FONDAZIONE MONDINO
Istituto Neurologico Nazionale a Carattere Scientifico | IRCCS

55° CONGRESSO SOCIETÀ ITALIANA DI NEUROLOGIA
Padova, 24-28 ottobre 2025
Centro Congressi Padova

UNIVERSITÀ DEGLI STUDI DI PAVIA
DIPARTIMENTO DI SCIENZE DEL SISTEMA NERVOSO E DEL COMPORTAMENTO

Serological quantitative, qualitative and functional profiling as biomarkers in LGI1 and CASPR2 associated disease (AD)

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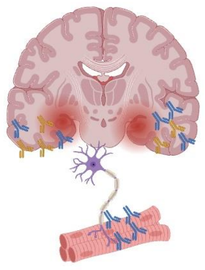
Introduction

Clinical manifestations in CNS and PNS with relapses and cognitive sequelae

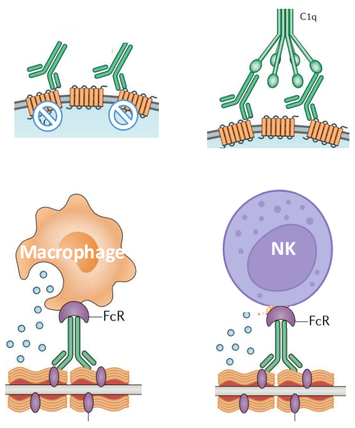
LGI1-IgG
CASPR2-IgG

Lack of biomarkers!

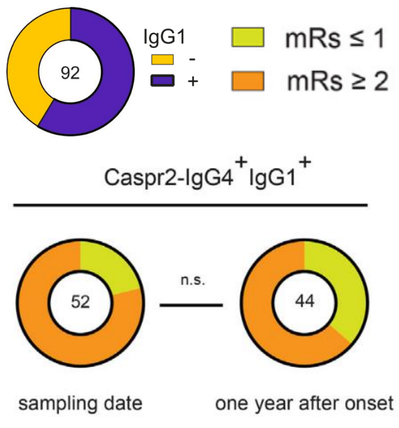
Autoimmune encephalitis
Morvan Syndrome
Neuromyotonia



IgG1/4 presence defines effector profile



CASPR2-IgG1 activate FcgammaRs and associate with worse outcome



Aim

<u>Aim 1</u>: To introduce a newly established simple in vitro experimental setting to test CDC, ADCC and ADCP

<u>Aim 2</u>: To explore IgG titers, Neurofilament light chain (NfL), CDC, ADCP and ADCC as biomarkers in CASPR2/LGI1-AD.

Materials and Methods

Study Algorithm

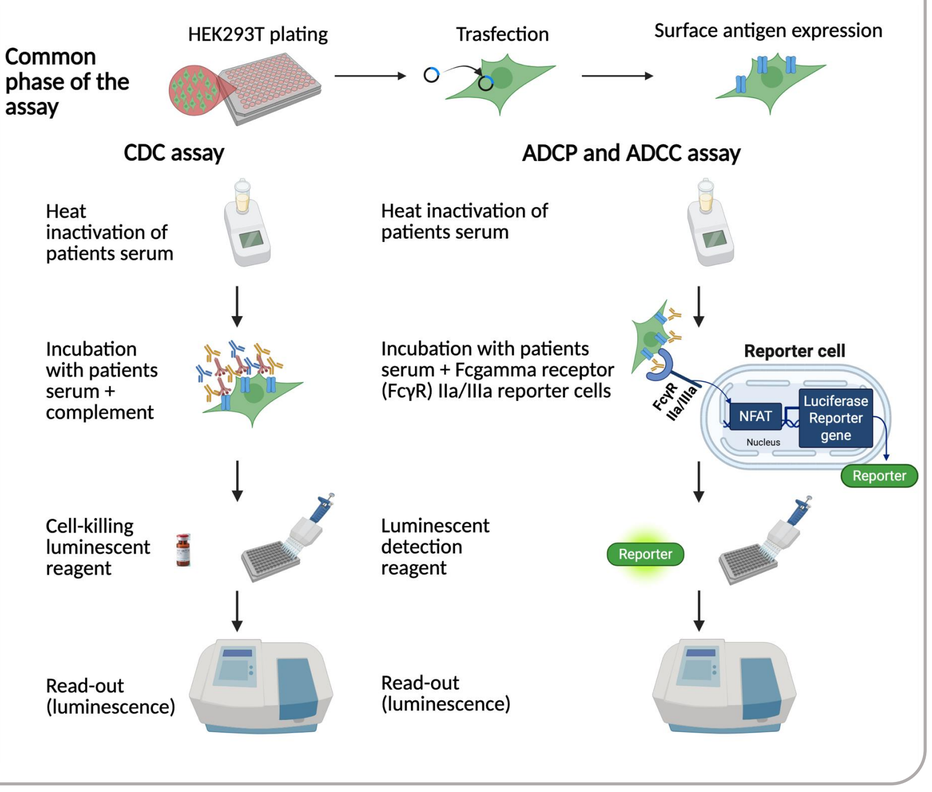
Patients sent for suspected autoimmune neurological syndrome n=5525

Patients tested positive for CASPR2 or LGI1-IgG on serum n=95

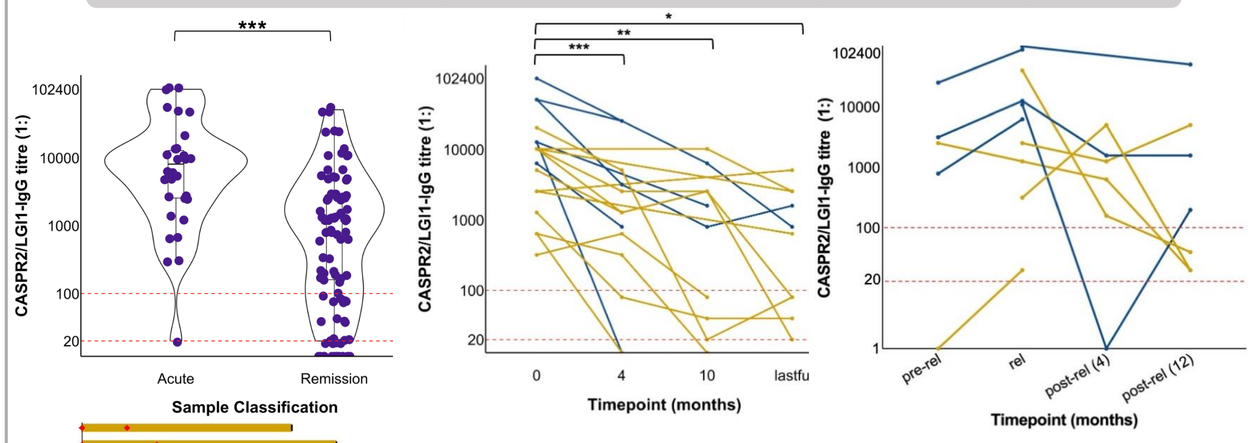
CASPR2/LGI1 confirmed autoimmune neurological syndrome n=55 (with longitudinal samples n=23)

CASPR2/LGI1-IgG subclasses, IgG endpoint titration, NfL (n=142), CDC, ADCC, ADCP (n=55)

In vitro experimental model to test antibody dependent- complement cytotoxicity (CDC), cell-phagocytosis (ADCP), cell-cytotoxicity (ADCC)



Results – I (Patients n=23, Samples n=142)

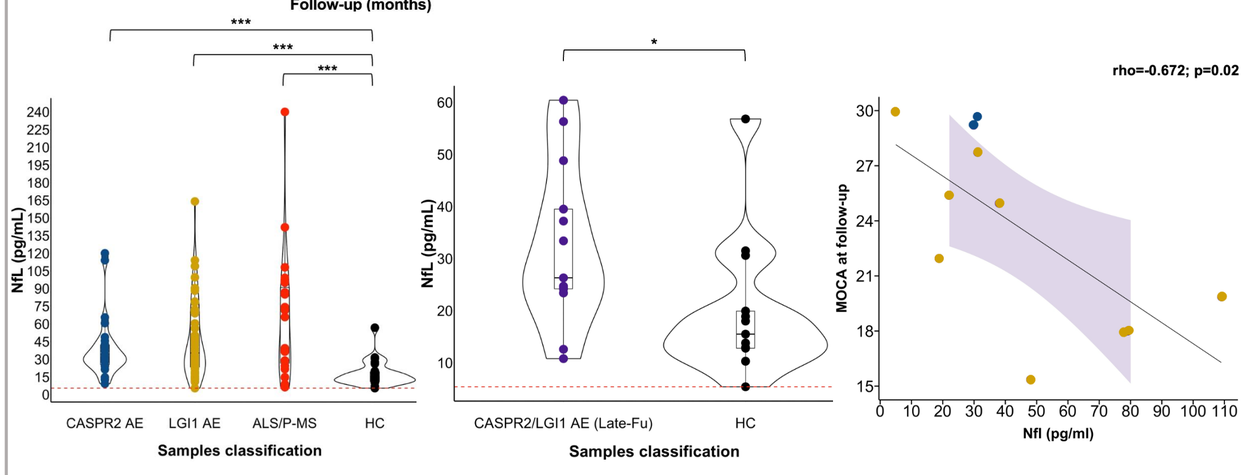


CASPR2/LGI1-IgG titers associated with disease phase

CASPR2/LGI1-IgG titers reduced over time

Relapses occurred with positive samples and with a titer increase

Conversion to negative associated with reduced relapse risk

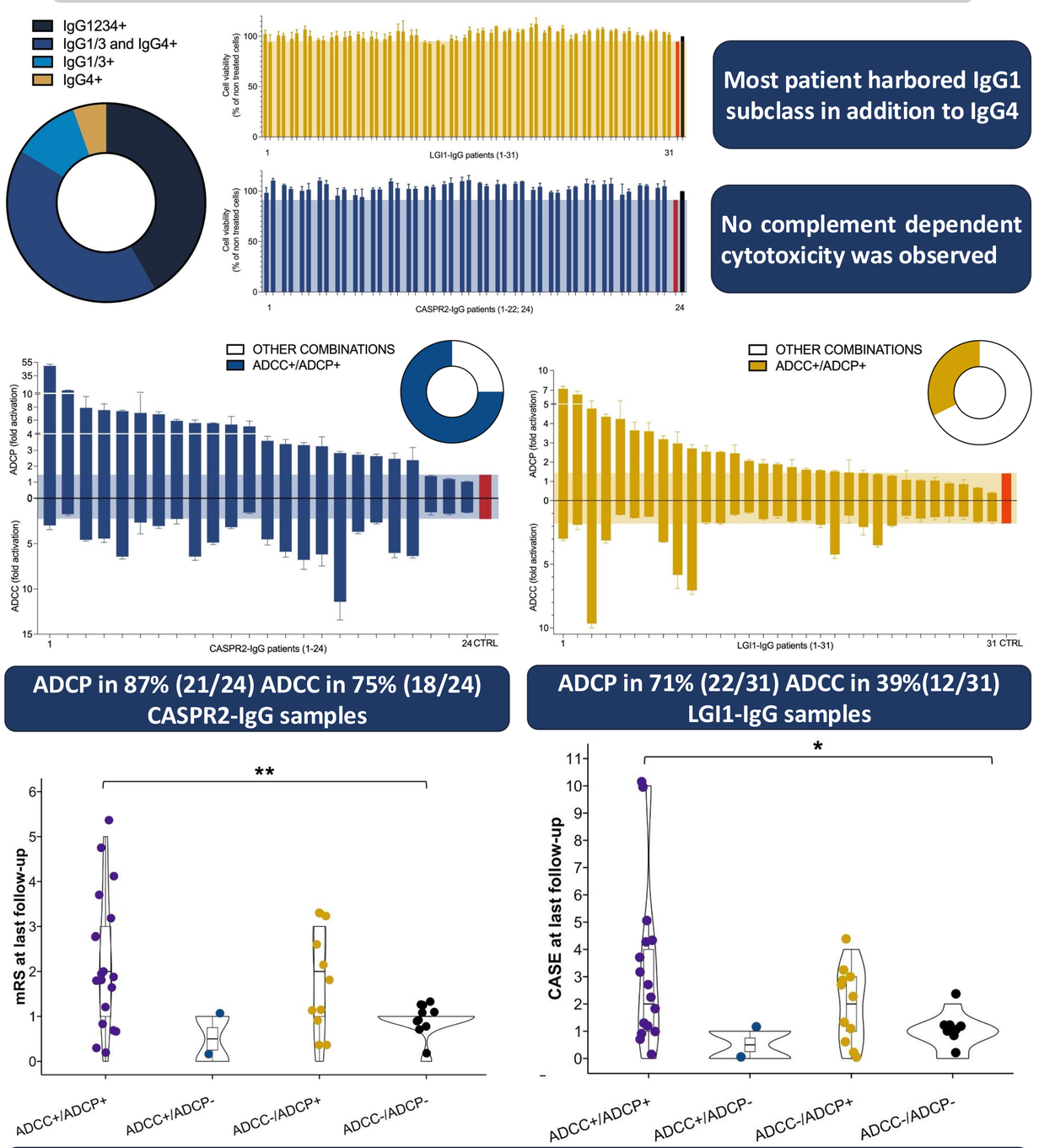


Overall NfL were increased compared to controls in LGI1/CASPR2-AD

NfL were persistently increased at follow-up

NfL at onset inversely correlated with MOCA score at follow-up

Results – II (Patients and samples n=55)



Most patient harbored IgG1 subclass in addition to IgG4

No complement dependent cytotoxicity was observed

ADCP in 87% (21/24) ADCC in 75% (18/24) CASPR2-IgG samples

ADCP in 71% (22/31) ADCC in 39%(12/31) LGI1-IgG samples

Concomitant presence of ADCP and ADCC associated with higher mRS and CASE score at 1 year follow-up

Conclusions

1) We implemented a new and simple to use in vitro assay to test ADCC and ADCP in autoantibody mediated disease.

2) CASPR2/LGI1-IgG titers could be useful to define the disease phase (especially relapses). Conversion to negative might be helpful to assess relapse risk. Elevated Nfl reflects increased axonal damage and might represent a useful prognostic biomarker. ADCP and ADCC are prominent effector functions in CASPR2-AD (and as a novelty in LGI-AD) and might be useful biomarkers to orient treatment strategies

References

Papi, C., Milano, C. & Spatola, 2024; Terroba-navajas, P., Spatola, M. & Chuquisana, O. 2025

Softwares and tools

R studio, graphpad and Biorender.com

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