

α -Synuclein pathology-related complement activation and clinical implications

MARIANNA RIZZO^{1,2}, IRENE CUMPLIDO-MAYORAL², SEBASTIAN PALMQVIST^{2,3}, RIK OSSENKOPPELE^{2,4}, ERIK STOMRUD^{2,3}, SHORENA JANELIDZE², PIERO PARCHI^{5,6}, ANGELA MAMMANA⁵, PIETER JELLE VISSER^{1,4,7}, OSKAR HANSSON², STEPHANIE J. B. VOS¹, and NIKLAS MATTSSON-CARLGREN^{2,3}

¹ Department of Psychiatry And Neuropsychology, Alzheimer Centrum Limburg, Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, Netherlands; ² Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Sweden; ³ Memory Clinic, Skåne University Hospital, Malmö, Sweden; ⁴ Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands; ⁵ IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; ⁶ Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; ⁷ Department of Neurobiology, Care Sciences And Society, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden.

Introduction

Dysfunction of the **complement system**, a key component of **innate immunity**, is implicated in **neurodegeneration** through excessive **neuroinflammation** and synaptic pruning. Complement activation has been linked to **α -synuclein pathology** *in vitro* and post-mortem, but *in vivo* associations remain unexplored, limiting understanding of complement roles in **early disease mechanisms** and **progression**.

Aims

To investigate associations between **α -synuclein pathology** and **CSF complement activation** and their **clinical implications**.

Methods

 **2132 participants** with neurodegenerative diseases or healthy controls from the **Swedish BioFINDER study 1-2**

 **CSF α -synuclein seed amplification assays (SAA; RT-QuIC)**

 **29 CSF complement proteins** (GO: 0006956) >limit of detection for >70% participants and meeting quality control criteria (quantified via CSF **Olink Explore 3072**)

 **Neuropsychological and motor assessment** (BL + FU)

1. **α -Synuclein pathology** $\longrightarrow$ **CSF complement proteins**
Linear regression; covariates: age, sex, mean CSF protein level; FDR correction

2. Differentially abundant proteins (DAPs) further assessed in **interaction** with **AD pathology** (CSF A β 42/40, tau PET), **APOE ϵ 4** carriership, **cognitive status** (CU/CI)

3. **α -Synuclein pathology** $\longrightarrow$ **Complement DAPs** $\longrightarrow$ **Cognitive and motor performance and decline**

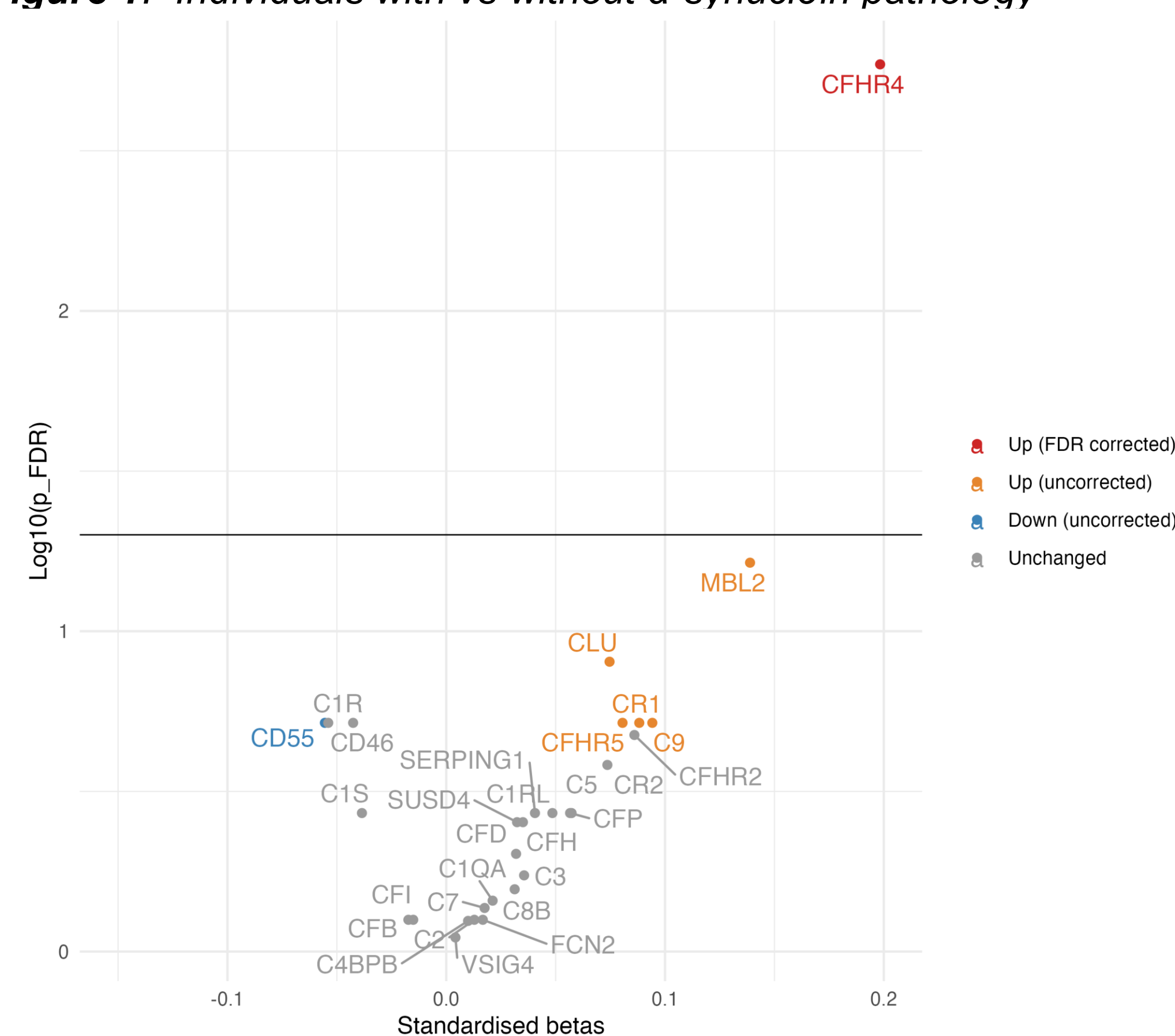
Mediation analyses for clinical outcomes associated with both α -synuclein pathology and DAPs; covariates: age, sex, mean CSF protein level, CSF A β 42/40 status, [for cognitive outcomes] education years

Results

	α -syn SAA- (N=1681)	α -syn SAA+ (N=451)	p-value	Total (N=2132)
Age	69 (10)	73 (8)	<0.001	70 (10)
Female sex	875 (52%)	152 (34%)	<0.001	1027 (48%)
Education years	13 (4)	13 (4)	0.200	13 (4)
APOE ϵ 4 carriers	838 (51%)	202 (49%)	0.500	1040 (50%)
MMSE	27 (4)	26 (4)	<0.001	27 (4)
Clinical diagnosis				
AD	213 (13%)	64 (14%)	<0.001	277 (13%)
DLB	1 (<0.1%)	50 (11%)		51 (2.4%)
MCI	392 (23%)	91 (20%)		483 (23%)
Normal	546 (32%)	31 (6.9%)		577 (27%)
PD	8 (0.5%)	98 (22%)		106 (5.0%)
PSP	55 (3.3%)	3 (0.7%)	0.004	58 (2.7%)
SCD	280 (17%)	38 (8.4%)		318 (15%)
Other or not determined	186 (11%)	76 (17%)		262 (12%)
Abnormal CSF A β 42/40	757 (46%)	222 (53%)		979 (47%)

Table 1. Sample characteristics

Figure 1. Individuals with vs without α -synuclein pathology

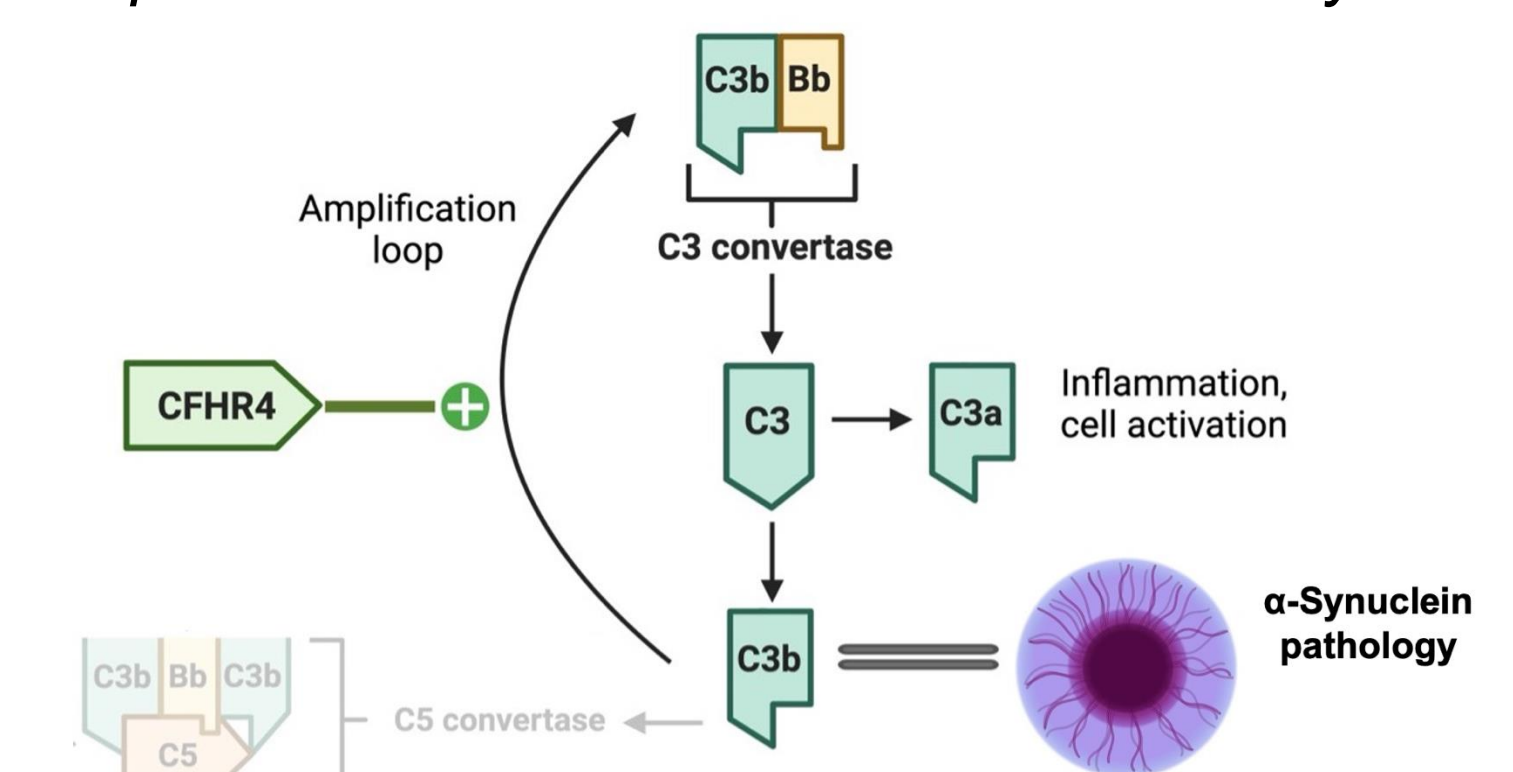


Complement DAPs

- Complement factor H-related 4 (CFHR4)** CSF levels were **upregulated** in individuals with **α -synuclein pathology** (b=0.198, p_{FDR}=0.002).
- CFHR4 is involved in **promoting alternative complement pathway activation** by competing with factor H and binding to C3b (amplification loop)
- No interactions** found with **amyloid** or **tau** pathology, **APOE ϵ 4** carriership, **cognitive status**

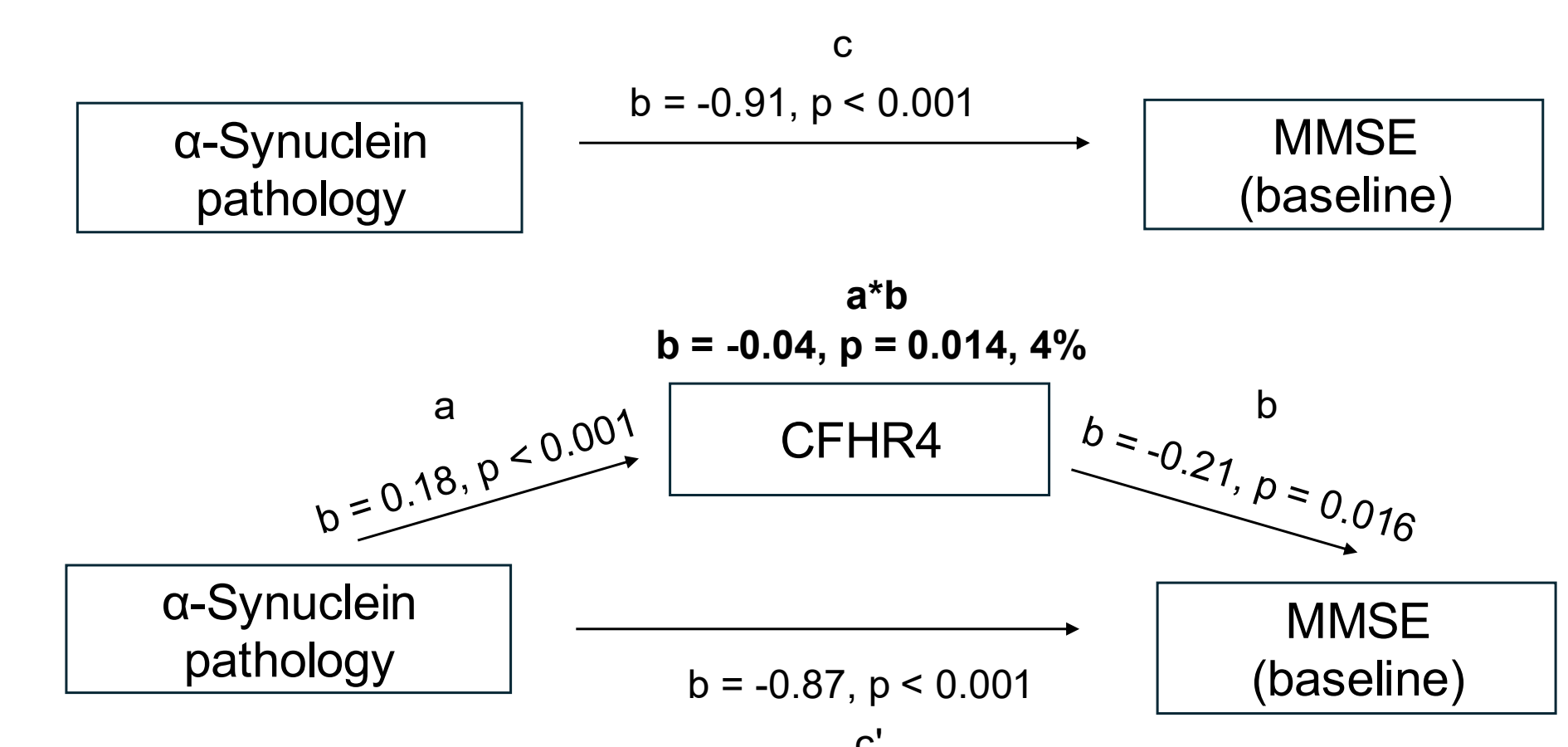
- CFHR4 levels were associated with genetic variants at the **CFHR4 locus**, not other loci (incl., SNCA locus)
- Strong association between **CSF and plasma** CFHR4 levels (b=0.695, p<0.001)

Figure 2. Proposed role of elevated CFHR4 with α -synuclein pathology



Clinical implications

- CFHR4 **partially** mediated α -synuclein pathology's effects on **cognitive performance** (across domains: MMSE, mPACC, TMT-B, symbol digit, ADAS delayed recall, VOSP cube), **motor performance** (CIMP-QUEST-Motor), and **attentional-executive decline** (animal fluency); **2-6%** effect mediated



Main conclusions

Our *in vivo* findings support **activation of the alternative complement pathway** positive-regulator CFHR4 **in response to α -synuclein pathology**, but do **not** provide evidence that this **strongly influences clinical disease manifestations**.

Complement components may **not** be therapeutically **targeted in isolation** in diseases primarily characterized by **α -synuclein pathology**, but clinical implications of downstream inflammatory components warrant further research.

Contact



Marianna Rizzo
Postdoctoral researcher
marianna.rizzo@maastrichtuniversity.nl