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Therapeutic Development for Frontotemporal Degeneration

There are no effective treatments for Frontotemporal Degeneration (FTD), however over the past five years there has been an explosion of new clinical trials and clinical development programs of therapeutics for different FTD syndromes. The most common genetic causes of familial FTD (fFTD) are mutations in *C9orf72*, *GRN* and *MAPT*, all of which are attractive therapeutic targets, and provide informative biomarkers for clinical trials that are underway or planned to begin soon. *GRN* (progranulin) mutations lead to loss of function through haploinsufficiency, and a Phase 3 clinical trial of a progranulin elevating monoclonal antibody is currently underway, as well as multiple Phase 1 trials of gene therapies aimed at raising brain *GRN* expression, and a genetically modified progranulin protein designed to cross the blood brain barrier. Additional small molecule approaches and gene therapy clinical trials are planned. *C9orf72* antisense oligonucleotide therapeutic trials began years ago for individuals with *C9orf72* amyotrophic lateral sclerosis, and are now beginning to include FTD patients, with more trials planned to begin soon. Two small molecule *C9orf72* trials are underway, and multiple gene therapy trials are planned. There are many promising candidate therapies for *MAPT* mutation carriers, however their low prevalence and clinical heterogeneity will require additional clinical trial design considerations. The largest number of disease-modifying agent trials for sporadic FTD have been in progressive supranuclear palsy, so far without success, but ongoing studies of symptomatic therapies such as intranasal oxytocin for behavioral variant FTD, and speech therapy and electrical stimulation for primary progressive aphasias (PPA) are beginning to produce results. A new anti-inflammatory agent trial is now underway for semantic variant PPA. The future of FTD therapeutic development seems very promising, with the potential to identify the first effective therapies within the next five years.