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Are there susceptibility factors for primary progressive aphasia?

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ABSTRACT

The determinants of selective vulnerability in neurodegenerative diseases remain elusive. The asymmetric loss of neurons in primary progressive aphasia offers a unique setting for addressing this question. Although no factor can yet account for the selective vulnerability of the left hemisphere language network to degenerative diseases, a few themes are emerging as potential targets of further investigation.

1. Introduction

Neurodegenerative diseases can be classified by the molecular nature of the proteinopathy, the cellular aspects of the pathology, the anatomical distribution of the neurosynaptic loss, or the clinical features of the resultant phenotype. No neurodegenerative disease is truly global, especially at the initial stages during which selective anatomical distributions determine distinctive clinical phenotypes. In the case of dementias, major subtypes such as those with predominantly *amnestic*, *visuospatial*, *comportmental* and *aphasic* impairments reflect the initially preferential involvement of mediotemporal, parietooccipital, prefrontal and temporosylvian cortices, respectively (Weintraub & Mesulam, 1993). The amnestic phenotype is also known as the dementia of the Alzheimer-type (DAT), the visuospatial phenotype as posterior cortical atrophy (PCA), the comportmental phenotype as behavioral variant frontotemporal dementia (bvFTD), and the aphasic phenotype as primary progressive aphasia (PPA).

In contrast to the consistent relationship between anatomy and clinical features, the relationship of the clinical picture to the underlying disease process in neurodegenerative dementia is anything but consistent. For example, the PPA phenotype can be caused by the neuropathology of either Alzheimer's disease (AD) or of frontotemporal lobar degeneration (FTLD). The FTLD in these patients can arise either sporadically or in conjunction with mutations that lead to dominantly inherited disease. Furthermore, identical mutations in dominantly inherited FTLD can cause different clinical patterns of impairment within the same family (Bird et al., 1999; Mesulam et al., 2007; Rademakers et al., 2007; Simon-Sanchez et al., 2012; Snowden et al., 2006). Similarly, Alzheimer pathology, known to display a predominantly limbic distribution of initial neurodegenerative change and a corresponding amnestic phenotype in the vast majority of cases, can have atypical distributions that occasionally lead to behavioral, visuospatial, or aphasic phenotypes, including PPA (Gefen et al., 2012; Mesulam et al., 2008). The phenotype in neurodegenerative disease therefore seems to reflect complex interactions between molecular factors that underlie neurosynaptic death, on one hand, and individual susceptibility factors that determine the anatomy of degeneration, on the other. The goal of this review is to introduce a few themes that may eventually become pertinent to the identification of factors underlying the selective susceptibility of the language network to neurodegeneration in PPA.

2. Search for genetic factors

2.1. Potential clues in GRN families

The majority of PPA cases associated with FTLD neuropathology are sporadic. However, PPA has also been reported in dominantly inherited forms of FTLD with mutations in *MAPT*, *GRN* or *C9orf72* (Cooper-Knock et al., 2012; Munoz, Ros, Fatas, Bermejo, & de Yebenes, 2007; Pickering-Brown et al., 2008; Simon-Sanchez et al., 2012). In the group of dominantly inherited dementias, the PPA phenotype has been described most frequently in families with a point mutation on chromosome 17 in the *GRN* gene that encodes

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progranulin and leads to a haploinsufficiency syndrome. In these families, some of the affected individuals may display the PPA phenotype while others display the bvFTD phenotype (Rademakers et al., 2007). There are, however, some exceptions. In two families, *GRN* mutations resulted in the PPA phenotype in all affected members (Mesulam et al., 2007). In the PPA1 family, three of four siblings had PPA. The mutation consisted of a single nucleotide deletion in exon 9. In the PPA3 family, two of three siblings had PPA. The mutation was a $C > T$ transition in exon 11. Both mutations resulted in a premature termination codon and a haploinsufficiency of progranulin. Affected members of both families showed FTLD-TDP Type A pathology, where inclusions containing the transactive response DNA-binding protein 43 (TDP-43) were asymmetrically distributed with a greater concentration in the left hemisphere language cortices (Gliebus et al., 2010). Families with this type of homogeneous PPA phenotype hold considerable promise for exploring factors that make the left hemisphere language network selectively susceptible to progranulin deficiency.

2.2. ApoE

As mentioned above, the PPA phenotype can emerge in association with the amyloid plaques and neurofibrillary tangles (NFT) of AD (Mesulam & Weintraub, 1992). However, in such cases, the NFTs have an atypical and clinically concordant distribution that is quite different from what is seen in DAT. Specifically, the NFTs in PPA display higher left-to-right and neocortical-to-entorhinal ratios than in patients with the DAT phenotype (Gefen et al., 2012). One question is whether the differential distribution of neurofibrillary degeneration in AD might be associated with differences of genetic background. This question was addressed in a study that looked at the prevalence of molecular forms of the Apolipoprotein E gene (*ApoE*). The ε4 allele of *ApoE* is a known genetic risk factor for typical AD, namely an age-related neurodegeneration associated with the amnestic DAT phenotype. In our autopsy series of patients *with proven Alzheimer pathology*, we found that the frequency of the ε4 allele was no higher in patients with the PPA phenotype than in the controls, whereas, as expected, the frequency of this allele was significantly higher in patients with the typical amnestic DAT phenotype (Gefen et al., 2012). It appears, therefore, that ε4 is not a general risk factor for *all* Alzheimer pathology, but *specifically* for the Alzheimer pathology that leads to the amnestic DAT phenotype and preferential atrophy of mediotemporal limbic cortices (Rogalski et al., 2011). Circumstantial support for this speculation comes from an experiment showing that neurologically intact subjects carrying at least one ε4 allele displayed reduced hippocampal volume, as if the ε4 allele might exert a developmental influence that makes medial temporolimbic structures more susceptible to involution and perhaps also to neurofibrillary pathology (Lind et al., 2006). Further exploration of how the ε4 allele of *ApoE* differentially influences the vulnerability of mediotemporal versus left perisylvian cortex to neurodegeneration may indirectly help to identify susceptibility factors for PPA.

2.3. Prion protein

One of the most interesting genetic clues related to selective vulnerability comes from the field of prion proteins. Two of the best-known phenotypes of genetic prionopathies are Creutzfeldt-Jacob disease, which causes predominantly cortical degeneration, and Fatal Familial Insomnia, which causes predominantly thalamic degeneration. Although the mutation of the prion protein gene (*PRNP*) is on codon 178 for both phenotypes, the nature of the polymorphism on codon 129 of *PRNP* influences whether the pathology is cortical or thalamic. One question is whether codon 129 polymorphisms also influence disease distribution in other degenerations.

In an initial investigation, we found that the methionine/valine (MV) polymorphism of codon 129 was overrepresented in PPA compared to controls, bvFTD, and motor neuron disease (Li et al., 2005). This preliminary finding raised the possibility that polymorphisms of codon 129 could influence the selective susceptibility of the language network to neurodegeneration even when the disease is not related to a prionopathy. However, two other studies (Premi et al., 2012; Rohrer et al., 2006), have failed to replicate our results. In the future, it may be useful to repeat this investigation in a larger group of PPA cases with known neuropathology.

2.4. Foxp2

Mutations of the forkhead box P2 gene (*FOXP2*) in the KE kindred has been linked to relatively specific speech and language impairments (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). This relationship has stimulated a great deal of interest in trying to identify whether *FOXP2* polymorphisms influence the susceptibility to PPA. In one study on patients with clinically diagnosed FTLD-spectrum syndromes, the rs1456031 and rs17137124 polymorphisms were associated with hypoperfusion in the left inferior frontal gyrus and lower verbal fluency (Padovani et al., 2010). However, these *FOXP2* polymorphisms did not differentiate PPA from controls (Premi et al., 2012). Of even greater interest is the finding that a polymorphism of *KIAA0319/TTRAP/THEM2, a* gene that is thought to be associated with dyslexia, influences the laterality of activation in the superior temporal sulcus (Pinel et al., 2012). In some way or another, these two genes seem to asymmetrically influence the activity of the two hemispheres, specifically within areas related to language function. Further work on these genes and their potential interactions with *GRN*, *ApoE* and *PRNP* remain promising avenues for exploring the putative molecular basis of selective vulnerability in PPA.

3. Search for developmental and acquired factors

3.1. Learning disability

A study in a group of 699 subjects found that a history of learning disability, including developmental dyslexia, is significantly higher in PPA patients and their first-degree relatives than either in controls or in patients with the DAT or bvFTD phenotypes (Fig. 1). In several of the PPA families there were unusually high concentrations of specific reading and spelling difficulties. For example, one of the PPA probands in this study reported that he did not learn to read until the age of 9–10 and that his spelling has always been poor. All three of his children and both granddaughters were reported as dyslexic. It is worth noting that the patient as well as all three sons managed to build successful careers emphasizing computers and sports. Another proband, who denied a personal history of learning disability, reported that all five of his siblings had difficulties with learning to read or spell. One of the PPA patients reported that his father was a stutterer. Dyslexia is known to run in families and has been associated with numerous genetic susceptibility loci (Cardon et al., 1994; Tzenova, Kaplan, Petryshen, & Field, 2004). If a sufficiently large PPA sample can be gathered, it may be possible, to explore if any of these genes are also risk factors for PPA. In some cases such susceptibility genes may interfere with the initial development of language and lead to developmental dyslexia, in others the effect may remain compen-