

Genetic Studies of Familial Vesicoureteral Reflux

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien,
Göteborgs universitet kommer att offentlig försvaras i Tallen, Drottning Silvias
barn- och ungdomssjukhus, SU/Östra, den 21 september 2018, kl. 9.00

av

Zsuzsa Ingulf Bartik

Fakultetsopponent:

Professor **Christian Radmayr**

Department of Urology, Medical University Innsbruck,
Innsbruck, Österrike

Avhandlingen baseras på följande delarbeten

- I. Bartik Z I, Nordenskjöld A, Sjöström S, Sixt R, Sillén U.
Hereditary Vesicoureteral Reflux: A Study of 66 Families.
Open Journal of Pediatrics 2015; 5: 304-313
- II. Zu S, Bartik Z, Zhao S, Sillen U, Nordenskjöld A.
Mutations in the *ROBO2* and *SLIT2* genes are rare causes of familial
vesico-ureteral reflux.
Pediatric Nephrology 2009; 24: 1501-1508
- III. Bartik Z I, Sillén U, Östenson M, Fransson S, Djos A, Sjöberg R-M, Martinsson T.
A genome-wide scan locating candidate regions of familial vesicoureteral reflux.
Manuscript.
- IV. Bartik Z I, Sillén U, Martinsson T, Djos A, Lindholm A, Fransson S.
Whole exome sequencing identifies *KIF26B*, *LIFR* and *LAMC1* mutations in
familial vesicoureteral reflux.
Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER



Genetic Studies of Familial Vesicoureteral Reflux

Zsuzsa Ingulf Bartik

Avdelningen för Pediatrik, Institutionen för Kliniska Vetenskaper, Sahlgrenska akademien, Göteborgs universitet, Sverige, 2018.

Abstract

Vesicoureteral reflux (VUR) is a common congenital anomaly with a high risk of recurrent urinary tract infections (UTI) and, as a consequence, scarring of the renal parenchyma. Additionally, high-grade reflux is often associated with congenital renal damage (hypodysplasia). A clear heredity is seen, although genetic factors are only known for a minority of cases. The aim of this thesis was to study the heritability and genetic contribution as well as to compare the differences between familial and sporadic VUR.

Study I compared clinical data from familial VUR with sporadic cases. Out of the 726 children with reflux that have been treated at Queen Silvia Children's Hospital between 1990 and 2004, 99 individuals (from 66 families) have reported relatives with VUR. A strong overrepresentation of maternal transmission of VUR was seen. The phenotype of VUR did not differ between familial and non-familial cases.

Study II investigated the contribution of *ROBO2* and *SLIT2* genes in familial VUR through mutation screening by direct sequencing in 54 unrelated patients with primary VUR. Six sequence variants were observed in *ROBO2* gene in the exon–intron boundary area, two of which were new, but none of them altered gene splicing. One *SLIT2* missense mutation was detected and predicted to alter the secondary structure of the protein. However, this variant did not segregate with VUR in the family. Gene variants in *ROBO2* and *SLIT2* are rare causes of VUR in humans.

Study III investigated 14 families from south-western Sweden with 3 or more affected members with primary VUR for shared genomic regions, possibly inherited from a common ancestor, and for recurrent copy-number variants in the families. A high-density SNP array was used for genotyping affected individuals and four controls. We found no unique haplotype region shared by most of the families, thus common founder mutation was excluded. However, subset of families shared different regions, six of them corresponding to previous linkage studies. We presented the genes and non-coding elements relevant for urinary tract development that are located within these regions. One CNV, a deletion at 5q31.1, segregated with VUR and hypodysplasia in one of the investigated families.

Study IV analysed 13 of the above-mentioned 14 families by whole-exome sequencing (WES) in order to find disease causing gene mutations. The findings were confirmed with segregation analysis based on Sanger sequencing in the whole family. We identified three novel variants that might affect function, in *LAMC1*, *KIF26B* and *LIFR* genes, in three families. *SALL1*, *ROBO2* and *UPK3A* gene variants, predicted to be deleterious, were excluded by segregation analysis. In all, we demonstrated likely causal gene mutation in 23% of the families.

In conclusion, severity of the disease did not differ between familial and non-familial VUR. Our studies show that VUR is a genetically highly heterogeneous malformation. WES in combination with a segregation study is a useful tool when it comes to confirming variants in known candidate genes and identifying new genes that might be involved in the pathogenesis of VUR.