Is posterior cortical atrophy an extreme phenotype of *GRN* mutations?

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INTRODUCTION

Posterior cortical atrophy (PCA)[1] is a rare neurodegenerative disorder affecting primary visual occipital, occipito-temporal and bi-parietal cortices. PCA is usually considered as atypical variant of Alzheimer's disease (AD) because most cases had AD pathology [2,3]. The genetic basis of PCA remains elusive. Mutations in *PSEN1*, *PRNP* and *IT15* genes have been identified in few patients [4,5,6]. A link between PCA and genetic forms of FTLD is supported by the recent identification of a *MAPT* mutation in one PCA case [7].

We identified a *GRN* mutation in a patient presenting with visual deficits, apperceptive visual agnosia and occipital cortical atrophy, fitting the criteria of PCA.

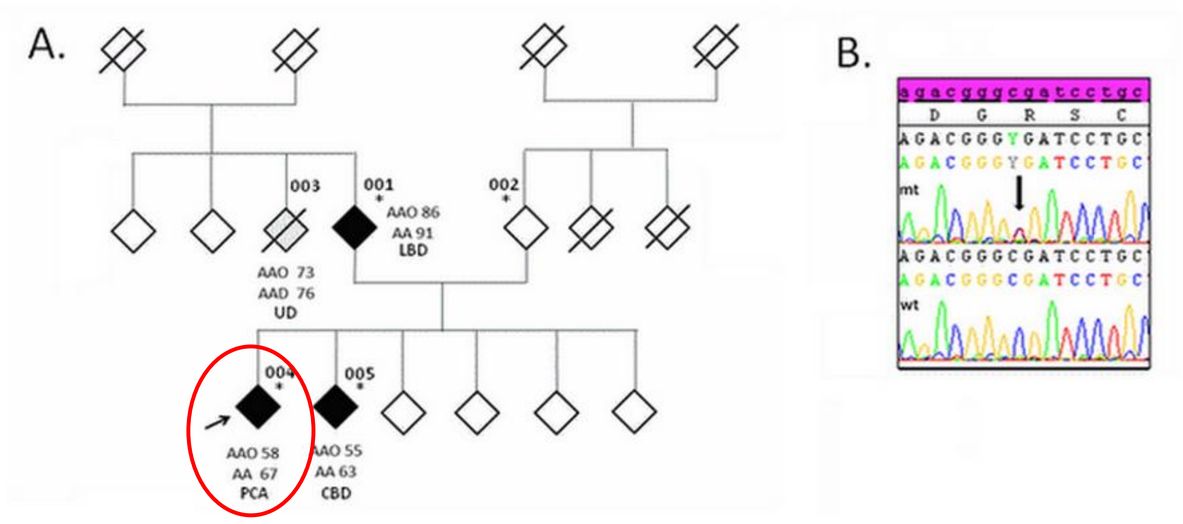
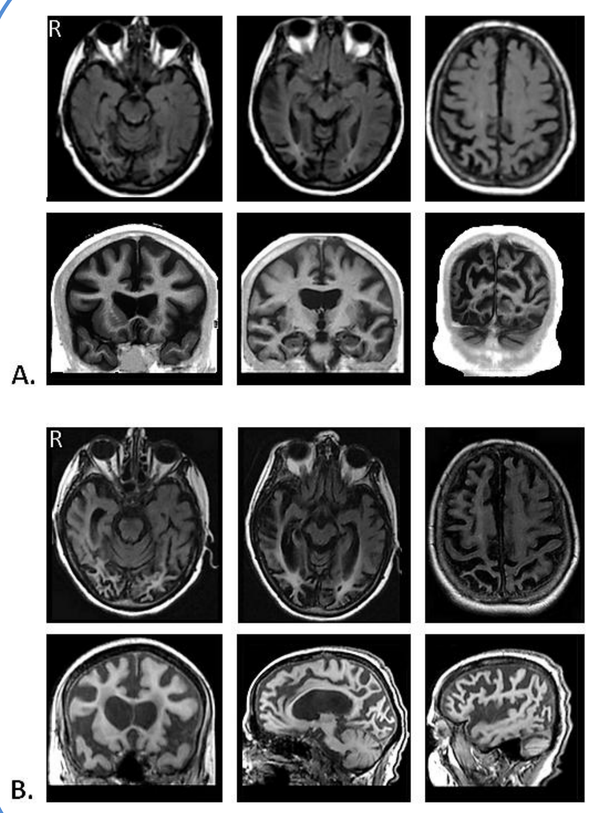


Figure 1. Family pedigree and *GRN* mutation.

A) Solid symbols indicate affected members, white symbols unaffected individuals; diamonds were used for confidentiality. AAO=age at onset; AA=actual age; AAD=age at death; LBD=Lewy Body disease; PCA=Posterior Cortical Atrophy; CBD=Corticobasal degeneration; UD=Unspecified dementia; asterisks indicate DNA availability. **B)** Chromatogram of the c.328C>T (p.Arg110*) mutation is in the upper half (bold arrow), the normal sequence below. mt=mutated; wt=wild type.



A. Axial and coronal slices, 2 years from onset

B. Axial, coronal and sagittal slices, 6 years from onset

Figure 2. MRI (FLAIR and T1-weighted sequences) of patient 004.

Tests	Score
MMSE	
Score (/30)	16*
Birmingham Object Recognition Battery	
Length Match (/30)	0
Size Match (/30)	0
Orientation Match (/30)	0
Position of Gap Match (/30)	0
Visual Object and Space Perception Battery	
Shape decision (/20)	10*
Incomplete letters (/20)	0
Silhouettes (/30)	0
Dot counting (/10)	0
Position discrimination (/20)	0
Picture naming (/80)	0
Identification of real objects	
Visual input (/10)	0
Tactile input (/10)	10
Auditory input (/3)	3
Olfactory input (/3)	3
Identification of living/non-living objects (/6)	3*
Identification of simples shapes (/4)	1*
Identification of colours (/20)	16
Movement perception	
Objects localization in space	Normal
Target tracking	Normal
Semantic knowledge battery (/78)	74
Executive functions	
Digit span backward	3*

Isaac Set Test	
15"	21
60"	49
Repetitions	4
Similarities (/19)	4*
Line bisection task	0
Symbol cancellation task	0
Words reading	0
Sentences reading	0
Letters identification (/6)	0
Writing words on dictation	
Regular (/10)	10
Irregular (/10)	9
Logatoms (/10)	10
Oral spelling of words (on dictation)	
Regular (/5)	5
Irregular (/5)	5
Logatoms (/5)	4
Reconstitution of words on spelling	
Regular (/5)	3
Irregular (/5)	3
Logatoms (/5)	2
Faces identification	
Facial Recognition Test (/54)	0
Famous and unknown faces recognition	0
Facial expression recognition (/10)	2*

Table 1. Neuropsychological profile of patient 004, right-handed, at age 60. Asterisks show scores under cut-off.

DISCUSSION

A p.Arg110* *GRN* mutation was identified in a patient with a clinical phenotype of PCA characterized by prominent visual deficits, apperceptive visual agnosia, alexia, prosopoagnosia with preservation of other cognitive functions. He presented predominant atrophy of the primary visual cortex, and of the parieto-occipital region that was in agreement with the criteria of visual/ventral variant of PCA[1, 7].

The clinical presentation of patient 004 was very unusual because isolated visual agnosia at onset has never been reported in *GRN* carriers, mostly presenting bvFTLD, PNFA or CBS. The distribution of atrophy was also different from *GRN* carriers, where usually involves frontal, temporal and parietal cortex but preserves occipital regions at onset [8].

GRN mutations are characterized by TDP-43 pathology and no pathological cases of PCA with TDP-43 inclusions have been described so far. In our patient, AD pathology cannot be surely excluded, in absence of brain pathology and CSF analyses. However, the patient did not carry the strong ApoE ε4 risk allele for AD and the atrophy rapidly progressed to severe diffuse cortical involvement.

CONCLUSION

This study extends the clinical spectrum of *GRN* mutations and demonstrates that, in rare cases, the pathology can be confined to posterior cortex at onset. *GRN* analyses could be indicated in PCA, particularly when the damages progress to anterior cerebral regions and a family history of dementia is present. FTLD genes analyses patient's cohorts will be necessary to better evaluate their genetic contribution to PCA. Finally, this study underlines a possible continuum in degenerative dementias, and highlights the limits of actual nosological boundaries. Clarifying these boundaries by identifying factors driving phenotypic heterogeneity will have important implications for the definition of new diagnosis criteria of degenerative dementias and clinical trial recruitment in the future.

REFERENCES

1). Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. *Lancet Neurol*. 2012;11:170-178. 2). Renner JA, Burns JM, Hou CE, McKeel DW Jr, Storandt M, Morris JC. Progressive posterior cortical dysfunction: a clinicopathologic series. *Neurology*. 2004;63:1175-1180. 3). Migliaccio R, Agosta F, Rascovsky K, et al. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology.* 2009;73:1571-1578. 4). Sitek EJ, Narożańska E, Pepłońska B, et al. A patient with posterior cortical atrophy possesses a novel mutation in the presenilin 1 gene. *PLoS One*. 2013;8:e6107 5). Depaz R, Haik S, Peoc'h K, et al. Long-standing prion dementia manifesting as posterior cortical atrophy. *Alzheimer Dis Assoc Disord.* 2012;26:289-292. 6). Caixeta L. Huntington's disease presenting as posterior cortical atrophy. *Arq Neuropsiquiatr*. 2011;69:407-408. 7) Rossi G, Bastone A, Piccoli E, et al. Different mutations at V363 MAPT codon are associated with atypical clinical phenotypes and show unusual structural and functional features. *Neurobiol Aging*. 2014;35:408-417. 8) Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. *Brain*. 2007;130:2636-2645.

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