An overview of Alzheimer's disease genetics

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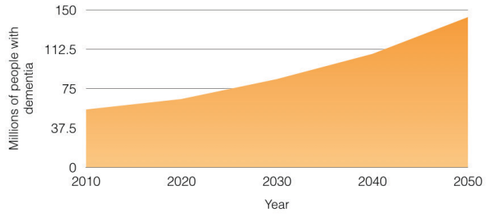
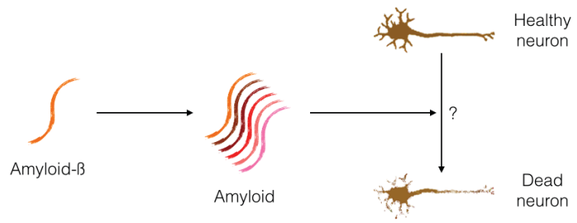
With advances in medicine, public health, and nutrition, people are living longer than ever before. Longevity comes at a price, however, as more and more of the elderly develop dementia. Alzheimer's disease (AD) is the most common form of dementia, affecting up to half of individuals by the time they are 80 years old1. Much of what we know about AD arises from the study of mutations in one or more genes associated with familial disease2. The identification of mutations that cause AD has completely changed the way both clinicians and scientists view the disorder. Instead of being an unfortunate 'mental condition', AD is now recognized as a progressive neurodegenerative disorder targeting the neural substrates of memory. Here, I will briefly discuss the growing epidemiologic concerns of AD in an aging population, then focus upon the biology of AD and how genetics has continually informed and directed ongoing investigations. I will pay particular attention to recent, unanswered questions in AD, including an intriguing link between AD and epilepsy3, new evidence suggesting an infectious component to neurodegeneration in AD4, and growing efforts to prevent the disease by co-opting the human immune system5. I will also summarize our efforts to determine the means by which AD spreads in the nervous system, and potential opportunities for therapy in this regard. Questions such as these are essential for truly understanding why neurons die in AD, and are fueling the next generation of treatments aimed at stopping the growing epidemic that is AD.





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I am a neurologist and a neuroscientist dedicated to investigating mechanisms of disease in dementia and motor neuron disease. Each patient I see is an additional reminder of the urgent need for a better understanding of how and why neurons die in these conditions. My overall goals are to change this fact, and successfully develop therapies capable of preventing disease.

As an undergraduate at the University of Pittsburgh, in Pittsburgh, PA, I worked with Lewis Jacobson, a geneticist studying signal transduction pathways in the nematode Caenorhabditis elegans. Importantly, this initial experience in the laboratory taught me an appreciation for the atmosphere of intellectual freedom to be found in research. Upon earning my Bachelors in Science (Biochemistry), I enrolled in the combined MD/PhD program at Washington University in St. Louis, MO, so that I could continue conducting research while training to become a physician. I was fascinated by prion diseases such as bovine spongiform encephalopathy (i.e., "Mad Cow Disease"), and joined the laboratory of Dr. David Harris, an authority on prion diseases, soon after the second year of medical school. Here, I constructed an animal model that allowed me to visualize the disease process in the brains of mice by fluorescence microscopy. It was also here that I met my future wife, who was also studying prion disease at Washington University at the time.

In 2006, I finished medical school, earned my PhD and began internship in medicine at Barnes Jewish Hospital, in St. Louis, MO. After the intern year, I moved to the University of California, San Francisco (UCSF), CA, for a residency in neurology. I then served as Chief Resident in charge of education for one year before beginning a research fellowship with Steve Finkbeiner at the Gladstone Institute of Neurological Diseases, in San Francisco, CA. With Dr. Finkbeiner, I applied innovative and powerful technology to the study of neurodegenerative diseases, and established some of the first models of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). In 2011, I transitioned to a Staff Scientist at the Gladstone Institutes and a Clinical Instructor at UCSF. During this time, I worked in the neurology clinic at San Francisco General Hospital and the UCSF ALS Center, with Dr. Cathy Lomen-Hoerth. I also trained with Dr. Bruce Miller, Director of the Memory and Aging Center at UCSF, an authority in behavioral neurology.

In 2013, I moved to the Neurology Department at the University of Michigan. Here, I am a member of the Neurodegenerative Disease Research Program, consisting of several laboratories that often collaborate with one another. My friend and mentor, Hank Paulson, a leader in neurodegeneration research, provides invaluable career and research advice. I work closely with pioneers in stem cell research and RNA biology, including Eva Feldman, Jack Parent and Vivian Cheung. My clinical practice focuses on patients with Alzheimer's disease, FTD, and the overlap between dementia and motor neuron diseases such as ALS. The chance to care for patients motivates my research and gives me the singular perspective of a physician scientist, clarifying the critical need for therapies that can stall or prevent the relentless progression of neurodegeneration.