Editorial

Bladder Conditions in Pediatric Patients: Genetics and Genomics

Pediatric patients, especially the youngest, have objective difficulties in explaining the source and characteristics of their physical discomfort. This is even more important in bladder conditions, which are sometimes characterized by hematuria in absence of other symptoms or pain. Thus, it is crucial for the physician to have a clear view of all possible problems affecting children; moreover, understanding the inheritance of such diseases is often a major help during diagnosis. In the present Special Issue, the most frequent causes of heritable bladder malfunctions are analyzed.

The group of Prof. Reutter, working in Bonn (Germany) presents a detailed report on the Bladder-Exstrophy-Epispadias Complex (BEEC). BEEC describes a wide spectrum of malformations, which affects the patient's life deeply. Alterations of the urogenital tract development may impair continence, sexual and renal functions. It is characterized by Epispadias (E) in its mildest phenotype, and Classic Bladder Exstrophy (CBE) in the intermediate and most common cases. More severe forms of BEEC include Persistent Cloaca (PC) or Urorectal Septal Malformation Sequence, imperforate anus, and the OEIS complex (omphalocele, exstrophy, imperforate anus, and spinal defects). Recent studies focusing on monozygotic twins and chromosomal aberrations were suggestive of causative genetic factors; this view has been recently further supported by the recent identification of copy number variations (CNVs), susceptibility regions and genes through the systematic application of array based analysis. Candidate genes and genome-wide association studies (GWAS) provide strong evidence in this scenario. In these pages, the Authors show an overview of the current knowledge about the genes mediating abnormal uro-rectal development leading to the BEEC, with a description of recently established murine models that provided new insights in the role of these genes. These studies allowed demonstrating the importance of *ISL1*-pathway in human and murine BEEC, and support the role of *SLC20A1* and *CELSR3* as the first BEEC candidate genes.

R. Piergentili

The group of Prof. Zangari, working in Rome (Italy) makes an extensive analysis of the genetics of bladder cancers affecting pediatric patients. Interestingly, some clinical features are typical of these patients, compared to their adult counterpart, such as the fact that non epithelial tumors are more common than epithelial ones, and Rhabdomyosarcoma (RMS) is the most common pediatric bladder tumor, while it is a rare tumor in adults; nonetheless, many other types of lesions may be found in children. The Authors report a deep study of all malignancies known and described in children, including RMS, urothelial neoplasms, malignant rhabdoid tumor and inflammatory myofibroblastic tumor. For each type, they provide the present knowledge about the genes that are recognized players in these malignancies, and their relationships among each other. The understanding of the genetics of bladder cancers in children is crucial for the correct identification of the lesion in times that are compatible with a good final prognosis.

The group of Prof. Porrello working in Chapel Hill (North Carolina, USA) takes advantage of a stringent analysis of available literature about the genetics of pediatric bladder cancers to discover two main classes of biological processes involved in this disease and, consequently, new potential therapeutic targets. In this original contribution, the Authors performed a Gene Ontology (GO)-based analysis using in-house developed algorithms. The identification of 21 genes in the literature allowed to identify two main classes of biological processes: cell regulation-based and differentiation/development-based. This analysis allowed to shed a new light on the genetics of pediatric bladder cancer; moreover, it allowed identifying some genes that should be experimentally re-assessed or evaluated as biomarkers (ACTA2), other genes that play pivotal roles in adult bladder cancer but only marginal roles in their pediatric counterpart (TP53, FGFR2) and, finally, genes that are new in this illness both in adults and in children (CTIP, WNT1).

The group of Dr Schultz, working in Curitiba - Paraná (Brazil) illustrates the current – and indeed very poor – knowledge about the Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) with a particular emphasis on the genetics of ureterocele. CAKUT form a group of heterogeneous disorders that affect the kidneys, ureters and bladder, with frequent asynchronous presentations and multiple CAKUT associations in the same individual. The ureterocele is a cystic dilation of the distal intramural ureter, resulting in obstruction of urine flow, dilation of both the ureter and renal pelvis, and the loss of renal function. Ureterocele development is dependent on formation and migration of the ureteric bud and its incorporation in the bladder. Consequently, understanding the molecular mechanisms involved in these processes is crucial for the comprehension of this condition, and consequently for the improvement of its management.

Finally, the group of Prof. Cobellis, working in Ancona (Italy) presents an updated report about the problem of vesicoureteric reflux, its implications, its relation with the prune-belly syndrome, and the state of the art about its genetic origins. Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder to the upper urinary tract. It is the most common congenital urological anomaly affecting 1-2% of children and 30-40% of patients with urinary tract infections. The clinical im-

portance of VUR is also due to it being a major risk factor for pyelonephritic scarring and chronic renal failure in children. The reflux is the result of a shortened intravesical ureter tract with an enlarged or erroneously positioned ureteric orifice. VUR is a complex genetic developmental disorder and its heterogeneous genetic pattern avoided for long times to identify single major loci or genes for primary VUR. It is likely that different forms of VUR with different genetic determinants are present. Recently, several possible candidate genes involved in the pathogenesis of VUR and related urinary tract malformations were reported. The Authors provide an up-to-date overview of these genes and their role in the development of such condition.

Roberto Piergentili

Guest Editor

Institute of Molecular Biology and Pathology at CNR (CNR-IBPM)
Department of Biology and Biotechnologies
Sapienza – Università di Roma
Italy