Linkage of Parkinsonism and Alzheimer's Disease with Lewy Body Pathology to Chromosome 12

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Funayama and colleagues[1] have reported linkage of a large family with autosomal dominant parkinsonism to the centromeric region of chromosome 12 between markers D12S1631 (50.9cM) and D12S339 (64.45cM). We find this report interesting not only because it identifies a novel locus for familial Parkinsonism,[1] but also because this same region of chromosome 12, between markers D12S1688 (42cM) and D12S1701 (62cM), previously has been linked to Alzheimer's disease in families containing at least one affected individual with Lewy bodies.[2] These individuals met neuropathological criteria for dementia with Lewy bodies, a phenotype containing elements of both dementia and parkinsonism. Taken together, these results raise the exciting possibility that a gene in the centromeric region of chromosome 12 may cause both dominant parkinsonism and dementia with Lewy bodies. Follow-up studies of this region would benefit from consideration of the data of both studies to find the gene responsible for dementia and parkinsonism on chromosome 12.

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Reply

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We thank Dr Scott and his colleagues for their interesting comment on our article reporting the newly found locus of autosomal dominant parkinsonism (*PARK8*) at 12p11.2-q13.1.[1] They pointed out that this chromosomal region overlaps that where a locus of late-onset familial Alzheimer's disease (*AD5*) with Lewy bodies has been mapped by them.[2] In the case of the *PARK8*-linked family, none of the patients exhibited dementia or other unusual features. Neuropathological examination was conducted in four cases, and all were diagnosed as "pure nigral degeneration." No Lewy bodies were detected in the substantia nigra, locus ceruleus, raphe nucleus, superior central nucleus, dorsal vagal nucleus, hypothalamus, substantia innominata, ventral tegmental area, or periventricular region. Furthermore, no NFTs or other accumulations were detected in any of the areas examined. No marked neuropathological changes were observed in other nuclei of the basal ganglia, such as the putamen, globus pallidus, subthalamic nucleus, red nucleus, and the cerebral cortex or cerebellar system.[3] These clinical and neuropathological characteristics of the *PARK8*-related patients suggest that the causal genes of *PARK8* and that of *AD5* would be distinct from each other. However, because the two loci are mapped to within a very small region on chromosome 12, it remains possible that this region contains a cluster of genes related in various different ways to nerve cell survival, mutations of which would result in different features of nervous system degeneration and functional disorder. Identification and functional analysis of the gene products of *PARK8* and *AD5* will provide an answer, and contribute greatly to clarifying the mechanism of both Parkinson's disease and Alzheimer's disease.

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Interleukin-12 p40 Polymorphism and Susceptibility to Multiple Sclerosis

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Van Veen and colleagues[1] reported an association of a single nucleotide polymorphism in the 3′ untranslated region of the interleukin (IL)–12p40 gene with multiple sclerosis (MS) in a Dutch case–control study. They observed that homozygous carriers of the B allele were significantly underrepresented in the MS group compared with the control group, suggestive for a protective effect conferred by carriage of this genotype (odds ratio, 0.20; 95% confidence interval, 0.07–0.60).[1] A similar, though not significant, trend was observed in a Northern Irish case–control study.[2] In the latter study, however, the control population was found not to be in Hardy–Weinberg equilibrium thus jeopardizing the validity of this observation. The B allele of this polymorphism is associated with reduced cellular production of IL-12p40 and originally was reported to be associated with resistance to insulin-dependent diabetes mellitus (IDDM).[3] In view of the well-documented disease-promoting role of IL-12 in both

Table. Transmission Disequilibrium Test of the Interleukin-12p40 B Allele in Northern Irish and Belgian Trio Multiple Sclerosis Families

Origin	Number of Families Typed	Number of Heterozygous Parents	B Allele Transmitted	B Allele Nontransmitted	χ^2	*P*
N. Irish	70	49	21	28	1.0	0.32
Belgian	142	106	55	51	0.15	0.70
Total	212	155	76	79	0.06	0.81

MS and IDDM, these reports call attention to the possibility that this polymorphism may represent a functional link similarly connecting the genetic susceptibility contexts and immune-related pathogeneses of both diseases.

In this study, we investigated association of the B allele of this polymorphism with MS in 212 trio MS families by means of the transmission disequilibrium test. Genotyping was performed on DNA samples from 142 Belgian and 70 Northern Irish families. In neither population were we able to detect parental transmission distortion of the B allele (Table). We used the affected family-based controls method to evaluate whether the homozygous genotype BB was underrepresented in MS patients compared with controls.[4] We did not find any statistically significant difference in BB genotype frequency between cases and controls ($\chi^2 = 0.06$). BB genotype frequency was 4.7% in the cases (5.6% in Belgian and 2.9% in Northern Irish cases) and 5.2% in the affected family-based controls (4.9% in Belgian and 5.7% in Northern Irish controls). Nevertheless, the power to detect in our data set an effect of a magnitude similar to that reported by van Veen and colleagues[1] amounted to 80% for a two-sided ($\alpha = 0.05$) and 88% for a one-sided ($\alpha = 0.05$) test.

The number of trio families used in the original IDDM study of Morahan and colleagues[3] was similar to that used in our study (235 and 212 families, respectively). Thus, the absence of any effect in the MS data set argues for a quantitatively distinct impact of the IL-12 p40 polymorphism in the genetic susceptibility contexts of MS and IDDM. Moreover, the very low nonparametric linkage scores for the chromosome region that harbors the IL-12 p40 gene (5q31-33) recorded in the recent meta-analysis of genome screens in MS sheds doubt on a major causative role for this gene in MS.[5] In conclusion, our findings argue against a functional/genetic role of this polymorphism in MS. A minor effect of the IL-12 p40 polymorphism in MS characterized by a recessive mode of inheritance is, however, difficult to exclude, and this may only be verifiable in an extremely large data set.

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Concerns with the Use of T2* Signal Intensity to Differentiate Hippocampal Subregions

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We wish to express our concerns with the quantitative magnetic resonance imaging methods on which the article by Small and colleagues[1] concludes that uncalibrated hippocampal T2* signal intensity (SI) can be used to differentiate age- or disease-related subregions. We argue that the inherent instability of this SI measure negates the assumption that it is comparable between individuals and imaging sessions. Their method used the averaged SI from the four brightest contiguous pixels within anatomical subregions on coronal gradient-echo images. Dependent variables were calculated by dividing this SI value by the global signal intensity of the whole slice and applying a logarithmic transformation prior to comparative statistics.

First, T2* images are extremely sensitive to magnetic susceptibility variations. T2* images of the medial temporal region are particularly prone to marked susceptibility effects caused by regional inhomogeneities (tissue–ventricle interface or air and bone in nearby sinuses). Aging-related brain changes and ventricular enlargement exacerbate this problem. Furthermore, head or body movement will add to these inhomogeneities amplifying error variation. Another difficulty in measuring raw SI signal relates to the assumption that instructing the subject to rest is sufficient to stabilize blood flow and blood oxygen level dependent signal regionally. This is not the experience of functional magnetic resonance imaging experiments in which control of cognitive baseline conditions requires much more care.

Second, SI is determined at the time of imaging after shimming and other calibrations. It is not an absolute measure of tissue density and is highly variable between sessions, such that interindividual comparisons would be a major source of error. Absolute measures, if this were possible, would require some form of preimaging standard phantom-based calibration and postimaging corrections, neither of

which were reported. In addition, their ratio computation would be expected to further increase the error variation (due to an additional variable added to the numerator and denominator introducing variation along a hyperbolic function).

Third, marked SI variability also is suggested by their data analysis. Although the base of logarithmic transformation was not reported, and assuming either base e or 10, the transformed ratios reported in their figures vary over a range of SI of subregions to whole slice by ±150 to 250%. This is at least an order of magnitude larger than is seen in functional magnetic resonance imaging experiments in which 5 to 10% increases are luxurious blood oxygen level dependent changes in SI. The distribution of ratio data before the logarithmic transformation is also not well described but may shed light on why there is such variability.

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Reply

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Every measurement has sources of error, but as Laplace's "law or errors" taught us 200 years ago, error need not paralyze us in fear. Rather, we can confront and exploit errors in any metric by acknowledging its existence, by making certain assumptions, and by controlling many sources of errors by multiple measurements. In the Neuron paper where our magnetic resonance imaging measure was introduced, we were careful in acknowledging many sources of error using T2*-weighted signal intensity. In fact, in that article we include a much longer list of sources of error than the rather trivial concerns expressed by Drs Darby and Tress. The main assumption about many sources of error is that if they are stochastic then multiple measurements—from neighboring regions of the same brain and across different brains—will cancel out their influence on an average measurement.

The first concern expressed by Drs Darby and Tress is that "T2* images are extremely sensitive to magnetic susceptibility." This, by itself, is not a concern but a compliment. The very reason for using T2*-weighted images is that they are sensitive to inhomogeneities caused by local variations in deoxyhemoglobin content and therefore might reflect function. Drs Darby and Tress point out that macroscopic variation—such as tissue–bone interface—might act as a source of error, and they are correct. This source of error, however, should influence neighboring regions, such as the entorhinal cortex and the subiculum, equally. The fact that different patterns of change in signal across the life span were observed in these regions suggests that these sources of error were stochastic and not systematic.

Another source of error that is presumably stochastic is the instability of measures of blood flow at "rest." I will assume that Drs Darby and Tress are familiar with the successful clinical use of positron emission therapy and single-photon emission computed tomography in detecting changes in blood flow measures at "rest." Measures of cerebral blood flow at rest detect changes in patients with structural brain damage, such as patients with Alzheimer's and Parkinson's disease, but also in patients with functional damage such as patients with depression. The magnitude of the systematic effect of brain dysfunction on signal intensity likely overshadows the stochastic and smaller sources of error that occur by subjects being in different states of rest.

The second and third points expressed by Drs Darby and Tress illustrates a source of error that no investigator has control over: errors in reading an article. They point out that T2*-weighted signal intensity "is not an absolute measure of tissue density … ." They need not protest, because this claim was never made in the article. They then raise a concern over the "transformed ratios reported in their figures." However, absolute not transformed ratios were used in the graphs of the figure.

Finally, beyond theoretical arguments, allaying concerns about systematic sources of error is best accomplished by correlating magnetic resonance imaging measures with independent cognitive measures. Indeed, as we reported, we found that normalized measures of T2*-weighted signal were selectively correlated with hippocampal-dependent memory performance.

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