A007 · An Open, Wet-Lab-Free In-Silico Pipeline for Allele-Specific Detection of Autosomal-Dominant Early-Onset Alzheimer's Disease Mutations

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Early-onset Alzheimer's disease (EOAD) is frequently caused by autosomal-dominant mutations in APP, PSEN1, and PSEN2, yet accessible, low-cost molecular screening tools for at-risk families remain limited. We present a fully in-silico, wet-lab-free proof-of-concept pipeline integrating tetra-primer amplification-refractory mutation system (ARMS) design, in-silico PCR validation, coarse-grained molecular dynamics modeling, and population-level coverage analysis for five well-characterized EOAD mutations (APP V717I, APP Swedish, PSEN1 E280A, PSEN1 M146L, PSEN2 N141I). Allele-specific primer pairs were designed using each mutation's reference genomic sequence and validated computationally via in-silico PCR, which confirmed correct allele-specific amplicon switching for three of five mutations (V717I, Swedish, E280A); redesign of the remaining two is in progress following an initial targeting discrepancy identified during verification. Duplex-level thermodynamic discrimination between matched and mismatched primer-template pairs is being characterized using oxDNA coarse-grained simulation, quantifying hydrogen-bond stability and structural fluctuation at the discriminating base. Population coverage was assessed against gnomAD (v4.1.1), identifying no common variants overlapping primer-binding sites for three mutations and minor, synonymous-variant caveats (population frequency up to 4.6%) for two. Together, these results outline a reproducible, open-access computational framework for evaluating allele-specific assay candidates prior to any wet-lab investment, with an integrated translation-confidence metric combining specificity, thermodynamic stability, and population robustness. This pipeline is presented explicitly as a computational proof-of-concept rather than a validated diagnostic tool.

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ABSTRACT

Early-onset Alzheimer's disease (EOAD) is frequently caused by autosomal-dominant mutations in *APP*, *PSEN1*, and *PSEN2*, yet accessible, low-cost molecular screening tools for at-risk families remain limited. We present a fully in-silico, wet-lab-free proof-of-concept pipeline integrating tetra-primer amplification-refractory mutation system (ARMS) design, in-silico PCR validation, coarse-grained molecular dynamics modeling, and population-level coverage analysis for five well-characterized EOAD mutations (APP V717I, APP Swedish, PSEN1 E280A, PSEN1 M146L, PSEN2 N141I). Allele-specific primer pairs were designed using each mutation's reference genomic sequence and validated computationally via in-silico PCR, which confirmed correct allele-specific amplicon switching for three of five mutations (V717I, Swedish, E280A); redesign of the remaining two is in progress following an initial targeting discrepancy identified during verification. Duplex-level thermodynamic discrimination between matched and mismatched primer-template pairs is being characterized using oxDNA coarse-grained simulation, quantifying hydrogen-bond stability and structural fluctuation at the discriminating base. Population coverage was assessed against gnomAD (v4.1.1), identifying no common variants overlapping primer-binding sites for three mutations and minor, synonymous-variant caveats (population frequency up to 4.6%) for two. Together, these results outline a reproducible, open-access computational framework for evaluating allele-specific assay candidates prior to any wet-lab investment, with an integrated translation-confidence metric combining specificity, thermodynamic stability, and population robustness. This pipeline is presented explicitly as a computational proof-of-concept rather than a validated diagnostic tool.