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Alzheimer's Disease Sequencing Project Discovery and Replication criteria for cases and controls: data from a community-based prospective cohort study with autopsy follow-up

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Structured abstract

Introduction—The Alzheimer's Disease Sequencing Project (ADSP) used different criteria for assigning case and control status from the discovery and replication phases of the project. We considered data from a community-based prospective cohort study with autopsy follow-up where participants could be categorized as case, control, or neither by both definitions, and compared the two sets of criteria.

Methods—We used data from the Adult Changes in Thought (ACT) study including DSM-IV criteria for dementia status, McKhann et al. criteria for clinical Alzheimer's Disease, and Braak and CERAD findings on neurofibrillary tangles and neuritic plaques to categorize the 621 ACT participants of European ancestry who died and came to autopsy. We applied ADSP discovery and replication definitions to identify controls, cases, and people who were neither controls nor cases.

Results—There was some agreement between the discovery and replication definitions. Major areas of discrepancy included the finding that only 40% of the discovery sample controls had sufficiently low levels of neurofibrillary tangles and neuritic plaques to be considered controls by the replication criteria, and the finding that 16% of the replication phase cases were diagnosed with non-AD dementia during life and thus were excluded as cases for the discovery phase.

Conclusions—These findings should inform interpretation of genetic association findings from the ADSP. Differences in genetic association findings between the two phases of the study may reflect these different phenotype definitions from the discovery and replication phase of the ADSP.

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Introduction

Study design is underemphasized in planning or interpretation of many genome-wide association studies (GWAS) and sequencing projects but may be extremely important [1]. Differences in phenotypic definition are important considerations in genetic epidemiology[2] and have important implications for the identification and confirmation of associations of genetic variants with specific phenotypes[3].

The Alzheimer's Disease Sequencing Project (ADSP) used different criteria for assigning case and control status from the discovery and replication phases of the project. We considered data from a community-based prospective cohort study with autopsy follow-up where participants could be categorized as case, control, or neither by both definitions, and compared the two sets of criteria.

Methods

Detailed methods for the Adult Changes in Thought (ACT) study have been published in several publications[4–6]. There have been three enrollment waves, each of which used the same methods. In each, a random sample of Seattle-area members of Group Health age ≥65 without established diagnoses of dementia and not living in a nursing home was invited to a screening visit. Cognition was measured with the Cognitive Abilities Screening Instrument[7], a 100-point cognitive functioning test. Consenting individuals with scores ≥86 were invited to enroll in the longitudinal study; those with scores ≤85 were evaluated with a comprehensive neuropsychological battery and neurological examination. Results were considered at a consensus conference and standardized criteria were completed, including the Diagnostic and Statistical Manual (DSM-IV) criteria for dementia[8] and the McKhann et al. for probable or possible Alzheimer's disease (AD)[9]. Consenting individuals who were found not to have dementia or AD were invited to enroll in the longitudinal study.

Participants received follow-up visits every two years either in their own homes or in a research clinic[10]. The CASI was again administered and the same cutoff value, follow-up procedures, and diagnostic criteria were used to identify incident cases of dementia and AD. To date the study has identified >1,000 dementia cases and >850 cases of AD.

Participants were invited to consider consent for autopsy at study visits; between 25–30% of the cohort have consented to autopsy. Detailed methods for autopsy evaluations have been published[11]. Standard work-up enables completion of criteria from the Consortium to Establish a Registry for AD (CERAD) for neuritic plaques[12] and as described by Braak and Braak for neurofibrillary tangles[13]. All study activities have been reviewed and approved by institutional review boards from Group Health and the University of Washington, and participants sign informed consent documents approved by those same boards.

The Alzheimer's Disease Sequencing Project (ADSP) used probable or possible AD as defined by the McKhann criteria to identify cases for the discovery phase; cognitively normal elderly individuals served as controls. For the replication phase, the ADSP defined a

case based on meeting DSM-IV criteria for dementia and having high levels of Braak and CERAD, while controls were defined as individuals who did not meet DSM-IV criteria for dementia during life and who had low levels of Braak and CERAD.

For this brief report we considered the subset of individuals from the ACT study who had data for both sets of criteria: people who had at least one follow-up study during life so they could have had incident dementia or AD, and people who had died and come to autopsy so they had data for CERAD and Braak stage. The initial stage of the ADSP focused on people with European ancestry so we limited analyses to that group. We performed simple tabulation and comparison of these two sets of criteria; all analyses were performed using Microsoft Excel.

Results

We considered data from 621 individuals of European ancestry who were members of the ACT study and had died and come to autopsy.

The comparison of discovery criteria (McKhann criteria for AD to define cases; cognitively normal elderly controls) vs. replication criteria (DSM-IV criteria for dementia plus high levels of Braak and CERAD to define cases; no dementia and low levels of Braak and CERAD to define controls) are shown in the Table.

Of the 621 ACT participants who died and came to autopsy, 341 (55%) were cognitively normal at the time of death and were controls by the discovery definition; 228 (37%) died with a diagnosis of AD and were cases by the discovery definition; and 52 (8%) died with a non-AD dementia diagnosis and were neither a case nor a control by the discovery definition.

There were 138 people who died without DSM-IV dementia who had low levels of Braak and CERAD who were controls by the replication definition (22%). Of these, nearly all were also controls by the discovery definition, though there were 204 people who died without dementia who had high Braak and/or CERAD levels at autopsy and were thus excluded from being considered controls in the replication sample. Of the 341 who were controls by the discovery definition, 137 (40%) were also controls by the replication definition, and the remaining 204(60%) had high levels of Braak and/or CERAD and were neither cases nor controls by the replication criteria.

There were 157 people who died with DSM-IV dementia who had high levels of Braak and CERAD at autopsy and who were cases by the replication definition (25%). Of these, 132 were diagnosed with AD during life (84% of the 157 who were cases for the replication definition) but 25 were diagnosed with non-AD dementia (16% of all cases for the replication definition) but nevertheless had sufficiently high levels of Braak and CERAD to be categorized as cases by the replication definition.

There were 326 people (52% of all autopsied participants) who were neither cases nor controls by the replication definition. Of these, 204 (63%) were cognitively normal at the time of death but had high levels of Braak and/or CERAD; 95 (29%) who had both dementia

and AD at the time of death but had low levels of Braak and/or CERAD, and 27 (8%) who had non-AD dementia at the time of death and had low levels of Braak and CERAD.

Discussion

We used data from a prospective community-based cohort study with autopsy follow-up to compare and contrast the criteria used to determine case vs. control status for the discovery and replication phases of the ADSP. Our findings are important for interpreting genetic association results from the two phases of the project. For the discovery phase, few people have autopsy data, so clinical criteria during life based on the McKhann et al. definition were used to define case status. It has long been appreciated that clinical criteria for AD are correlated with neuropathology findings of neuritic plaques and neurofibrillary tangles, but that correlation is not particularly strong, especially in those who die at extreme old ages. This understanding is reflected in the finding here that fully 60% (204 of 341) of those who would be considered controls by the discovery criteria are excluded by the replication definition. About 2/5 of the “control” sample in the ADSP discovery phase should also have low levels of plaques and tangles, but 3/5 should be expected to have high levels of plaques and tangles.

The ADSP used a more inclusive dementia criterion for the replication stage case definition, including anyone who died with DSM-IV dementia, as opposed to the subset who died with McKhann criteria for AD. Of the 157 people who were considered cases by the replication criteria, 25 (16%) had dementia other than AD diagnosed during life.

Conclusion

The scientific community should be keenly aware of these differences between criteria for the discovery and replication phases of the ADSP. Differences in genetic association findings between the two phases of the study may reflect these different phenotype definitions.

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Research in Context

Systematic review

The authors searched PubMed and Google. There do not appear to be any publications or websites detailing differences between phenotype definitions in the Discovery and Replication phases of the Alzheimer's Disease Sequencing Project (ADSP). Some websites refer to "autopsy confirmation" in the replication phase but specifics and implications are not spelled out.

Interpretation

There are important differences in "controls" and "cases" defined from the ADSP discovery and replication phases. About 60% of "control" participants from the discovery criteria likely have high levels of Alzheimer's pathology. About 16% of "case" participants from the replication criteria were likely to have been diagnosed with dementia other than Alzheimer's disease during life. These results have important implications for interpretation of findings from the ADSP.

Future directions

Careful analyses will need to be performed to understand the implications of using a different phenotypic definition for the two phases of the ADSP.

Table

Characterization of European ancestry ACT participants who died and came to autopsy using the discovery and replication criteria of the Alzheimer's Disease Sequencing Project (ADSP)

	Replication controls	Replication cases	Replication neither cases nor controls	Totals
Discovery controls	137	0	204	341 (55%)
Discovery cases	1	132	95	228 (37%)
Discovery neither cases nor controls	0	25	27	52 (8%)
Totals	138 (22%)	157 (25%)	326 (52%)	621