

Saethre–Chotzen Phenotype With Learning Disability and Hyper IgE Phenotype in a Patient Due to Complex Chromosomal Rearrangement Involving Chromosomes 3 and 7

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The authors describe on a Brazilian girl with coronal synostosis, facial asymmetry, ptosis, brachydactyly, significant learning difficulties, recurrent scalp infections with marked hair loss, and elevated serum immunoglobulin E. Standard lymphocyte karyotype showed a small additional segment in 7p21[46,XX,add(7)(p21)]. Deletion of the *TWIST1* gene, detected by Multiplex Ligation Probe-dependent Amplification (MPLA) and array-CGH, was consistent with phenotype of Saethre–Chotzen syndrome. Array CGH also showed deletion of four other genes at 7p21.1 (*SNX13*, *PRPS1L1*, *HD9C9*, and *FERD3L*) and the deletion of six genes (*CACNA2D2*, *C3orf18*, *HEMK1*, *CISH*, *MAPKAPK3*, and *DOCK3*) at 3p21.31. Our case reinforces *FERD3L* as candidate gene for intellectual disability and suggested that genes located in 3p21.3 can be related to hyper IgE phenotype. © 2012 Wiley Periodicals, Inc.

Key words: *TWIST1* gene microdeletion; Saethre–Chotzen syndrome; hyper-IgE syndrome; array-CGH; *CISH* gene; *FERD3L* gene; *DOCK3* gene

INTRODUCTION

Saethre–Chotzen syndrome or acrocephalosyndactyly type III [OMIM 101400] is an autosomal dominant inheritance condition characterized by craniosynostosis, mainly of the coronal sutures, facial asymmetry, brachydactyly, partial soft tissue syndactyly, and other skeletal anomalies. There is a remarkable inter- and intra-familial phenotypic variability and mild cases can be misdiagnosed [Dollfus et al., 2002; Passos-Bueno et al., 2008]. It is caused by different heterozygous mutation in the *TWIST1* gene (7p21) that results in haploinsufficiency [revised by Passos-Bueno et al., 2008]. In some instances, the phenotype is caused by microdeletion or deletion in chromosomal region 7p21 comprising the whole *TWIST1* gene. Additional signs such as intellectual disability, learning difficulties, short stature, microcephaly, vertebral anomalies, respiratory, and circulatory tract pathology, and allergies had

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also been observed in these individuals with large *TWIST1* gene deletions [Johnson et al., 1998; Chun et al., 2002; Cai et al., 2003; de Heer et al., 2005; Schluth-Bolard et al., 2008; Busche et al., 2011]. Hyper IgE syndrome [OMIM 147060 and 243700] is a rare primary immunodeficiency disorder, characterized by chronic eczema, recurrent staphylococcal skin and lung infections, and increased serum IgE. Non-immunological findings include coarse facial appearance with minor facial dysmorphism, skeletal involvement, and dental anomalies [Johnson et al., 1998; Domingo et al., 2008; Freeman and Holland, 2008]. Two types of Hyper IgE syndrome had been described: an autosomal dominant form (Job syndrome) [OMIM 147060], caused by heterozygous mutations in the *STAT3* gene (17q21), and an autosomal recessive form [OMIM 243700], caused by mutations in *TYK2* gene (19p13.2) and *DOCK8* gene

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(9p24.3) [Minegishi et al., 2007; Freeman and Holland, 2008; Minegishi, 2009; Schimke et al., 2010; Zhang et al., 2010].

Here we present on a Brazilian girl with 7p21 and 3p21.31 microdeletions, identified by array comparative genomic hybridization (CGH), who had Saethre–Chotzen phenotype, significant learning difficulties and hyper IgE syndrome. Clinical and molecular aspects were discussed.

CLINICAL REPORT

The patient (Fig. 1A–L), a girl born in 1997, is the only child of an unrelated 21-year-old mother and 20-year-old father. The mother was referred as having brachydactyly of fingers and toes, clinodactyly of the second and five fingers, and broad halluces. Clinodactyly of the second and five fingers were also referred in the maternal great-grandfather. The pregnancy was uncomplicated and delivery occurred at term. The birth weight was 3.350 g (50th centile) and length was 46 cm (3rd centile). Plagiocephaly and eyelids ptosis were noted at birth. After 3 years of age, she started to present recurrent scalp infections, which resulted in transient alopecia. Other chronic infections such as pneumonias, dermatitis, or abscesses were not observed. Motor development was normal.

Clinical examination at age 5 years (Fig. 1D–F) showed weight of 14.3 kg, height of 90 cm, and OFC of 45 cm (all below 3rd centile). She had microbrachycephaly, coronal synostosis, partial alopecia, low set ears with prominent crura and hypoplastic lobule, asymmetric face, hypoplastic supraorbital ridge at right, prominent eyes, eyelids ptosis at left, hypoplastic midface, anteverted nares, open mouth, brachydactyly of fingers, ulnar clinodactyly of fingers two, radial clinodactyly of fingers five, and toes brachydactyly. The halluces were broad and there were mild toes 2–3 and 4–5 syndactyly (Fig. 2A–C). Complementary investigations showed elevated serum IgE (355 IU/ml); normal brain CT scan and renal ultrasound. In the follow-up, at age 7 and 10 years, she presented behavior disturbance and marked learning disabilities. At this time, she had suffered various episodes of hair loss.

CYTOGENETIC AND MOLECULAR ANALYSIS

Cytogenetic analysis of peripheral blood lymphocytes from the patient, performed using standard techniques and processed by G-banding chromosomes (550 bands), detected additional small segment in 7p21 [46,XX,add(7)(p21)]. FISH was not performed. To determine if *TWIST1* gene was deleted in the patient, Multiplex Ligation Probe-dependent Amplification (MLPA) was performed with the commercially available kit SALSA P080 Craniofacial Disorders (www.mlpa.com—MRCHolland, Amsterdam). DNA denaturation and hybridization, probe ligation and PCR reactions were carried out according to the manufacturer's instructions. Electrophoresis and analysis were performed using the MegaBACE™ 1,000 DNA analysis system and Fragment Profiler software (GE Healthcare, Life Sciences, Cleveland, Ohio). Statistical analysis of the results was carried out upon the transfer of Fragment Profiler results to an excel spreadsheet (National Genetics Reference Laboratory Manchester, NGRL). Results of normalized relative peak heights of gene-specific and control probes show that probes of *TWIST1* gene have relative peak heights of approximately 0.5 when

compared to normal pool results, indicating that the patient is hemizygous for this region. Array-comparative genomic hybridization (aCGH) GeneChip® Human Mapping 500K Array Set platform (Affymetrix®, Santa Clara, CA) was performed according to the manufacturer's recommendation. After DNA labeling, hybridization, washing and staining steps, the slide was scanned in GeneChip® Scanner 3000 7G (Affymetrix®). Raw data were generated using the GeneChip Command Console Software (Affymetrix®) and, after normalization, DNA copy number changes were assessed with the Genotyping Console™ Software (Affymetrix®), using default parameters. We detected on aCGH a deletion of band 7p21.1 between the SNP_A-2268171 to SNP_A-4272203 with a maximum size of 1,969 kb, spanning from positions 17518427 to 19486999 bp and encompassing five Reviewed RefSeq genes, including the *TWIST1* gene [UCSC Genome Browser on Human March 2006 (NCBI36/hg18)]. We also detected on aCGH a deletion of band 3p21.31 between the probes SNP_A-1871167 and SNP_A-2044672 with a maximum size of 356K, spanning from positions 50382348 to 50738038 bp and encompassing six Reviewed RefSeq genes. The parents were not available to clinical, cytogenetics, and molecular evaluation.

DISCUSSION

The girl here described presents facial appearance, coronal synostosis, facial asymmetry, ptosis, and extremities abnormalities, which are typical features of Saethre–Chotzen syndrome. In addition this patient also presents recurrent alopecia and increased serum IgE that fit in the diagnosis of hyper IgE syndrome. Non-immunological findings of hyper IgE syndrome/Job syndrome were not found. Overlapping of some clinical features between Saethre–Chotzen syndrome and hyper IgE syndrome had been observed in some instances. Craniosynostosis, typical sign of Saethre–Chotzen syndrome had been reported in a few cases with autosomal dominant hyper IgE syndrome [Hoeger et al., 1985; Freeman and Holland, 2008], while recurrent infections and eczema, common in the hyper IgE syndrome, was observed in some cases with Saethre–Chotzen syndrome [Etzioni et al., 1990; de Heer et al., 2005]. The occurrence of these distinct conditions in the same patient was observed only once in a boy reported by Boeck et al. [2001]. Molecular analysis of the *TWIST1* gene, in this case, with an intragenic deletion of 11 bp on position 127 (c.127del11), confirmed the diagnosis of Saethre–Chotzen. This mutation was also detected in the patient's mother, who had mild facial phenotype of Saethre–Chotzen syndrome, without any immunodeficiency. The authors commented that, probably, the 11bp deletion causes the Saethre–Chotzen phenotype and another unknown genetic defect would be responsible for the hyper IgE phenotype.

In our case, the conventional cytogenetic showed an unknown additional chromosome segment in 7p21.1 region and, the MLPA showed a reduction about 50% of the *TWIST1* gene, when compared to normal control, indicating that the Saethre–Chotzen phenotype, in this patient, is caused by deletion of *TWIST1* gene in one of the alleles. This deletion was confirmed by aCGH that showed an interstitial 7p21.1 deletion, spanning about 1.9 Mb and encompassing *TWIST1* gene and four neighbor genes. However, as observed in previously published cases with Saethre–Chotzen

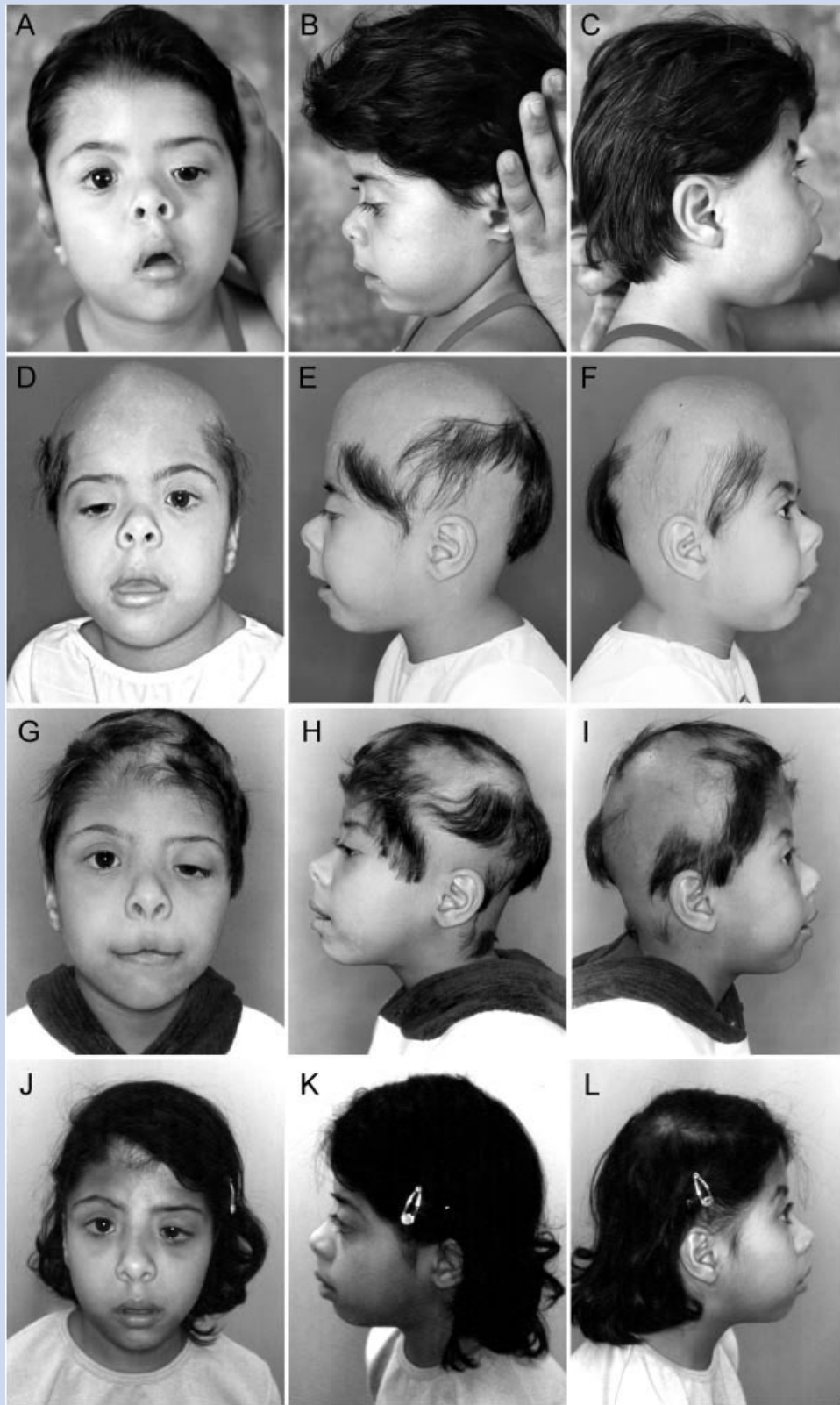


FIG. 1. A–L: Clinical aspects of the patient at age 2 years (A–C); 5 years (D–F); 6 years (G–I); and 7 years and 10 months (J–L).

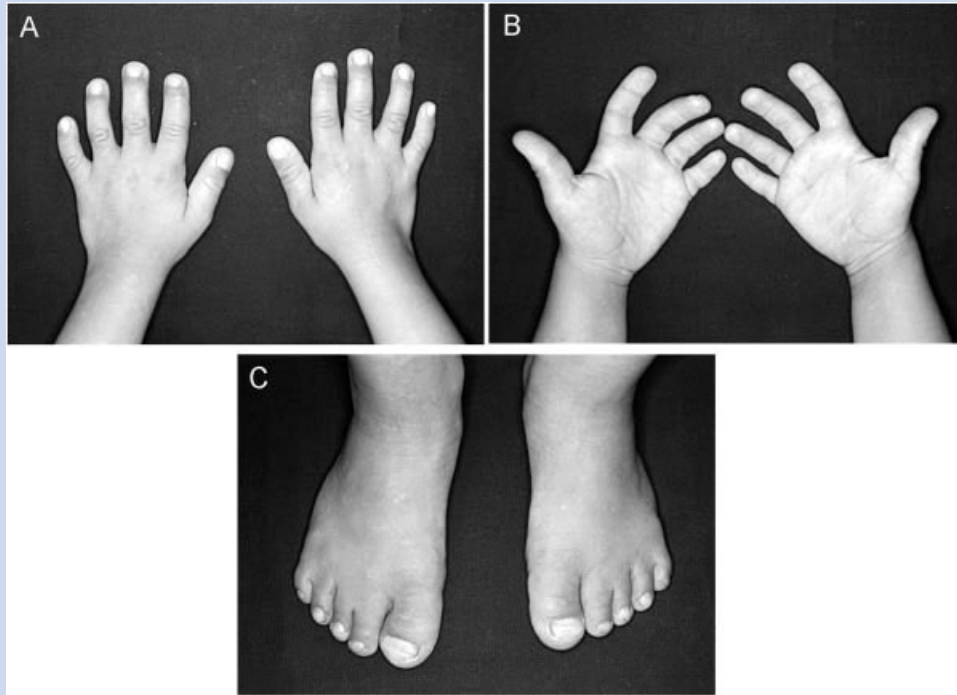


FIG. 2. A–C: Hands and feet of the patient.

phenotype caused by deletions in chromosome 7p21.1, our patient had also significantly learning disabilities [Johnson et al., 1998; Kosan and Kunz, 2002; Cai et al., 2003; Schluth-Bolard et al., 2008; Busche et al., 2011]. Some authors had suggested that 7p21.3 microdeletion results in a contiguous gene syndrome with *TWIST1* gene being responsible for craniosynostosis and another gene(s) accounting for intellectual disability [Johnson et al., 1998; Schluth-Bolard et al., 2008; Busche et al., 2011]. The deletion observed in our patient was relatively small, encompassing four other genes. One of them, the *FERD3L* gene (RefSeq NM_152898), had been considered a potential candidate gene to intellectual disability in cases with microdeletion of 7p21.3 [Johnson et al., 1998; Schluth-Bolard et al., 2008; Busche et al., 2011]. This gene, also called *N-TWIST*, coding a basic helix-loop-helix transcription factor that binds the E-box, functioning as an inhibitor of transcription, being expressed in the developing central nervous system of mouse, chick and drosophila [Segev et al., 2001; Verzi et al., 2002; Mansour et al., 2011]. The influence of *FERD3L* in human nervous central system is yet unknown but the presence of marked microcephaly in patients with *FERD3L* deletion has been suggested that it is associated to brain growth and development [Busche et al., 2011]. Our patient reinforces the hypothesis that *FERD3L* gene is a potential candidate for intellectual disability. Besides the *FERD3L* gene, other deleted gene in 7p21.1 region, in our case, was the *HDAC9* gene (RefSeq NM_014707) that encodes a protein of the histone deacetylase family. Histone deacetylases (HDACs) catalyze the removal of the acetyl group from the lysine residues in the N-terminal tails of nucleosomal core histones, resulting in a more compact chromatin structure, a configuration that is generally associated with repression of transcription. The *HDAC9*

gene has several alternative splice isoforms and the transcripts are expressed at high level in brain and skeletal muscle [Petrie et al., 2003]. It regulates a wide variety of normal and abnormal physiological functions, including cardiac growth, T-regulatory cell function, neuronal disorders, muscle differentiation, development, and cancer [Méjat et al., 2005; Yuan et al., 2010; Yan et al., 2011]. Like in our case, deletion of *HDAC9* gene was observed in other patients with Saethre–Chotzen phenotype and mental retardation caused by 7p21 microdeletion [Johnson et al., 1998; Busche et al., 2011]. Therefore, it is possible that the *HDAC9* gene may also contribute to the occurrence of intellectual disability.

In addition, the present case shows a 354 kb microdeletion in 3p21.31. Unfortunately, the DNA sample of the parents was not available to clarify if this is a de novo deletion, and we were also not able to perform a FISH test to clarify a possible complex rearrange involving the chromosomes 3 and 7. This microdeletion encompass the *CACNA2D2*, *C3orf18*, *HEMK1*, *CISH*, and *MAPKAPK3* genes and the upstream untranslated region, exon 1, and part of the intron1–2 of the *DOCK3* gene. According to Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER, from DECIPHER consortium, <http://decipher.sanger.ac.uk/>) deletions encompassing 3p21.31 result in abnormal phenotypes, characterized mainly by intellectual disability/developmental delay. Copy number variations, in normal control, were not observed in three (*HEMK1*, *CISH*, and *MAPKAPK3*) of these six genes (Database of Genomic Variants: <http://projects.tcag.ca>). Thus, in our patient, this deletion could be influencing the phenotype. One of these genes, *CISH* gene (NM_013324), is a member of suppressor of cytokine signaling

family proteins that controls interleukin-2 signaling [Khor et al., 2010]. The increase of *CISH* activity, in turn, leads to blocks the cytoplasmic docking and activation of signal transducer and activator of transcription 5 (SAT5), inhibiting downstream cytokine signaling. Variants of *CISH* gene were associated with susceptibility to diseases caused by diverse infectious pathogens [Khor et al., 2010]. Our patient had recurrent infection of the scalp leading to alopecia areata and, collapse of immune privilege in follicle hair has been considered as cause of alopecia areata [Gilhar, 2010; Petukhova et al., 2010]. The later authors showed some genomic regions that contribute to disease susceptibility, including one locus on chromosome 4p27, that contain the interleukin (*IL*)-2/*IL*-21 genes. Considering that *CISH* gene is a suppressor of cytokine, it is possible that deletion of the one *CISH* allele, in our patient, has deregulated cytokine signaling and influenced the immunological phenotype. Other interesting gene closed in 3p21.31 deleted region is the *DOCK3* gene (RefSeq NM_004947), a member of the dedicator of cytokine protein (DOCK) family of guanine nucleotide exchange factors (GEFs), specifically expressed in the central nervous system. In our patient, the deletion encompassed the upstream regulation region, probably leading to haploinsufficiency of *DOCK3* gene. Disruption of *DOCK3* gene was observed in a family co-segregating an early-onset behavior/developmental condition with a pericentric inversion of chromosome 3 (p14;q21) [de Silva et al., 2003]. These authors considered the possibility of the *DOCK3* gene to be involved in pathway of this neuropsychological condition. Other interesting fact is that a member of the DOCK family, the *DOCK8* gene, causes an autosomal recessive form of hyper IgE recurrent infection syndrome (OMIM 243700) [Zhang et al., 2010; Su, 2010]. If the haploinsufficiency of the *DOCK3* gene could have influenced the behavior and immunological phenotype in our patient remains to be clarified.

In summary, our patient display clinical findings that fit into both diagnoses: Saethre–Chotzen syndrome and hyper IgE syndrome. The deletion of the *TWIST1* gene is responsible for the Saethre–Chotzen phenotype and the deletion of the *FERD3L* gene reinforces it as a candidate for intellectual disability. Besides it is possible that the 3p21 deletion is causative of immunological findings in our patient, however, it is not possible to exclude this deletion as a fortuity finding, since the parents' DNA samples were not available for study. Further studies are necessary to clarify if *CISH* and *DOCK3* genes are related to hyper IgE syndrome.

REFERENCES

- Boeck A, Kosan C, Ciznar P, Kunz J. 2001. Saethre–Chotzen syndrome and hyper IgE syndrome in a patient with a novel 11bp deletion of the *TWIST* gene. *Am J Med Genet* 104:53–56.
- Busche A, Graul-Neumann LM, Zweier C, Rauch A, Klopocki E, Horn D. 2011. Microdeletions of chromosome 7p21, including *TWIST1*, associated with significant microcephaly, facial dysmorphism, and short stature. *Eur J Med Genet* 54:256–261.
- Cai J, Goodman BK, Patel AS, Mulliken JB, Van Maldergem L, Hoganson GE, Paznekas WA, Ben-Neriah Z, Sheffer R, Cunningham ML, Daentl DL, Jabs EW. 2003. Increased risk for developmental delay in Saethre–Chotzen syndrome is associated with *TWIST* deletions: An improved strategy for *TWIST* mutation screening. *Hum Genet* 114:68–76.
- Chun K, Teebi AS, Jung JH, Kennedy S, Laframboise R, Meschino WS, Nakabayashi K, Scherer SW, Ray PN, Teshima I. 2002. Genetic analysis of patients with the Saethre–Chotzen phenotype. *Am J Med Genet* 110:136–143.
- de Heer IM, de Klein A, van den Ouweland AM, Vermeij-Keers C, Wouters CH, Vaandrager JM, Hovius SE, Hoogeboom JM. 2005. Clinical and genetic analysis of patients with Saethre–Chotzen syndrome. *Plast Reconstr Surg* 115:1894–1902.
- de Silva MG, Elliott K, Dahl HH, Fitzpatrick E, Wilcox S, Delatycki M, Williamson R, Efron D, Lynch M, Forrest S. 2003. Disruption of a novel member of a sodium/hydrogen exchanger family and *DOCK3* is associated with an attention deficit hyperactivity disorder-like phenotype. *J Med Genet* 40:733–740.
- Dollfus H, Biswas P, Kumaramanickavel G, Stoetzel C, Quillet R, Biswas J, Lajeunie E, Renier D, Perrin-Schmitt F. 2002. Saethre–Chotzen syndrome: Notable intrafamilial phenotypic variability in a large family with Q28X *TWIST* mutation. *Am J Med Genet* 109:218–225.
- Domingo DL, Freeman AF, Davis J, Puck JM, Tianxia W, Holland SM, Hart TC. 2008. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. *Oral Dis* 14:73–81.
- Etzioni A, Obdeanu N, Benderly A, Gershoni-Baruch R. 1990. Saethre–Chotzen syndrome associated with defective neutrophil chemotaxis. *Acta Paediatr Scand* 79:375–379.
- Freeman AF, Holland SM. 2008. The hyper-IgE syndromes. *Immunol Allergy Clin North Am* 28:277–291.
- Gilhar A. 2010. Collapse of immune privilege in alopecia areata: Coincidental or substantial? *J Invest Dermatol* 130:2535–2537.
- Hoeger PH, Boltshauser E, Hitzig WH. 1985. Craniosynostosis in hyper IgE syndrome. *Eur J Pediatr* 144:414–417.
- Johnson D, Horsley SW, Moloney DM, Oldridge M, Twigg SR, Walsh S, Barrow M, Njolstad PR, Kunz J, Ashworth GJ, Wall SA, Kearney L, Wilkie AO. 1998. A comprehensive screen for *TWIST* mutations in patients with craniosynostosis identifies a new microdeletion syndrome of chromosome band 7p21.1. *Am J Hum Genet* 63:1282–1293.
- Khor CC, Vannberg FO, Chapman SJ, Guo H, Wong SH, Walley AJ, Vukcevic D, Rautanen A, Mills TC, Chang KC, Kam KM, Crampin AC, Ngwira B, Leung CC, Tam CM, Chan CY, Sung JJ, Yew WW, Toh KY, Tay SK, Kwiatkowski D, Lienhardt C, Hien TT, Day NP, Peshu N, Marsh K, Maitland K, Scott JA, Williams TN, Berkley JA, Floyd S, Tang NL, Fine PE, Goh DL, Hill AV. 2010. *CISH* and susceptibility to infectious diseases. *N Engl J Med* 362:2092–2101.
- Kosan C, Kunz J. 2002. Identification and characterization of the gene *TWIST NEIGHBOR (TWISTNB)* located in the microdeletion syndrome 7p21 region. *Cytogenet Genome Res* 97:167–170.
- Méjat A, Ramond F, Bassel-Duby R, Khochbin S, Olson EN, Schaeffer L. 2005. Histone deacetylase 9 couples neuronal activity to muscle chromatin acetylation and gene expression. *Nat Neurosci* 8:313–321.
- Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, Karasuyama H. 2007. Dominant-negative mutations in the DNA-binding domain of *STAT3* cause hyper-IgE syndrome. *Nature* 448:1058–1062.
- Minegishi Y. 2009. Hyper-IgE syndrome. *Curr Opin Immunol* 21:487–492.
- Mansour AA, Nissim-Eliraz E, Zisman S, Golan-Lev T, Schatz O, Klar A, Ben-Arie N. 2011. *Foxa2* regulates the expression of *Nato3* in the floor plate by a novel evolutionarily conserved promoter. *Mol Cell Neurosci* 46:187–199.
- Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM Number: {OMIM 101400}; {2/11/2008}; World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>

- Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University Baltimore, MD. MIM Number: {OMIM 147060}: {1/7/2010}: World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>
- Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University Baltimore, MD. MIM Number: {OMIM 243700}: {11/30/2009}: World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>
- Passos-Bueno MR, Serti Eacute AE, Jehee FS, Fanganiello R, Yeh E. 2008. Genetics of craniosynostosis: Genes, syndromes, mutations and genotype-phenotype correlations. *Front Oral Biol* 112:107–143.
- Petrie K, Guidez F, Howell L, Healy L, Waxman S, Greaves M, Zelent A. 2003. The histone deacetylase 9 gene encodes multiple protein isoforms. *J Biol Chem* 278:16059–16072.
- Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P, Lee A, Chen WV, Meyer KC, Paus R, Jahoda CA, Amos CI, Gregersen PK, Christiano AM. 2010. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* 466:113–117.
- Segev E, Halachmi N, Salzberg A, Ben-Arie N. 2001. Noto3 is an evolutionarily conserved bHLH transcription factor expressed in the CNS of *Drosophila* and mouse. *Mech Dev* 106:197–202.
- Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, Rieber N, Cremer R, Maass E, Dopfer R, Reichenbach J, Wahn V, Hoenig M, Jansson AF, Roesen-Wolff A, Schaub B, Seger R, Hill HR, Ochs HD, Torgerson TR, Belohradsky BH, Renner ED. 2010. Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol* 126:611–617.
- Schluth-Bolard C, Till M, Labalme A, Rey C, Banquart E, Fautrelle A, Martin-Denavit T, Le Lorc'h M, Romana SP, Lazar V, Edery P, Sanlaville D. 2008. TWIST microdeletion identified by array CGH in a patient presenting Saethre–Chotzen phenotype and a complex rearrangement involving chromosomes 2 and 7. *Eur J Med Genet* 51:156–164.
- Su HC. 2010. Dedicator of cytokinesis 8 (DOCK8) deficiency. *Curr Opin Allergy Clin Immunol* 10:515–520.
- Verzi MP, Anderson JP, Dodou E, Kelly KK, Greene SB, North BJ, Cripps RM, Black BL. 2002. N-twist, an evolutionarily conserved bHLH protein expressed in the developing CNS, functions as a transcriptional inhibitor. *Dev Biol* 249:174–190.
- Yan K, Cao Q, Reilly CM, Young NL, Garcia BA, Mishra N. 2011. Histone deacetylase 9 deficiency protects against effector T cell-mediated systemic autoimmunity. *J Biol Chem* 286:28833–28843.
- Yuan Z, Peng L, Radhakrishnan R, Seto E. 2010. Histone deacetylase 9 (HDAC9) regulates the functions of the ATDC (TRIM29) protein. *J Biol Chem* 285:39329–39338.
- Zhang Q, Davis JC, Dove CG, Su HC. 2010. Genetic, clinical, and laboratory markers for DOCK8 immunodeficiency syndrome. *Dis Markers* 29: 131–139.