Biomarkers in Down syndrome can help us understand Alzheimer's disease

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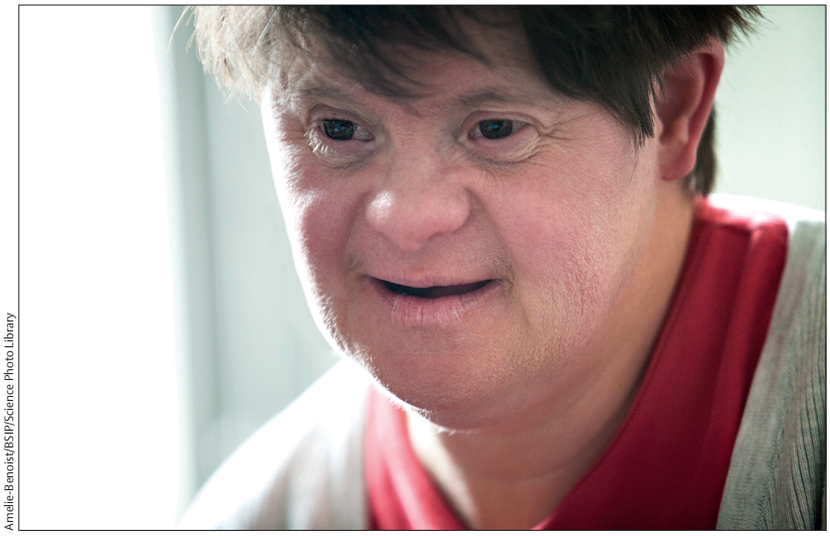
Down syndrome is associated with increased risk of developing early-onset Alzheimer's disease, primarily because of the overexpression of the *APP* gene on chromosome 21. People with Down syndrome, as a form of genetically determined Alzheimer's disease, represent one of the largest cohorts at risk of early-onset Alzheimer's disease because virtually all adults with Down syndrome will develop Alzheimer's disease by age 40 years.[1] However, the age range for the onset of cognitive decline is wide (from <50 years to >70 years).[2] The characterisation of the preclinical phases of Alzheimer's disease is crucial for early diagnosis in this susceptible group of people.



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A hypothesised model has been proposed for late-onset Alzheimer's disease, which has also been applied to autosomal dominant Alzheimer's disease, consisting of early amyloid β (Aβ) deposition, followed by hyperphosphorylated tau protein accumulation that is subsequently followed by neurodegeneration, termed AT(N).[3] Based on the AT(N) criteria, a long preclinical phase due to the presence of Alzheimer's disease pathology occurs more than 15 years before an individual develops overt cognitive symptoms. In *The Lancet*, an exciting study by Juan Fortea and colleagues essentially applied the AT(N) model as a framework for adults with Down syndrome.[4] We commend this team on their thorough cross-sectional examination of a large cohort of adults with Down syndrome and euploid controls across a wide age range. For this study, Fortea and colleagues assessed multiple Alzheimer's disease biomarkers (including from blood samples, cerebrospinal fluid samples, PET, MRI, and cognitive testing) in 388 participants with Down syndrome (174 [45%] women; 257 [66%] asymptomatic, 48 [12%] prodromal Alzheimer's disease, and 83 [21%] Alzheimer's disease dementia) and 242 euploid controls. The authors observed that Alzheimer's disease in people with Down syndrome had a long preclinical phase, in which biomarkers followed a predictable order of changes that began more than two decades before the onset of symptoms. Prodromal Alzheimer's disease in this cohort was diagnosed at a median age of 50·8 years (IQR 47·5–54·1), and Alzheimer's disease dementia at 53·7 years (49·5–57·2), with some biomarkers changing as early as the third decade of life. Fortea and colleagues noted similarities between biomarkers reflecting Alzheimer's disease pathogenesis in individuals with Down syndrome and individuals with late-onset and autosomal dominant Alzheimer's disease. These results provide strong evidence that studies of people with Down syndrome can inform research on late-onset and autosomal dominant Alzheimer's disease.

The existing AT(N) model, developed for late-onset Alzheimer's disease and as applied here for people with Down syndrome, does not yet incorporate potential roles for inflammation and cerebrovascular disease, which are often seen in adults with Down syndrome.[5,6] Additionally, moving forward, future studies should assess other risk factors, including the role of sex,[7] genetics (eg, apolipoprotein E-ε4 allele and other genes on chromosome 21),[8] and other co-occurring medical conditions in people with Down syndrome, which might influence the age of onset or slope of change of biomarkers, such as those described by Fortea and colleagues. Interesting differences in biomarkers in individuals with Down syndrome noted by the authors include differences in plasma $A\beta_{1-42}$ concentrations (58% higher in adults with Down syndrome than in controls across the whole Down syndrome age span) and hippocampal atrophy (people with Down syndrome had smaller hippocampi across their lifespans than did controls). Fortea and colleagues also found features of Alzheimer's disease in individuals with Down syndrome that are more similar to those of autosomal dominant Alzheimer's disease than those of late-onset Alzheimer's disease, such as early striatal Pittsburgh compound B binding.[9] Moving forward, it will be crucial to characterise not only similarities of Alzheimer's disease in people with Down syndrome to late-onset Alzheimer's disease, but also important differences that might also guide future clinical trials. It will also be important to observe how biomarkers described in Fortea and colleagues' study, and the possible addition of novel proteomic or metabolomic approaches, relate to incident dementia in this cohort over time.

Exciting opportunities for people with Down syndrome to participate in and contribute to research in Alzheimer's disease continue to evolve (eg, the

Alzheimer's Biomarker Consortium for Down Syndrome and Horizon21).[10] In the past, adults with Down syndrome have not been included in Alzheimer's disease clinical trials. Such trials admittedly pose additional challenges for people with Down syndrome (and possible risks) compared with those for the general population regarding recruitment and feasibility of completing all the assessments. Therefore, Fortea and colleagues emphasise that people with Down syndrome are able and willing to participate in multimodal studies needed for clinical trials. Biomarker studies, as reported here and by other teams,[11] are crucial and will serve as a foundation for the design of clinical trials for Alzheimer's disease in people with Down syndrome.[12] Biomarker criteria can be used to streamline the recruitment of people with Down syndrome for clinical trials. Additionally, biomarker characterisation will be useful for future precision medicine approaches and important for the development of effective interventions within this high-risk population.[13] Biomarker research in people with Down syndrome has important contributions and implications for the general population, especially for individuals with late-onset Alzheimer's disease.

We declare no competing interests. We both contributed equally.

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For the **Alzheimer's Biomarker Consortium for Down Syndrome** see https://www.nia.nih.gov/research/abc-ds