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Mapping of a gene responsible for dermatitis in NOA (Naruto Research Institute Otsuka Atrichia) mice, an animal model of allergic dermatitis

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Abstract The NOA (Naruto Research Institute Otsuka Atrichia) mouse is an animal model of allergic or atopic dermatitis, a condition characterized by ulcerative skin lesions with accumulation of mast cells and increased serum IgE. These features of the murine disease closely resemble human atopy and atopic disorders. We performed linkage analysis in NOA back-cross progeny, as a step toward identifying and isolating a gene responsible for the NOA phenotype. We crossed NOA mice with five other murine strains (C57BL/6J, IQI, C3H/HeJ, DBA/2J, and BALB/cByJ) and then bred back-cross animals. Using microsatellite markers, we scanned the entire genomes of 559 N2 offspring from the five parental strains. Linkage analysis revealed a significant association between ulcerative skin lesions and markers on murine chromosome 14. Statistical analysis indicated that the critical region was assigned to the vicinity of D14Mit236 and D14Mit160.

Key words Atopic dermatitis · Animal model · Linkage analysis · Chromosome 14

Introduction

Atopy and atopic disorders, multifactorial diseases resulting from combinations of genetic and environmental influences, have been increasing significantly in Western countries (Coleman et al. 1997). Genetic associations were noted many years ago through observations of familial aggregation (Cooke and Vander Veer 1916; Rajka 1960). Although a large number of genetic investigations have been reported, the ways in which certain genes may predispose individuals to these diseases or contribute to their development are still not well understood because of the etiological complexity in humans. Hence, an animal model that develops a disease whose phenotype resembles human atopic diseases could be a promising approach. Appropriate murine models have already contributed to investigations into the pathogenesis of other multifactorial diseases in humans, such as asthma, diabetes mellitus, and essential hypertension (Blyth et al. 1996; Kloting et al. 1997; Joshi et al. 1997). From this point of view the Naruto Research Institute Otsuka Atrichia (NOA) mouse, a strain that develops severe ulcerative skin lesions that are associated with accumulation of mast cells, and also shows a significantly increased level of serum IgE (Kondo et al. 1997), is likely to be a good model for investigating genetic factors that underlie the development of severe allergic dermatitis.

From among various approaches we chose to attempt to localize such genes in NOA mice by linkage analysis. The mode of inheritance of dermatitis in NOA mice was recessive inheritance with incomplete penetrance. Here we report the chromosomal location of a major locus associated with the development of severe allergic dermatitis in this murine strain, and document evidence that differences in genetic background among the parental strains used for breeding back-cross animals significantly affected the incidence of skin lesions.

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Materials and methods

Animals

NOA mice, a strain developed at the Naruto Research Institute Otsuka Pharmaceutical Factory, (Naruto, Japan), were bred at Clea Japan (Shirakawa, Japan). We crossed male NOA mice with female mice with five different genetic backgrounds (strains C57BL/6J, IQI, C3H/HeJ, DBA/2J,

and BALB/cByJ). We then back-crossed only the female F1 progeny, because female NOA mice are unable to provide milk to their offspring due to dermatitis on their nipples. N2 offspring were examined for the absence or presence of ulcerative skin lesions.

Linkage studies

Genomic DNAs were isolated from the tail tips of the N2 population by standard techniques (Siracusa et al. 1989; Pavan and Tilghman 1994). We initially scanned the entire genome of each animal, using microsatellite markers selected at 10- to 20-cM intervals. Also examined were markers adjacent to genes whose homologues may be candidates for human atopic disorders, such as interleukin (IL)4 (Marsh et al. 1994), IL5 (Kapp and Zeck-Kapp 1991), IL4R (Hershey et al. 1997), HLA (Levine et al. 1972; Marsh et al. 1991; Blumenthal et al. 1992), and FCεRIβ (Cookson et al. 1989; Sandford et al. 1993; Shirakawa et al. 1994). Primer sequences for amplifying each marker locus were obtained through the database at the Mouse Genome Informatics (MGI) web site (distributed via World Wide Web, URL: http://mgd.niai.affrc.go.jp/strtools.html). Oligonucleotide primers were synthesized by means of the Oligo 1000M DNA Synthesizer (Beckman, Palo Alto, CA, USA). Polymerase chain reaction (PCR) amplifications were performed as described by Dietrich and associates (1992). PCR conditions for most primers involved a denaturation step at 94°C for 2 min, followed by 35 cycles of 94°C for 30 s, 55°C–57°C for 30 s, 72°C for 30 s, and extension at 72°C for 7 min, in a Gene Amp PCR system 9,600 (Perkin Elmer Cetus, Norwalk, CT, USA). PCR products were electrophoresed on 4% agarose or 6% polyacrylamide gels, and stained with ethidium bromide.

Statistical analysis

The number of affected or non-affected mice, and whether each was a recombinant, were calculated for each marker locus. To identify the locus associated with dermatitis, the resulting segregation ratios were analyzed by the χ^2 test.

Results

Among a total of 559 N2 offspring examined, 158 (28.3%) developed ulcerative skin lesions (Table 1). These lesions developed as early as 6 weeks of age in DBA/2J, 13 weeks in BALB/cByJ, 18 weeks in IQI and C57BL/6J, and 24 weeks in C3H/HeJ descendants (Fig. 1). The incidence was not consistent with an autosomal recessive mode, and it clearly differed according to parental strain. The incidence of skin lesions when we used IQI (27.1%), DBA/2J (31.4%), or BALB/cByJ (38.8%) as parental strains was about three times higher than that among C57BL/6J (10.6%) or C3H/HeJ (12.2%) N2 progeny.

In a whole-genome scan, using a total of 243 markers on 19 autosomal chromosomes, the number of informative

Table 1. Ratio of affected mice among N2 offspring

Strain of F1 parent	Dermatitis+	Total	Susceptibility(%)
C57BL	9	85	10.6
IQI	19	70	27.1
C3H	6	49	12.2
DBA	58	185	31.4
BALB	66	170	38.8
	158	559	28.3

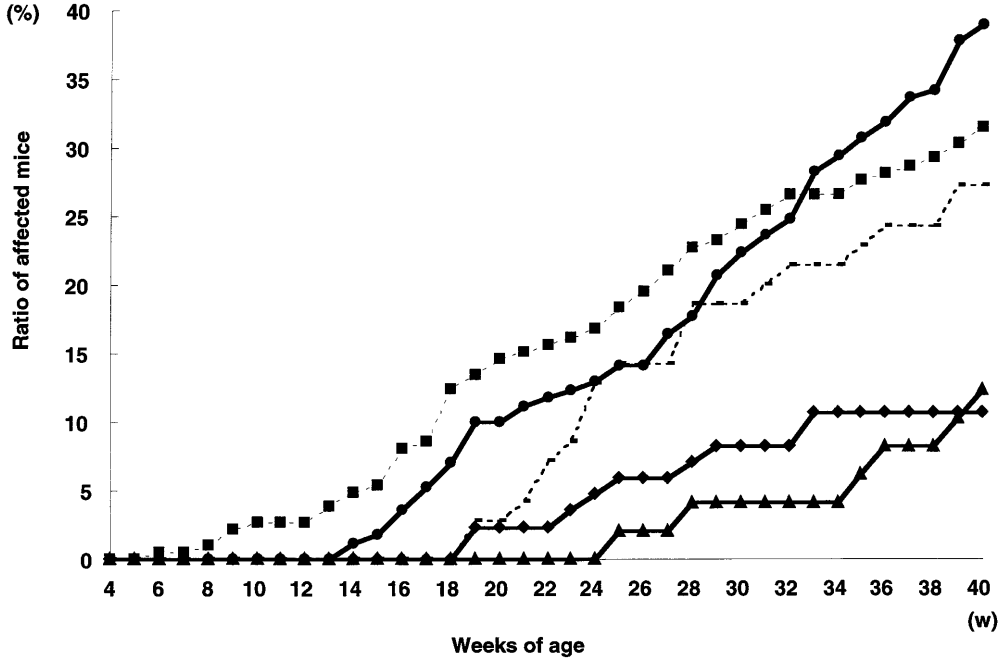

Fig. 1. Incidence of dermatitis in N2 offspring. The *vertical axis* indicates the ratio of the number of affected mice to the total number of N2 progeny. Strains: C57BL (n = 85; *diamonds*; IQI (n = 70; *small rectangles on dashed line*; C3H (n = 49; *triangles*; DBA (n = 185; *squares*); BALB (n = 170; *closed circles*)

Fig. 2. Whole-genome scan, using 243 markers on 19 murine autosomes. The numbers of affected or non-affected mice, and whether recombinant or not, are shown for each marker locus. *IL10* (interleukin 10), *FcεRIγ* (high-affinity immunoglobulin E receptor γ), *FcεRIα* (high-affinity immunoglobulin E receptor α), *CD72* (CD72 antigen), *TCRβ* (T-cell receptor-β), *IL4R* (interleukin 4 receptor), *IL4* (interleukin 4), *IL5* (interleukin 5), *IgH* (immunoglobulin H), *TCRγ* (T-cell receptor-γ), *IL9* (interleukin 9), *TCRα* (T-cell receptor-α), *MHC* (major histocompatibility complex), and *FcεRIβ* (high-affinity immunoglobulin E receptor β) have been reported as candidate genes for atopic dermatitis in humans. *Homo*, Homozygous; *hetero*, heterozygous

	cM	Dermatitis+		Dermatitis-		Total
		Homo	Hetero	Homo	Hetero	
D1Mit 432	15.0	33	37	109	115	294
D1Mit 213	25.7	14	18	54	45	131
D1Mit 380	36.9	28	34	75	71	208
D1Mit 7	41.0	28	33	54	44	159
D1Mit 415	52.0	21	23	23	25	92
D1Mit 157	58.7	30	30	57	41	158
D1Mit 187	62.0	24	27	64	61	176
IL10	69.9					
D1Mit 196	71.5	31	24	46	38	139
D1Mit 42	78.0	20	22	24	24	90
D1Mit 145	87.4	20	24	21	27	92
FCεRIγ	93.3					
FCεRIα	94.2					
D1Mit 206	95.8	21	16	58	66	161
D1Mit 291	101.5	37	37	82	92	248
D1Mit 209	110.4	7	5	34	43	89
D2Mit 521	15.3	19	25	27	19	90
D2Mit 369	27.3	8	11	30	21	70
D2Mit 379	38.3	25	38	56	42	161
D2Mit 332	48.1	10	18	42	63	133
D2Mit 58	60.0	5	15	21	32	73
D2Mit 255	69.0	20	30	26	25	101
D2Mit 194	81.4	30	33	55	43	161
D2Mit 226	96.0	11	17	49	39	116
D3Mit 221	2.4	38	34	84	83	239
D3Mit 268	13.8	24	19	22	26	91
D3Mit 182	23.3	24	20	23	25	92
D3Mit 199	33.7	15	13	55	50	133
D3Mit 141	45.2	23	21	24	24	92
D3Mit 158	52.5	15	13	32	24	84
D3Mit 110	64.1	19	30	85	84	218
D3Mit 200	77.3	20	24	23	25	92
D3Mit 129	85.0	21	23	23	25	92
D4Mit 235	1.9	7	5	33	42	87
D4Mit 172	8.6	26	18	47	51	142
D4Mit 108	12.1	30	21	46	76	173
D4Mit 272	21.9	27	17	17	31	92
CD72	22.5					
D4Mit 26	42.5	33	30	48	51	162
D4Mit 145	44.5	28	24	49	76	177
D4Mit 146	53.6	23	21	19	29	92
D4Mit 203	60.0	32	31	70	77	210
D4Mit 233	69.0	21	20	19	26	86
D4Mit 160	76.0	23	21	21	27	92
D5Mit 346	1.0	8	20	24	31	83
D5Mit 294	8.0	14	22	82	97	215
D5Mit 386	14.0	9	18	22	34	83
D5Mit 182	24.0	12	16	27	28	83
D5Mit 254	34.0	16	27	26	22	91
D5Mit 134	41.0	19	25	45	51	140
D5Mit 93	54.0	23	21	23	24	91
D5Mit 338	59.0	23	24	69	86	202
D5Mit 161	70.0	22	22	21	27	92
D5Mit 31	80.0	15	13	25	28	81
D6Mit 1	3.0	17	10	52	49	128
D6Mit 17	17.5	13	31	30	18	92
TCRβ	20.5					
D6Mit 273	19.0	17	38	67	57	179
D6Mit 243	30.5	13	31	30	17	91
D6Mit 213	37.0	2	5	34	38	79
D6Mit 55	50.0	11	8	20	31	70
D6Mit 110	63.9	11	17	29	27	84
D6Mit 137	71.0	14	14	26	28	82
D7Mit 178	1.5	31	32	44	55	162
D7Mit 117	11.0	13	15	27	28	83
D7Mit 27	23.0	17	27	27	21	92
D7Mit 230	44.0	19	25	25	23	92
D7Mit 206	60.0	38	37	105	114	294
IL4R	62.0					
D7Mit 15	71.0	36	35	84	85	240
D8Mit 155	1.0	17	11	27	28	83
D8Mit 258	15.0	42	45	106	97	290
D8Mit 65	22.5	26	29	60	66	181
D8Mit 128	31.0	34	28	35	53	150
D8Mit 107	43.0	5	7	38	38	88
D8Mit 113	52.0	31	32	66	82	211
D8Mit 200	60.1	15	10	24	25	74
D8Mit 56	73.0	20	23	19	29	91

	cM	Dermatitis+		Dermatitis-		Total
		Homo	Hetero	Homo	Hetero	
D9Mit 90	7.7	25	19	20	28	92
D9Mit 286	17.5	4	8	32	45	89
D9Mit 133	43.0	7	24	56	68	155
D9Mit 181	48.0	26	35	43	54	158
D9Mit 214	61.2	9	18	58	69	154
D10Mit 168	9.0	39	24	47	52	162
D10Mit 106	20.0	14	12	29	25	80
D10Mit 42	41.5	18	26	27	21	92
D10Mit 134	57.9	18	26	27	20	91
D10Mit 237	67.5	17	27	30	18	92
D10Mit 297	75.4	13	15	23	33	84
D11Mit 74	0.0	17	29	62	45	153
D11Mit 80	10.0	34	27	47	51	159
D11Mit 110	19.0	32	30	47	52	161
IL4	28.0					
IL5	28.0					
D11Mit 140	28.0	34	27	75	73	209
D11Mit 320	39.3	24	32	62	64	182
D11Mit 36	48.5	18	20	24	24	86
D11Mit 286	52.0	21	23	27	21	92
D11Mit 99	59.5	24	20	27	21	92
D11Mit 199	62.0	34	29	48	48	159
D11Mit 128	73.0	23	21	22	22	88
D12Mit 106	8.7	16	12	27	29	84
D12Mit 46	17.0	12	7	23	26	68
D12Mit 210	28.0	9	10	25	25	69
D12Mit 214	37.0	15	13	29	27	84
IgH	58.0					
D12Mit 19	58.0	19	19	27	21	86
D13Mit 16	0.0	7	12	23	28	70
D13Mit 3	9.0	10	19	61	65	155
TCRγ	10.0					
D13Mit 179	30.0	15	12	36	20	83
IL9	33.0					
D13Mit 290	40.4	25	19	23	23	90
D13Mit 147	51.0	25	21	60	47	153
D13Mit 213	59.0	42	29	54	50	175
D13Mit 151	71.0	53	36	80	75	244
D14Mit 10	3.0	25	19	23	25	92
D14Mit 14	10.0	44	18	39	56	157
TCRα	19.5					
D14Mit 234	22.5	39	5	17	31	92
D14Mit 113	25.0	46	6	51	74	177
D14Mit 236	32.5	101	2	17	39	159
D14Mit 160	40.0	85	5	53	101	244
D14Mit 225	42.5	50	3	32	40	125
D14Mit 165	52.0	56	16	42	59	173
D15Mit 13	6.7	17	24	24	24	89
D15Mit 111	17.8	19	23	22	24	88
D15Mit 121	29.3	33	23	53	72	181
D15Mit 234	40.9	15	13	27	29	84
D15Mit 159	52.0	25	18	48	56	147
D15Mit 149	60.0	22	20	22	25	89
D16Mit 131	4.3	2	9	34	41	86
D16Mit 110	21.0	22	20	20	27	89
D16Mit 84	32.3	4	8	39	38	89
D16Mit 76	43.0	4	8	46	29	87
D16Mit 152	57.0	26	18	19	29	92
D17Mit 113	6.5	22	22	26	22	92
D17Mit 173	11.8	26	29	62	62	179
MHC	18.6					
D17Mit 24	20.4	14	17	65	64	160
D17Mit 39	30.2	9	7	18	31	65
D17Mit 89	36.0	34	29	46	50	159
D17Mit 122	51.9	24	20	22	26	92
D17Mit 130	55.7	25	18	21	22	86
D18Mit 64	2.0	23	31	60	54	168
D18Mit 111	11.0	6	6	43	34	89
D18Mit 17	20.0	11	8	24	20	63
D18Mit 105	25.0	15	13	24	31	83
D18Mit 209	41.0	15	13	22	34	84
D18Mit 7	50.0	18	26	24	24	92
D19Mit 59	0.5	2	6	37	40	85
D19Mit 68	6.0	30	16	53	53	152
FcεRIβ	8.0					
D19Mit 16	15.0	23	21	21	27	92
D19Mit 106	22.0	41	34	87	90	252
D19Mit 88	34.0	20	22	22	26	90
D19Mit 123	51.0	15	13	63	58	149
D19Mit 71	54.0	28	19	51	54	152

Table 2. Association of dermatitis and microsatellite markers on chromosome 14

Primer	Dermatitis(+) cM	Homo	Hetero	χ^2	*P*
D14Mit10	3.0	7	6	0.14	0.7040
D14Mit14	10.0	44	18	13.47	<0.001
TCRα	19.5				
D14Mit234	22.5	40	5	27.99	<0.001
D14Mit113	25.0	46	6	33.68	<0.001
D14Mit236	32.5	101	2	86.89	<0.001
D14Mit160	40.0	89	5	86.62	<0.001
D14Mit225	42.5	46	3	31.79	<0.001
D14Mit165	52.0	56	16	22.42	<0.001

Homo, Homozygous; hetero, heterozygous

cases at a given locus varied because informativeness at each locus was different depending on the parental strain from which the N2 progeny had been derived. We found no significant associations between dermatitis and any marker loci lying in regions syntenic to human chromosomal regions that contain candidate genes thought to be associated with human atopic disorders (Fig. 2). However, we found a significant linkage between skin lesions and markers in the middle of mouse chromosome 14. As shown in Table 2, the most likely position to contain alleles conferring susceptibility to dermatitis was assigned to the vicinity of D14Mit236 and D14Mit160 ($\chi^2 = 86.89$; $P < 0.001$ for D14Mit236 and $\chi^2 = 86.62$; $P < 0.001$ for D14Mit160; Table 2).

Discussion

Atopy and atopic disorders are considered to be multifactorial diseases involving both genetic and environmental influences (Coleman et al. 1997). Since the environmental and nutritional conditions affecting atopic patients vary enormously, it is extremely difficult to identify genes that confer susceptibility or that are associated with the etiology of these diseases in humans. Hence, an animal model that resembles the human phenotype could contribute to investigations of the pathogenesis of atopic disorders. The NOA mouse can serve that function.

In the study reported here, the incidence of dermatitis in N2 offspring was higher when we crossed NOA mice with BALB/cByJ, IQI, or DBA/2J strains than when C57BL/6J and C3H/HeJ mice were the parental strains (Table 1). Moreover, the age of disease onset in descendants of BALB/cByJ or DBA/2J mice was earlier than in the others (Fig. 1). Recently, Leung (1997) reported that the immunoregulatory disorder known as atopic dermatitis in humans resulted from an imbalance of the helper T-lymphocytes that release cytokines. At present, murine and human CD4+ T-helper cells are classified as either Th-1 or Th-2 on the basis of their cytokine-expression profiles (Mosmann et al. 1986). Th-1 cells are characterized by the secretion of γ-interferon (IFN-γ); Th-2 cells are known to produce interleukin (IL)-4. IFN-γ inhibits the differentiation of Th-2 cells and suppresses IgE synthesis (Vercelli and Geha 1993; Lung 1997). Thepen et al. (1996) have indicated that elevated production of IgE and Th-2 cytokines plays an important role in the pathogenesis of atopic dermatitis. Among the five mouse strains we mated with the NOA mice, BALB/cByJ and DBA/2J are known to have Th-2-dominant immunity (Heinzel et al. 1993; Shankar and Titus 1995). The N2 progeny from those parental lines exhibited a higher incidence and earlier onset of the disease than did descendants of C57BL/6J or C3H/HeJ mice, which carry Th-1-dominant immunity (Heinzel et al. 1993; Shankar and Titus 1995). Our results therefore support the idea that Th-2 dominant immunity increases susceptibility to, and is associated with, atopic dermatitis.

Among a total of 158 affected mice examined, 153 had a hairless phenotype. Therefore we examined the Hairless (*hr*) gene on mouse chromosome 14 (Cachon-Gonzalez et al. 1994) for its level of expression and possible genetic alterations. However, as we found no genetic changes or altered levels of expression in those experiments, it is unlikely that *hr* plays any important role in dermatitis among NOA mice.

Our linkage study based on genome-wide scanning strongly indicated that a gene capable of conferring susceptibility to atopic dermatitis lies within an interval of approximately 17.5 cM between D14Mit113 and D14Mit225 on mouse chromosome 14. The murine T-cell receptor-alpha (*TCR*-α) gene, whose product modifies specific IgE responses (Moffatt et al. 1994), is located in the proximal part of the candidate region. However, markers D14Mit14 and D14Mit234 near the TCR-α locus revealed relatively frequent recombination with respect to the dermatitis phenotype, while distal markers were involved in fewer recombination events. Therefore we assume that TCR-α is not a likely candidate for dermatitis in NOA mice. A computer search of databases, including the mouse-human comparative map, failed to identify in the region any other murine homologues of genes that had been reported as candidates for this disease in humans. Nevertheless, since this 17.5-cM region of murine chromosome 14 must contain dozens of genes, it will be useful to construct a more detailed genetic map with a view toward positional cloning of the putative dermatitis-associated gene.

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