〔Symposium I〕

A 28 (Symp. I)

COMMON DISEASES AND GENETICS: AN INTRODUCTORY REMARKS

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Studies on genetic factors for common diseases are steadily progressing using techniques for molecular genetics. The elucidation of genotypes strongly associated with a common disease makes it possible to prevent the disease by early diagnosis followed by controls of environmental factors and life styles, and medication in some cases. Analysis of the genes and/or genotypes for LDL receptor and apolipoprotein(a) is a case in point for the prevention of coronary heart disease. Molecular genetic studies of common diseases such as atherosclerosis have also clarified the presence of extreme heterogeneity in genetic factors: a major gene is involved in some families and an interaction of a major gene and a polymeric gene is responsible for in some individuals. In addition, the presence of polymorphic defective genes such as plasminogen with type I mutation and apolipoprotein E2 have been reported.

In this symposium, three specialists will report recent progress of molecular and clinical genetic studies on atherosclerosis and diabetes mellitus .

A 29 (Symp. I)

ATHEROSCLEROSIS AND GENETICS: CLINICAL ASPECTS OF GENETIC DISORDERS OF LIPOPROTEIN METABOLISM.

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Elevated levels of low-density lipoprotein (LDL) are strongly associated with coronary atherosclerosis, while those of high-density lipoprotein (HDL), known as "antiatherogenic" lipoprotein, are negatively correlated with coronary heart disease (CHD). Familial hypercholesterolemia (FH) is a common, autosomal dominant disorder occurring in approximately one in 500 people in Japan as well as in Western countries. FH is frequently associated with premature CHD, and 65% of the heterozygotes and all the homozygotes die of CHD. FH is characterized by a defect in LDL metabolism produced by mutations in the LDL receptor gene. The human LDL receptor gene is in the short arm of chromosome 19. We found 4 new variants of the LDL receptor gene - FH-Tonami-1, FH-Tonami-2, FH-Okayama, and FH-Kanazawa - through analysis of DNA samples from the members of 200 unrelated Japanese families. The ligand protein of LDL responsible for its recognition by the LDL receptor is apolipoprotein B (apo B)-100. We found two patients with familial defective apolipoprotein B-100 (FDB) which gives rise to a dominantly inherited increase in plasma LDL concentration and produces clincial and biochemical signs indistinguishable from those of classical FH.

Familial hyper-HDL-emia has been known to be associated with longevity due to resistance to atherosclerosis, a condition called "longevity syndrome". The plasma cholesteryl-ester transfer protein (CETP), a hydrophobic glycoprotein with a molecular mass of 74,000, facilitates the transfer of cholesteryl esters from HDL to lipoproteins containing apolipoprotein B. We recently found a family with increased HDL levels produced by the CETP deficiency due to a point mutation (G-->A) in the splice donor site of intron 14 of the CETP gene. We found the same CETP gene mutation in four families from three different regions of Japan. There was no evidence of premature atherosclerosis in the families with DETP deficiency. The lipoprotein profile of the persons with CETP deficiency is potentially antiatherogenic and may be associated with an increased life span.

A 30 (Symp. I)

GENETIC RISK FACTORS FOR ATHEROSCLEROSIS. Tadao ARINAMI (Dept. Med. Genet., Univ. of Tsukuba, Tsukuba)

Genes associated with premature coronary heart disease (CHD) or possibly involved in CHD in the Japanese population are reported. Family studies on the low density lipoprotein (LDL) receptor gene showed that most, if not all, relatively severe hereditary hypercholesterolemia associated with Achilles tendon xanthomas is caused by a defect of the LDL receptor gene, and that the origins of the mutant LDL receptor genes generally differ among different pedigrees. As to the genetic polymorphism of apolipoprotein E (apoE) which is under the control of three common alleles and associated with hypercholesterolemia, sequence analysis in 34 $\varepsilon 2$ alleles and in 75 $\varepsilon 4$ alleles revealed that 30 (about 90%) of the $\varepsilon 2$ alleles are the type for the $Arg_{158} \rightarrow Cys$ substitution and all $\varepsilon 4$ alleles are the type for $Cys_{112} \rightarrow Arg$ substitution. Serum Lp(a) levels are fairly determined by genetic factors, particularly highly polymorphic molecular weights of apolipoprotein (a) (apo(a)). At least 24 phenotypes of apo(a) are identified by our modified electrophoretic method. The distribution of apo(a) phenotypes is found to be similar to those reported in Caucasians. Association of high level plasma Lp(a) concentrations with CHD is also presented in the Japanese population. An inactive plasminogen phenotype, M5, is found in 2–4 % of the Japanese. Our data indicate that M5 is identical with plasminogen Tochigi ($Ala_{601} \rightarrow$ Thr).

A 31 (Symp. I)

MOLECULAR GENETICS OF NON INSULIN DEPENDENT DIABETES MELLITUS(NIDDM) TAKASHI KADOWAKI Third Department of Internal Medicine, University of Tokyo, Tokyo, Japan 113

NIDDM is a genetic disorder characterized by insulin resistance and ß-cell dysfunction. Mutations in the insulin receptor and insulin genes can cause diabetes. Mutations in the insulin receptor gene have been identified in patients with extreme insulin resistance such as well as obesity and NIDDM. To screen patients with diabetes for mutations in these genes and the GLUT4 gene,we have been employing direct sequencing and/or single-strand conformation polymor-phisms of PCR-amplified genomic DNA. Relevance of mutations identified in these genes to the pathogenesis of NIDDM will be discussed.

A 32

POSSIBLE MAPPING OF THE GENE RESPONSIBLE FOR TRANSIENT ABNORMAL MYELOPOIESIS (TAM) AT 21q11.2. Kyohko ABE, Naoki HARADA (Kyushu Med. Sci. Nagasaki Labor., Nagasaki), Han-Xiang DENG, Norio NIIKAWA (Dept. Hum. Genet., Nagasaki Univ. Sch. Med.), Ichiro MATSUDA (Dept. Pediatr., Kumamoto Univ. Sch. Med.), Yoshimitsu FUKUSHIMA (Div. Med. Genet., Saitama Child. Hosp.), Yasuhiko KANEKO (Dept. Labor. Med., Saitama Cancer Ctr.), Tadashi KAJII (Dept. Pediatr., Yamaguchi Univ. Sch. Med.)

The parental origin of the extra chromosome # 21 was studied in 20 patients with trisomy 21-associated TAM, using chromosome heteromorphisms as markers; this was combined a study of RFLPs in 5 patients. Of these, 10 were shown to result from duplication of a parental #21, viz, maternal in 8 and paternal in 2. A patient showed a 47,XY,-21,+inv(21)(q11.2q22.13)mat,+inv(21)(q11.2q22.13)mat karyotype. These findings supported our hypothesis of "disomic homozygosity" of a mutant gene on #21 in 21-trisomic cells as being a mechanism responsible for the occurrence of TAM. It also suggests that the putative TAM gene is located either at 21q11.2 or at 21q22.13, assuming that the gene is interrupted at either site due to the inv(21). The study of 5 patients using RFLPs detected a cross-over site on the duplicated #21 between 21q11.2 and 21q21.3. The combined observations finally suggest that the TAM gene is located at 21q11.2.

A 33

PARENTAL ORIGIN OF MUTATION OF RB GENE IN THE DEVELOPMENT OF RETINOBLASTOMA. Masao S. SASAKI, Mitsuo KATO, Yosuke EJIMA, and Kanji ISHIZAKI (Radiation Biol. Center, Kyoto Univ., Kyoto)

Loss of function mutation of RB gene is responsible for the development of retinoblastoma. The new mutations are either germinal or somatic, leading to the development of sporadic bilateral and sporadic unilateral retinoblastoma, respectively. We studied the parental origin of new germinal mutations involving RB gene and that of chromosomes which harbor the initial somatic mutations by the use of polymorphic chromosome- and DNA-markers on chromosome 13 in the normal somatic and tumor cells. As a result, 11 out of 12 chromosome mutations (gross interstitial deletions and translocations involving 13q14) and 4 out of 4 subvisible mutations of the germinal origin were of the paternal origin. In the sporadic unilateral tumors, the paternally derived allele was lost in 5 out of 7 tumors. Examination of the loss of heterozygosity (LOH) on chromosome 13 revealed that the frequency of LOH was much higher (86%) in the sporadic unilateral tumors as compared with that in the bilateral tumors (48%). When these observations are combined, it is assumed that approximately 70% of the initial somatic mutations are deletion mutations which are themselves manifested as LOH and also show a strong bias towards the paternally derived copy of genes. The preferential involvement of paternally derived RB gene in the development of sporadic unilateral tumors indicates the germinal origin of mutations possibly mediated by pre-mutations and/or mutational mosaicism.

A 34

CHROMOSOME ABNORMALITIES OBSERVED IN RENAL CELL CARCINOMA FROM A PATIENT WITH VON HIPPEL-LINDAU SYNDROME. Mitsuaki A. YOSHIDA[1], Taro SHUIN[2], Naoki SAKAI[2], Tatsuro IKEUCHI[1] and Akira TONOMURA[1] ([1]Dept. Cytogenet., Med. Res. Inst., Tokyo Med. & Dent. Univ., Tokyo, [2]Dept. Urology, Sch. Med., Yokohama City Univ., Yokohama)

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant disorder characterized by predisposition to a variety of benign and malignant tumors in certain organs. The most frequent clinical lesions are retinal angiomas, cerebellar hemangioblastomas, renal cell carcinomas(RCC) and pheochromocytomas. The RCC is particularly a frequent cause of death in this disorder. Chromosome study was performed on a renal cell carcinoma developed in a Japanese patient with sporadic VHL syndrome. Detailed analysis with Q-banding technique demostrated monosomy #3 and trisomy #5 as highly clonal abnormalities. These numerical changes were simultaneously identified in approximately 77 % of metaphases analyzed. Trisomy of chromosome 7 was also observed in two metaphases without showing the chromosome 3 abnormality. These findings were consistent with the data from VHL-RCCs published by others. The literature study including the present case indicated that the commonly deleted region in VHL-RCCs was #3p14-pter, which includes the site of a putative tumor suppressor gene(s), #3p14-p21, associated with the development of sporadic RCC.

A 35

CHROMOSOME REARRANGEMENT, t(6;14)(p21.1;q32.3), IN THREE PATIENTS WITH PLASMA CELL LEUKEMIA OR MULTIPLE MYELOMA.
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Recurrent rearrangements of chromosome 14q32.3 have been known in human mature B-lymphoid malignancies. We recognized a t(6;14)(p21.1;q32.3) in three patients with plasma cell leukemia or multiple myeloma. Case 1 was a non-producer type plasma cell leukemia. Chromosome analysis by short-term culture of peripheral leukocytes revealed abnormal karyotype: 46,XX, del(1)(p13), t(6;14)(p21.1;q32). Case 2 was a multiple myeloma (Bence Jones-lambda type) associated with acute myelogenous leukemia. Karyotype of bone marrow cells showed 46,XY,-15,t(6;14)(p21.1;q32.3),+der(15)t(1;15)(q23;q24). Case 3 was a multiple myeloma (Bence Jones-lambda type) with systemic subcutaneous metastasis. Karyotype from a subcutaneous nodule showed 49,XY,-1,-6,+9,-14,+17,i(1)(p32),del(14)(q22q32),+der(14)t(6;14)(p21.1;q32.3),+mar1,+mar2. Thus, t(6;14) may constitute a new class of the specific translocations involved in B-cell malignancies. We discess the clinical, hematological, immunological, and cytogenetic aspects of plasma cell neoplasia with t(6;14).

A 36

GIANT RING AND GIANT MARKER CHROMOSOMES, BEING APART IN TWO CLONES OF BONE MARROW CELLS WITH A Ph POSITIVE ACUTE LYMPHOCYTIC LEUKEMIA.
Tamiko SHINOHARA(Dept. Hum.Cytogenet., Japan Red Cross Med. Centr., Tokyo). Kouichi INOKUCHI, Kazuo DAN and Takeo NOMURA(Dept. Internal Medicine, Nihon Medical Collage, Tokyo)

The cytogenetic analysis of bone marrow cells from a 54 year-old woman with a Ph positive acute lymphocytic leukemia(ALL L2) is reported. The patient was pointed out enlarged lymph nodes of the neck and was admitted to the Nihon Med. Collage Hospital in July 1990. Her bone marrow aspirate was hypercellular, contained 88.4% blasts, which were POX, SBB and NBest negative, TdT positive. Surface marker study showed that CD10, CD19 and HLA-DR were positive. She was diagnosed as ALL L2. Chromosome analysis of bone marrow cells showed 46,XX,-1,t(9;22)(q34;q11),del(9)(p13),+Giant r/46,XX,-1,t(9;22)(q34;q11),del(9)(p13),+Giant m/46,XX. Giant r was 87%, giant m 3%. Giant ring chromosome seemed to include the abnormal chromosome, 1pter→cen→1q32::1q21→1q32::1q23→1q32::1q25→1qter. Moreover, giant marker chromosome had a tandem duplication of 1q(q21→q32) and had a translocation of 1q(q23→q32::q25→q32) to the terminal of the short arm of No.1 invertively. We considered that giant marker chromosome was made of giant ring chromosome in which second q32 region probably separated. We report very rare chromosome abnormalities in bone marrow cells of ALL L2 patient.

A 37

CHROMOSOME INSTABILITY IN THE LYMPHOCYTES OF MULTIPLE ENDOCRINE NEOPLASIA(TYPE I AND TYPE II).
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The multiple endocrine neoplasia type I and type II(MEN I, MEN II) are autosomal dominant disorders in which tumors or hyperplasia are formed in two or more organs such as parathyroid glands and anterior pituitary. Lymphocyte chromosomes from a MEN I patient having anterior pituitary tumor(from her sisters and children also) and five MEN II patients with medullary thyroid carcinoma were studied for the genetic instability. In one MEN I patient, chromosome type aberrations such as dicentrics, rings, minutes and deletions were found in 20% of the observed cells. In three of the five MEN II patients a slight increase of this type of aberration was also detected in 6.4, 4.3 and 1.1% of the observed cells, respectively. Frequencies of spontaneous chromatid type aberration in both MEN I and II patients were not significantly higher than these of controls. In the five MEN II patients, no increase of MTX-induced chromatid breaks nor unique fragile sites were observed. High incidence of chromosome instability in the lymphocytes of MEN I and II patients presents interesting observation to understand the genetic pathology prone to the tumor development or acquition of more advanced stage tumors.

A 38

CYTOGENETIC STUDY IN MINUTE MARKER CHROMOSOME ON MPDS AND MDS
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We performed the cytogenetic investigation on 6 cases of patients of MPDS (MMM/1 case) and MDS(RA/2 cases, RAEB/3 cases). It's average age was 66.5 years old. And the karyotypes with missing normal #20 chromosome and with small metacentric chromosome were observed in each case. Then, in order to establishthe mechanism for the derivation of this metacentric marker chromosome, we performed C-band, NOR, and *In Situ* chromosome hybridyzation with D20Z1 alpha-satellite DNA and telomere oligo DNA.
These minute metacentric chromosomes were identified as psu dic(20)(qter→q13:: q11→cen→p11::p11→q11::q13→qter) by previous conventional banding and molecular genetic procedures. Moreover, the hypothetical mechanism of its derivation was thought to be caused from the two steps; first, interstitial deletion of long arm of #20 chromosome, second, the deletion of short arm of its 20q- and the sister union through replication.

A 39

CYTOGENETIC AND MOLECULAR-GENETIC FINDINGS IN JAPANESE WILMS' TUMOR. Yasuhiko KANEKO, Chieko HOMMA, Nobuo MASEKI, Masaharu SAKURAI, Hiroyuki MIYOSHI (Saitama Cancer Center, Ina, Saitama)

The incidence of Wilms' tumor in Asian children was only one half of that in Caucasian children. We studied the chromosome and molecular-genetic patterns in the Japanese tumors and compared them with those reported in the Caucasian tumors, to clarify whether the difference in the incidence reflects differences in karyotype or genetic changes. There were no difference in the distribution of the tumor cell ploidies or in the presence of the tumors with the 11p13 abnormalities between the two populations. Homozygous deletion of WT1 in 11p13 was found in 8% (3/37) of the Japanese tumors and 3% (3/95) of the Caucasian tumors. LOH of the 11p13-pter region and that limited to the 11p15-pter region were found in 26% (5/19) and 0% (0/19), respectively, of the Japanese tumors. LOH of the 11p13-pter region and that of the 11p15-pter region were found in 16% (13/79) and 14% (11/79), respectively, of the Caucasian tumors. The increased incidence may be caused by that Caucasian children may have more tumors with the genetic changes not involving WT1 than Japanese children.

A 40

ABERRANT EXPRESSION OF HUMAN IL-3 GENE IN A LUNG CANCER CELL LINE. Takeshi OTSUKA, Takanori TESHIMA, Tsunefumi SHIBUYA, Mine HARADA, Hironobu Satoh, Yoshiyuki NIHO
(The 1st Dept. Int. Med., Kyushu Univ. Fukuoka)

Based on the previous experiment, human lung cancer cell line (KMNT) was revealed to express IL-3 gene constitutively. However, the IL-3 gene transcript was about 400 bases shorter than that expressed in activated peripheral blood mononuclear cells. By RT-PCR analysis, this transcript did not have sequences of 3' untranslated region of IL-3 gene. By sequencincing of the cDNA, there were two mutations at the 3' untranslated region and poly A tails attached at the position 631 , which is 291 bp 5' upstream of the reported poly A attaching site. There was no alteration of the sequence in the open reading frame and its gene product was observed by in situ hybridization by using antibodies against human IL-3.

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SEPARATION OF PROTEIN FACTORS CORRESPONDING TO THE SEVEN COMPLEMENTATION GROUPS OF XERODERMA PIGMENTOSUM AND ITS APPLICATION TO A DIAGNOSIS. Masaru YAMAIZUMI, Satoshi TATEISHI, Seiichi MORI and Tatsuo SUGANO (Inst. Medical Genetics, Kumamoto Univ. Medical School, Kumamoto)

Hela cell extract contains factors which correct the defect of DNA repair in XP cells belonging to the seven complementation groups (A-G). These factors could be separated each other by gel-filtration and heat treatment. These results strongly suggest that the seven complementation groups correspond to seven independent DNA repair genes. We applied these complementation group specific factors to a diagnosis of a new patient who was suspected to be XP. He is eight years old and showed moderate photo-sensitivity. Do value of his fibroblasts was 4 J/m^2 and UDS was about 50% of that of normal cells. Microinjection of T4 endonuclease V restored UDS at a normal level, suggesting that DNA repair of pyrimidine dimers is defective in this patient. Complementation tests revealed that this patient belonged to group D of xeroderma pigmentosum.

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MOLECULAR ANALYSIS OF GROUP A XERODERMA PIGMENTOSUM GENE, XPAC GENE. Kiyoji TANAKA, Ichiro SATOKATA, Iwai MIYAMOTO, Naoyuki MIURA, Kunimitsu IWAI(Inst. Mol. Cell. Biol., Osaka Univ., Osaka)

We cloned human DNA repair gene which complements the defect of group A xeroderma pigmentosum(XP) and named it XPAC gene(XP group A complementing gene). Human XPAC cDNA encodes a protein consisting of 273 amino acids. The expected MW of the protein is about 31KDa and it contains a C4 type zinc-finger motif. Polyclonal antiserum was raised against a recombinant XPAC protein and on its use for immunoprecipitation and SDS-PAGE analysis, two bands of 40 K and 38KDa were detected in normal human cells, but not in XP2OSSV, a group A XP cells. Microinjection of the recombinant XPAC protein into group A XP cells restored UV-induced unscheduled DNA synthesis in group A XP cells. Gel retardation assay using 80mer oligonucleotides as probe revealed that the recombinant XPAC binds to DNA. We identified three different mutations in Japanese group A XP patients. These are G to C transversion at the 3' splice acceptor site of intron 3, and two nonsense mutations in exon 3 and 6 of the XPAC gene.

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Towards Targeted Disruption of XPAC Gene in Mice. Shunsuke YUBA[1], Kunimitsu IWAI[1], Tomoyuki TOKUNAGA[2], Yoko KATO[3], Yukio Tsunoda[3], and Kiyoji TANAKA[1].([1]Inst.Mol.Cell.Biol. Osaka Univ., [2]Cent.Res.Lab. Nippon Zenyaku Kogyo Co.Ltd., [3]Fac.Agr. Kinki Univ.)

Xeroderma pigmentosum (XP) is an autosomal recessive disease, characterized by a high incidence of skin cancer and frequent neurological disorders. Recently we cloned a mouse DNA repair gene that complements the defect of group A XP and named it the XPAC gene. Model mice of XP group A would be of great value for determining the physiological role of it and testing therapeutic regimes. One of the XPAC alleles was disrupted at high frequency in mouse embryonic stem (ES) cells by its replacement with neo. We have reintroduced such ES lines into blastocysts and obtained a chimeric mouse. The screening for germ-line transmission of the ES genome is going to start. Furthermore,in order to examine the consequence of the disruption of the mouse XPAC gene, we isolated a diploid ES line with both alleles of it disrupted using a previously targeted line and second drug resistance marker,hyg. The characters in vitro of the three lines, wild-type, heterozygous and homozygous mutant lines, are under investigation.

A 44

A METHOD WITH QUINOLINE DERIVATIVE FOR THE DIFFERENTIAL STAINING OF SISTER CHROMATIDS. Misako GOMI, Tadahisa KOGURE (Dept. Legal Med., St. Marianna Univ. Sch. Med., Kawasaki) and Kouchi MAMBA (Dept. Vet. Anat., Yamaguchi Univ., Yamaguchi)

Peripheral human leukocytes were grown 2 cell cycles in the presence of BrdU and then treated by the sister chromatid differential staining technique. Slides were stained in 5 μ g/ml Bis (2 - quinolyl) - 9, 10 - anthryl dihydrazone in acetic acid at room temperture for 0.5~1hr, washed in 1/15M Sorensen phosphate buffer (pH6.8) and observed. Those regions of a chromosome which had replicated twice in the presence of BrdU were pale staining and in a part of chromsomes sisten chromatid exchanges were observed.

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TRANSITION OF PHENOTYPIC DIMORPHISM WITH REGARD TO SPONTANEOUS SISTER CHROMATID EXCHANGE IN BLOOM'S SYNDROME LYMPHOBLASTOID CELL LINES. Kouichi TATSUMI (Dept. Mol. Oncol., Kyoto Univ. Kyoto), Takayuki KURIHARA (Med. Res. Ins., Kanazawa Medical Univ., Ishikawa) and Izumi ARITA (Dept. Pediat., Takashima Hospital, Shiga)

We recently established four lymphoblastoid cell lines by infecting with Epstein-Barr virus(EBV) the peripheral blood of four Japanese patients with Bloom's syndrome(BS). During the course of propagating these cell lines, two of them exhibited the dimorphism regarding spontaneous sister chromatid exchange (SCE), i.e., a mixed population consisted of cells with extremely high SCE level that was a characteristic of BS and cells with low SCE level indistinguishable from that of normal control cells. On the other hand, both of the remaining two cell lines maintained a monomorphic population with high SCE level at least until 30 weeks after EBV infection. The proportion of the cells with high SCE level in the cell lines with dual phenotype declined as the population doubling numbers increased with time and eventually became undetectable. These observations suggest that the somatic mosaicism in the B-lymphocytes pool of some BS patients *in vivo* and the selective pressure against the cells with high SCE level *in vitro* are responsible for occasional establishment of BS LCLs exclusively with low spontaneous SCE level.

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MALIGNANCY IN NEUROFIBROMATOSIS TYPE 1

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Fifity-seven cases (0.22%) of neurofibromatosis type 1 (NF1) with childhood malignancy found among 26,084 cases of Japan Children's Cancer Registry during 1969 and 1989 confirmed our previous reports; NF1 increased the risk of some childhood malignancies; and epithelial cancers frequently observed in adults, both with NF1 and in the general population, were not developed in childhood in either group. Moreover, Rhabdomyosarcoma was liable to develop in urogenital organs in NF1 with onset age in infant when most genitourinary rhabdomyosarcomas occur in the general population. Leukemia with NF1 occurred mainly at 3-4 years of age, which was the peak age of general childhood leukemia. Age at diagnosis of optic glioma and malignant Schwannoma with NF1 distributed throughout childhood as well as the general population.

The age-specific, organ-dependent carcinogenesis in NF1 reflecting those in the general population implies that NF1 gene, which has been suspected to control the activity of ras gene, may play a role in different organs at a specific stage in life.

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GENE ANALYSES OF THE NEUROFIBROMATOSIS TYPE 1 PATIENTS WITH MALIGNANT SCHWANNOMA

:Shun'ichi SAWADA, Arihito OHTA, Mariko HONDA, and Michihito NIIMURA :Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan

Cloning and sequence analysis of the neurofibromatosis (NF1) gene mapped to 17q11.2, showed homology between a portion of this sequence to the GTPase activating protein family. Malignant schwannomas (MS) are noted with high frequency in patients with NF1. MS were found in 15 of our 1,120 patients (1.3 per cent) with NF1. In this study, using oncogene probes and DNA markers for different regions of chromosome 17, we analyzed benign and malignant tumors from 2 NF1 patients. Amplification and over-expression of oncogenes were seen in none of these tumors. Both benign and malignant tumors had no abnormalities with D17Z1 and HHH202 DNA markers. Scanning exons of the NF-1 gene using PCR-SSCP did not show any genetic change, but we did detect aberrations of the p53 gene.