alzheimer's research&therapy

COMMENTARY

Pinpointing key mechanisms in Alzheimer's disease development

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Abstract

van Exel and colleagues present an elegant study testing relationships between vascular and inflammatory traits and the risk of Alzheimer's disease (AD) development. They compared middle-aged offspring of AD cases with similar offspring of nondemented parents and observed greater inflammatory response to challenge and increased hypertension in those at high genetic risk. These observations join a growing body of evidence implicating inflammation/innate immunity as a crucial component in disease development. Recent discoveries of new risk genes for Alzheimer's disease also implicate innate immunity and to some extent vascular health as potentially important in pathogenesis. Further identification and refinement of putative disease mechanisms is likely as the genetic architecture of AD is uncovered through current large-scale association and sequencing studies.

The reason most of us in the field of complex genetics search for genes that contribute to disease development is that these genes will pinpoint mechanisms of primary importance to pathogenesis. Using a variation on this theme, van Exel and colleagues sought to identify traits associated with genetic risk before the development of Alzheimer's disease (AD) [1]. The study used an elegant design to identify primary events related to disease susceptibility in those at high genetic risk. By comparing middle-aged offspring of AD cases with similar offspring of nondemented parents, the authors observed increased proinflammatory responses and increased hypertension in those at genetic risk. These individuals showed no overt signs of cognitive decline. The authors did not observe changes in cholesterol or inflammatory markers circulating in the blood, which could indicate either that the disease process was not yet established or that these were not good biomarkers for AD development. The greater proinflammatory responses to inflammatory challenge and the increased hypertension observed in those at high genetic risk, however, may indicate a predisposition that contributes to AD development in the future.

The idea that changes in inflammation/innate immunity are associated with AD is not new. Numerous studies have shown markers of inflammation to be increased in AD sufferers, both in the brain and peripherally (reviewed in [2]). What is new is the idea that inflammatory processing makes a direct contribution to disease development – that it is part of a causal pathway to disease. Hypertension has also been highlighted as a risk factor for AD in previous epidemiological studies, although the results have been mixed [3]. What the van Exel study now suggests, however, is that this risk is mediated through genetic susceptibility.

These findings become more interesting when juxtaposed with those emerging from recent genetic studies, including our own. The advent of powerful genome-wide association studies has at last provided firm evidence for new risk genes for Alzheimer's disease. We identified two new susceptibility genes for AD – *CLU* and *PICALM* [4] – and when we put our data together with a similar study undertaken by a French group, a third gene was added to the list, *CR1* [5]. Both *CLU*, coding for clusterin, and *CR1*, complement receptor 1, are involved in inflammation/innate immunity. Clusterin is a complement inhibitor and can suppress complement activation observed in AD, and *CR1* helps instigate the adaptive immune response [6].

Both apolipoprotein E, a known risk factor for AD, and clusterin regulate cholesterol and lipid metabolism of the brain, which is disturbed in AD. It is possible that their effects on the processing of cholesterol in the periphery could in turn affect hypertension, amongst others processes. Of course, these molecules have other functions that may contribute to disease development, so we must remain cautious in our interpretation. Noteworthy, however, is that a variety of research strategies are producing independent evidence converging on the

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primary roles of inflammatory processing and vascular health in AD development.

We already know that genes play an important role in AD development, with studies showing heritability of between 56 and 79% [4]. It is therefore encouraging that further work characterising the genetic architecture of AD is well underway. Larger genome-wide association studies involving tens of thousands of AD cases and controls should report their findings within the year. These results will no doubt identify several more common susceptibility genes conferring risk for AD. In addition, advances in sequencing technologies will allow large-scale interrogations of coding regions in the genome likely to detect rare variants of strong effect. Together these research strategies will map out much of the genetic architecture of AD in the near future. But most importantly, these genetic research strategies will give us the best indication yet of the mechanisms that contribute directly to AD development.

Abbreviations
AD, Alzheimer's disease.

Competing interests
Patent application submitted for genes identified in reference [4]. The author declares that they have no other competing interests.

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