Genetics of neurofibromatosis 1 in Japan: mutation rate and paternal age effect

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Summary. We have performed formal genetic studies on 26 patients (14 males, 12 females) with neurofibromatosis 1 (von Recklinghausen’s disease, NF1) in Japan. Family studies of 74 members of 18 kindreds revealed that 50% of the cases were caused by a new mutation; the mutation rate was assumed to be 7.3–10.5 × 10⁻⁵. A tendency of paternal age effect, which was not accounted for by the maternal age effect, was observed, but live-birth order had no significant effect. Genetic linkage of neurofibromatosis 1 to the NF1 gene or the genetic marker in the pericentric region of chromosome 17 was established in 3 informative families.

Introduction

Von Recklinghausen neurofibromatosis (neurofibromatosis 1: NF1) is one of the most frequent and clinically important autosomal dominant disorders, with an incidence of 1.3–2.5 × 10⁻⁴ (Crowe et al. 1956). The mutation rate was reported to be 4.4–4.9 × 10⁻⁵ in Russia, 2.4–4.3 × 10⁻⁵ in Sweden and 3.1–10.4 × 10⁻⁵ in South East Wales (Sergeyev 1975; Samuelsson and Akesson 1988; Huson et al. 1989). Sergeyev (1975) reported an increasing birth order effect and an increasing paternal age effect. Riccardi et al. (1984) described paternal age as a factor related to new mutations. In their analysis, mean paternal age was 32.8 and mean maternal age was 27.4, both of which were significantly higher than those of the control populations. The effect of advanced paternal age was not accounted for by the increase in maternal age. On the other hand, Huson et al. (1989) reported no paternal age effect. Jadayel et al. (1990) found 12 cases of paternal origin among 14 new mutations (85.7%) using RFLPs (restriction fragment length polymorphisms) as a genetic marker, but they observed no paternal age effect.

Baker et al. (1987) and Seizinger et al. (1987) first presented the evidence for the genetic linkage of NF1 to the region of chromosome 17, using RFLPs. Subsequently, tightly linked markers for the NF1 gene, such as the pHHH202, EW200 series, have been reported (White et al. 1987; Fain et al. 1987); more recently, Cawthon et al. (1990) have determined the sequence of major segment of the NF1 gene.

The frequency of NF1 in live births was reported to be about 4.5 × 10⁻⁴ in Japan (Takeshita et al. 1984). No systematic formal genetic studies on NF1 have however been performed in Japanese and Asian patients. We have tried to clarify new mutation rates and other genetic features in Japanese patients with NF1.

Materials and methods

We examined 74 members of 18 kindreds with 26 patients at our special clinic for von Recklinghausen’s disease in the hospital of the University of Tsukuba. The 26 patients with NF1 were diagnosed according to the criteria of the National Institutes of Health Consensus Development Conference (1988). We have also carried out physical examination and slit lamp eye examination of the family members in order to avoid overlooking any possible signs of NF1. Figure 1 illustrates pedigrees of all familial cases (7 kindreds). Second cousin marriage was observed in one family (family 16) and parental consanguinity was suspected in one family (family 12).

Statistical analysis of paternal and maternal age was performed by Wilcoxon signed rank test, and logistic regression analysis using SAS (SAS User’s Guide 1985a, b) on a HITAC M240D at the Research Computer Center, Teikyo University School of Medicine.

Peripheral blood was collected from the 74 members of 18 kindreds and from 62 unrelated healthy Japanese adults. Chromosome analysis was carried out in 20 out of 26 patients using high-resolution chromosomal G-banding.

In order to perform linkage studies, genomic DNA was isolated according to the method of Kunkel et al. (1977). DNA was cut with the restriction enzymes BclI, RsaI, XmnI, electrophoresed on agarose gels and transferred to nitrocellulose filters by Southern blotting (Southern 1975). The probe at the NF1 locus was a 424-bp fragment amplified by the PCR (polymerase chain reaction); this
Fig. 1. Pedigrees of 7 familial cases. ♀, Normal female (45 years old); ♂, 2 normal males; ■, affected male (1 year 8 months old); □, tumor resection; □, suspected affected male. ♦ abortion, ♂, died at one week.