Report

A Novel Primary Immunodeficiency with Specific Natural-Killer Cell Deficiency Maps to the Centromeric Region of Chromosome 8

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We describe four children with a novel primary immunodeficiency consisting of specific natural-killer (NK) cell deficiency and susceptibility to viral diseases. One child developed an Epstein-Barr virus–driven lymphoproliferative disorder; two others developed severe respiratory illnesses of probable viral etiology. The four patients are related and belong to a large inbred kindred of Irish nomadic descent, which suggests autosomal recessive inheritance of this defect. A genomewide scan identified a single 12-Mb region on chromosome 8p11.23-q11.21 that was linked to this immunodeficiency (maximum LOD score 4.51). The mapping of the disease-causing genomic region paves the way for the identification of a novel pathway governing NK cell differentiation in humans.

Natural killer (NK) cells are circulating cytotoxic lymphocytes lacking antigen-specific T-cell and B-cell receptors (Yokoyama and Plougastel 2003; Moretta and Moretta 2004; Vivier et al. 2004; Lanier 2005). They have been shown to exert potent and nonredundant antiviral activity in the mouse (Brown et al. 2001; Casanova et al. 2001; Lee et al. 2001; Smith et al. 2002; French and Yokoyama 2003; Yokoyama and Plougastel 2003; Desrosiers et al. 2005; Lodoen and Lanier 2005), but their function in human host defenses remains unclear, partly because of the lack of well-defined inherited disorders associated with a specific deficiency in NK cell development (Orange 2002). A previously healthy girl who presented with disseminated varicella-zoster virus (VZV) infection at age 13 years, which was followed by cytomegalovirus (CMV) pneumonitis and cutaneous herpes simplex virus (HSV) infections, was described as lacking NK cells (Biron et al. 1989). However, this patient has since died of aplastic anemia, which suggests that she may have had an acquired, global hematopoietic condition (Orange 2002). A second patient was recently described who had NK cell deficiency and recurrent varicella infections, which led to death at age 2 years (Etzioni et al. 2005). The parents were consanguineous, and viral infections had begun early in life, which suggests that this child had an inherited defect. However, NK cell counts were not determined before the first viral infection in these two unrelated patients, and VZV has been shown to decrease NK cell counts in otherwise healthy children (Vossen et al. 2005).

We recently described the first reported form of familial NK cell deficiency in two affected sisters without T-cell lymphopenia (Bernard et al. 2004). The older child died from CMV infection, whereas the second child remained healthy at age 7 years and had a persistent lack of NK cells with no diagnosed viral infection (C.E., E.J., and J.-L.C., unpublished data). This strongly suggests that the NK cell deficiency was an inherited defect in this family. Furthermore, like the two previously mentioned reports, these findings are consistent with the hypothesis that this immunodeficiency leads to susceptibility to herpes viruses, such as CMV, VZV, HSV, and Epstein-Barr virus (EBV). The molecular basis of the NK cell deficiency was found to be excessive lymphoid apoptosis with impaired survival responses to interleukin 2 (IL-2) and IL-15 (C.E., E.J., and J.-L.C., unpublished data). However, these two siblings have a more generalized condition, because they also displayed severe in-

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trauterine growth retardation, mild facial dysmorphy, and neutropenia. There is therefore no known Mendelian disorder associated exclusively with selective NK cell deficiency (McKusick 1998). We describe here a large consanguineous kindred with NK cell deficiency in four members, including one patient with EBV-driven lymphoproliferative disorder and two patients with severe pneumonitis of probable viral origin. We also show that this novel NK cell–specific primary immunodeficiency is autosomal recessive and maps to the centromeric region of chromosome 8.

The index case patient (P3) was born in 1996 (fig. 1). At age 18 mo, he presented with failure to thrive, hepatomegaly, splenomegaly, and peripheral lymphadenopathy. His condition may have reflected primary EBV infection but remained unexplained. It eventually resolved without treatment. The patient had previously had relatively benign viral infections of childhood, with recurrent respiratory tract infections, herpetic stomatitis, and molluscum contagiosum. At age 2 years and 9 mo, he developed an EBV-related lymphoproliferative disorder in the small bowel, and the resulting tumor was surgically removed. Neither chemotherapy nor immunotherapy was given. Immunohistochemical staining of the lesion showed morphologic appearances of malignant lymphoma with infiltrative and destructive growth and atypical cytology, but classification was difficult. Results of immunohistochemical staining for the B-cell marker CD20 and the EBV latent membrane protein antigen were positive in many large cells. A draining lymph node biopsy specimen showed infiltration with reactive histiocytes, and a blood smear provided evidence of hemophagocytosis by monocytes. The patient has remained well since his recovery. He is currently 9 years old and is not receiving treatment.

Two of the three other affected family members experienced frequent lung infections: P2 (born in 1991) and P4 (born in 1997). P2 was found to have foci of bronchiectasis, a probable consequence of severe viral illnesses. In 2004, P4 had a serious infection, and a lung biopsy specimen showed changes suggestive of viral infection; however, CMV was not detected, and adenovirus was suspected but not proven. P1, born in 1999, was less severely ill than the others and has had no documented viral infectious diseases. At the last follow-up in 2005, the four patients had improved clinically, although both P2 and P4 continued to experience repeated respiratory infections without a specific etiologic agent identified. There was no documented intrauterine growth retardation; however, all four patients were <3rd percentile for height and weight at their first presentation, a probable consequence of recurrent infections, and this below-average growth has continued. Serological tests for EBV (testing for immunoglobulin M [IgM] to viral capsid antigen and IgG to EBV nuclear antigen) were paradoxically negative for P3 at 4 and 9 years old,

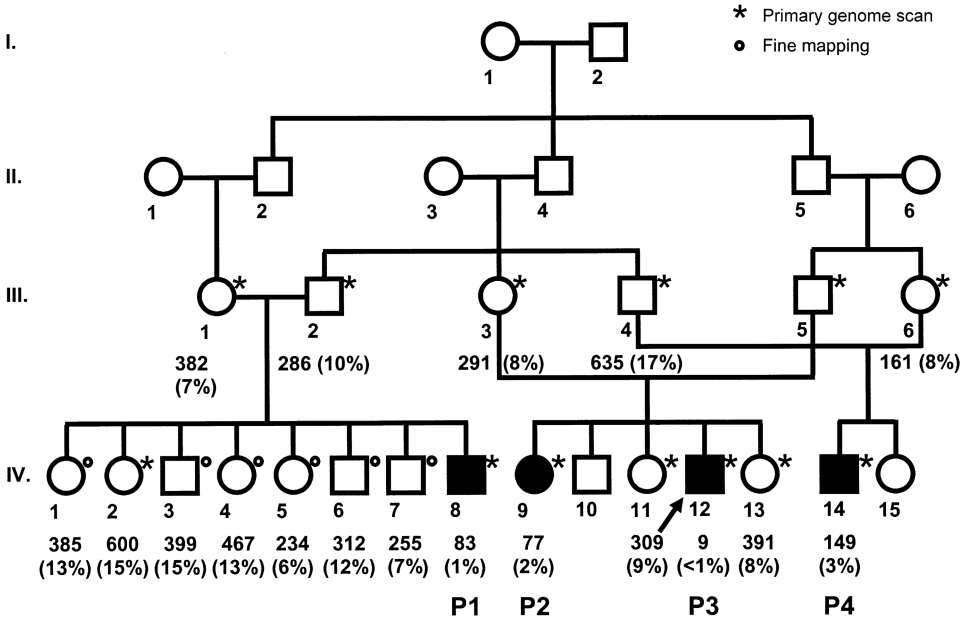

Figure 1 Pedigree of the family. Individuals represented by a symbol with an asterisk (*) were available for genotyping (primary genome scan), whereas individuals represented by a symbol with a small circle were genotyped for only 8p12-q12.2 (fine mapping). The absolute NK cell count (measured in cells/mm^3 of whole blood) and the percentage of lymphocytes that were NK cells in the first whole-blood sample analyzed are indicated for each individual tested.

whereas the other three patients tested positive for IgG to EBV nuclear antigen. Serological tests for HSV were positive for all four patients, serological tests for VZV were positive for P1 and P4 but negative for P2 and P3, and serological tests for CMV were negative for all four patients. P3 also mounted an antibody response to HSV and to mumps, measles, and rubella viruses (possibly because of vaccination). This patient had no antibodies against CMV and VZV.

Immunological investigations were performed for the proband shortly after removal of the lymphoproliferative lesion, and a specific lack of NK cells in the blood was found (table 1). When initially phenotyped in 1998, P3 showed an NK cell count of 9 cells ($CD3^-$, $CD16^+$, and $CD56^+$) per mm^3 of whole blood (<1% of lymphocytes) by flow cytometry (methods available on request). We checked whether the NK cell deficiency was persistent by testing whole-blood samples from P3 on four other occasions (twice in 1998, once in 2002, and once in 2003). NK cell counts were very low on all occasions: 40, 43, 37, and 6 cells/mm^3 (equivalent to 0%–2% of lymphocytes). We looked for a similar phenotype in other family members. Three additional family members (P1, P2, and P4) had very low NK cell counts. Whole-blood samples from P2 were tested seven times, and the absolute NK cell counts were 77 and 32 cells/mm^3 in 2000 and 174, 43, 30, 90, and 24 cells/mm^3 in 2003 (1%–3%). The NK cell counts of samples from P4 were 149 cells/mm^3 in 2000, 30 and 29 cells/mm^3 in 2001, and 50 and 116 cells/mm^3 in 2002 (1%–3%). Whole-blood samples from P1 were tested eight times. At age 1 year, P1 had an NK cell count of 83 cells/mm^3. In 2001, two samples from P1 were analyzed, with NK cell counts of 174 and 181 cells/mm^3. His NK cell counts were 81 and 90 cells/mm^3 in 2002, 128 and 128 cells/mm^3 in 2003, and 137 cells/mm^3 at the last phenotyping in 2005 (1%–4%). On some occasions, the absolute number of NK cells was in the normal range in P1, because of the production of large numbers of lymphocytes, but the percentage of NK cells remained low (<4%). Thus, 4 individuals from this kindred (P1, P2, P3, and P4) were found to have much lower counts (generally <100 cells/mm^3) and percentages (always <4%) of NK cells in blood than those of the 14 healthy family members tested (including 9 children) and of age-matched unrelated healthy children (table 1) (Comans-Bitter et al. 1997). One adult (III.6) with an NK cell count of 161 cells/mm^3 was not considered to be NK cell deficient because the NK cell percentage reached 8%.

Consistent with the small number of NK cells present, NK cell activity was also impaired. No NK cytotoxic activity was detected for P3 after the incubation of peripheral blood mononuclear cells (PBMCs) with the erythroleukemia K562 cell line or of IL-2–activated PBMCs with Daudi cells. T cells expressing the NK cell marker CD56 were also fewer in number in the two patients tested (P3 and P2) than in age-matched healthy controls. NK T cells ($CD3^+$ and $TCRV\alpha24^+/V\beta11^+$) were rare in P1 (0.02% of lymphocytes) and were present at normal levels (0.16%, 0.92%, and 0.22%) in three siblings with normal NK cell counts. The immunological workup for the four NK-deficient patients was otherwise unremarkable, with normal numbers of total lymphocytes, B cells ($CD19^+$), T cells ($CD3^+$), and $CD4^+$ and $CD8^+$ T cells, with the possible exception of P3, who presented with subnormal numbers of $CD8^+$ T cells. Finally, T cells from P3 proliferated normally on stimulation by mitogens (concanavalin A and phytohemagglutinin), and B cells were able to mount antigen-specific antibody responses. Owing to the difficulties of not having regular access to blood samples from the patients, the expression of NK receptors unfortunately could not be studied. Classic and alternative complement levels and phagocytic respiratory-burst test results were normal. These 4 individuals thus presented with a selective and profound deficiency of NK cells in blood, unlike the 14 healthy family members tested. Moreover, three of the NK-deficient patients were tested before the onset of any unusual infectious disease associated with EBV infection. This suggests that the documented NK cell deficiency in the index patient was a cause, rather than a consequence, of the EBV-driven lymphoma. Nevertheless, although unlikely, we cannot exclude on solely clinical grounds the possibility that NK deficiency in the four patients was a consequence of viral illness.

The kindred lives in Ireland, and its members are all of Irish nomadic descent (fig. 1). The kindred is inbred, with multiple loops of consanguinity. The members of the fourth generation belong to three sibships. The parents of each sibship are consanguineous, and the parents of the three sibships are related to each other. The parents of the first sibship (III.1 and III.2) are first cousins, and the parents of the second (III.3 and III.5) and third (III.6 and III.4) sibships are doubly first cousins. These three couples are also related to each other. The observation of NK cell deficiency in four related patients from an extended inbred kindred suggested that this immunological phenotype was inherited as an autosomal recessive trait and that NK deficiency was the predisposing factor to viral infections. We tested this hypothesis by performing a genomewide scan by homozygosity mapping in this family (Lander and Botstein 1987). In a primary screen, 13 informative family members (fig. 1) were studied by genotyping a panel of 388 highly informative microsatellite markers covering the entire genome at intervals of ~10 cM (ABI Prism Linkage Mapping set 2, version 2.5 [Applied Biosystems]). Genetic distances between markers were derived from the Marshfield database. Because of the complexity of the family structure, the analysis was performed by splitting

Table 1

Parameters of Blood Samples from the Four Patients and Healthy Controls

	Samples from Patient[a]				Healthy Controls[b]		
Parameter	P1 ($n = 8$)	P2 ($n = 7$)	P3 ($n = 5$)	P4 ($n = 5$)	Age Group 1 ($n = 33$)	Age Group 2 ($n = 35$)	Age Group 3 ($n = 23$)
Age range[c] (years)	1–6	9–12	2–7	3–5	2–5	5–10	10–16
Lymphocytes[d]	5,195 (2,879–7,221)	1,567 (1,238–4,197)	2,443 (1,895–4,037)	4,281 (3,891–5,374)	3,300 (1,700–6,900)	2,800 (1,100–5,900)	2,200 (100–5,300)
B cells ($CD19^+$)[d]	1,400 (835–2,273)	247 (156–932)	538 (446–794)	1,266 (1,099–1,430)	800 (200–2,100)	500 (200–1,600)	300 (200–600)
T cells ($CD3^+$)[d]	3,651 (1,900–5,145)	1,343 (1,011–3,231)	1,850 (1,366–3,285)	2,775 (2,647–3,903)	2,300 (900–4,500)	1,900 (700–4,200)	1,500 (800–3,500)
$CD3^+$ and $CD4^+$ cells[d]	2,821 (1,256–3,490)	941 (383–2,190)	1,507 (1,040–3,084)	1,844 (1,679–2,680)	1,300 (500–2,400)	1,000 (300–2,000)	800 (400–2,100)
$CD3^+$ and $CD8^+$ cells[d]	852 (482–1,313)	620 (337–884)	188 (77–386)	1,034 (876–1,332)	800 (300–1,600)	800 (300–1,800)	400 (200–1,200)
NK cells ($CD3^-$, $CD56^+$, and $CD16^+$):							
Count[d]	128 (81–181)	32 (24–90)	37 (6–43)	50 (29–149)	400 (100–1,000)	300 (90–900)	300 (70–1,200)
Percentage[e] (%)	1–4	1–3	0–2	1–3	4–23	4–26	6–27

Note.—Normal values of the healthy controls were studied by Comans-Bitter et al. (1997).

[a] n = Number of blood samples from the patient.

[b] n = Number of healthy children tested to establish the normal values.

[c] For patients, range of ages at which samples were obtained; for healthy controls, range of ages for all children in that group.

[d] Data are cells/mm^3. For patients, values are median and range. For healthy controls, values are median and interquartile range (i.e., 5th–95th percentiles).

[e] For patients, the range of percentages of lymphocytes that were NK cells; for healthy controls, the interquartile range of the percentages of lymphocytes that were NK cells.

the pedigree into two parts. Two-point and multipoint LOD score values were calculated using GENEHUNTER (Kruglyak et al. 1996) and MERLIN (Abecasis and Wigginton 2005), under the assumption that the gene responsible for the defect was fully penetrant and autosomal recessive. We identified six chromosomal regions that were possibly linked with NK cell deficiency—that is, with a multipoint LOD score >1 after the primary genomewide scan.

In these regions (2p21, 2p15, 6q27, 7p22.2, 8p12-q12.2, and 8q24.13), we genotyped additional microsatellites (4, 3, 2, 2, 8, and 19 microsatellites, respectively) in the 13 members of the family who had been genotyped previously. This fine mapping increased the LOD score in only one region, 8p12-q12.2, which had already yielded the highest LOD score in the primary screen. We then genotyped 10 additional microsatellites in this region. The 18 markers covering the region were also genotyped in six additional healthy siblings of P1 (fig. 1). The results of the multipoint linkage analysis are shown in figure 2. A maximum LOD score of 4.51 was obtained at marker *D8S532*. The region of interest (8p11.23-q11.21) overlaps the centromeric region of chromosome 8 and ranges from *D8S1821* to *D8S1745* (3.2 cM). The four patients are homozygous for the same haplotype in this region. This corresponds to a physical distance of 12 Mb that contains 59 genes. Thirteen of the genes have been described as being expressed in lymphoid cells (*DKFZp586M1819, FNTA, VDAC3, GOLGA7, INDO, BLP1, PLEKHA2, TACC1, UBE2V2, CEBPD, IKBKB, POLB*, and *PRKDC*). Twelve knockout mice for genes in this region have been generated, including two mutants of lymphoid-expressed genes (*Polb, Prkdc, Snal2, Chrna6, Chrnb3, Vdac3, Plat, Ap3m2, Sfrp1, Adam2, Adam9*, and *Ank1*). One knockout (*Prkdc*) mouse presented with a lack of both T and B cells, but NK cells were not studied. In conclusion, our genomewide scan clearly identified a locus located on chromosome 8p11.23-q11.21 that is responsible for NK cell deficiency in this family, providing strong evidence that the patients had viral infections as a consequence of a primary defect of NK cell development.

We describe here the first multiplex kindred with a primary, selective deficit of NK cells. The four related

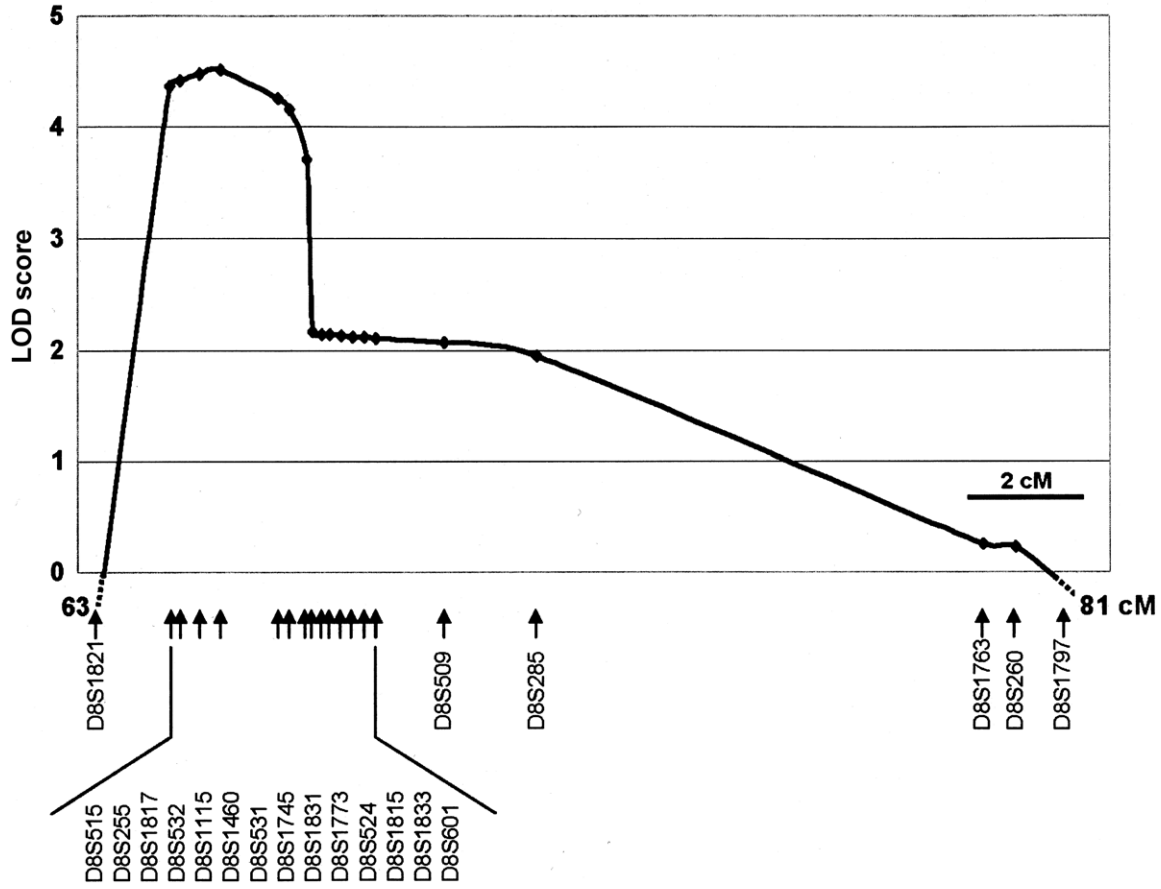

Figure 2 Multipoint linkage analysis of chromosome region 8p12-q12.2 by homozygosity mapping. Microsatellite positions are given in cM. A total of nine microsatellites were genotyped between *D8S1821* and *D8S1745*.

patients from a large inbred kindred of Irish nomadic descent had very small numbers of NK cells in blood. The other two cases of possible NK cell deficiency reported in the literature (Biron et al. 1989; Etzioni et al. 2005) were sporadic, so it is unclear whether NK cell deficiency was heritable, whereas heritability was clear in the multiplex kindred described here. The observation that three of the four children in whom the NK cell defect was found were ill with viral disease suggests that NK cell deficiency was a cause, rather than a consequence, of viral disease, such as the EBV-driven lymphoma diagnosed in the index patient. Moreover, that patient was seronegative for EBV nuclear antigen, which is reminiscent of the abnormal EBV serology documented in patients with the related disorder X-linked lymphoproliferative syndrome, characterized by low cytotoxic activity of NK cells and predisposition to EBV-driven lymphoma (Nichols et al. 2005). Unlike the two siblings we described in a previous study, who additionally had neutropenia, facial dysmorphy, and severe intrauterine growth retardation (Bernard et al. 2004), these four patients displayed no overt biological and clinical abnormalities other than NK cell deficiency and viral susceptibility, with the possible exception of growth retardation that may or may not have been secondary to infection. Above all, the conclusive identification (LOD score 4.51) of a single chromosomal region linked to NK cell deficiency by homozygosity mapping unambiguously indicates that NK cell deficiency was indeed inherited as a Mendelian trait and was probably responsible for susceptibility to viruses. We cannot exclude the possibility that the disease-causing locus governed susceptibility to viruses, which in turn resulted in NK deficiency. This is unlikely, however, because one of the four patients had NK deficiency in the absence of any known severe viral disease. The kindred studied therefore define a novel Mendelian disorder that should be registered in the McKusick catalog of Mendelian conditions of man (McKusick 1998). The identification of a region on chromosome 8 linked to NK cell deficiency should facilitate the search for the disease-causing gene. One of the patients with sporadic disease who were previously described as having NK cell deficiency, who was born to consanguineous parents (Etzioni et al. 2005), is heterozygous in this region (data not shown), which excludes the involvement of this candidate region in that patient's condition.

The occurrence of EBV-driven lymphoproliferative disorder in our index patient suggests that human NK cells are involved in anti-EBV immunity, antitumor immunity, or both. Three of the four patients were seropositive and controlled EBV primo-infection well clinically, which suggests that NK deficiency was involved in impaired control of latent EBV infection or tumor genesis rather than that of EBV primo-infection. Two of the four patients appeared to be vulnerable to other viruses—notably, those associated with pulmonary disease—although no specific virus could be documented. The patients were, however, resistant to other viruses, including some herpes viruses such as HSV and VZV, perhaps because of residual levels of NK cells. A longer follow-up period is required before we can draw firm conclusions about the range of susceptibility and resistance to viruses and tumors in these patients. The viral susceptibility of our index patient seems to be similar but not identical to those of the children described in previous studies who were given a diagnosis of possible NK cell deficiency, whose EBV status was unknown or negative, and who had VZV, HSV, and CMV infections (Biron et al. 1989; Bernard et al. 2004; Etzioni et al. 2005). Therefore, as in mice (Casanova et al. 2001; Lee et al. 2001; French and Yokoyama 2003), NK cells seem to be important for the control of viruses in humans. Interindividual differences in viral disease susceptibility may reflect the complex interplay between host and environmental factors in the course of infection (Casanova and Abel 2004, 2005). Clearly, more families with inherited NK cell deficiency must be identified before we can reach a comprehensive understanding of the function of human NK cells in host defenses. The identification of the genomic region on chromosome 8p11.23-q11.21 that controls NK cell development in our kindred should nonetheless shed new light on NK cell development.

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