steadily increases. One possibility by which HHT mutations may result in reduction of fitness, especially in women, would be lower reproductive fitness. Interestingly, vascular complications were shown to be exacerbated during pregnancy [Neau et al., 1988; Gammon et al., 1990; Revelaqua et al., 1992]. Another implication of the significant level of mutations is that *ENG* may have a relatively high mutation rate. At present, however, we do not have definitive evidence regarding the mutation rate of *ENG* in this population.

The variability of mutations indicates that we should screen for family-specific mutations in places of community-specific mutations for accurate diagnosis. Mutational searches to detect family-specific mutations failed in two families. For one of two families a family history of vascular complications was not proven and thus, HHT of this kindred may not be affected by a *ENG* mutation but rather by an *ALK1* mutation as reported previously [Johnson et al., 1996] or another type of HHT [Piantanida et al., 1996; Wallace and Shovlin, 2000]. Alternatively, the absence of mutations may suggest technological or other unknown difficulties, also as reported previously [Shovlin et al., 1997]. Therefore, as suggested previously [Cymerman et al., 2000], additional effort to detect *ENG* expression levels may be necessary. Although it was demonstrated that two major founder mutations can explain the high prevalence of HTT in Netherlands Antilles [Gallione et al., 2000], we believe that approaches using known mutations with the assumption of a founder mutation cannot be applied for screening purposes even in isolated populations due to large false negative rates. Our current conclusion is in accord with an observation on *ALK-1* mutations, which reported more than two mutations in a local cluster of HTT in the county of Fyn, Denmark [Kjeldsen et al., 2001].

We found 23 affected cases in a cluster in county A that included, however, only populations traceable by family interview and did not include exact numbers of offspring in each pedigree. Therefore, the number of patients was likely to be underestimated. A conservative estimate of the total population affected by HHT in this county could be obtained by assuming that an affected adult (age 30 years and above) has two children, one of whom would be affected by HHT. The number of children is based on the typical birth rate in Japan in the 1990s. Based on this assumption, five cases from SB-2, seven cases from SB-3, and one case from SB-6 may be added, leading to an estimated number of 36. Thus, from these cases we postulated that the population prevalence of HHT ranges from 23 (1:8,000) to 36 (1:5,000) of 170,000 people in county A. This estimated prevalence is roughly comparable to those reported in European and U.S. populations [Porteus et al., 1992; Guttmacher et al., 1994; Kjeldsen et al., 1999]. The present results contradict the traditional view that HHT is rare among Asians [Haitjema et al., 1996] and suggest that this view may be associated with poor recognition of HHT by physicians. In support of the concept that HHT is as common in Japan as in Europeans is the early work of Miyoshi et al. [1976] from the Southern prefecture of Tokushima. These authors conducted clinical genetic studies from five families with HHT and estimated a prevalence rate of 2–9 affected individuals per 100,000 population in Tokushima. We believe that approaches based on clinical epidemiology and genetics are critical to trace high-risk subjects in families with HHT. Such systematic follow-up will substantially improve the clinical course and prognosis by preventing unnecessary morbidity and mortality of affected persons.

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［Ⅲ］研究成果の刊行に関する一覧表

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