Jie Song
Dr. sc. hum.

A next generation sequencing approach to identify mutations in pulmonary arterial hypertension with a functional assessment of *bone morphogenic protein receptor type 2* promoter variants

Fach/Einrichtung: Innere Medizin
Doktorvater: Herr Prof. Dr. med. Ekkehard Grünig

Pulmonary arterial hypertension (PAH) is a rare autosomal dominant pulmonary vascular disease with reduced penetrance. The current common diagnostic procedure is Sanger sequencing of the three major genes (*BMPR2*, *ACVRL1* and *ENG*). Mutations have been identified in the *BMPR2* gene as a predominant PAH causing gene in about 85% hereditary PAH (HPAH) and 25% of idiopathic PAH (IPAH) cases. However, the penetrance of *BMPR2* is only about 27% indicating that other modifiers such as promoter variants may contribute to disease manifestation.

In this work, a new PAH-specific gene panel was designed to enrich genes of interest. Next generation sequencing was used to assess the coding sequence and intron/exon boundaries of 12 known disease genes and 17 candidate genes. Mutations in the gene *BMPR2*, *ACVRL1*, *ENG* or *EIF2AK4* were identified in 59% patients by panel and Sanger sequencing. In addition, 12 VUS were found in seven genes. A sensitivity and specificity of 100% was met after quality parameters were adjusted and Sanger technique was additionally applied.

In addition, nine *BMPR2* promoter variants have been identified in IPAH/HPAH patients and their effect on gene expression was investigated. In the functional analysis, seven of the nine variants led to a significantly decreased transcriptional activity in comparison to the wild-type. However, the decreased transcriptional level did not correlate with the clinical manifestation in the HPAH families.

Based on the results, the new PAH-specific gene panel presented in this study allowed for the first time the assessment of all known PAH genes and further candidates at once with a saving of time and cost. This new approach is changing the routine diagnostic genetic testing in PAH patients. Moreover, this study identified new variants in the *BMPR2* promoter region but combined with the analysis of pedigrees the variants may not have relate causatively to the PAH phenotype.