Symposium I. Part 1

SI-1

Mechanisms of occurrence of genetic diseases
Chairperson: Norio Niikawa, M.D. (Department of Human Genetics, Nagasaki University School of Medicine)

Recently developed molecular-genetics techniques, such as the positional cloning and candidate gene approach, made it possible to isolate and characterize the genes responsible for various genetic diseases. Consequently, this leads to understanding of not only their molecular pathology but also hitherto unknown mechanisms for the disease occurrence. In this symposium, five speakers presented their work and discussed on the topics in the field of medical genetics, especially focusing the mechanisms for the occurrence of genetic diseases. The topics presented included "genomic imprinting relevant to genetic diseases", "complex TRH/GH/PRL deficiency due to a Pit-1 gene mutation as the first transcriptation factor disease in man", an autoimmune disease-sensitivity gene linked to HLA markers", "molecular genetics of Alzheimer disease", and "a DNA-instability region and the occurrence of myotonic dystrophy".

S 1

GENOMIC IMPRINTING AND ITS RELEVANCE TO GENETIC DISEASES Norio NIIKAWA (Dept. Hum. Genet., Nagasaki Univ. Sch. Med., Nagasaki)

Genomic imprinting is a newly observed gene-expression mechanism, through which one of the parental alleles is marked before fertilization to reduce its expression in offspring. In other words, each allele in a child is different in expression depending on its parental derivation. I presented several examples of genetic diseases, where the imprinting may play an important role in their causes.

Supportive evidence for the imprinting in man has been provided by the observation of abnormal phenotypes (growth deficiency/overgrowth) in persons with uniparental disomy (UPD). UPD in man has been observed in chromosomes 4mat, 6pat, 7mat, 11pat, 14pat, 14mat, 15pat, 15mat, and 22mat. Mouse experiments of the igf2 showed that growth deficiency occurs only in offspring who inherits the paternal mutant gene, while normal development was observed when the maternal mutant gene is inherited. In addition, the mouse embryo with a certain type overgrowth usually inherits excess copies of the paternal igf2. These findings indicated that the igf2 is maternally imprinted. A human analogy to the latter condition in the mouse may be Beckwith-Wiedemann syndrome (BWS). From clinical and cytogenetic data in BWS patients, it is suggested that an excess of the active paternal IGF2 located at 11p15.5 causes the syndromes. In Prader-Willi syndrome (PWS) and Angelman syndrome (AS), 15q11-q13 deletion and UPD with selective parent-of-origin have been observed. This suggests that they occur through the following imprinting mechanism: in PWS, the maternal gene is imprinted and the paternal gene lacking may lead to the disorder, and vice versa in AS. Other examples of imprinting-related disorders in man include Huntington disease, myotonic dystrophy, neurofibromatosis I, fragile X syndrome, Wilms tumor, and retinoblastoma. The imprinting may explain unusual inheritance, anticipation phenomenon, or preferential parent-of-origin of LOH in these disorders.

S 2

MUTATIONS IN PIT-1 GENE FROM PATIENTS WITH MULTIPLE PITUITARY DEFICIENCIES. Fumio ENDO, Kohji OHTA, and Ichiro MATSUDA
Dept. Pediatr, Kumamoto Univ. Sch. Med., Kumamoto;

Pit-1 is a pituitary-specific transcription factor that binds to and transactivates promoters of growth hormone- and prolactin-encoding genes. Pit-1 was coded in PIT-1 locus. Mutations of PIT-1was first described in dwarf mouse trains of Jackson dwarf and Snell dwarf in which a hypoplasia of anterior pituitary and a combined deficiency of GH, PRL and TSH were observed. These studies prompted us to analyze gene mutations in human who showed combined pituitary hormone deficiency of GH, PRL and TSH. We analyzed the Pit-1 gene of five Japanese patients. In three patients, we identified three point mutations in the Pit-1 gene, Pro24Leu, Arg143Gln, and Arg271Trp, located on the major transactivation region, POU-specific domain, and POU-homeo domain, respectively. When other mutations of Pit-1 gene are taking into account, it is suggested that mutant Pit-1 proteins act as dominant-negative mutant (in POU-homeo domain and transactivation region) and a recessive mutant (in POU-specific domain). Two (Pro24Leu and Arg143Gln) of three mutations are novel mutations. The Pit-1 deficiency is the first disorder which involves transcription factor whose target genes are well characterized.

S 3

MOLECULAR GENETICS OF ALZHEIMER'S DISEASE.
(Shoji TSUJI (Dept. Neurol., Brain Res. Inst., Niigata Univ., Niigata)

Senile plaques and neurofibrillary tangles have been identified as neuropathological hallmarks for Alzheimer's brain. Detailed biochemical analyses have revealed the components of these structures, which has further advanced our understanding of the mechanisms of pathophysiology of Alzheimer's disease.

Among the neuropathological findings of Alzheimer's disease, senile plaques have been known to be highly specific to Alzheimer's disease. Biochemical analysis has revealed that β-protein is a principal component of the senile plaque. Molecular cloning of a cDNA for the β-protein has shown that β-protein is derived from a much larger precursor protein, amyloid precursor protein (APP).

Very recently a mis-sense mutation in exon 17 of the APP gene has been identified in families early-onset familial Alzheimer's disease. The mutation substitutes isoleucine for valine which is present 3 amino acids down-stream from the carboxy terminus of the β-protein. The discovery prompted world-wide extensive studies. To date the mutation has been identified in 5 Japanese families and 4 Caucasian families. More interestingly two different mutations involving the ^{717}Val have been discovered. Another mutation invloving an amino acid near the amino-terminus of the β-protein has also been identified. These results raise a possibility that these mis-sense mutation affect the processing of the APP resulting in deposition of the β-protein.

S 4

GENETIC CONTROL OF IMMUNE RESPONSE AND SUSCEPTIBILITY TO AUTOIMMUNE DISEASES BY *HLA*-LINKED GENE(S)

Yasuharu NISHIMURA (Div. Immunogenet., Dept.Neurosci. and Immunol., Kumamoto Univ. Grad. Sch. Med. Sci., Kumamoto), Nobuhiro KAMIKAWAJI, Hideyuki YOSHIZUMI, Akinori KIMURA and Takehiko SASAZUKI (Dept. Genet., Med.Inst.Bioreg., Kyushu Univ., Fukuoka)

Genetic analysis of immune response to streptococcal antigen in human revealed that low responsiveness to antigen was controlled by an *HLA*-linked dominant trait through induction of $CD8^+$ immuno-suppressive T cells. Low responsiveness was strongly associated with particular alleles of the *HLA-DQ* locus and $CD4^+$ T cells recognizing an antigenic peptide in the context of HLA-DQ molecule was observed in low but not in high responders. This DQ restricted T cells propagated a proliferation of autoreactive $CD8^+$ cytotoxic T cells specific to HLA-B molecule expressed on antigen presenting cells to downregulate immune response by killing antigen presenting cells. Thus low responsiveness to streptococcal antigen was controlled by a particular combination of *HLA-B* and *DQ* alleles. The frequencies of particular *HLA-B, DR* and *DQ* alleles were increased in patients with autoimmune diseases such as rheumatoid arthritis and insulin dependent diabetes mellitus indicating a presence of *HLA*-linked susceptibility genes to these diseases. One possible mechanism for the association between *HLA* alleles and autoimmune diseases is that a polymorphism determined by *HLA* genes in immune response to unknown antigens triggering autoimmunity controls the susceptibility to autoimmune diseases.

S 5

THE GENE FOR MYOTONIC DYSTROPHY AND HERITABLE UNSTABLE DNA SEQUENCES

Tetsuro MIKI (Dept. Geriat. Med., Osaka Univ. Med. Sch., Osaka)

Myotonic dystrophy (DM) is the most common form of muscular dystrophy affecting adults in caucasian and Japanese populations, with a prevalence of 5.5 per 100,000 individuals in Japan. An unstable DNA region has detected in Japanese patient with DM. Affected individuals have larger DNA fragments than their normal siblings and the size of the band correlates with the age of onset and severity of symptoms within families. Our result that the gene responsible for myotonic dystrophy in Japanese had been closely linked to the DNA markers, D19S19 and APOC2, located to 19q13.2-13.3 had supported the absence of genetic heterogeneity between Caucasian and Japanese. We investigated 40 patients and 58 normal siblings from unrelated families, and 7 so-called sporadic cases. The increase in size correlated with the severity of symptoms, as had been reported for caucasians. This cDNA provide an direct, easy and predictive test for prenatal and presymptomatic diagnosis in Japanese population.

Symposium I. Part 2

SI-2

Clinical application of medical genetics: the present and future. Yoshimitsu Fukushima (Saitama Children's Medical Center, Iwatsuki)

Concerning with what human genetics should be, the following keywords were proposed at 8th International Congress of Human Genetics in Washington D.C. last year, i.e., "Internationalization", "Molecularization", "Medicalization" and "Socialization". In Japan, the former two keywords, international collaborative effort and molecular research, seems to be satisfactorily performed, but the other issues on clinical application, genetic service, education and social recognition, seems to be very behindhand.

This symposium will focus on medicalization and socialization of human genetics in Japan. After introduction of "Clinical Geneticist, the Japanese Board of Medical Genetics" and proposals from a journalist, all of participants and speakers will discuss on these issues.

S 6

PRESENT STATUS AND PROSPECT OF CERTIFICATION OF CLINICAL GENETICISTS. Tadashi KAJII (Dept. Pediatr., Yamaguchi Univ. School Med., Ube)

The Committee on Certification of Medical Geneticists was established in 1990. The individuals who were in practice of clinical genetics or who entered a clinical genetics training program prior to April 1, 1991 became eligible for certification in clinical genetics. So far, 216 clinical geneticists have been certified by the committee and 47 institutions were designated as training centers. The individuals who entered training after April 1, 1991 will become eligible for certification examination in October 1994 or later. There are currently 58 such candidates in training.

Certification in clinical cytogenetics is being discussed, and is expected to be enacted soon.

S 7

UNDERSTANDING TOWARDS MEDICAL GENETICS AND THE ROLE OF PHYSICIANS AND MASS MEDIA. Kunihiko KUMAMOTO (Div. Science News , NHK, Tokyo)

We at NHK have broadcast of Jan. 17,1992 a program called "Can you select your child's life?" on PRIME 10. The program looks at the present prenatal testing today and the advanced technolgy as well as interviewing those couples who have had their fetus be diagnosed where it has brought about major discussion and debate both domestically and abroad. At the same time, we compare two cases one in the U.S. a Chicago couple who can go to a genetic counsellor easily to discuss about genetics and their child, and a case in Japan's Shizuoka Prefecture where a couple knowing that the wife is a hemophiliac but nevertheless was not able to get information on prenatal testing beforehand. Major hospitals in the U.S. have outpatients for the clinical genetics branch, and there are approximately 1000 genetic counsellors in the U.S. Whilst in the U.S. such medical genetics advancement is being utilized in the clinical field, Japan is quite behind. So, I feel that we the mass media people (through correct information transmission) together with those physicians and researchers of medical genetics (making systems where medical information could be carried forward) should work together to come up with a better way to handle things.

Symposium II.

S 8

CHROMOSOME TRANSLOCATIONS AND MOLECULAR MECHANISM IN LEUKEMIA. Yasuhiko KANEKO (Dept. Lab. Med., Saitama Cancer Center, Saitama)

Various translocations are found in half of leukemias. There have been 61 translocations specific for certain types of leukemias reported previously (Human Gene Mapping 11). 37 genes have been cloned from the breakpoint regions and characterized. The translocations found in lymphocytic leukemia usually involve immunoglobulin genes or T-cell receptor genes and result in transcriptional deregulation of the counterpart oncogenes. Those in myelocytic leukemia result in the production of chimeric mRNA and protein. Transcriptionally deregulated oncogenes or chimeric proteins transform normal hematopoietic cells to leukemic cells.

We have cloned the AML1 and MTG8 genes from the 21q22 and 8q22 regions, respectively, of the 8;21 translocation associated with acute myeloblastic leukemia (M2). The chimeric protein has DNA binding domains and seems to deregulate the transcription of an unknown target gene. The RT-PCR method to detect minimal amount of the chimeric AML1-MTG8 mRNA may be useful for monitoring small numbers of leukemic cells during the course of the disease.