Explorative genetic study of Neuromedin B (*NMB*) in behavioral variant Frontotemporal Dementia

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BACKGROUND

The behavioral variant of Frontotemporal dementia (bvFTD) is the most common presentation of Frontotemporal Lobar Degeneration. This variant is characterized by early and progressive behavioral dysinhibition, apathy, loss of empathy, compulsive behaviors, and hyperorality (1).

The cortical atrophy in early bvFTD involves the anterior cingulate (ACC) and frontoinsular (FI) cortex (2). This pattern corresponds to the cortical regions harboring von Economo neurons (VENs), that are exclusively found in layer V of the ACC and FI (3). VENs have been shown to be selectively affected in early bvFTD (4). VENs are large bipolar neurons located in frontoinsular and anterior cingulate cortex (fig.1), immunoreactive for several peptides like activating-transcription factor 3 (ATF3), interleukin 4 receptor (IL4Rα), and neuromedin B (NMB) (5).

The NMB gene is located at 15q25.2 and encodes neuromedin B, a member of the bombesin-like peptide family. These peptides influence a variety of physiological functions, including regulation of food intake, body temperature, social interaction, behavioral responses to stress, and pain perception. NMB exerts its effect by binding to its cell surface receptor (NMB-R). Upon agonist binding, several intracellular signaling cascades, including phospholipase, calcium mobilization and protein kinase C (PKC), are activated. Polymorphisms of the *NMB* gene have been previously associated with abnormal eating behavior in adults.

AIM OF THE STUDY

The purpose of our study was to evaluate the frequency of *NMB* gene mutations in a dataset of Italian patients with bvFTD and in healthy controls.

METHODS

- We recruited 125 unrelated patients with bvFTD (72 men, 53 women; mean age ±SD= 68.6± 8.4 years) attending the Memory Clinic of the Department of Neuroscience "Rita Levi Montalcini" of the University of Torino. The diagnosis of bvFTD was made according to Rascovsky et al. criteria.
- A group of 62 healthy controls (34 men, 28 women; mean age ± SD= 71.8 ± 6.9 yrs) served as control.
- DNA for genetic analysis was extracted from peripheral blood leukocytes. All the three exons of the *NMB* gene (Ref Seq NM_205858.1) were sequenced.
- The clinical characteristics of bvFTD patients carrying *NMB* gene mutations were examined.
- *In silico analysis.* PolyPhen-2, SIFT and SNAP were used for predicting the effects of the exonic mutations. The substitutions were considered deleterious if at least two out of three computational software predicted the genetic variant as not neutral. We also analyzed the intronic variants with ASSPP, Splicing Finder, Netgene to evaluate whether the substitutions modify the splicing sites.
- Demographic and clinical data were analyzed using SPSS 21.

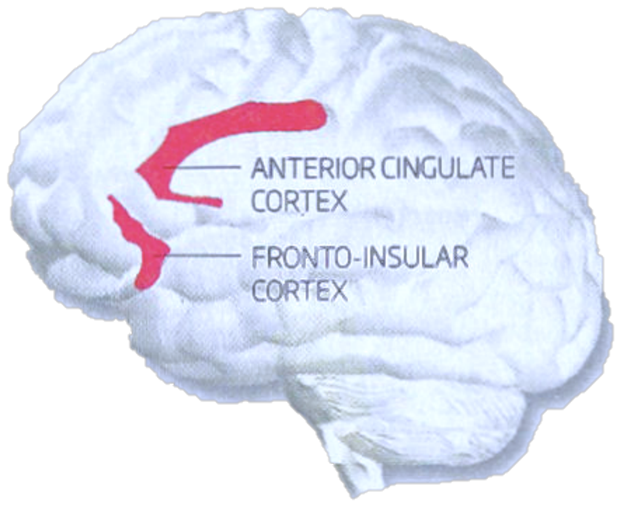

Figure 1. von Economo neurons located in frontoinsular and anterior cingulate cortex.

RESULTS

- In patients with bvFTD, we found five missense mutations 7GA, P73T, M120K, M120I and G138R. Three substitutions were new heterozygous variants in the coding region of *NMB* gene (G7A, M120K, G138R), none of which were found in healthy controls (table 1).
- *In silico* analysis suggested a pathogenic role for two out of three missense substitutions.
- Furthermore, two new genetic variants in the intronic region were found in bvFTD patients (table 2). Computational software predicted that these genetic variants do not affect the splicing sites.
- No significant difference in clinical features was found between bvFTD patients carrying NMB genetic variants and remaining patients.

Exon	Change, bp	Variant	dbSNP	MAF bvFTD	MAF controls	PolyPhen-2	SIFT	SNAP
Exon 1	c.20 G>C	7GA	New	0.012	0	DEL	DEL	NEU
Exon 2	c.217 C>A	P73T	rs1051168	0.406	0.210	NEU	NEU	NEU
Exon 3	c.364 T>A	M120K	New	0.005	0	NEU	NEU	NEU
Exon 3	c.365 G>A	M120I	rs17598561	0.088	0.062	NEU	NEU	NEU
Exon 3	c.823 G>A	G138R	New	0.029	0	DEL	DEL	DEL

Table 1. *NMB* exonic genetic variants in patients with bvFTD and controls. MAF: minor allele frequency; DEL: deleterious; NEU: neutral.

Intron	Change, bp	MAF bvFTD	MAF controls	dbSNP
Intron 1	c.157+47G>A	0.052	0	new
Intron 2	c.330+135 G>A	0.059	0	new
Intron 2	c.331–36 C>T	0.006	0.016	rs117966434

Table 2. *NMB* intronic genetic variants in patients with bvFTD and controls. MAF: minor allele frequency.

DISCUSSION

In the present study, we aimed to assess the prevalence of neuromedin B genetic variants in patients with behavioral variant frontotemporal dementia. In this Italian cohort, we found several gene mutations and in silico analysis suggested a pathogenetic role for two of them.

To the best of our knowledge, this is the first study that investigated the *NMB* gene in bvFTD and our results must be viewed cautiously. The low number of patients examined is the main limitation of this study. However, the patients involved in the study performed extensive clinical, neuropsychological and neuroradiological investigations. In addition, in all patients, clinical diagnosis was supported by analysis of cerebrospinal fluid biomarkers.

Neurobiological mechanisms linking *NMB* to frontotemporal dementia are, at present, unclear.

In conclusion, our study provided preliminary data suggesting an involvement of Neuromedin B gene in bvFT. Additional studies, in larger populations, are needed to better investigate the prevalence of *NMB* mutations in the different clinical subtypes of Frontotemporal Lobar Degeneration.

References

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