Diagnostic Modeling of Systemic Lupus Erythematosus Based on New and Traditional Autoantibodies: Demonstration of Feasibility

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Introduction

- SLE is a clinically and genetically heterogeneous disease with a high demand for biomarkers to improve early diagnosis.
- Autoantibodies (AABs) are important in aiding the clinical diagnosis of SLE, with some few AABs, anti-double-stranded DNA (dsDNA), anti-Smith (Sm), and anti-ribosomal P (riboP) being highly associated with SLE.
- We have recently identified novel AABs in SLE (1) and developed quantitative ELISA-prototypes for five new AABs.
- The objectives of this study were to evaluate the diagnostic value of novel AABs and to screen for an optimized combination of novel and traditional AABs using logistic regression to increase the diagnostic accuracy of SLE testing.

Methods

- Serum samples were obtained from 156 SLE patients with European ancestry at the rheumatology department of the Heinrich-Heine University (Düsseldorf, Germany), and Hannover Medical School (Hannover, Germany).
- Traditional diagnostic AABs were measured using IVD assays. Table 1 shows the characteristics of the study cohort and frequency of known diagnostic autoantibodies in SLE and control samples. Optimized marker combinations of new and traditional markers were tested using logistic regression modeling and receiver operating curve analysis (ROC).

Table 1: Sample demographics and diagnostic assay results among SLE and control samples

	SLE	RA	SjS	SSc	PM/DM	HC
Number	156	36	31	39	22	77
Age (years) S.D.	46.89 (14.37)	52.19 (12.88)	51.52 (18.19)	52.92 (12.59)	57.58 (12.14)	45.6 (12.59)
Gender F (%)	46.58	51.37	52.79	52.23	49.50	45.47
dsDNA (%)	32.05	0	6.45	2.56	0	0
Sm (%)	14.74	0	3.23	5.13	0	2.60
Ribosomal P (%)	25.64	2.78	0	7.69	0	1.30
Cardiolipin (%)	25.64	2.78	12.90	12.82	4.55	1.30
SSA/Ro52 (%)	17.95	0	58.06	15.38	13.64	0
SSA/Ro60 (%)	28.21	2.78	58.06	7.69	9.09	2.60
SSB/La (%)	16.03	0	61.29	2.56	9.09	3.90
CCP (%)	5.77	83.33	6.45	7.69	4.55	2.60
Jo1 (%)	0.64	0	0	5.13	18.18	1.30
Scl70 (%)	1.28	0	3.23	38.46	4.55	0
CENPB (%)	1.92	0	3.23	43.59	4.55	0

Results

ELISA development

- Prototype bead based ELISAs were developed for five novel antigens described in (1). When comparing 156 SLE patients with 203 control samples, the area under the curve (AUC) of the five novel SLE ELISAs ranged from 0.6 to 0.74.
- The performance of the anti-MVP ELISA was assessed in the sample set and compared to Luminex measurements. The Pearson's correlation coefficient of the ELISA values with Luminex signal intensities was R=0.83 indicating successful platform transfer.

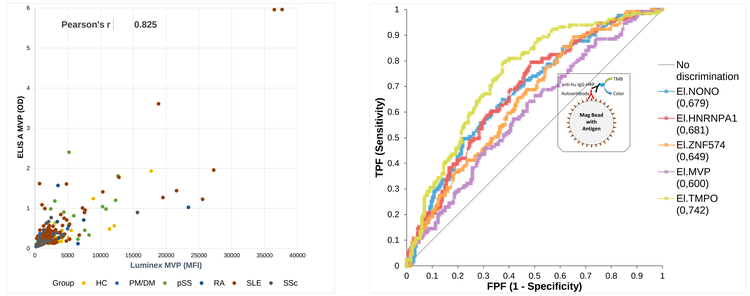

Fig. 2: Performance of new bead-based ELISAs

Testing strategy

Since none of the traditional diagnostic tests has sufficient sensitivity, it may be possible to combine the information to diagnose SLE. Logistic regression models were built and compared for a combination of traditional markers and combinations of new and traditional markers as shown in Fig.3.

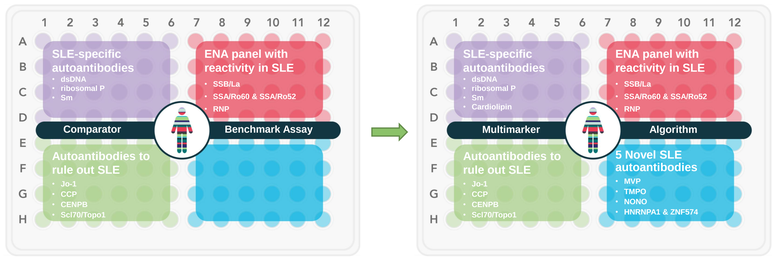

Fig. 3: Comparison of benchmark assay vs Protagen marker panel

Exploration of multimarker panels

- The individual contribution of new markers to a logistic regression model based on traditional markers was assessed by plotting the probability of each model against each other.

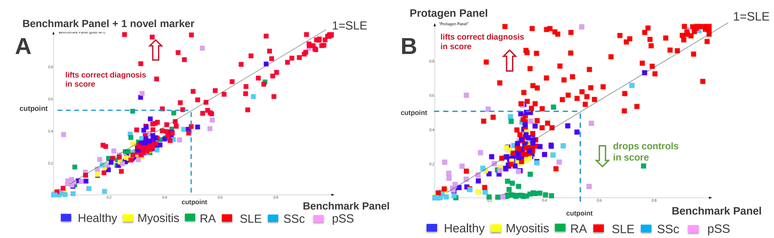

Fig. 4: Contribution of markers to the diagnostic perfomance of multimarker panels
A) Benchmark panel vs benchmark panel plus 1 novel marker
B) Benchmark panel vs novel multimarker panel

- Compared to a logistic regression with traditional assays, a logistic regression with novel markers was superior with increased sensitivity of 17% without loss of specificity.

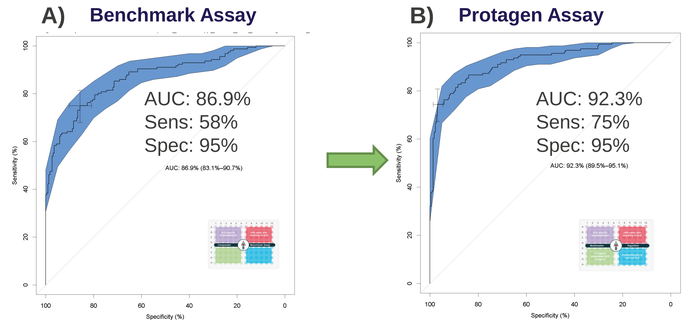

Fig. 5: ROC analysis of multimarker models based on A) traditional markers and B) a combination of new and traditional markers

Conclusions

This study demonstrates the feasibility of combining test results of novel and traditional AABs using logistic regression to increase the diagnostic accuracy for SLE. Further studies are required to assess the impact of different ethnicities on marker selection and algorithm performance.

(1) Budde P, Zucht H-D, Vordenbäumen S, Goehler H, Fischer-Betz R, Gamer M, et al. Multiparametric detection of autoantibodies in systemic lupus erythematosus. Lupus. 2016 Jul 1;25(8):812–22