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Clinical and Genetic Distinction of Schimke Immuno-Osseous Dysplasia and Cartilage-Hair Hypoplasia

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To the Editor

Previously we had proposed that cartilage-hair hypoplasia (CHH) and Schimke immuno-osseous dysplasia (SIOD) could be caused by defects in the same biological pathway. This was based on the shared features of skeletal dysplasia, defective T cell proliferation, and impaired lymphocytic production of and responsiveness to interleukin-2 [Boerkoel et al., 2000]. We now show that these two disorders are molecularly as well as phenotypically distinct.

SIOD has been associated with biallelic mutations in the swi/snf-related matrix-associated actin-dependent regulator of chromatin, subfamily-a-like-1 gene (SMARCA1) [Boerkoel et al., 2002], and CHH has been associated with biallelic mutations of RNase mitochondrial RNA processing gene (RMRP) [Ridanpää et al., 2001]. RMRP mutations have also been identified in metaphyseal dysplasia without hypotrichosis, anauxetic dysplasia, and some cases of kyphomelic dysplasia and Omenn syndrome [Bonafe et al., 2005; Thiel et al., 2005; Roifman et al., 2006; Martin and Li, 2007]. Due to the variation in severity of the clinical and radiographic phenotypes of the allelic mutations in RMRP, these conditions could be called CHH-anauxetic dysplasia or CHH-spectrum [Thiel et al., 2007].

SIOD is an autosomal recessive multisystem disorder. The features of SIOD include spondyloepiphyseal dysplasia, defective cellular immunity with opportunistic infections, progressive nephropathy leading to renal failure, hyperpigmented macules, thin hair and dysmorphic facial features [Schimke et al., 1971; Ehrich et al., 1988; Spranger et al., 1991; Boerkoel et al., 2000; Stormon et al., 2002]. Less frequently associated features include hypothyroidism, migraine-like headaches, atherosclerosis and cerebral ischemia and enteropathy [Kaitila et al., 1998; Boerkoel et al., 2000; Kilic et al., 2005].

CHH is also an autosomal recessive multisystem disorder. Its features include disproportionate short-limbed short stature, metaphyseal chondrodysplasia, hypoplastic hair, defective cellular and humoral immunity, macrocytic anemia, neuronal dysplasia of intestine (expressed as malabsorption or Hirsch-sprung disease), limited elbow extension, ligamentous laxity, and

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predisposition to cancer [McKusick et al., 1965; Makitie et al., 1992b, 2000b, 2002; Makitie and Kaitila, 1993; Hermanns et al., 2006].

To test whether mutations of RMRP genocopy mutations of SMARCAL1, we assembled a cohort of 29 patients who fulfilled the diagnostic criteria of SIOD but did not have detectable SMARCAL1 mutations [Clewning et al., 2007b]. These patients were very similar to those in which we had identified SMARCAL1 mutations, although they had a lower prevalence of hyperpigmented macules, cerebral ischemia and migraine-like headaches and a higher prevalence of developmental and academic delay (Table I).

Patients referred to this study gave informed consent approved by the Institutional Review Board of Baylor College of Medicine or the University of British Columbia (H-9669 or C06-0283). The clinical data for patients were obtained from questionnaires completed by the referring physician as well as from medical records and summaries provided by that physician.

Using genomic DNA extracted from peripheral blood, we sequenced the whole known promoter and transcript region of the RMRP gene as previously described [Thiel et al., 2005]. By this analysis, we did not detect RMRP mutations in this cohort of SIOD patients. Therefore, in agreement with the phenotypic differences, RMRP mutations are not a frequent cause of SIOD.

The RMRP gene encodes the untranslated RNA subunit of the ribonucleoprotein endoribonuclease, RNase MRP, which is involved in ribosome assembly and cell-cycle regulation. Analysis of mutations identified in human patients has showed altered ribosomal processing with associated changes in cytokine signaling and cell cycle progression. RMRP defects affect cellular proliferation by dysregulation of the cell cycle. Inhibition cellular proliferation in some cell types appears to arise from RMRP defects impeding cell cycle progression via decreased degradation of some mRNAs and increased gene expression. Also, RMRP defects upregulate cytokine expression and cell-cycle regulatory genes in leukocytes; this may underlie the immunodeficiency and increased risk of malignancies, particularly lymphomas, in CHH patients [Ridanpää et al., 2001; Hermanns et al., 2005; Martin and Li, 2007; Thiel et al., 2007].

The SMARCAL1 gene encodes a member of the SNF2 family of chromatin remodeling proteins. Although its *in vivo* function has not been defined, *in vitro* SMARCAL1 has homology to snf2 enzymes, recognizes DNA structure, binds nucleosomes and has DNA-dependent ATPase activity [Muthuswami et al., 2000; Coleman et al., 2003; Flaus et al., 2006]. Most of the disease features of SIOD arise from cell-autonomous loss of functional SMARCAL1 enzyme [Elizondo et al., 2006]. From clinical studies, it does not appear that SMARCAL1 is involved in DNA repair [Boerkoel et al., 2000]; however, it has been suggested that this multisystem disease is the result of a defect in selective cellular proliferation because its phenotype is consistent with short stature from impaired chondrogenesis, T-cell deficiency from impaired proliferation, azoospermia from impaired spermatogenesis, and occasionally bone marrow failure from impaired blood precursor proliferation [Clewning et al., 2007a]. Supporting this hypothesis, the T lymphocytes from SIOD patients proliferate poorly in response to cytokine or mitogenic stimuli [Boerkoel et al., 2000]. Although, the mechanism by which SMARCAL1 regulates cellular proliferation remains undefined, its role in cellular proliferation may resemble that of other SWI/SNF members such as Brm and Brg, which are necessary for neural stem cell renewal and differentiation [Lessard et al., 2007].

Although the overlap of some features among SIOD and CHH patients might lead to misdiagnosis upon initial evaluation, the following features help distinguish SIOD and the classical CHH, the portion of the RMRP disease spectrum for which much clinical, biochemical, and radiographic data are available. First, a disproportionately short spine

suggests SIOD, whereas disproportionately short, rhizomelic limbs and short fingers with joint laxity suggest CHH [Makitie and Kaitila, 1993; Lücke et al., 2006]. Second, hyperpigmented macules are commonly observed in SIOD but not CHH [Boerkoel et al., 2000; Clewing et al., 2007b]. Third, evidence of renal disease, such as hypertension and proteinuria, are early common features of SIOD but not of CHH [Boerkoel et al., 2000; Clewing et al., 2007b]. Fourth, atherosclerosis and cerebral vascular accidents presenting as migraine-like headaches, cerebral ischemia, or cognitive deficiency are common in SIOD but not in CHH. Fifth, in vitro assessment of the mitogenic response of patient B cells is deficient in CHH but normal in the vast majority of SIOD patients [Pierce and Polmar, 1982; Makitie et al., 1998, 2000b; Boerkoel et al., 2000]. Sixth, anemia in CHH is usually transient and macrocytic, not microcytic, whereas it is usually persistent and normocytic or microcytic in SIOD [Makitie et al., 2000a; Boerkoel et al., unpublished work]. Seventh, spine and hip radiographs of SIOD patients nearly always show ovoid and flat vertebrae and hypoplastic femoral heads and acetabular roofs but are usually normal in CHH patients [Makitie et al., 1992a; Glass and Tiffet, 1999; Boerkoel et al., 2000] although the vertebral and epiphyseal abnormalities can be observed in anauxetic dysplasia [Horn et al., 2001; Thiel et al., 2005, 2007].

The major radiological manifestations in CHH are generalized metaphyseal dysplasia presenting as characteristic abnormalities of the metaphyses in childhood, shortening and thickening of the tubular bones prominently affecting the distal femur, proximal tibia, metacarpals, metatarsals, and phalanges. Also, the distal fibulae are disproportionately long and the phalangeal epiphyses are commonly cone-shaped [Makitie et al., 1992a; Giedion, 1998; Hermanns et al., 2006; Lachman, 2006].

All of the SIOD patients tested for RMRP mutations met the diagnostic criteria for SIOD. Therefore, the absence of RMRP mutations in this cohort of SIOD patients suggests that the diagnostic criteria for SIOD effectively distinguish between SIOD and CHH and that RMRP mutations do not cause SIOD.

In summary, SIOD and CHH are multisystem disorders that share some phenotypic features and affect cytokine signaling and cellular proliferation. However, careful clinical, biochemical and radiological evaluation of these patients distinguishes between these two conditions, and (with the possible exception of anauxetic dysplasia) suggests the appropriate molecular testing for confirmation of the diagnosis. Moreover, mutations of RMRP, the gene mutated in CHH, are not a cause of SIOD.

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REFERENCES

- Boerkoel CF, O'Neill S, Andre JL, Benke PJ, Bogdanovic R, Bulla M, Burguet A, Cockfield S, Cordeiro I, Ehrlich JH, Frund S, Geary DF, Ieshima A, Illies F, Joseph MW, Kaitila I, Lama G, Leheup B, Ludman MD, McLeod DR, Medeira A, Milford DV, Ormala T, Renner-Primec Z, Santava A, Santos HG, Schmidt B, Smith GC, Spranger J, Zupancic N, Weksberg R. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. *Eur J Pediatr* 2000;159:1–7. [PubMed: 10653321]

- Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, Andre JL, Bogdanovic R, Burguet A, Cockfield S, Cordeiro I, Frund S, Illies F, Joseph M, Kaitila I, Lama G, Loirat C, McLeod DR, Milford DV, Petty EM, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Spranger J, Stein A, Thiele H, Tizard J, Weksberg R, Lupski JR, Stockton DW. Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. *Nat Genet* 2002;30:215–220. [PubMed: 11799392]
- Bonafe L, Dermitzakis ET, Unger S, Greenberg CR, Campos-Xavier BA, Zankl A, Ucla C, Antonarakis SE, Superti-Furga A, Reymond A. Evolutionary comparison provides evidence for pathogenicity of RMRP mutations. *PLoS Genet* 2005;1:e47. [PubMed: 16244706]
- Clewing JM, Antalfy BC, Lücke T, Najafian B, Marwedel KM, Hori A, Powel RM, Safo Do AF, Najera L, SantaCruz K, Hicks MJ, Armstrong DL, Boerkoel CF. Schimke immunoosseous dysplasia: A clinicopathological correlation. *J Med Genet* 2007a;44:122–130. [PubMed: 16840568]
- Clewing JM, Fryssira H, Goodman D, Smithson SF, Sloan EA, Lou S, Huang Y, Choi K, Lucke T, Alpay H, Andre JL, Asakura Y, Biebuyck-Gouge N, Bogdanovic R, Bonneau D, Cancrini C, Cochat P, Cockfield S, Collard L, Cordeiro I, Cormier-Daire V, Cransberg K, Cutka K, Deschenes G, Ehrlich JH, Frund S, Georgaki H, Guillen-Navarro E, Hinkelmann B, Kanariou M, Kasap B, Kilic SS, Lama G, Lamfers P, Loirat C, Majore S, Milford D, Morin D, Ozdemir N, Pontz BF, Proesmans W, Psoni S, Reichenbach H, Reif S, Rusu C, Saraiva JM, Sakallioglu O, Schmidt B, Shoemaker L, Sigaudy S, Smith G, Sotsiou F, Stajic N, Stein A, Stray-Pedersen A, Taha D, Taque S, Tizard J, Tsimaratos M, Wong NA, Boerkoel CF. Schimke immunoosseous dysplasia: Suggestions of genetic diversity. *Hum Mutat* 2007b;28:273–283. [PubMed: 17089404]
- Coleman MA, Miller KA, Beernink PT, Yoshikawa DM, Albala JS. Identification of chromatin-related protein interactions using protein microarrays. *Proteomics* 2003;3:2101–2107. [PubMed: 14595808]
- Ehrlich JHH, Offner G, Schirg E, Helmchen U, Brodehl J. Minderwuchssyndrom mit Skelettdysplasien und focal segmental sklerosierender Glomerulonephritis. *Monatsschr Kinderheilkd* 1988;136:6.
- Elizondo LI, Huang C, Northrop JL, Deguchi K, Clewing JM, Armstrong DL, Boerkoel CF. Schimke immuno-osseous dysplasia: A cell autonomous disorder? *Am J Med Genet Part A* 2006;140A:340–348.
- Flaus A, Martin DM, Barton GJ, Owen-Hughes T. Identification of multiple distinct Snf2 subfamilies with conserved structural motifs. *Nucleic Acids Res* 2006;34:2887–2905. [PubMed: 16738128]
- Giedion A. Phalangeal cone-shaped epiphyses of the hand: Their natural history, diagnostic sensitivity, and specificity in cartilage-hair hypoplasia and the trichorhinophalangeal syndromes I and II. *Pediatr Radiol* 1998;28:751–758. [PubMed: 9799296]
- Glass RB, Tift CJ. Radiologic changes in infancy in McKusick cartilage-hair hypoplasia. *Am J Med Genet* 1999;86:312–315. [PubMed: 10494084]
- Hermanns P, Bertuch AA, Bertin TK, Dawson B, Schmitt ME, Shaw C, Zabel B, Lee B. Consequences of mutations in the non-coding RMRP RNA in cartilage-hair hypoplasia. *Hum Mol Genet* 2005;14:3723–3740. [PubMed: 16254002]
- Hermanns P, Tran A, Munivez E, Carter S, Zabel B, Lee B, Leroy JG. RMRP mutations in cartilage-hair hypoplasia. *Am J Med Genet Part A* 2006;140A:2121–2130.
- Horn D, Rupprecht E, Kunze J, Spranger J. Anauxetic dysplasia, a spondylometaphyseal dysplasia with extreme dwarfism. *J Med Genet* 2001;38:262–265. [PubMed: 11370632]
- Kaitila I, Savilahti E, Ormala T. Autoimmune enteropathy in Schimke immunoosseous dysplasia. *Am J Med Genet* 1998;77:427–430. [PubMed: 9632175]
- Kilic SS, Donmez O, Sloan EA, Elizondo LI, Huang C, Andre JL, Bogdanovic R, Cockfield S, Cordeiro I, Deschenes G, Frund S, Kaitila I, Lama G, Lamfers P, Lucke T, Milford DV, Najera L, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Stajic N, Stein A, Taha D, Wand D, Armstrong D, Boerkoel CF. Association of migraine-like headaches with Schimke immuno-osseous dysplasia. *Am J Med Genet Part A* 2005;135A:206–210.
- Lachman, RS. Taybi and Lachman's radiology of syndromes, Metabolic disorders and skeletal dysplasias. Mosby; Philadelphia: 2006.
- Lessard J, Wu JI, Ranish JA, Wan M, Winslow MM, Staahl BT, Wu H, Aebersold R, Graef IA, Crabtree GR. An essential switch in subunit composition of a chromatin remodeling complex during neural development. *Neuron* 2007;55:201–215. [PubMed: 17640523]

- Lücke T, Franke D, Clewing JM, Boerkoel CF, Ehrich JH, Das AM, Zivicnjak M. Schimke versus non-Schimke chronic kidney disease: An anthropometric approach. *Pediatrics* 2006;118:e400–e407. [PubMed: 16816006]
- Makitie O, Kaitila I. Cartilage-hair hypoplasia—Clinical manifestations in 108 Finnish patients. *Eur J Pediatr* 1993;152:211–217. [PubMed: 8444246]
- Makitie O, Marttinen E, Kaitila I. Skeletal growth in cartilage-hair hypoplasia. A radiological study of 82 patients. *Pediatr Radiol* 1992a;22:434–439. [PubMed: 1437368]
- Makitie O, Rajantie J, Kaitila I. Anaemia and macro-cytosis—Unrecognized features in cartilage-hair hypoplasia. *Acta Paediatr* 1992b;81:1026–1029. [PubMed: 1290847]
- Makitie O, Kaitila I, Savilahti E. Susceptibility to infections and in vitro immune functions in cartilage-hair hypoplasia. *Eur J Pediatr* 1998;157:816–820. [PubMed: 9809821]
- Makitie O, Juvonen E, Dunkel L, Kaitila I, Siimes MA. Anemia in children with cartilage-hair hypoplasia is related to body growth and to the insulin-like growth factor system. *J Clin Endocrinol Metab* 2000a;85:563–568. [PubMed: 10690856]
- Makitie O, Kaitila I, Savilahti E. Deficiency of humoral immunity in cartilage-hair hypoplasia. *J Pediatr* 2000b;137:487–492. [PubMed: 11035826]
- Makitie OM, Tapanainen PJ, Dunkel L, Siimes MA. Impaired spermatogenesis: An unrecognized feature of cartilage-hair hypoplasia. *Ann Med* 2001;33:201–205. [PubMed: 11370774]
- Makitie O, Heikkinen M, Kaitila I, Rintala R. Hirschsprung's disease in cartilage-hair hypoplasia has poor prognosis. *J Pediatr Surg* 2002;37:1585–1588. [PubMed: 12407544]
- Martin AN, Li Y. RNase MRP RNA and human genetic diseases. *Cell Res* 2007;17:219–226. [PubMed: 17189938]
- McKusick VA, Eldridge R, Hostetler JA, Ruangwit U, Egeland JA. Dwarfism in the Amish. II. Cartilage-Hair Hypoplasia. *Bull Johns Hopkins Hosp* 1965;116:285–326. [PubMed: 14284412]
- Muthuswami R, Truman PA, Mesner LD, Hockensmith JW. A eukaryotic SWI2/SNF2 domain, an exquisite detector of double-stranded to single-stranded DNA transition elements. *J Biol Chem* 2000;275:7648–7655. [PubMed: 10713074]
- Pierce GF, Polmar SH. Lymphocyte dysfunction in cartilage-hair hypoplasia: Evidence for an intrinsic defect in cellular proliferation. *J Immunol* 1982;129:570–575. [PubMed: 6806374]
- Ridanpää M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, van Venrooij W, Pruijn G, Salmela R, Rockas S, Makitie O, Kaitila I, de la Chapelle A. Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. *Cell* 2001;104:195–203. [PubMed: 11207361]
- Roifman CM, Gu Y, Cohen A. Mutations in the RNA component of RNase mitochondrial RNA processing might cause Omenn syndrome. *J Allergy Clin Immunol* 2006;117:897–903. [PubMed: 16630949]
- Schimke RN, Horton WA, King CR. Chondroitin-6-sulphaturia, defective cellular immunity, and nephrotic syndrome. *Lancet* 1971;2:1088–1089. [PubMed: 4106927]
- 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. [PubMed: 2066860]
- Spranger JW, Brill PW, Poznanski A. Bone dysplasias: An atlas of genetic disorders of skeletal development. Oxford University Press; Oxford: 2002.
- Stormon M, Friedman J, King S, Cutz E, Furuya KN. An unusual case of diarrhea in schimke immuno-osseous dysplasia. *J Pediatr Gastroenterol Nutr* 2002;35:369–371. [PubMed: 12352531]
- Thiel CT, Horn D, Zabel B, Ekici AB, Salinas K, Gebhart E, Ruschendorf F, Sticht H, Spranger J, Müller D, Zweier C, Schmitt ME, Reis A, Rauch A. Severely incapacitating mutations in patients with extreme short stature identify RNA-processing endoribonuclease RMRP as an essential cell growth regulator. *Am J Hum Genet* 2005;77:795–806. [PubMed: 16252239]
- Thiel CT, Mortier G, Kaitila I, Reis A, Rauch A. Type and level of RMRP functional impairment predicts phenotype in the cartilage-hair hypoplasia-anaxetic dysplasia spectrum. *Am J Hum Genet* 2007;81:519–529. [PubMed: 17701897]

TABLE I

Features of SIOD Patients Compared to Those of CHH Patients*

Features	SIOD patients with SMARCAL1 mutation	SIOD patients without SMARCAL1 mutation	CHH patients
Dysmorphism			
Hair hypoplasia	(21/41) 55%	(20/30) 67%	(81/87) 93%
Broad low nasal bridge	(33/49) 67%	(20/31) 65%	NO
Bulbous nasal tip	(38/48) 79%	(21/31) 68%	NO
Hyperpigmented macules	(39/51) 76%	(14/31) 45%	NO
Protuberant abdomen	(42/49) 86%	(25/32) 78%	NO
Skeleton and growth			
Disproportionate short stature	(13/14) 93%	(9/12) 75%	(104/108) 96%
Decreased sitting height	(8/8) 100% ^c	(2/2) 100% ^c	(0/108) 0%
Scoliosis	(2/53) 4%	(1/37) 3%	(18/86) 21%
Lumbar lordosis	(40/48) 83%	(19/29) 66%	(72/85) 85%
Limited elbow extension	NO	NO	(79/86) 92%
Ligamentous laxity	NO	NO	(81/85) 95%
Skeletal radiographic findings			
Spondyloepiphyseal dysplasia	(39/46) 85%	(18/29) 62%	NO
Metaphyseal dysplasia	(2/53) 4%	NR	(82/82) 100%
Coned phalangeal epiphyses	(0/53) 0%	(0/37) 0%	(42/47) 89%
Development			
Delayed development	(9/45) 20%	(14/29) 48%	NO
Academic delay	(4/23) 17%	(8/15) 53%	NO
Endocrine			
Serologic hypothyroidism	(17/34) 50%	(13/29) 45%	NO
Hematology and immunology			
Lymphopenia	(40/47) 85%	(14/25) 56%	(51/79) 65% ^a
T-cell count	Reduced	Reduced	Reduced
Reduced CD4 ⁺ T cells	(18/18) 100%	(5/6) 83%	(17/30) 57%
Reduced CD8 ⁺ T cells	(13/16) 81%	(4/6) 67%	(8/30) 27%
Reduced CD4 ⁺ /CD8 ⁺	(6/16) 38%	(5/10) 50%	(10/31) 32%
B-cell count	Normal	Normal	Usually normal
Response to T-cell mitogens	Reduced	Reduced	Reduced
Response to B-cell mitogens	Normal	Reduced	Reduced
Recurrent infections	(24/51) 47%	(22/33) 67%	(58/103) 56%
Neutropenia	(19/41) 46%	(10/29) 34%	(21/79) 27% ^a
Anemia ^a	(25/42) 60%	(17/31) 55%	(67/85) 79%
Thrombocytopenia	(14/46) 30%	(8/30) 27%	NR
Nephrology			
Hypertension	(42/47) 89%	(25/32) 78%	NR
Nephrotic syndrome	(47/51) 92%	(27/32) 84%	NO
Progressive renal failure	(36/46) 78%	(19/31) 61%	NO
Dialysis or graft	(30/49) 61%	(14/32) 44%	NO
Neurology			
TIA's	(22/45) 49%	(6/30) 20%	NO
Strokes	(19/43) 44%	(6/27) 22%	NO
Migraine-like headaches	(21/40) 53%	(5/16) 31%	NO
Gastrointestinal			
Autoimmune enteropathy	(1/53) 2%	NR	NR
Malabsorption	(1/53) 2%	NR	(2/21) 9.5%
Hirschsprung disease	(0/53) 0%	(0/37) 0%	(13/147) 8.8%
Other features			
Impaired spermatogenesis	(2/2) 100%	NR	(11/11) 100%
Malignancies ^b	(2/53) 4%	(0/37) 0%	(9/123) 7.3%
Basal cell carcinoma	NO	NO	(10/123) 8.1%

NR, not reported; NO, not observed.

* This table was compiled from Pierce and Polmar [1982], Makitie et al. [1992a,b, 1998, 2001, 2002], Makitie and Kaitila [1993], Giedion [1998], Glass and Tift [1999], Boerkoel et al. [2000], Spranger et al. [2002], Hermanns et al. [2006], Lachman [2006], Lücke et al. [2006] and Clewing et al. [2007a,b] and unpublished data [Kaitila, unpublished work; Boerkoel et al., unpublished work]. The figures for CHH are derived from studies constituted from Amish and Finnish patients with classical type of the CHH spectrum.

^a Anemia in SIOD normocytic or microcytic, in CHH macrocytic and hypoplastic; childhood values.

^b EBV-positive and negative non-Hodgkin lymphoma.

^c Measured in patients with disproportionate short stature.