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（要　旨）
(Summary)

Amyloid plaques, primarily composed of misfolded 42-residue amyloid-β (Aβ42) fibrils, are a defining characteristic of Alzheimer's disease (AD). In familial Alzheimer's disease (FAD), particularly in patients with the Arctic (E22G) mutation, these plaques are notable for containing a higher proportion of Aβ40 within their cores compared to sporadic AD cases. Despite the significance of the E22G mutation, the structural characteristics of misfolded E22G Aβ40 fibrils have not been well defined, which poses a challenge for understanding the early stages of FAD and impedes therapeutic development. In this study, we present a unique atomic model for E22G Aβ40 fibrils that exhibits a distinct twisted fibril morphology. Our findings are based on a comprehensive analysis that integrates cryo-electron microscopy (cryo-EM) and solid-state nuclear magnetic resonance (SSNMR) data. The resultant model reveals a characteristic W-shaped parallel β-sheet arrangement, marking the first *in vitro* characterization of the E22G Aβ40 fibril structure. Additionally, the E22G Aβ40 fibrils displayed hallmark amyloid characteristics, such as low thioflavin-T (ThT)

fluorescence and a less compact, unbundled morphology, reminiscent of cotton-wool plaques found in FAD. Kinetic studies provide compelling evidence that E22G Aβ40, rather than Aβ42, may serve as a catalyst for Aβ misfolding in the context of FAD. This misfolding can subsequently facilitate the cross-seeding of wild-type (WT) Aβ40/Aβ42, leading to further aggregation. These findings offer unprecedented insights into the role of the Arctic mutation in promoting Alzheimer's disease through the accumulation of Aβ40 and its potential for cross-propagation, thereby enhancing our understanding of the molecular mechanisms underlying familial Alzheimer's disease.