The environmental and genetic impact of spatial cluster analysis in ALS

Spatial scan statistics can be instrumental in stimulating etiologic research by detecting specific disease clusters. Successful examples include the maps produced by the US National Cancer Institute in the 1970s, identifying areas of high mortality rates from nasal cancer associated with furniture-manufacturing industries, and oral cancer in regions where snuff use was common.

Amyotrophic lateral sclerosis (ALS) heritability estimates from twin studies range from 61% to 76%, meaning that both genetic and environmental influences are at play in causing this disease, many of which remain to be discovered.

Using a nationwide population-based design from 1995 to 2013, this elegant study shows that there were no high-risk clusters of ALS in Ireland, although lower patient numbers than expected were found in 2 areas, which could not be explained by underascertainment.

This study has several strong points that buttress the conclusions: the population-based, complete case ascertainment avoids the pitfalls of identifying artificial clusters around a center of expertise and avoids missing real clusters elsewhere; a correction for multiple testing; and the use of a new method that allows for the detection of clusters with irregular shapes.

The areas of lower-than-average ALS risk can be interpreted as pointing to both environmental and genetic influences. The recently published genome of the Netherlands showed that the genetic composition of people in the north of the Netherlands is different compared with people living in the south, with an effective physical distance of only 200 miles. These differences became even more striking when rare genetic variation was considered. It is highly likely that many rare genetic variants are far more important in explaining heritability in ALS than common variation. This means that regional differences in ALS risk may help us find both new environmental and important genetic risk factors, and that larger but well-designed studies, such as this one, are needed. The growing collaborations among several population-based registers within Europe (e.g., the Euro-MOTOR project) will be instrumental in achieving this.


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Disclosure: The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.