

Language impairment in the genetic forms of behavioural variant frontotemporal dementia

Kiran Samra¹, Amy M. MacDougall², Arabella Bouzigues¹, Martina Bocchetta¹, David M. Cash¹, Caroline V. Greaves¹, Rhian S. Convery¹, John C. van Swieten³, Harro Seelaar³, Lize Jiskoot³, Fermin Moreno^{4,5}, Raquel Sanchez-Valle⁶, Robert Laforce⁷, Caroline Graff^{8,9}, Mario Masellis¹⁰, Maria Carmela Tartaglia¹¹, James B. Rowe¹², Barbara Borroni¹³, Elizabeth Finger¹⁴, Matthias Synofzik^{15,16}, Daniela Galimberti^{17,18}, Rik Vandenberghe^{19,20,21}, Alexandre de Mendonça²², Chris R Butler^{23,24}, Alexander Gerhard^{25,26}, Simon Ducharme^{27,28}, Isabelle Le Ber^{29,30,31,32}, Pietro Tiraboschi³³, Isabel Santana^{34,35}, Florence Pasquier^{36,37,38}, Johannes Levin^{39,40,41}, Markus Otto⁴², Sandro Sorbi^{43,44}, Jonathan D. Rohrer^{1*}, Lucy L. Russell^{1*}, on behalf of the Genetic FTD Initiative (GENFI)[#]

*joint senior authors

[#]List of consortium authors in acknowledgements

¹Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK

²Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

³Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands

⁴Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Spain

⁵Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain

⁶Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain

⁷Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, QC, Canada

⁸Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden

⁹Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital, Solna, Sweden

¹⁰Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada

¹¹Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada

¹²Department of Clinical Neurosciences, University of Cambridge, UK

¹³Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

¹⁴Department of Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada

¹⁵Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany

¹⁶Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

¹⁷Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milan, Italy

¹⁸University of Milan, Centro Dino Ferrari, Milan, Italy

¹⁹Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium

²⁰Neurology Service, University Hospitals Leuven, Leuven, Belgium

²¹Leuven Brain Institute, KU Leuven, Leuven, Belgium

²²Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

²³Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK

²⁴Department of Brain Sciences, Imperial College London, UK

²⁵Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK

²⁶Departments of Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Germany

²⁷Department of Psychiatry, McGill University Health Centre, McGill University, Montreal, Québec, Canada

²⁸McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Québec, Canada

²⁹Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

³⁰Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

³¹Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

³²Reference Network for Rare Neurological Diseases (ERN-RND)

³³Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy

³⁴University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

³⁵Center for Neuroscience and Cell Biology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

³⁶Univ Lille, France

³⁷Inserm 1172, Lille, France

³⁸CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France

³⁹Department of Neurology, Ludwig-Maximilians Universität München, Munich, Germany

⁴⁰German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

⁴¹Munich Cluster of Systems Neurology (SyNergy), Munich, Germany

⁴²Department of Neurology, University of Ulm, Germany

⁴³Department of Neurofarba, University of Florence, Italy

⁴⁴IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

Corresponding author:

Dr Lucy L. Russell, Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, l.russell@ucl.ac.uk

Online only (supplementary) material

Number of supplementary tables: 2

Number of supplementary figures: 0

Supplementary Table 1. Neuropsychology assessment scores for the bvFTD groups and controls. Bold items are significantly different to controls; ^asignificantly impaired compared to *C9orf72* mutation carriers, ^bsignificantly impaired compared to *GRN* mutation carriers, ^csignificantly impaired compared to *MAPT* mutation carriers.

Supplementary Table 2. Correlations between the linguistic symptoms and left hemisphere regional brain volumes in each genetic group. Rho is shown for each correlation, with significant values shown highlighted and in bold. Abbreviations: comp = comprehension.

Supplementary Table 1. Neuropsychology assessment scores for the bvFTD groups and controls. Bold items are significantly different to controls; ^asignificantly impaired compared to *C9orf72* mutation carriers, ^bsignificantly impaired compared to *GRN* mutation carriers, ^csignificantly impaired compared to *MAPT* mutation carriers.

	Controls	<i>C9orf72</i>	<i>GRN</i>	<i>MAPT</i>
Trail Making Test Part A (max 150s)	30.8 (13.4)	60.4 (31.8)	84.1 (41.2) ^c	45.1 (17.1)
Trail Making Test Part B (max 300s)	73.5 (34.7)	195.0 (89.3)	218.4 (112.8)	146.5 (88.3)
D-KEFS Color-Word Interference Test (max 180s)	52.4 (13.1)	110.0 (47.7)	88.7 (50.9)	79.5 (35.5)
Digit Symbol test (max in 90s)	51.8 (12.3)	27.8 (11.9)	22.6 (12.8)	33.2 (8.7)
Digit Span Forwards (/12)	7.8 (1.9)	6.3 (2.7)	6.2 (2.7)	7.8 (2.6)
Digit Span Backwards (/12)	6.4 (2.0)	4.3 (2.1)^c	4.3 (2.8)	6.5 (3.2)
Block Design (/71)	46.0 (14.2)	18.8 (14.5)^c	11.8 (9.8)^c	37.7 (14.9)
FCSRT - free recall (/48)	30.5 (7.1)	16.7 (7.4)	6.7 (10.0)^a	10.4 (7.3) ^a
FCSRT - free + cued recall (/48)	45.3 (4.8)	39.5 (8.5)	18.3 (16.4)^a	28.3 (12.4) ^a
FCSRT - free delayed recall (/16)	11.4 (2.8)	6.3 (3.8)	2.9 (4.3)	3.3 (4.2)
FCSRT - free + cued delayed recall (/16)	15.2 (1.7)	13.8 (2.6)	8.7 (7.0)	10.1 (4.5) ^a
Mini-SEA: Faux-Pas test (/40)	34.7 (4.9)	26.7 (7.5)	21.8 (5.6)^c	30.6 (7.3)
Mini-SEA: Facial Emotion Recognition Test (/35)	28.2 (3.3)	20.9 (4.6)	17.1 (5.5)^c	23.4 (6.0)

Supplementary Table 2. Correlations between the linguistic symptoms and left hemisphere regional brain volumes in each genetic group. Rho is shown for each correlation, with significant values shown highlighted and in bold. Abbreviations: comp = comprehension.

		Impaired articulation	Decreased fluency	Impaired grammar	Impaired word retrieval	Impaired speech repetition	Impaired sentence comp	Impaired single word comp	Dyslexia	Dysgraphia	Impaired functional communication
Inferior frontal gyrus	C9orf72	-0.64	-0.26	0.21	-0.04	-0.39	0.14	0.16		-0.07	-0.11
	GRN	0.08	0.62	0.58	0.47	0.58	0.08		-0.25	0.25	0.20
	MAPT		-0.87		-0.56		-0.22	-0.79	-0.79	-0.45	-0.39
Insula	C9orf72	-0.45	-0.54	0.08	-0.39	-0.09	-0.07	0.21		0.46	-0.58
	GRN	-0.58	0.24	0.58	-0.17	0.58	-0.30		-0.25	0.25	-0.26
	MAPT		-0.58		-0.51		0.58	-0.16	-0.16	-0.40	-0.39
Motor Cortex	C9orf72	-0.59	-0.65	-0.29	-0.51	-0.30	-0.11	0.03		0.20	-0.26
	GRN	-0.41	0.24	-0.08	0.05	-0.08	-0.04		0.41	0.25	0.31
	MAPT		0.29		0.32		-0.22	0.63	0.63	-0.22	0.46
Temporal pole	C9orf72	-0.21	-0.36	-0.34	-0.38	0.26	0.05	0.34		0.30	0.01
	GRN	-0.58	-0.04	0.41	-0.13	0.41	-0.73		-0.41	0.00	-0.40
	MAPT		-0.14		0.09		0.76	0.16	0.16	-0.09	0.15
Superior temporal gyrus	C9orf72	-0.18	-0.42	-0.26	-0.27	0.09	-0.10	0.37		0.15	-0.13
	GRN	-0.41	0.01	0.58	0.13	0.58	-0.78		-0.25	0.25	-0.53
	MAPT		-0.14		-0.21		0.04	0.00	0.00	-0.45	-0.54
Supratemporal region	C9orf72	-0.40	-0.42	0.05	-0.12	-0.39	0.14	0.50		0.11	-0.42
	GRN	-0.08	0.03	0.58	0.33	0.58	-0.73		-0.41	0.25	0.31
	MAPT		-0.14		-0.09		0.76	0.32	0.32	-0.27	-0.08
Angular gyrus	C9orf72	-0.08	-0.03	0.08	0.37	0.30	0.40	0.24		0.13	-0.07
	GRN	-0.58	-0.11	0.41	-0.36	0.41	-0.54		-0.41	0.00	-0.50
	MAPT		0.29		0.30		-0.80	-0.16	-0.16	0.13	0.08