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Paternal Uniparental Isodisomy of Chromosome 6 Causing a Complex Syndrome Including Complete IFN- γ Receptor 1 Deficiency

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Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare primary immunodeficiency associated with clinical disease caused by weakly virulent mycobacterial species. Interferon gamma receptor 1 (IFN- γ R1) deficiency is a genetic etiology of MSMD. We describe the clinical and genetic features of a seven-year-old Italian boy suffering from MSMD associated with a complex phenotype, including neonatal hyperglycemia, neuromuscular disease, and dysmorphic features. The child also developed necrotizing pneumonia caused by *Rhodococcus equi*. The child is homozygous for a nonsense mutation in exon 3 of *IFNGR1* as a result of paternal uniparental disomy (UPD) of the entire chromosome 6. This is the first reported case of uniparental disomy resulting in a complex phenotype including MSMD.

Keywords

Mycobacterium; uniparental disomy; IFN- γ

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Introduction

Mendelian susceptibility to mycobacterial disease (MSMD, OMIM# 209950) is a rare primary immunodeficiency (PID) associated with clinical disease caused by weakly virulent mycobacterial species, such as bacille Calmette-Guerin (BCG) vaccines and environmental mycobacteria (EM) [Filipe-Santos et al., 2006; Casanova et al., 1996]. Patients are also susceptible to *Mycobacterium tuberculosis* [Alcais et al., 2005; Jouanguy et al., 1997; Picard et al., 2002]. With the exception of salmonellosis, which affects about half of affected individuals, other infectious diseases are rarely reported in these patients, although the range of infections identified is increasing [Chapgier et al., 2006; Filipe-Santos et al., 2006; MacLennan et al., 2004]. Up to five autosomal genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12RB1*, and *IL12B*) and one X-linked (*NEMO*) MSMD-causing gene have been reported [Filipe-Santos et al., 2006; Vogt et al., 2008]. The first genetic etiology of MSMD was described in 1996, with null recessive mutations in *IFNGR1*, which encodes the IFN- γ receptor 1 (IFN- γ R1) ligand-binding chain [Jouanguy et al., 1996; Newport et al., 1996]. The human *IFNGR1* gene is located on chromosome 6q23.3. Two forms of complete IFN- γ R1 deficiency have been described, both with and without surface expression of the receptor [Dorman et al., 2004]. Complete IFN- γ R1 deficiency remains the most severe etiology of MSMD, as it is associated with early-onset MSMD and a poor prognosis [Dorman et al., 2004]. Hematopoietic stem cell transplantation may be curative; however, it is associated with a high rate of graft rejection, probably due to the high levels of circulating IFN- γ [Chantraine et al., 2006; Horwitz et al., 2003; Moilanen et al., 2009; Reuter et al., 2002; Roesler et al., 2004; Rottman et al., 2008]. Up to 90 complete IFN- γ receptor 1 deficient patients have been reported worldwide; most are homozygous, but some are compound heterozygous for null *IFNGR1* alleles [Dorman et al., 2004; Filipe-Santos et al., 2006; Glosli et al., 2008; Lee et al., 2009; Muszlak et al., 2007; Noordzij et al., 2007; Okada et al., 2007; Storgaard et al., 2006]. We investigated an Italian boy with MSMD associated with neuromuscular disease, neonatal hyperglycemia and dysmorphic features, who was homozygous for an *IFNGR1* mutant allele inherited from his father but not found in his mother.

Clinical Report

The patient was born in 2002 to nonconsanguineous Italian parents. The birth was induced at 37 weeks and one day due to a decrease in fetal movements, oligohydramnios and intrauterine growth retardation (IUGR). Neonatal examination showed major axial hypotonia, ligamentous laxity, campodactyly, club foot, small hands and feet, hypoplasia of the nails of the hands, and cryptorchidism, retrognathia, macroglossia and high palate. At birth, the child presented with respiratory distress, resulting in a need for nasal oxygen therapy for two months. Hyperglycemia was detected and the patient received insulin during the first 48 hours of life to control glycemia. At the age of two years, the patient presented with high fever daily over a period of three months, accompanied by hepatomegaly and cervical and inguinal lymphadenopathy. Computerized tomography scans showed pulmonary hilum and intra-abdominal lymph node enlargement. Cervical lymph node biopsy showed granulomatous lymphadenopathy with abscesses suggestive of EM disease, and a positive culture was obtained for *Mycobacterium fortuitum*. Treatment with antimycobacterial agents (including clarithromycin, rifampin, ethambutol, ciprofloxacin and rifabutin) was initiated and maintained for 15 months.

There was no family history of muscular dystrophy or mycobacterial disease and the patient was not vaccinated with BCG. It was hypothesized that the patient had MSMD in the context of a complex developmental syndrome. The patient remained asymptomatic until the age of five years, when he presented with necrotizing pneumonia. Bronchoalveolar lavage

(BAL) samples tested negative for *Mycobacterium* spp. Gram-positive coccobacilli were found in the BAL sample and a history of recent exposure to soil containing horse feces was reported. *Rhodococcus equi* was therefore assumed to be the etiologic agent and antibiotic treatment was initiated, leading to successful recovery.

The patient was fed through a nasogastric tube until the age of five years due to problems with oral feeding. The muscular hypotonia gradually improved and the patient was able to stand unaided and walk with the assistance of a walking frame from the age of four years. At last patient's follow up cognitive development and language skills were appropriate for age six years.

The Patient's karyotype as studied by G-banded method was normal. A muscle biopsy at the age of one month suggested primary muscle disease (generalized moderate atrophy of type 2 fibers). An electromyogram showed morphological changes to motor units typical of highgrade myogenic disease. Creatine kinase levels were high at the age of one month (243 U/l), but had normalized by the next assessment at the age of two months. At the age of two years the patient had inconclusive laboratory findings such as leukocyte counts, serum immunoglobulins and complement components C3, C4 and CH50. Mitogen-driven T-cell proliferation was normal. The patient was seronegative for HIV. The IL12-23/IFN- γ circuit was evaluated to search for MSMD etiologies.

We collected blood samples from the patient and his parents after obtaining informed consent. Blood cells from the patient responded to BCG + IL-12 and produced IFN- γ , but did not secrete IL-12p40 and IL-12p70 in response to stimulation with BCG + IFN- γ (Figs 1A, 1B, 1C). Plasma IFN- γ level was 104 pg/ml. These results were suggestive of complete IFN- γ R1 or IFN- γ R2 deficiency [Feinberg et al., 2004]. We then cultured Epstein Barr virus-transformed B lymphocytes (EBV-B), as previously described [Dupuis et al., 2003].

Genomic DNA was extracted from leukocytes and EBV-B cell lines and *IFNGR1* exons were amplified and sequenced [Dupuis et al., 2003]. The known sequences from Ensembl (<http://www.ensembl.org>) were aligned by CLUSTALW multiple sequence alignment (<http://align.genome.jp>). We identified an apparently homozygous nucleotide substitution at position 13840 in exon 3, resulting in a new nonsense mutation (Y113X) upstream from the transmembrane domain of IFN- γ R1 (Fig 2A). These results suggested a diagnosis of recessive, complete IFN- γ R1 deficiency. We assessed the IFN- γ response of the patient's EBV-B cells by carrying out an electrophoretic mobility shift assay [Dupuis et al., 2000] in which these cells were stimulated with IFN- γ , using a gamma activating sequence (GAS) probe. EBV-B cells from the patient presented a complete deficiency of GAS-binding proteins after IFN- γ stimulation, as shown by comparisons with control cells (Fig 1D). These results suggested that the patient had complete IFN- γ R1 deficiency, due to a new, apparently homozygous nonsense mutation in exon 3. However, intrafamilial segregation of the mutant allele of the *IFNGR1* gene showed that the patient's father was heterozygous for the Y113X mutation, whereas his mother carried only the wild-type allele of *IFNGR1* (Fig 2).

In order to further investigate the mode of inheritance of the Y113X mutation, we genotyped the patient and his parents with the genome-wide SNP 6.0 array (Affymetrix, Santa Clara, CA) including 909,622 SNPs. Genotyping was highly successful, with call rates of 99.0, 98.8, and 98.9% in the patient, father, and mother, respectively. In particular, the call rate for the patient on chromosome 6 (out of 56,400 SNPs) was 98.8%, with a proportion of no calls equally distributed over the chromosome (Fig 3C). Examination of the genotypes at the chromosome 6 of the patient shows an overall loss of heterozygosity, without heterozygous calls along the whole chromosome (Fig 3B), a pattern that was not observed on any other

chromosomes, as exemplified in figure 3A with chromosome 1. Examination of mother-patient transmissions showed that all maternal chromosomes except chromosome 6 were compatible with a Mendelian inconsistency rate of < 0.004 , while chromosome 6 displayed a considerable rate of Mendelian inconsistencies (0.172), which were equally distributed over chromosome 6 (Fig 3C). These results confirm that the mother is indeed the biological mother of the patient, although she did not transmit any part of her chromosome 6 to her child. Examination of father-patient transmissions showed that all paternal chromosomes, including 6, are compatible with the patient with Mendelian inconsistencies rate < 0.006 . As well as for the mother, Mendelian inconsistencies of paternal origin were equally distributed on chromosome 6 (Fig 3C). All these data strongly support the view that both copies of chromosome 6 of the patient were inherited from the father, characterizing a paternal UPD of the whole chromosome.

Discussion

UPD is defined as the inheritance of a pair of homologous chromosomes from a single parent [Engel, 1980]. If the two chromosomes are identical, the UPD is described as isodisomic; if the two chromosomes are not identical, the UPD is described as heterodisomic UPD. It is associated with two main types of developmental risk: the inheritance of a recessive trait and the occurrence of imprinting disorders. The clinical phenotype for an autosomal recessive disorder depends on the gene mutated. Most of the known imprinted genes are critical regulators of growth and development [Fowden et al., 2006; Hurst and McVean, 1997]. To date, up to three PIDs resulting from autosomal recessive disorders due to UPD have been reported: Chediak-Higashi syndrome (OMIM# 214500; chromosome 1), cartilage-hair hypoplasia (OMIM# 250250; chromosome 9) and familial hemophagocytic lymphohistiocytosis (OMIM# 603553; chromosome 10). To our knowledge, UPD has never previously been associated with MSMD. Our patient with UPD6 presented with MSMD, neonatal hyperglycemia, muscular disease and dysmorphic features.

The duplicated chromosomes harboring a mutant *IFNGR1* gene account for the recessive form of MSMD in this child despite the presence of the heterozygous mutation in only one of his parents. The recessive nonsense mutation in exon 3 gave rise to a premature stop codon and complete IFN- γ R1 deficiency. The severe clinical features of MSMD in our patient are consistent with those of other IFN- γ R1-deficient patients [Dorman et al., 2004], with an early onset of symptoms and disseminated infection with rapidly growing mycobacteria, *Mycobacterium fortuitum* in this case. Three years after the initial onset of symptoms, the patient presented with necrotizing pneumonia thought to be caused by *R. equi*, an emerging pathogen of humans [Weinstock and Brown 2002] that had not previously been identified in IFN- γ R1-deficient patients. With the exception of salmonellosis [Dorman et al., 2004], few infections have been described in patients with complete IFN- γ R1 deficiency. Those detected in other patients include cytomegalovirus [Cunningham et al., 2000; Dorman et al., 1999], human herpesvirus 8 [Camcioglu et al., 2004], *Listeria monocytogenes* [Roesler et al., 1999] and *Histoplasma capsulatum* [Jouanguy et al., 1999; Zerbe and Holland, 2005] infections. However, each of these infections occurred in only one to three patients, making it difficult to draw definitive conclusions concerning the extent to which these infections truly reflect genetic predisposition. *Rhodococcus equi* is a Gram-positive facultative intracellular pathogen that infects foals, cattle and wild birds, among other animals [von Bargen and Haas 2009]. Foals display a defect in IFN- γ production at birth and there is evidence that the immune response to *Rhodococcus equi* depends on the production of IFN- γ [Breathnach et al., 2006; Giguere et al., 1999; Hines et al., 1997]. *Rhodococcus equi* is a rarely documented pathogen in human populations [von Bargen and Haas 2009]. *Rhodococcus equi* was first described as a human pathogen in 1967, in a patient on immunosuppressive treatment for autoimmune hepatitis [Golub et al., 1967]. Most cases of

human *Rhodococcus equi* infection involve patients taking immunosuppressive treatment or infected with HIV [Arya et al., 2004; Corti et al., 2009; von Bargen and Haas 2009]. The most common presentation of *Rhodococcus equi* in immunodeficient patients is necrotizing pneumonia, with or without sepsis [Sistla et al., 2009]. One patient suffering from chronic granulomatous disease presented pneumonia caused by *Rhodococcus equi* [Soler-Palacin et al., 2007]. Our patient's history suggests that *Rhodococcus equi* may be a potential pathogen in patients with IFN γ -R1 deficiency, and even perhaps in patients with other genetic etiologies of MSMD.

The first UPD6 conferring a recessive disorder was reported in 1990 as a recessive deficiency of the C4 component of the complement system in a girl with systemic erythematous lupus [Welch et al., 1990]. Imprinting disorder due to paternal UPD6 affecting the 6q24-q25 region leads to transient neonatal diabetes (OMIM# 601410). Six published cases of five recessive disorders resulting from either entire or segmental UPD6 have been described: complete C4 deficiency, congenital adrenal hyperplasia, methylmalonic acidemia and agenesis of pancreatic beta cells progressive degenerative disease due to mutation in SCA17 gene [Abramowicz et al., 1994; Kotzot, 2008]. Our patient is the first reported case of IFN- γ R1 deficiency in which the recessive disorder results from UPD6. Reported cases of UPD6 not involving recessive disorders have highly heterogeneous phenotypes, ranging from an absence of symptoms to growth retardation, developmental retardation and organ dysgenesis [Kotzot, 2001]. Two genes on human chromosome 6 are known to be paternally imprinted (*PLAGL1* and *HYMAI*), two others are predicted to be paternally imprinted (*MRAP2* and *BRP44L*), and two more are predicted to be maternally imprinted (*FAM50B* and *BTNL2*) [Luedi et al., 2007] (www.geneimprint.com). Only *PLAGL1*, located in the 6q24-q25 region, has been associated with a clinical disorder, transient neonatal diabetes mellitus (TNDM; OMIM# 601410). Twenty-four patients with segmental or complete paternal UPD6 without autosomal recessive disorders have been reported and are listed in Table I [Aviram et al., 2008; Bittencourt et al., 1997; Bonet Alcaina et al., 2002; Bryke 2004; Cave et al., 2000; Christian et al., 1999; Cockwell et al., 2006; Das et al., 2000; Diatloff-Zito et al., 2007; Eggermann et al., 2001; Felix et al., 2007; Gardner et al., 1998; Hermann et al., 2000; Kenny et al., 2009; Marquis et al., 2000; Milenkovic et al., 2006; Milenkovic et al., 2001; Smith et al., 1999; Temple et al., 1995; Valerio et al., 2001; Whiteford et al., 1997]. The abnormal findings common to these patients may be attributed to imprinting disorders. Most of these patients (n=21) developed TNDM, with and without dysmorphic features. One patient was asymptomatic, with UPD of the entire chromosome 6 identified during HLA typing to identify potential donors for bone marrow transplantation for β -thalassemia major [Bittencourt et al., 1997]. Our patient presented at least seven of the features reported in paternal UPD6 patients: IUGR, macroglossia and other craniofacial dysmorphisms, small hands and feet, club foot, muscular hypotonia and motor retardation. The precise period during which TNDM may be considered to occur has not been precisely defined [Barbetti, 2007; Shield, 2000]. Our patient's neonatal hyperglycemia may therefore be considered to be consistent with this well characterized paternal UPD6 imprinting disorder.

Our patient also presented with several features not previously reported in paternal UPD6 patients: cryptorchidism, hypoplasia of the nails on his hands, campodactyly, kyphosis and prominent heels. The clinical phenotype of our patient, except for the symptoms related to MSMD, probably resulted from the disruption of imprinting balance. However, we cannot exclude the possibility of another recessively inherited mutation contributing to some phenotypes, such as the muscle disease.

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References

- Abramowicz MJ, Andrien M, Dupont E, Dorchy H, Parma J, Duprez L, Ledley FD, Courtens W, Vamos E. Isodisomy of chromosome 6 in a newborn with methylmalonic acidemia and agenesis of pancreatic beta cells causing diabetes mellitus. *J Clin Invest.* 1994; 94(1):418–21. [PubMed: 7913714]
- Alcais A, Fieschi C, Abel L, Casanova JL. Tuberculosis in children and adults: two distinct genetic diseases. *J Exp Med.* 2005; 202:1617–1621. [PubMed: 16365144]
- Arya B, Hussian S, Hariharan S. *Rhodococcus equi* pneumonia in a renal transplant patient: a case report and review of literature. *Clin Transplant.* 2004; 18:748–752. [PubMed: 15516256]
- Aviram R, Kidron D, Silverstein S, Lerer I, Abeliovich D, Tepper R, Dolfin Z, Markovitch O, Arnon S. Placental mesenchymal dysplasia associated with transient neonatal diabetes mellitus and paternal UPD6. *Placenta.* 2008; 29:646–649. [PubMed: 18486206]
- Barbetti F. Diagnosis of neonatal and infancy-onset diabetes. *Endocr Dev.* 2007; 11:83–93. [PubMed: 17986829]
- Bittencourt MC, Morris MA, Chabod J, Gos A, Lamy B, Fellmann F, Antonarakis SE, Plouvier E, Herve P, Tiberghien P. Fortuitous detection of uniparental isodisomy of chromosome 6. *J Med Genet.* 1997; 34:77–78. [PubMed: 9032654]
- Bonet Alcaina M, Garcia-Algar O, Herrero Perez S, Mombiola Vidal R, Perez Jurado LA, Mur Sierra A. Transient neonatal diabetes associated with uniparental isodisomy of chromosome 6. *An Esp Pediatr.* 2002; 56:567–570. [PubMed: 12042155]
- Breathnach CC, Sturgill-Wright T, Stiltner JL, Adams AA, Lunn DP, Horohov DW. Foals are interferon gamma-deficient at birth. *Vet Immunol Immunopathol.* 2006; 112:199–209. [PubMed: 16621024]
- Bryke, CR.; G, AT.; Israel, J. Evolution of a complex phenotype in a unique patient with a paternal uniparental disomy for every chromosome cell line in a normal biparental inheritance cell line [Abstract 831]. The American Society of Human Genetics; Toronto, Canada: 2004.
- Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, Kaner G, Demirkesen C, Plancoulaine S, Emile JF, Gessain A, Casanova JL. HHV-8-associated Kaposi sarcoma in a child with IFN γ R1 deficiency. *J Pediatr.* 2004; 144:519–523. [PubMed: 15069403]
- Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, Stephan JL, Bernaudin F, Bordigoni P, Turck D, Lachaux A, Albertini M, Bourrillon A, Dommergues JP, Pocard MA, Le Deist F, Gaillard JL, Griscelli C, Fischer A. Idiopathic disseminated bacillus Calmette-Guerin infection: a French national retrospective study. *Pediatrics.* 1996; 98(4 Pt 1):774–778. [PubMed: 8885960]
- Cave H, Polak M, Drunat S, Denamur E, Czernichow P. Refinement of the 6q chromosomal region implicated in transient neonatal diabetes. *Diabetes.* 2000; 49:108–113. [PubMed: 10615957]
- Chantraine CF, Bruwier A, Brichard B, Largent V, Chappier A, Feinberg J, Casanova JL, Stalens JP, Vermeylen C. Successful hematopoietic stem cell transplantation in a child with active disseminated Mycobacterium fortuitum infection and interferon-gamma receptor 1 deficiency. *Bone Marrow Transplant.* 2006; 38:75–76. [PubMed: 16715106]
- Chappier A, Boisson-Dupuis S, Jouanguy E, Vogt G, Feinberg J, Prochnicka-Chalufour A, Casrouge A, Yang K, Soudais C, Fieschi C, Santos OF, Bustamante J, Picard C, de Beaucoudrey L, Emile JF, Arkwright PD, Schreiber RD, Rolinck-Werninghaus C, Rosen-Wolff A, Magdorf K, Roesler J, Casanova JL. Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. *PLoS Genet.* 2006; 2(8):e131. [PubMed: 16934001]

- Christian SL, Rich BH, Loeb C, Israel J, Vasa R, Kittikamron K, Spiro R, Rosenfield R, Ledbetter DH. Significance of genetic testing for paternal uniparental disomy of chromosome 6 in neonatal diabetes mellitus. *J Pediatr*. 1999; 134:42–46. [PubMed: 9880447]
- Cockwell AE, Baker SJ, Connarty M, Moore IE, Crolla JA. Mosaic trisomy 6 and maternal uniparental disomy 6 in a 23-week gestation fetus with atrioventricular septal defect. *Am J Med Genet A*. 2006; 140A:624–627. [PubMed: 16470696]
- Corti M, Palmero D, Eiguchi K. Respiratory infections in immunocompromised patients. *Curr Opin Pulm Med*. 2009; 15:209–217. [PubMed: 19276812]
- Cunningham JA, Kellner JD, Bridge PJ, Trevenen CL, McLeod DR, Davies HD. Disseminated bacille Calmette-Guerin infection in an infant with a novel deletion in the interferon-gamma receptor gene. *Int J Tuberc Lung Dis*. 2000; 4:791–794. [PubMed: 10949334]
- Das S, Lese CM, Song M, Jensen JL, Wells LA, Barnoski BL, Roseberry JA, Camacho JM, Ledbetter DH, Schnur RE. Partial paternal uniparental disomy of chromosome 6 in an infant with neonatal diabetes, macroglossia, and craniofacial abnormalities. *Am J Hum Genet*. 2000; 67:1586–1591. [PubMed: 11038325]
- Diatloff-Zito C, Nicole A, Marcelin G, Labit H, Marquis E, Bellanne-Chantelot C, Robert JJ. Genetic and epigenetic defects at the 6q24 imprinted locus in a cohort of 13 patients with transient neonatal diabetes: new hypothesis raised by the finding of a unique case with hemizygotic deletion in the critical region. *J Med Genet*. 2007; 44:31–37. [PubMed: 16971482]
- Dorman SE, Picard C, Lammas D, Heyne K, van Dissel JT, Baretto R, Rosenzweig SD, Newport M, Levin M, Roesler J, Kumararatne D, Casanova JL, Holland SM. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. *Lancet*. 2004; 364:2113–2121. [PubMed: 15589309]
- Dorman SE, Uzel G, Roesler J, Bradley JS, Bastian J, Billman G, King S, Filie A, Schermerhorn J, Holland SM. Viral infections in interferon-gamma receptor deficiency. *J Pediatr*. 1999; 135:640–643. [PubMed: 10547254]
- Dupuis S, Doffinger R, Picard C, Fieschi C, Altare F, Jouanguy E, Abel L, Casanova JL. Human interferon-gamma-mediated immunity is a genetically controlled continuous trait that determines the outcome of mycobacterial invasion. *Immunol Rev*. 2000; 178:129–137. [PubMed: 11213797]
- Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, Yang K, Chapgier A, Eidenschenk C, Eid P, Al Ghonaium A, Tufenkeji H, Frayha H, Al-Gazlan S, Al-Rayes H, Schreiber RD, Gresser I, Casanova JL. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet*. 2003; 33:388–391. [PubMed: 12590259]
- Eggermann T, Marg W, Mergenthaler S, Eggermann K, Schemmel V, Stoffers U, Zerres K, Spranger S. Origin of uniparental disomy 6: presentation of a new case and review on the literature. *Ann Genet*. 2001; 44:41–45. [PubMed: 11334617]
- Engel E. A new genetic concept: uniparental disomy and its potential effect, isodisomy. *Am J Med Genet*. 1980; 6:137–143. [PubMed: 7192492]
- Feinberg J, Fieschi C, Doffinger R, Feinberg M, Leclerc T, Boisson-Dupuis S, Picard C, Bustamante J, Chapgier A, Filipe-Santos O, Ku CL, de Beaucoudrey L, Reichenbach J, Antoni G, Balde R, Alcais A, Casanova JL. Bacillus Calmette Guerin triggers the IL-12/IFN-gamma axis by an IRAK-4- and NEMO-dependent, non-cognate interaction between monocytes, NK, and T lymphocytes. *Eur J Immunol*. 2004; 34:327632–84.
- Felix TM, Tansey MJ, Patil SR, Murray JC, Dagle JM. Double paternal nondisjunction in an infant with transient neonatal diabetes mellitus and Klinefelter syndrome. *Am J Med Genet A*. 2007; 143A:895–898. [PubMed: 17366578]
- Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. *Semin Immunol*. 2006; 18:347–361. [PubMed: 16997570]
- Fowden AL, Sibley C, Reik W, Constancia M. Imprinted genes, placental development and fetal growth. *Horm Res*. 2006; 65 3:50–58. [PubMed: 16612114]

- Gardner RJ, Robinson DO, Lamont L, Shield JP, Temple IK. Paternal uniparental disomy of chromosome 6 and transient neonatal diabetes mellitus. *Clin Genet*. 1998; 54:522–525. [PubMed: 9894800]
- Giguere S, Wilkie BN, Prescott JF. Modulation of cytokine response of pneumonic foals by virulent *Rhodococcus equi*. *Infect Immun*. 1999; 67:5041–5047. [PubMed: 10496876]
- Glosli H, Stray-Pedersen A, Brun AC, Holtmon LW, Tonjum T, Chapgier A, Casanova JL, Abrahamsen TG. Infections due to various atypical mycobacteria in a Norwegian multiplex family with dominant interferon-gamma receptor deficiency. *Clin Infect Dis*. 2008; 46(3):e23–27. [PubMed: 18171304]
- Golub B, Falk G, Spink WW. Lung abscess due to *Corynebacterium equi*. Report of first human infection. *Ann Intern Med*. 1967; 66:1174–1177. [PubMed: 6067513]
- Hermann R, Laine AP, Johansson C, Niederland T, Tokarska L, Dziatkowiak H, Ilonen J, Soltesz G. Transient but not permanent neonatal diabetes mellitus is associated with paternal uniparental isodisomy of chromosome 6. *Pediatrics*. 2000; 105(1 Pt 1):49–52. [PubMed: 10617703]
- Hines SA, Kanaly ST, Byrne BA, Palmer GH. Immunity to *Rhodococcus equi*. *Vet Microbiol*. 1997; 56:177–185. [PubMed: 9226832]
- Horwitz ME, Uzel G, Linton GF, Miller JA, Brown MR, Malech HL, Holland SM. Persistent *Mycobacterium avium* infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency. *Blood*. 2003; 102:2692–2694. [PubMed: 12805054]
- Hurst LD, McVean GT. Growth effects of uniparental disomies and the conflict theory of genomic imprinting. *Trends Genet*. 1997; 13:436–443. [PubMed: 9385840]
- Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. *N Engl J Med*. 1996; 335:1956–1961. [PubMed: 8960475]
- Jouanguy E, Lamhamedi-Cherradi S, Altare F, Fondaneche MC, Tuerlinckx D, Blanche S, Emile JF, Gaillard JL, Schreiber R, Levin M, Fischer A, Hivroz C, Casanova JL. Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid bacillus Calmette-Guerin infection and a sibling with clinical tuberculosis. *J Clin Invest*. 1997; 100:2658–2664. [PubMed: 9389728]
- Jouanguy E, Lamhamedi-Cherradi S, Lammas D, Dorman SE, Fondaneche MC, Dupuis S, Doffinger R, Altare F, Girdlestone J, Emile JF, Ducoulombier H, Edgar D, Clarke J, Oxelius VA, Brai M, Novelli V, Heyne K, Fischer A, Holland SM, Kumararatne DS, Schreiber RD, Casanova JL. A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. *Nat Genet*. 1999; 21:370–378. [PubMed: 10192386]
- Kenny AP, Crimmins NA, Mackay DJ, Hopkin RJ, Bove KE, Leonis MA. Concurrent Course of Transient Neonatal Diabetes with Cholestasis and Paucity of Interlobular Bile Ducts: A Case Report. *Pediatr Dev Pathol*. 2009; 1
- Kotzot D. Complex and segmental uniparental disomy (UPD): review and lessons from rare chromosomal complements. *J Med Genet*. 2001; 38:497–507. [PubMed: 11483637]
- Kotzot D. Complex and segmental uniparental disomy updated. *J Med Genet*. 2008; 45:545–556. [PubMed: 18524837]
- Lee WI, Huang JL, Lin TY, Hsueh C, Wong AM, Hsieh MY, Chiu CH, Jaing TH. Chinese patients with defective IL-12/23-interferon-gamma circuit in Taiwan: partial dominant interferon-gamma receptor 1 mutation presenting as cutaneous granuloma and IL-12 receptor beta1 mutation as pneumatocele. *J Clin Immunol*. 2009; 29:238–245. [PubMed: 18972195]
- Luedi PP, Dietrich FS, Weidman JR, Bosko JM, Jirtle RL, Hartemink AJ. Computational and experimental identification of novel human imprinted genes. *Genome Res*. 2007; 17:1723–1730. [PubMed: 18055845]
- MacLennan C, Fieschi C, Lammas DA, Picard C, Dorman SE, Sanal O, MacLennan JM, Holland SM, Ottenhoff TH, Casanova JL, Kumararatne DS. Interleukin (IL)-12 and IL-23 are key cytokines for immunity against *Salmonella* in humans. *J Infect Dis*. 2004; 190:1755–1757. [PubMed: 15499529]
- Marquis E, Robert JJ, Benezech C, Junien C, Diatloff-Zito C. Variable features of transient neonatal diabetes mellitus with paternal isodisomy of chromosome 6. *Eur J Hum Genet*. 2000; 8:137–140. [PubMed: 10757646]

- Milenkovic T, Martic J, Robinson DO, Mackay DJ, Petrovic K, Zdravkovic D. Transient neonatal diabetes mellitus in an infant with paternal uniparental disomy of chromosome 6 including heterodisomy for 6q24. *J Pediatr Endocrinol Metab.* 2006; 19:1353–1357. [PubMed: 17220064]
- Milenkovic T, Zdravkovic D, Gardner RJ, Ignjatovic M, Jankovic B. Transient neonatal diabetes mellitus in a child with paternal uniparental disomy of chromosome 6. *J Pediatr Endocrinol Metab.* 2001; 14:893–895. [PubMed: 11515730]
- Moilanen P, Korppi M, Hovi L, Chapgier A, Feinberg J, Kong XF, Boisson-Dupuis S, Arola M, Casanova JL, Saarinen-Pihkala UM. Successful Hematopoietic Stem Cell Transplantation from an Unrelated Donor in a Child with Interferon Gamma Receptor Deficiency. *Pediatr Infect Dis J.* 2009; 28:658–660. [PubMed: 19451859]
- Muszlak M, Chapgier A, Barry Harivelo R, Castella C, Cremades F, Goulois E, Laporte R, Casanova JL, Ranaivoarivony V, Hebert JC, Santiago J, Picard C. Multifocal infection due to *Mycobacterium intracellulare*: first case of interferon gamma receptor partial dominant deficiency in tropical French territory. *Arch Pediatr.* 2007; 14:270–272. [PubMed: 17223023]
- Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, Levin M. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. *N Engl J Med.* 1996; 335:1941–1949. [PubMed: 8960473]
- Noordzij JG, Hartwig NG, Verreck FA, De Bruin-Versteeg S, De Boer T, Van Dissel JT, De Groot R, Ottenhoff TH, Van Dongen JJ. Two patients with complete defects in interferon gamma receptor-dependent signaling. *J Clin Immunol.* 2007; 27:490–496. [PubMed: 17514500]
- Okada S, Ishikawa N, Shirao K, Kawaguchi H, Tsumura M, Ohno Y, Yasunaga S, Ohtsubo M, Takihara Y, Kobayashi M. The novel IFNGR1 mutation 774del4 produces a truncated form of interferon-gamma receptor 1 and has a dominant-negative effect on interferon-gamma signal transduction. *J Med Genet.* 2007; 44:485–491. [PubMed: 17513528]
- Picard C, Fieschi C, Altare F, Al-Jumaah S, Al-Hajjar S, Feinberg J, Dupuis S, Soudais C, Al-Mohsen IZ, Genin E, Lammas D, Kumararatne DS, Leclerc T, Rafii A, Frayha H, Murugasu B, Wah LB, Sinniah R, Loubser M, Okamoto E, Al-Ghonaïm A, Tufenkeji H, Abel L, Casanova JL. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Genet.* 2002; 70:336–348. [PubMed: 11753820]
- Reuter U, Roesler J, Thiede C, Schulz A, Classen CF, Oelschlagel U, Debatin KM, Friedrich W. Correction of complete interferon-gamma receptor 1 deficiency by bone marrow transplantation. *Blood.* 2002; 100:4234–4235. [PubMed: 12393576]
- Roesler J, Horwitz ME, Picard C, Bordigoni P, Davies G, Koscielniak E, Levin M, Veys P, Reuter U, Schulz A, Thiede C, Klingebiel T, Fischer A, Holland SM, Casanova JL, Friedrich W. Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. *J Pediatr.* 2004; 145:806–812. [PubMed: 15580206]
- Roesler J, Kofink B, Wendisch J, Heyden S, Paul D, Friedrich W, Casanova JL, Leupold W, Gahr M, Rosen-Wolff A. *Listeria monocytogenes* and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFNGammaR1) deficiency: mutational analysis and evaluation of therapeutic options. *Exp Hematol.* 1999; 27:1368–1374. [PubMed: 10480427]
- Rottman M, Soudais C, Vogt G, Renia L, Emile JF, Decaluwe H, Gaillard JL, Casanova JL. IFN-gamma mediates the rejection of haematopoietic stem cells in IFN-gammaR1-deficient hosts. *PLoS Med.* 2008; 5(1):e26. [PubMed: 18232731]
- Shield JP. Neonatal diabetes: new insights into aetiology and implications. *Horm Res.* 2000; 53 1:7–11. [PubMed: 10895036]
- Sistla S, Karthikeyan S, Biswas R, Parija SC, Patro DK. Acute osteomyelitis caused by *Rhodococcus equi* in an immunocompetent child. *Indian J Pathol Microbiol.* 2009; 52:263–264. [PubMed: 19332935]
- Smith A, Jauch A, Slater H, Robson L, Sandanam T. Syndromal obesity due to paternal duplication 6(q24.3-q27). *Am J Med Genet.* 1999; 84:125–131. [PubMed: 10323737]
- Soler-Palacin P, Margareto C, Llobet P, Asensio O, Hernandez M, Caragol I, Espanol T. Chronic granulomatous disease in pediatric patients: 25 years of experience. *Allergol Immunopathol (Madr).* 2007; 35:83–89. [PubMed: 17594870]

- Storgaard M, Varming K, Herlin T, Obel N. Novel mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infections. *Scand J Immunol.* 2006; 64:137–139. [PubMed: 16867158]
- Temple IK, James RS, Crolla JA, Sitch FL, Jacobs PA, Howell WM, Betts P, Baum JD, Shield JP. An imprinted gene(s) for diabetes? *Nat Genet.* 1995; 9:110–112. [PubMed: 7719335]
- Valerio G, Franzese A, Palmieri A, Mackay DJ, Gardner RJ, Temple IK. Central precocious puberty in a girl with triple X syndrome and neonatal diabetes mellitus associated with paternal isodisomy of chromosome 6. *J Pediatr Endocrinol Metab.* 2001; 14:897–900. [PubMed: 11515731]
- Vogt G, Bustamante J, Chappier A, Feinberg J, Boisson Dupuis S, Picard C, Mahlaoui N, Gineau L, Alcais A, Lamaze C, Puck JM, de Saint Basile G, Khayat CD, Mikhael R, Casanova JL. Complementation of a pathogenic IFNGR2 misfolding mutation with modifiers of N-glycosylation. *J Exp Med.* 2008; 205:1729–1737. [PubMed: 18625743]
- von Barmen K, Haas A. Molecular and infection biology of the horse pathogen *Rhodococcus equi*. *FEMS Microbiol Rev.* 2009; 33:870–891. [PubMed: 19453748]
- Weinstock DM, Brown AE. *Rhodococcus equi*: an emerging pathogen. *Clin Infect Dis.* 2002; 34:1379–1385. [PubMed: 11981734]
- Welch TR, Beischel LS, Choi E, Balakrishnan K, Bishof NA. Uniparental isodisomy 6 associated with deficiency of the fourth component of complement. *J Clin Invest.* 1990; 86:675–678. [PubMed: 2384609]
- Whiteford ML, Narendra A, White MP, Cooke A, Wilkinson AG, Robertson KJ, Tolmie JL. Paternal uniparental disomy for chromosome 6 causes transient neonatal diabetes. *J Med Genet.* 1997; 34:167–168. [PubMed: 9039998]
- Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. *Clin Infect Dis.* 2005; 41(4):e38–41. [PubMed: 16028145]

Figure 1. IL12-23/IFN- γ circuit evaluation. Cytokine production of whole blood cells from the patient, his father and mother, and a healthy control. ELISA data for blood after 48 hours of activation. **A**, IFN- γ production at 48 hours. **B**, IL-12p40 production at 48 hours. **C**, IL-12p70 production at 48 hours. **D**, IFN- γ receptor-mediated cell responses evaluated by electrophoretic mobility shift assay with nuclear extracts (5 μ g) from EBV-B cells from one healthy control and the patient not stimulated or stimulated for 30 minutes with 10³ and 10⁵ IU/ml IFN- γ or 10⁵ IU/ml IFN- α . The results shown are representative of two independent experiments

Figure 2. Mutation in the *IFNGR1* gene. **A**, Analysis of the genomic sequence of the *IFNGR1* gene. The patient carries a T>A mutation in exon 3, leading to a nonsense mutation (Y113X). The father is heterozygous for the same mutation and the mother presents the wild-type allele. All sequences are shown in sense orientation. **B**, Pedigree of the family. The proband is represented by a black symbol and indicated by an arrow.

Figure 3.

SNP 6.0 array analysis of patient's chromosome 6. Schematic representation of the genotype calls (denoted as AA, AB and, BB) for the SNPs along the entire chromosomes 1 (panel A) and 6 (panel B). Chromosome 1 presents a typical distribution of AA, AB, and BB genotypes while no heterozygous AB calls are observed for chromosome 6. Panel C presents the proportion of errors observed along the entire chromosome 6 of the patient for mother-patient transmissions (blue line), father-patient transmissions (red line), and genotype calls (green line).

UPD6 symptoms not resulting from autosomal recessive disorders.

Table I

ID	Karyotype	UPD6	TNDM	IUGR	Craniofacial dysmorphism ^a	Abdominal wall defects ^b	Bone and joints defects ^c	Muscular hypotonia	Motor retardation	Heart defect ^d	Reference
	47,XY	P(I)	x	x	x		x	x	x		Presented in this paper
1	47,XXX	P (I)	x	x	x	x				x	Valerio, 2001
2	46,XY	P (I)	x		x	x					Milenkovic et al, 2001
3	46,XX	P (I)	x		x						Cave et al, 2000
4	46,XY	P (I)	x	x	x		x	x			Christian et al, 1999
5	46,XX	P (I)	x		x	x					Bonet Alcaina et al, 2002
6	46,XX	P (I)	x		x						Hermann et al, 2000
7	46,XX	P (I)	x	x							Gardner, 1998
8	46,xx	P (I for 6q->24)	x	x	x						Das et al, 2000
9	46,XX	P (I for p12; H for q24-24.3)	x	x	x						Aviram et al, 2008
10	47,XXY	P (H)	x		x						Felix, 2007
11	46,XX	P (I; H for 6q24)	x	x	x						Milenkovic et al, 2006
12	46XX	P (I)	x	x							Robinson et al, 1998
13	not informed	P (I) *	x	x			x	x	x	x	Diatloff-Zito et al, 2007
14	not informed	P (I) *	x								Diatloff-Zito et al, 2007
15	46,XX	P (I)	x								Marquis et al, 2000
16	46,XX	P (I)	x								Temple et al, 1995
17	46,XX/47XX,+r(6)	P (I for 6q23->qter)	x								Temple et al, 1995
18	46,XY	P (I)	x								Whiteford, 1997
19	46xx	P (I)	x								Kenny et al, 2009
20	not informed	P (I)	x								Eggermann et al, 2001
21	46,xx	P (I) ***	x					x			Bryke et al. 2004
22	46,XY	P (I for 6q23->qter)			x		x				Smith et al, 1999
23	46,XX	P (I)				x				x	Cockwell et al, 2006
24	46,XX	P (I)									Bittencourt et al, 1997

^I P= paternal origin. M= maternal origin. I= isodisomy. H= heterodisomy.
^a, includes macroglossia as the main symptom (n=10).

b includes umbilical hernia (n= 3) and exomphalos (n=1).
c includes small hands and feet (n=1), club foot (n=2) and delayed bone maturation (n=1).

d includes septal defects (n=2) and mitral valve insufficiency (n=1).

* only markers for the region 6q24 were considered in this patient.

** genome-wide UPD. Patient 8 died from neonatal sepsis. Patients 13 and 14 were studied specifically for UPD in the region 6q24. Patient 17 presented with mild, unspecified dysmorphic features. Patient 19 developed cholestasis, due to a paucity of interlobular bile ducts. Patient 21 presented genome-wide UPD with symptoms of UPD 11, 14, 15 and 20 in addition to UPD6. Patient 23 died in the uterus. Patient 24 is asymptomatic.