EGF-Receptor Ligands in Atrial Fibrillation – From Genomic Evidence to the Identification of New Players

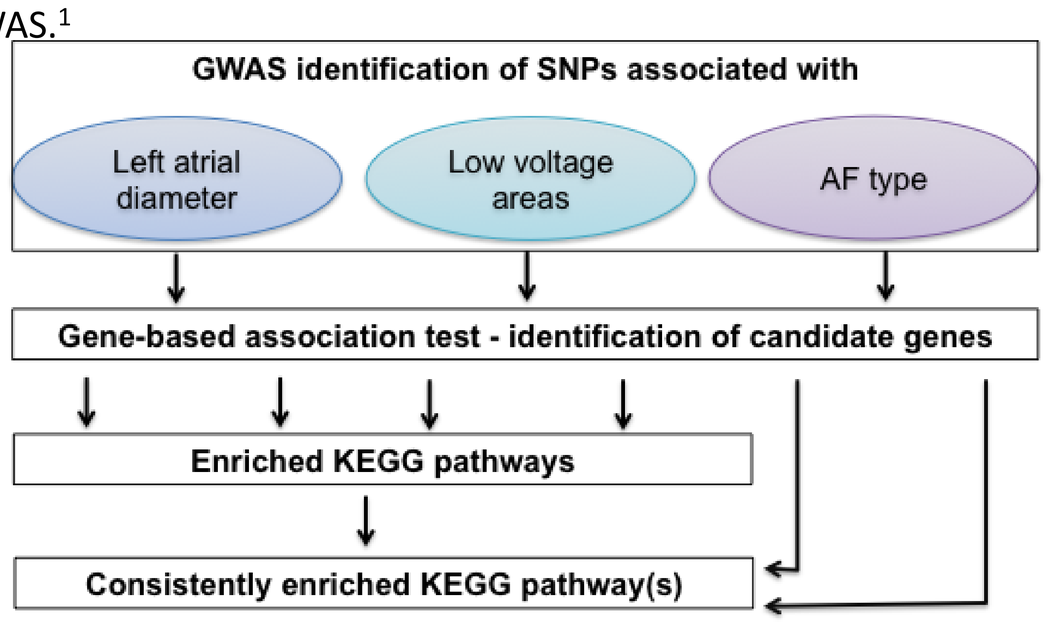
Petra Büttner[1], Sarah Werner[1], Philipp Sommer[2], Ralph Burkhardt[4], Samira Zeynalova[3,4], Ronny Baber[4], Andreas Bollmann[2,4] Daniela Husser-Bollmann[2,4], Joachim Thiery[4], Gerhard Hindricks[2], Holger Thiele[1], Jelena Kornej[2,3,4]

[1] Heart Center Leipzig at University of Leipzig, Department of Internal Medicine/Cardiology, Leipzig, Germany
[2] Heart Center Leipzig at University of Leipzig, Department of Electrophysiology, Leipzig, Germany
[3] Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany
[4] LIFE – Leipzig Research Center of Civilization Diseases, University of Leipzig, Leipzig, Germany

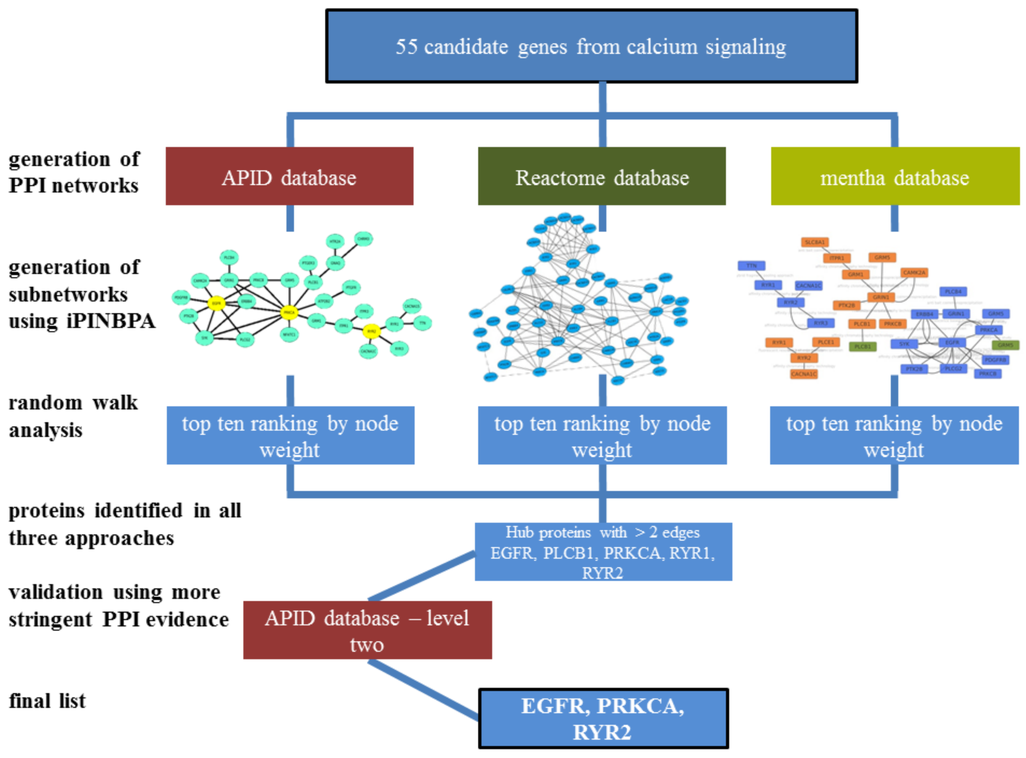
Background

Atrial fibrillation (AF) is underpinned by a multitude of contributing and currently only partially identified pathomechanisms, an individual genetic background, comorbidities and risk factors. Recently we demonstrated an association between genetic variants in the gene locus of the epidermal growth factor receptor (EGFR) and AF progression applying stepwise bioinformatical analyses.

Step 1: Identification of candidate genes associated with AF based on GWAS.[1]



Step 2: Identification of AF-associated central pathway regulators.[2]



Purpose

In this study we analyzed peripheral and cardiac levels of the circulating EGFR ligands EGF and HB-EGF in AF patients before and after catheter ablation and compared them with no-AF controls.

Patients and Methods

Cohort characteristics

	Controls*	AF patients	p-value
	n=41	n=234	
Age	65 (58-73)	65 (57-73)	0.949
Males, n (%)	22 (54)	136 (58)	0.594
BMI (kg/m²)	26 (23-30)	29 (26-33)	<0.001
Diabetes mellitus, n (%)	2 (5)	56 (24)	0.006
Hypertension, n (%)	8 (20)	192 (82)	<0.001
left atrial diameter, mm	36 (32-42)	44 (39-48)	<0.001
Ejection fraction, %	63 (60-66)	59 (50-65)	<0.001
Creatinine, µmol/l	69 (61-77)	83 (73-95)	<0.001
HG-EGF, pg/ml	24 (15-36)	72 (49-102)	<0.001
EGF, pg/ml	17 (11-28)	66 (44-96)	<0.001

Table 1. Characterization of AF cohort and controls Table. Data presented as median (interquartile rage) or n (%).
* Controls are participants of the epidemiological LIFE Adult Study.[3]

EGF and HB-EGF were measured using Luminex screening assays according to the manufacturer's instructions (biotechne, Wiesbaden, Germany).

Results

Result 1: EGF and HB-EGF levels are significantly increased in atrial fibrillation.
Result 2: EGF levels are further significantly higher in left atrial cardiac blood.

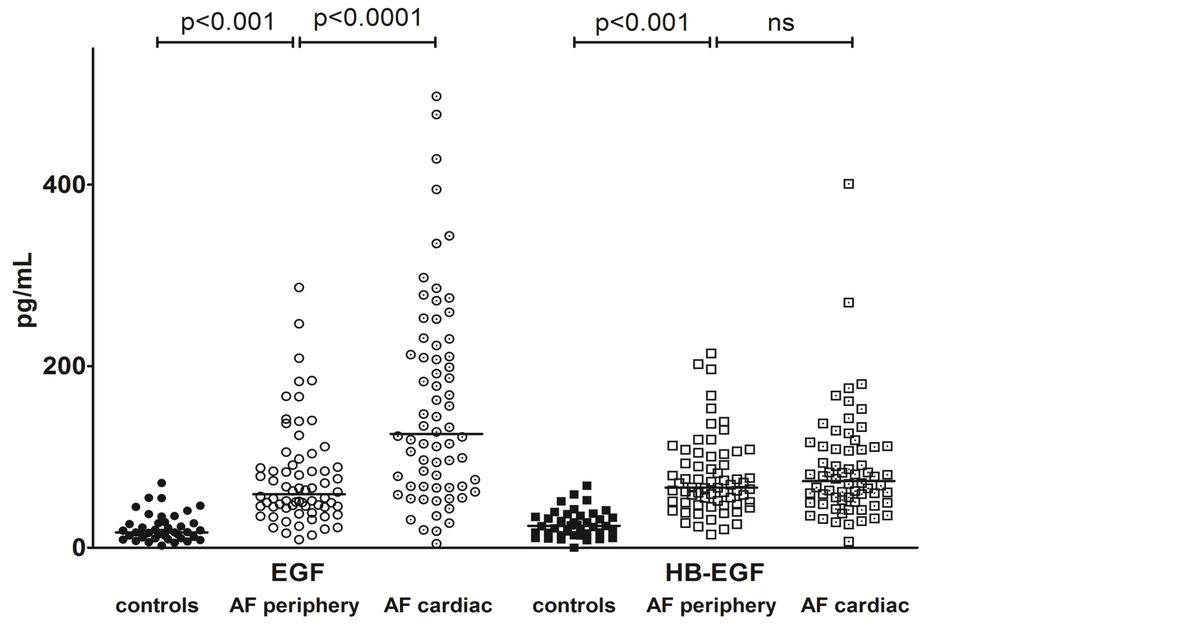


Figure 1: Plasma levels of EGF and HB-EGF in controls and paired samples AF patients from peripheral blood and cardiac blood from the left atrium. Filled symbols stand for controls; clear symbols indicate peripheral blood; clear symbols with a dot indicate cardiac blood.

Result 3: Peripheral levels of EGF and HB-EGF correlate with cardiac levels.

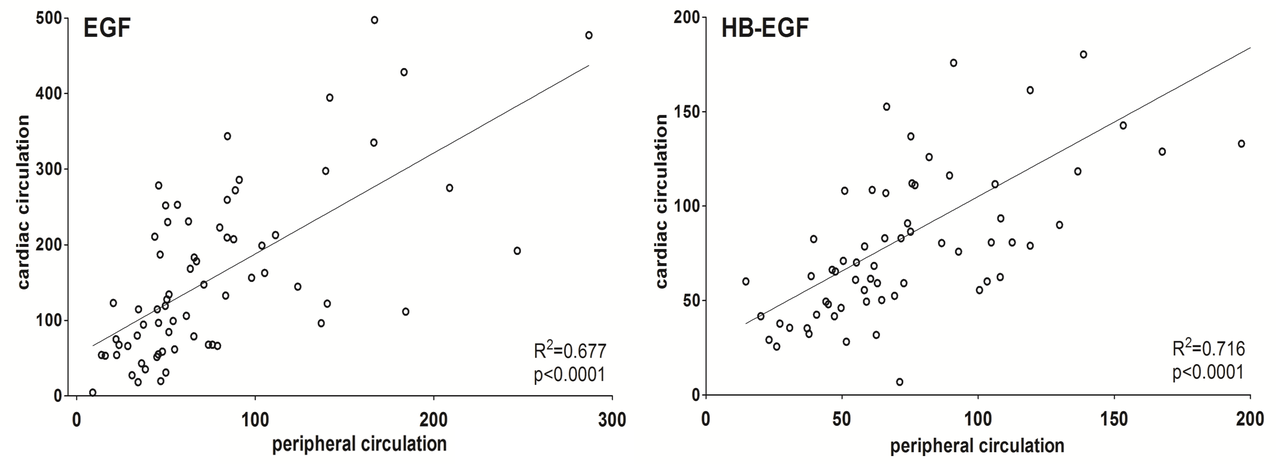


Figure 2: Correlation of EGF and HB-EGF levels in 67 paired samples from cardiac and peripheral blood of AF patients. Regression-coefficient was calculated using Spearman's rank-order correlation.

Result 4: EGF and HB-EGF levels at baseline and at follow up are not associated with AF recurrence

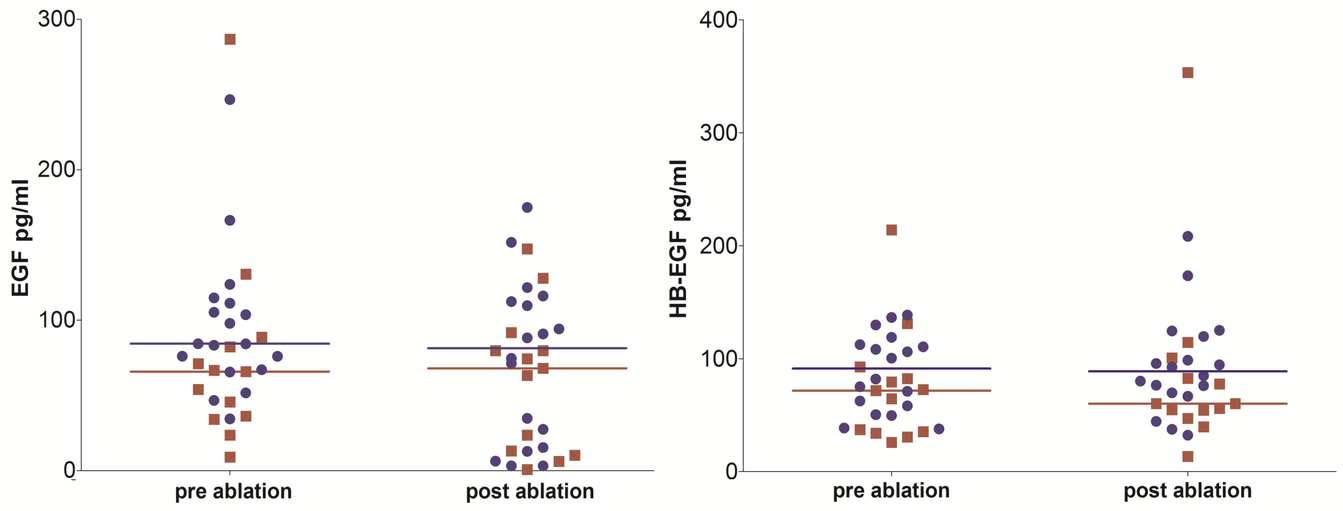


Figure 3. EGF and HB-EGF levels in paired samples from AF patients before catheter ablation (pre ablation) and 12-18 months post ablation. Blue circles indicate patients with restored sinus rhythm (blue line indicates group median), red squares indicate patients with recurring AF (red line indicates group median).

Conclusions

Circulating EGF and HB-EGF are significantly increased in AF with important implications for altered EGFR signaling. Levels do not decrease following sinus rhythm restoration potentially as a consequence of persisting underlying pathomechanisms leading to AF perpetuation and recurrences. Left atrial EGF levels are higher than peripheral levels indicating that circulating EGF may originate here.

Funding

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Contact: Petra Büttner
petra.buettner@medizin.uni-leipzig.de

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