
	IV.1 (Proband aged 6 months)	*III.2 (father)*	*III.4 (uncle)*	*II.2 (grandmother)*	
Immunoglobulin values (mg/dl)					
IgG (total)	150 (control ranges: 280–680)	252	245	588	1410 ± 250
IgG1	ND	75	77	350	940 ± 190
IgG2	ND	15	13	287	320 ± 130
IgG3	ND	162	155	40	100 ± 45
IgG4	ND	0	0	11	62 ± 48
IgM	36 (control ranges: 40–84)	5.6	2.2	ND	53 ± 20
IgA	8 (control ranges: 10–58)	38	38	ND	194 ± 58
IgD	<2 (low)	2.2	1.8	ND	>3
CD19 (B cells) %	0	1 (low)	0	0	
Surface IgM (%)	0	<1	0	0	

ND: not determined.

The proband's father (case 2, III.2, fig 1) had recurrent episodes of respiratory infections, and had *Streptoccocus pneumoniae* meningitis at the age of 22, which led to investigation of his immune status (table 1). He had dissociated hypogammaglobulinaemia involving mainly IgG, IgA, and IgM with IgG1, IgG2, and IgG4 deficiency. Very few B cell lymphocytes could be detected using a CD19 specific antibody. He had normal T cell lymphocyte counts and functions. IV immunoglobulin substitution was initiated.

Fig 4 shows distal limb abnormalities including bilateral flexion contractures of the interphalangeal joints of the thumbs, hypoplasia of the thumbs, overlapping first and second toes, and skin syndactyly of toes 3-4. *X* rays showed brachymesophalangism of toes 2-5 with only two phalanges on the fifth toes and short metacarpophalangeal and interphalangeal articular distances of fingers (not shown). He had epispadias and his son (case 1) was born using artificial insemination.

Dysmorphic features consisted of mild hypertelorism (interpupillary distance of 6.5 cm), deep periorbital ridges, fullness of periorbital regions, mandibular hypoplasia, and a thin chin (fig 1). He had severe, non-progressive, bilateral, sensorineural deafness considered to be a consequence of his meningitis. Intelligence, height, and weight were

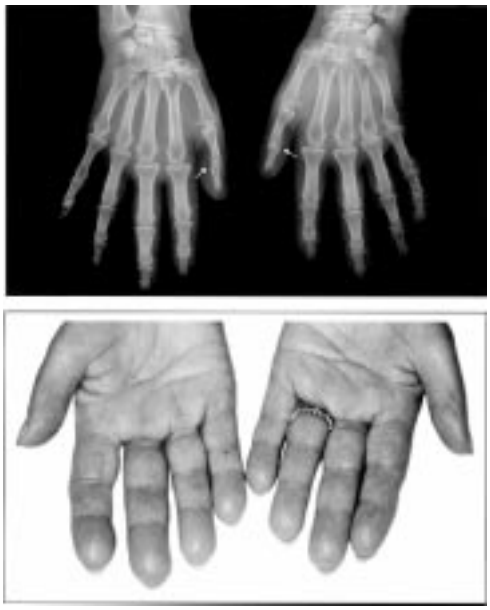

Figure 5 Paternal grandmother of the proband (case 4). (Top) Symphalangism of both thumbs is indicated by arrows. (Bottom) Absence of flexion crease of thumbs.

normal. Standard chromosome studies on blood lymphocytes showed no anomalies.

The proband's paternal uncle (case 3, III.4, fig 1) had a similar disease history to his brother (case 2) with recurrent respiratory infections and a *Streptoccocus pneumoniae* meningitis. He had dissociated hypogammaglobulinaemia with marked deficiency of IgG, IgA, and IgM and IgG1, IgG2, and IgG4 subclasses. No B cell lymphocytes could be detected (table 1). Bilateral symphalangism of the thumbs, epispadias which required surgical correction, and hypertelorism were noted. He had bilateral deafness considered to result from his meningitis, but which was not further investigated. He died from post-hepatitis cirrhosis. His blood karyotype performed using standard methods showed normal chromosomes.

The paternal grandmother of the proband (case 4, II.2, fig 1) had a humoral immune deficiency with slight IgG, IgG1, and IgG4 deficiencies but no detectable B cell lymphocytes (table 1) and normal T cell lymphocyte numbers and functions (lymphocyte proliferation after exposure to PHA). She had bilateral contractures of the interphalangeal joints of the thumbs and symphalangism of the thumbs as shown by *x* rays (fig 5), but no urogenital anomalies. Her parents were known to be healthy and her father was 38 years old at the time of her conception.

Discussion

Here, we report on a striking combination of congenital anomalies, including B cell immunodeficiency, distal limb malformations, urogenital anomalies, and mild dysmorphic features in four members of a single three generation family. We propose the acronym BILU (B cell Immunodeficiency, Limb anomalies, and Urogenital malformations) as a means to make this association of signs easier to remember. Two of the four affected subjects (cases 2 and 3) also had deafness and one was obese (the proband, case 1). However, deafness started after a *Streptococcus pneumoniae* meningitis in both cases and the type of deafness was sensorineural and non-progressive in case 2 (not studied in case 3), suggesting that this feature may not be part of the BILU syndrome. Also, obesity in case 1 was associated with a unfavourable psychosocial status and, in our opinion, should not be considered as a specific sign. The occurrence of one male to male transmission together with the intrafamilial variability in phenotypic expression of the disease suggests autosomal dominant inheritance of the trait. Alternatively, an infracytogenetic chromosomal rearrangement might be responsible for the disease phenotype. However, the latter hypothesis is unlikely since neither mental retardation nor growth delay was observed in the affected subjects. This combination of congenital anomalies including B cell immunodeficiency appears unique and thus may represent an as yet undescribed autosomal dominant MCA syndrome.

Several short limbed dwarfisms/skeletal dysplasias (SLSD) have been found to be associated with immunodeficiency.[1] Ammann *et al*[2] proposed a classification based on the immune defect. Type 1 includes early lethal SLSD with combined humoral (B cell) and cell mediated (T cell) immunodeficiency. Patients with type 1 SLSD appear to form a heterogeneous group.[3] Some have adenosine deaminase (ADA) deficiency.[3 4] Several reports have described type 1 SLSD cases associated with features of Ommen syndrome, namely eosinophilia, reticuloendotheliosis, alopecia, and ichthyosiform skin lesions.[3 5–7] Type 2, less common than type 1, includes SLSD and T cell immunodeficiency, an association reminiscent of the cartilage-hair hypoplasia syndrome (CHH, MIM 250250), a metaphyseal dysplasia with short stature, fine and sparse blond hair, chronic neutropenia, and abnormal cellular immunity.[8 9] This autosomal recessive condition has been mapped to chromosome 9p13.[10] Type 3 (two sibs reported by Ammann *et al*[2]) comprises SLSD with antibody mediated (B cell) immunodeficiency. It should be noted that skeletal phenotypes overlap considerably between these categories, apart from CHH which appears to be a genetically homogeneous condition. It is questionable whether this classification is relevant with regard to the underlying molecular pathology.

In the family presented here, the diagnosis of SLSD can easily be excluded since the patients do not have short stature. Moreover, urogenital anomalies are not commonly observed in SLSD. The pattern of congenital anomalies reported here shows some overlap with that of a 6 year old boy born to first cousin parents of Turkish origin described by Braegger *et al*.[11] This patient had panhypogammaglobulinaemia, hypospadias, bilateral cryptorchidism, and distal limb anomalies comprising short hands and digits, short middle phalanges of the fifth fingers, and mild skin syndactyly of the toes. However, we believe that we are dealing with a different condition since this boy also displayed

mental retardation, ischiadic hypoplasia, renal dysfunction without any obstructive uropathy, and marked facial dysmorphism. He had neither symphalangism nor limitation of flexion of the thumbs.

We will briefly describe other immunoosseous syndromes with short stature. Each of these conditions also appears to be different from the BILU syndrome. Schimke immunoosseous dysplasia (MIM 242900) includes short trunk skeletal dysplasia, glomerulonephritis with immune complex formation, and a defect of T cell maturation.[12 13] Ainsworth *et al*[14] reported a syndrome of selective IgG2 deficiency with severe growth retardation of prenatal onset, developmental delay, distal limb hypotrophy, dental anomalies, and eczematous skin.[14] The Say-Barber-Miller syndrome includes B cell deficiency, short stature, hypoplastic patellae, multiple joint anomalies, microcephaly, mental retardation, hypogonadism, and unusual facies.[15 16] Two female sibs with hypogammaglobulinaemia, multiple epiphyseal dysplasia, prenatal growth deficiency, microcephaly, mental retardation, cataracts, enamel hypoplasia, and downward slanting palpebral fissures were reported by Toriello *et al*.[17] Unique combinations of immunodeficiency and skeletal dysplasia, such as those reported by Lichtenstein *et al*,[18] Castriota-Scanderbeg *et al*,[19] and Kultursay *et al*,[20] should also be mentioned. Rare disorders such as Shokeir syndrome (MIM 274190) combine B cell deficiency and/or immunoglobulin abnormalities and a radial ray defect.[21 22] Brewer *et al*[23] reported a male infant with low immunoglobulin values and bilateral radial aplasia, but this child also had anomalies absent in our patients, namely severe prenatal and postnatal growth retardation and markedly increased spontaneous chromosome breaks in leucocytes. This latter case may be related to the group of autosomal recessive chromosome breakage disorders including Fanconi anaemia. Finally, associations of B cell deficiency with alopecia, but without osseous anomalies, have also been reported by Ipp *et al*.[24]

Careful examination of the skeletal and urogenital systems in patients with B cell immunodeficiency may hopefully lead to the identification of other cases similar to those observed in the family described here. The diagnostic importance of two rare signs observed in the family presented here, namely epispadias (cases 2 and 3) and symphalangism (cases 3 and 4), is worth noting. Each of these two signs may suggest the diagnosis of BILU syndrome when associated with B cell immunodeficiency. Finally, this observation raises the question of which gene(s) might be involved in three different developmental fields, such as the immune, skeletal, and urogenital systems.

We thank Mrs A Reumert-Kazès for her help with writing this manuscript.

1 Ming JE, Stiehm ER, Graham JM Jr. Immunodeficiency as a component of recognizable syndromes. *Am J Med Genet* 1996;**66**:378-98.
2 Ammann AJ, Sutliff W, Millinchick E. Antibody-mediated immunodeficiency in short-limbed dwarfism. *J Pediatr* 1974;**84**:200-3.
3 MacDermot KD, Winter RM, Wigglesworth JS, Strobel S. Short stature/short limb skeletal dysplasia with severe combined immunodeficiency and bowing of the femora: report of two patients and review. *J Med Genet* 1991;**28**:10-17.
4 Cederbaum SD, Kaitila I, Rimoin DL, Stiehm ER. The chondro-osseous dysplasia of adenosine deaminase deficiency with severe combined immunodeficiency. *J Pediatr* 1976;**89**:737-42.
5 Schofer O, Blaha I, Mannhardt W, Zepp F, Stallmach T, Spranger J. Ommen phenotype with short-limbed dwarfism. *J Pediatr* 1991;**118**:86-9.
6 Gatti RA, Platt N, Pomerance HH, Hong R, Langer LO, Kay HE, Good RA. Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of short-limbed dwarfism and ectodermal dysplasia. *J Pediatr* 1969;**75**:675-84.
7 Gotoff SP, Esterly NB, Gottbrath E, Liebner EJ, Lajvardi SR. Granulomatous reaction in an infant with combined immunodeficiency disease and short-limbed dwarfism. *J Pediatr* 1972;**80**:1010-7.
8 Lux SE, Johnston RB Jr, August CS, Say B, Penchaszadeh VB, Rosen FS, McKusick VA. Chronic neutropenia and abnormal cellular immunity in cartilage-hair hypoplasia. *N Engl J Med* 1970;**282**:231-6.
9 McKusick VA, Eldridge R, Hostetler JA, Egeland JA, Ruangwit U. Dwarfism in the Amish. II. Cartilage-hair hypoplasia. *Bull Johns Hopkins Hosp* 1965;**116**:285-326.
10 Sulisalo T, Klockars J, Makitie O, Francomano CA, de la Chapelle A, Kaitila I, Sistonen P. High-resolution linkage-disequilibrium mapping of the cartilage-hair hypoplasia gene. *Am J Hum Genet* 1994;**55**:937-45.
11 Braegger C, Bottani A, Hallé F, Giedion A, Leumann E, Seger R, Willi U, Schinzel A. Unknown syndrome: ischiadic hypoplasia, renal dysfunction, immunodeficiency, and a pattern of minor congenital anomalies. *J Med Genet* 1991;**28**:56-9.
12 Schimke RN, Horton WA, King CR, Martin NL. Chondroitin-6-sulfate mucopoly-saccharidosis in conjunction with lymphopenia, defective cellular immunity and the nephrotic syndrome. *Birth Defects* 1974;**10**:258-66.
13 Spranger J, Hinkel GK, Stoss H, Thoenes W, Wargowski D, Zepp F. Schimke immuno-osseous dysplasia: a newly recognized multisystem disease. *J Pediatr* 1991;**119**: 64-72.
14 Ainsworth SB, Baraitser M, Mueller RF, Massey RF. Selective IgG2 subclass deficiency - a marker for the syndrome of pre/postnatal growth retardation, developmental delay, hypotrophy of distal extremities, dental anomalies and eczema. *Clin Dysmorphol* 1997;**6**:139-6.
15 Say BA, Barber N, Miller GC, Grogg SE. Microcephaly, short stature, and developmental delay associated with a chemotactic defect and transient hypogammaglobulinaemia in two brothers. *J Med Genet* 1986;**23**:355-9.
16 Perandones C, Cerretini RI, Vargas Vera RM, Aranda EI, Alba LG, Pivetta OH. Microcephaly, characteristic facies, joint abnormalities, and deficient leucocyte chemotaxis: a further case of the syndrome of Say *et al*. *J Med Genet* 1996;**33**:227-9.
17 Toriello HV, Horton WA, Oostendorp A, Waterman DF, Higgins JV. An apparently new syndrome of microcephalic primordial dwarfism and cataracts. *Am J Med Genet* 1986; **25**:1-8.
18 Lichtenstein JR. A "new" syndrome with neutropenia, immune deficiency, and multiple congenital anomalies (spondylolysis, open posterior cervical arches, ulnar deviation of fingers, carp mouth). *Birth Defects* 1972;**8**:178-90.
19 Castriota-Scanderbeg A, Mingarelli R, Caramia G, Osimani P, Lachman RS, Rimoin DL, Wilcox WR, Dallapiccola B. Spondylo-mesomelic-acrodysplasia with joint dislocations and severe combined immunodeficiency: a newly recognised immuno-osseous dysplasia. *J Med Genet* 1997;**34**: 854-6.
20 Kultursay N, Taneli B, Cavusoglu A. Pseudoachondroplasia with immune deficiency. *Pediatr Radiol* 1988;**18**:505-8.
21 Shokeir MHK. Short stature, absent thumbs, flat facies, anosmia and combined immune deficiency (CID). *Birth Defects* 1978;**14**:103-16.
22 Semmekrot BA, Haraldsson A, Weemaes CMR, Smeets DFCM, Geven WB, Brunner HG. Absent thumb, immune disorder, and congenital anemia presenting with hydrops fetalis. *Am J Med Genet* 1992;**42**:736-40.
23 Brewer CM, Grace E, Stark, GD, Gregory DW, Howell RT, Fitzpatrick DR. Genomic instability associated with limb defects: case report and review of the literature. *Clin Dysmorphol* 1997;**6**:99-109.
24 Ipp MM, Gelfand EW. Antibody deficiency and alopecia. *J Pediatr* 1976;**89**:728-31.

Chromosome 2 interstitial deletion (del(2)(q14.1q21)) associated with connective tissue laxity and an attention deficit disorder

K L Baker, M I Rees, P W Thompson, R T Howell, T R Cole, H E Hughes, M Upadhyaya, D Ravine

J Med Genet 2001;**38**:493–496

Medical Genetics Service for Wales, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK
K L Baker
P W Thompson
H E Hughes
M Upadhyaya
D Ravine

Department of Psychological Medicine and Medical Genetics, University of Wales College of Medicine, Cardiff, UK
M I Rees

Department of Molecular Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand
M I Rees

Regional Cytogenetics Centre, Southmead Hospital, Bristol, UK
R T Howell

West Midlands Regional Clinical Genetics Service, Birmingham, UK
T R Cole

Correspondence to:
Dr Ravine
ravine@cardiff.ac.uk

EDITOR—Reports of interstitial deletions involving the long arm of chromosome 2 are uncommon.[1–10] Among these, there are only four which involve the region q14q21. We report a further case with a paternally derived de novo interstitial deletion of chromosome 2q14.1q21.

Case report

The proband was a male born by spontaneous vaginal delivery at term following an uneventful pregnancy. The parents are healthy, unrelated, and white. Birth weight was 4140 g (97th centile). Early childhood was complicated by hypotonia and recurrent sleep apnoea which resolved following adenoidectomy at 2 years of age. Otherwise, his medical history showed the normal range of intercurrent childhood viral illnesses. While childhood linear growth was rapid, during the second year there was considerable concern about poor weight gain. At 6 years of age he was noted to have a high, bossed forehead with a large head circumference (90-97th centile). A thoracolumbar kyphoscoliosis and a mild sternal depression was noted. He attended normal school although moderate learning difficulties were experienced. An attention deficit defect was identified and managed with the aid of methylphenidate hydrochloride. At 15 years of age, he was tall and thin (height 176 cm, 80th centile; weight 43.3 kg, 5th centile) with an associated moderate thoracolumbar kyphoscoliosis and pectus carinatum deformity. While the upper segment:lower segment ratio was 0.804, it was apparent that spinal height was somewhat reduced by the curvature of the scoliosis. The span measurement was 175 cm and head circumference was 56.0 cm (60th centile). He was a generally thinly muscled adolescent with little subcutaneous tissue. Some mild proximal upper limb weakness was detected and winging of the scapulae was evident, particularly on the right side. Examination of the musculature around the scapulae showed that the trapezius muscles were absent or possibly extremely hypoplastic. Ophthalmic examination showed normal fundi with no evidence of corneal or anterior chamber abnormalities, lens opacities, or dislocation. Other than findings of brisk lower limb reflexes, no other neuromuscular signs were present. No striae were evident. The forehead was high and the mandible was prominent owing to obtuse angulation. The ears were low set and dysplastic with some overfolding of the pinnae. The palate was high arched. Puberty had started, with stage 4 pubic hair development and a testicular volume of 25 ml. Cardiac echocardiography showed a mild degree of aortic root dilatation (aortic diameter 2.9 cm, calculated body surface area of 1.5 m^2) but otherwise normal cardiac anatomy. Cytogenetic studies showed a small proximal interstitial deletion on the long arm of chromosome 2 (46,XY,del(2)(q14.1-21)). Before this result, no syndromic diagnosis was immediately apparent, although the occurrence of a high birth weight, a markedly prominent forehead in early childhood (fig 1A, B), and later development of mandibular prominence, hypotonia, and disproportionately long limbs had raised the question of Sotos syndrome.[11] No bone age assessments were performed earlier in childhood and it was concluded that there were insufficient features present to confirm this diagnosis. Later photographs taken in mid childhood (fig 1C-F) were not supportive of the diagnosis.

In view of the phenotype observed in this child and the rarity of interstitial deletions within this region of chromosome 2, it was decided to delineate the breakpoints of the deletion further by both fluorescence in situ hybridisation and microsatellite analysis. FISH analysis with three YACS identified a region of deletion defined by YAC694-d-4. The deleted YAC contains marker D2S110 which provided an anchor point for the microsatellite work. Microsatellite markers (Genethon map) were selected and loss of heterozygosity analysis further defined the deletion within a genetic distance of approximately 10-12 cM and involves markers ranging from 2q14.1 to 2q21.1 (fig 2). The loss of alleles was paternal for all markers and the patient displayed only the maternal alleles for the deleted region.

Discussion

Common clinical features among the few reports of proximal interstitial deletions of chromosome 2 involving the region q14.1q21 include developmental delay, microcephaly, defects of the corpus callosum, prominence of the forehead, low set and malformed ears, cardiac anomalies, and a tendency to recurrent, severe infections (table 1). Our case has some