families (Families 1, 3, 4, and 5) shared FAF-relevant haplotypes, which strongly indicated the presence of a founder effect in Japanese FAF. This interpretation was also in accordance with the findings of previous studies conducted on two Japanese FAF families [29]. In Family 2 where there are no other affected family members, there is only a 196-kb segment of the shared haplotype at most, which spans two haploblocks. These observations suggest that presence of the founder haplotype is less likely in Family 2. II-1 is the only affected individual in Family 2, and the parents of II-1 died in their 80s and 90s without any symptoms suggesting FAF. To evaluate the penetrance associated with the p.Asp187Asn mutation, we analyzed the cumulative age at onset of the initial clinical symptoms in all the individuals described in the literature (n=38) [4, 8, 10–19, 22, 24, 31, 32–36] or in this study (n=6). As shown in Fig. 3b, 72.7 % of the patients develop symptoms by 50s, 95.4 % by 60s, and all the patients by 70s, which indicates that the p.Asp187Asn mutation is completely penetrant by 70s. Thus, the parents of II-1 in Family 2 are unlikely to carry the mutation considering the ages of the parents and the high penetrance associated with the p.Asp187Asn mutation. Taken together with the observation that only a very small segment of the founder haplotype was observed in Family 2, these observations strongly support the possibility of a de novo mutation event in Family 2. In accordance with this interpretation, the mutation involves the CpG sequence, a mutation hot spot. The possibility of a *de novo* mutation, however, could not be confirmed because the parents were unavailable for the analysis.

In conclusion, the present study demonstrated that the clinical presentations of patients with FAF are considerably broad despite the finding that all the patients carry the same c.654G>A (p.Asp187Asn) mutation. Detailed haplotype analyses demonstrated a founder mutation in most of the Japanese families with FAF, except for a sporadic patient in whom a *de novo* mutation event is suggested as the origin of the mutation.

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