for APC and MEN IIa. I will describe our recent progress on these diseases and introduce general strategies for isolating a gene after the first linkage is detected with DNA markers on the genomic map.

SII-2. AN APPROACH BY THE CHROMOSOME STUDY. Shin-ichi SONTA (Inst. Develop. Res., Aichi Pref. Colony, Kasugai)

In cases with an unknown disease of dominant inheritance, chromosomes of the patient are usually analyzed at first, because cases with a certain chromosome abnormality always show abnormal phenotypes. The abnormal region of DNAs which causes genetic disorders may be various in size. They are, for instance, abnormal arrangements of DNAs, deletion of genes, and duplication of chromosome segments. The chromosome abnormalities are all morphological changes of segments distinguishable by optical microscope. The size of chromosome segments distinguishable as abnormal ones became very small by the recently improved techniques such as the high resolution banding techniques. However, individuals even with an addition or deletion of a very tiny segment of the chromosome, with the exception of a part of sex chromosomes and heterochromatic segments, have some phenotypical expression different from normal phenotypes.

Most living individuals with "balanced" structural rearrangements, which were either transmitted from the parent or occurred *de novo*, usually have no abnormal phenotype. Only a few persons with such rearrangements, however, very often show some abnormal phenotype.

Using experimental animals, we can obtain cases with "balanced" chromosome rearrangements by X-irradiation. In such "balanced" rearrangements, they may accompany the structural abnormality of DNAs and a gene at the breakpoint. If this is true, we could use the rearranged chromosome as a marker of the presence of abnormalities on DNAs and genes. The results of chromosomal observation of gametes, embryos and offspring from experimental animals with X-irradiation indicated that some cases with "balanced" rearrangements arrested at various developmental stages and some live offspring with such rearrangements evidenced some abnormal phenotypes. Furthermore, the results also indicated that some cases homozygous for "balanced" rearrangements were recessive lethal, whereas the heterozygotes have no abnormal phenotype.

These results suggest that some of the "balanced" structural rearrangements accompany abnormalities of a tiny invisible segment of the chromosome, genes or DNAs at the breakpoint and the neighboring region. The difference between dominant and recessive expression may well be due to a difference of the gene or the part of gene affected by X-irradiation.

SII-3. USE OF TRANSGENIC MICE FOR DISSECTING THE MOLECULAR MECHANISM OF AMYLOID DEPOSITION IN FAMILIAL AMYLOIDOTIC POLYNEUROPATHY. K. YAMAMURA,[1] S. WAKASUGI,[1] S. YI,[2] F. TASHIRO,[1] T. IWANAGA,[1] S. MAEDA,[3] K. TAKAHASHI[2] and K. SHIMADA[3] ([1]Inst. Med. Genet., [2]Dept. Pathol., and [3]Dept. Biochem. Kumamoto Univ. Med. Sch., Kumamoto)

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant disorder characterized by extracellular deposition of amyloid fibrils and by prominent peripheral and

autonomic nerve involvement. Although the gene responsible for this disease has been identified as the transthyretin (TTR) gene and well characterized at molecular level, many questions, such as the mechanism of amyloid deposition, remain to be elucidated. We formely produced two lines of transgenic mice by introducing the human mutant TTR gene containing its own promoter (0.6-hTTR30) or metallothionein promoter (MT-hTTR30). In these two lines the total serum concentrations of human mutant TTR are the same. However, the onset of amyloid deposition in MT-hTTR30 lines was 6 months of age and was 9 months earlier than that in the 0.6-hTTR30 lines. These results suggest that the concentration of homo-tetramers composed of human mutant TTR but not amount of human mutant TTR molecule is found to for amyloid deposition.

To analyze the role of the human serum amyloid P component (SAP) which is a minor component of amyloid fibrils, we also produced SAP transgenic mice. Interestingly, the serum levels of human SAP were roughly proportional to the number of copies integrated and were higher than that of the human serum in three lines. These mice were mated with MT-hTTR30 transgenic to obtain mice carrying both genes. In these mice the onset of amyloid deposition was not accerelated, but the amyloid deposition in renal glomeruli is much more prominent suggesting that the presence of human SAP can alter the tissue distribution of amyloid deposition.

Strangely enough, there were no amyloid deposits in peripheral nervous tissues where amyloid deposition is commonly observed in FAP patients. These results suggest that the production of mutant TTR molecule in the choroid plexus is important for the amyloid deposition in these tissues.