Supplementary Appendix

Rare single nucleotide and copy number variants and the etiology of congenital obstructive uropathy: implications for genetic diagnosis

Dina F Ahram PhD[1*], Tze Y Lim MSc[1*], Juntao Ke PhD[1*], Gina Jin BS[1*], Miguel Verbitsky PhD[1], Monica Bodria MD[2], Byum Hee Kil BS[1], Debanjana Chatterjee PhD[1], Stacy E Piva BS[1], Maddalena Marasa MD[1], Jun Y Zhang PhD[1], Enrico Cocchi MD[1], Gianluca Caridi BS[2,3], Zoran Gucev MD[4], Vladimir J Lozanovski MD[4,5], Isabella Pisani MD[6], Claudia Izzi MD[7], Gianfranco Savoldi MD[8], Barbara Gnutti MS[8], Valentina P Capone MD[1,9], William Morello MD[9], Stefano Guarino MD[10], Pasquale Esposito MD[11,12], Sarah Lambert MD[13], Jai Radhakrishnan MD[1], Gerald B Appel MD[1], Natalie S Uy MD[14], Maya K Rao MD[1], Pietro A Canetta MD[1], Andrew S Bomback MD[1], Jordan G Nestor MD[1], Thomas Hays MD, PhD[15], David J Cohen MD[1], Carolina Finale NA[16], Joanna A E van Wijk MD, PhD[17], Claudio La Scola MD[18], Olga Baraldi MD[19], Francesco Tondolo MD[19], Dacia Di Renzo PhD[20], Anna Jamry-Dziurla BS[21], Alessandro Pezzutto MD[22], Valeria Manca MD[23], Adele Mitrotti MD[1,24], Domenico Santoro MD[25], Giovanni Conti MD[26], Marida Martino MD[27], Mario Giordano MD[27], Loreto Gesualdo MD[24], Lada Zibar MD, PhD[28,29], Giuseppe Masnata MD[23], Mario Bonomini MD[22], Daniele Alberti[30], Gaetano La Manna MD[31], Yasar Caliskan MD[32], Andrea Ranghino MD[16], Pierluigi Marzuillo MD[10], Krzysztof Kiryluk[1], Grażyna Krzemień MD[33], Monika Miklaszewska MD[34], Fangming Lin[14], Giovanni Montini MD[9,35], Francesco Scolari MD[36], Enrico Fiaccadori MD[6], Adela Arapović[37,38], Marijan Saraga MD[37,38], James McKiernan[39], Shumyle Alam MD[39,40], Marcin Zaniew MD[41], Maria Szczepańska MD[42], Agnieszka Szmigielska MD[33], Przemysław Sikora MD[43], Dorota Drożdż MD[34], Malgorzata Mizerska-Wasiak MD[33], Shrikant Mane PhD[44], Richard P Lifton MD, PhD[44], Velibor Tasic MD[4], Anna Latos-Bielenska MD[21], Ali G Gharavi MD[1], Gian Marco Ghiggeri MD[2,3], Anna Materna-Kiryluk MD[21], Rik Westland MD, PhD[17], Simone Sanna-Cherchi MD[1]

[1]Department of Medicine, Division of Nephrology, Columbia University, New York, New York, USA
[2]Division of Nephrology and Renal Transplantation, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[3]Laboratory on Molecular Nephrology, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[4]Medical Faculty of Skopje, University Children's Hospital, Skopje, Macedonia
[5]Department of General, Visceral and Transplant Surgery, University Hospital Heidelberg, Germany
[6]Unità Operativa Nefrologia, Azienda Ospedaliero-Universitaria di Parma, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy
[7]Division of Nephrology and Department of Obstetrics and Gynecology, ASST Spedali Civili of Brescia, Brescia, Italy
[8]Medical Genetics Laboratory, ASST-Spedali Civili, Brescia, Italy
[9]Pediatric Nephrology, Dialysis and Transplant Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, via della Commenda 9, Milan, Italy

[10]Department of Woman and Child and of General and Specialized Surgery, Università degli Studi della Campania "Luigi Vanvitelli", Naples, 80138, Italy
[11]Department of Internal Medicine, University of Genoa, Genova, Italy.
[12]Unit of Nephrology, IRCCS San Martino Polyclinic Hospital, Genoa, Italy
[13]Yale School of Medicine/Yale New Haven Health System, New Haven, CT, USA
[14]Department of Pediatric, Division of Pediatric Nephrology, Columbia University Irving Medical Center NewYork-Presbyterian Morgan Stanley Children's Hospital in New York, NY, USA
[15]Department of Pediatrics, Division of Neonatology, Columbia University, New York, NY, USA
[16]Nephrology, Dialysis and Renal Transplantation Unit, Azienda Ospedaliera Universitaria Ospedali Riuniti Umberto I, Lancisi, Salesi of Ancona, Ancona, Italy
[17]Department of Pediatric Nephrology, Emma Children's Hospital, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands
[18]Department of Pediatrics, Nephrology and Dialysis Unit, Azienda Ospedaliero Universitaria Sant'Orsola-Malpighi, Via Massarenti 11, Bologna, 40138, Italy
[19]Nephrology, Dialysis and Renal Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Massarenti 9, Bologna, Italy
[20]Pediatric Surgery of "G. d'Annunzio" University of Chieti-Pescara and "Spirito Santo" Hospital of Pescara, Italy
[21]Polish Registry of Congenital Malformations, Chair and Department of Medical Genetics, University of Medical Sciences, 61-701 Poznan, Poland
[22]Department of Medicine, Nephrology and Dialysis Unit, SS Annunziata Hospital, "G. d'Annunzio" University, Chieti, Italy
[23]Department of Pediatric Urology, Azienda Ospedaliera Brotzu, Cagliari, Italy
[24]Department of Emergency and Organ Transplantation, Section of Nephrology, University of Bari, Bari, Italy
[25]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[26]Department of Pediatric Nephrology, Azienda Ospedaliera Universitaria "G. Martino", Messina, Italy
[27]Pediatric Nephrology and Dialysis Unit, Pediatric Hospital "Giovanni XXIII", Bari, Italy
[28]Department of Nephrology, University Hospital Merkur, Zagreb, Croatia
[29]Faculty of Medicine University Josip Juraj Strossmayer in Osijek, Osijek, Croatia
[30]Pediatric Surgery, University of Brescia, Brescia, Italy
[31]IRCCS Azienda Ospedaliera di Bologna, Nephrology, Dialysis and Kidney Transplant Unit, St. Orsola University Hospital, Via Massarenti 9, Bologna, 40100, Italy
[32]Division of Nephrology, Saint Louis University School of Medicine, Saint Louis, Missouri, USA
[33]Department of Pediatrics and Nephrology, Medical University of Warsaw, Warsaw, Poland
[34]Department of Pediatric Nephrology and Hypertension, Jagiellonian University Medical College, Krakow, Poland
[35]Department of Clinical Sciences and Community Health, Giuliana and Bernardo Caprotti Chair of Pediatrics, University of Milano, Milano, Italy
[36]Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Division of Nephrology and Dialysis, University of Brescia and ASST Spedali Civili of Brescia, Brescia, Italy
[37]Department of Pediatrics, University Hospital of Split,, Split, Croatia
[38]School of Medicine, University of Split, Split, Croatia
[39]Department of Urology, Columbia University Irving Medical Center, New York, NY, USA
[40]Division of Pediatric Urology, MUSC Health-University Medical Center, Charleston, SC, USA
[41]Department of Pediatrics, University of Zielona Góra, Zielona Góra, Poland
[42]Department of Pediatrics, FMS in Zabrze, Medical University of Silesia, Katowice, Poland
[43]Department of Pediatric Nephrology, Medical University of Lublin, Lublin, Poland
[44]Yale Center for Mendelian Genomics (YCMG), New Haven, CT, USA

*These authors contributed equally

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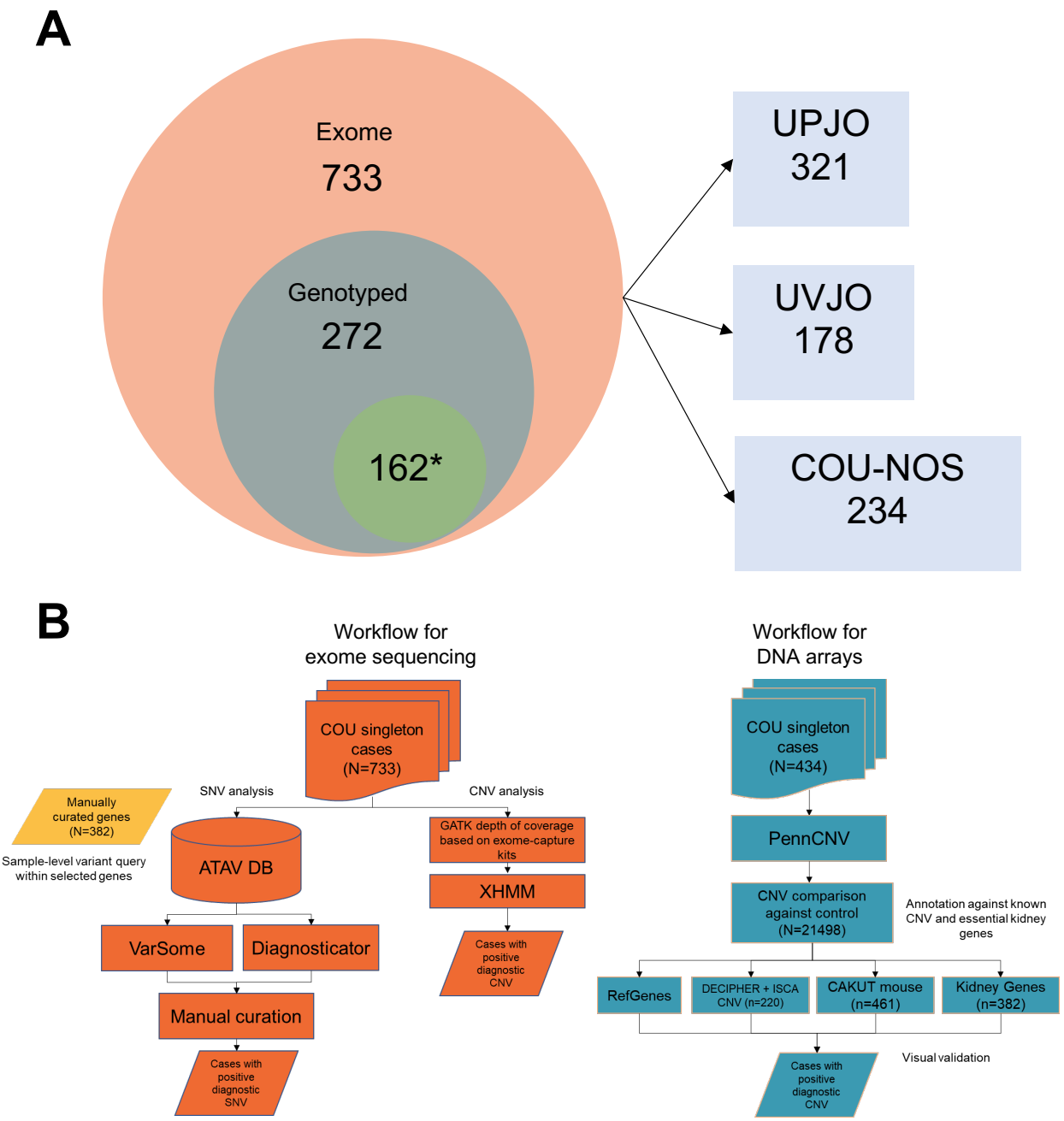
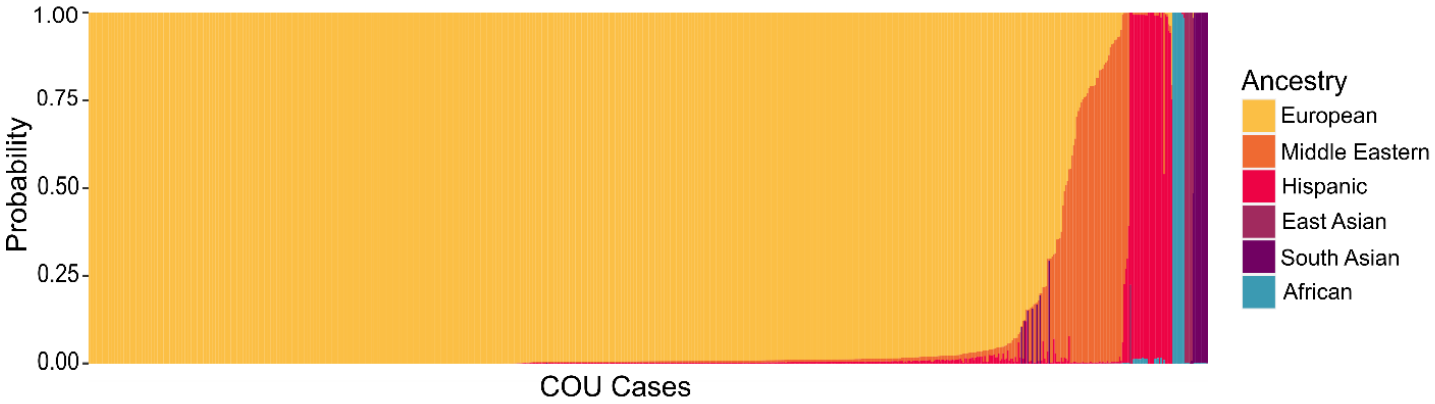
Supplementary Figure S1. Study cohort and analytical workflow for SNV and CNV analyses



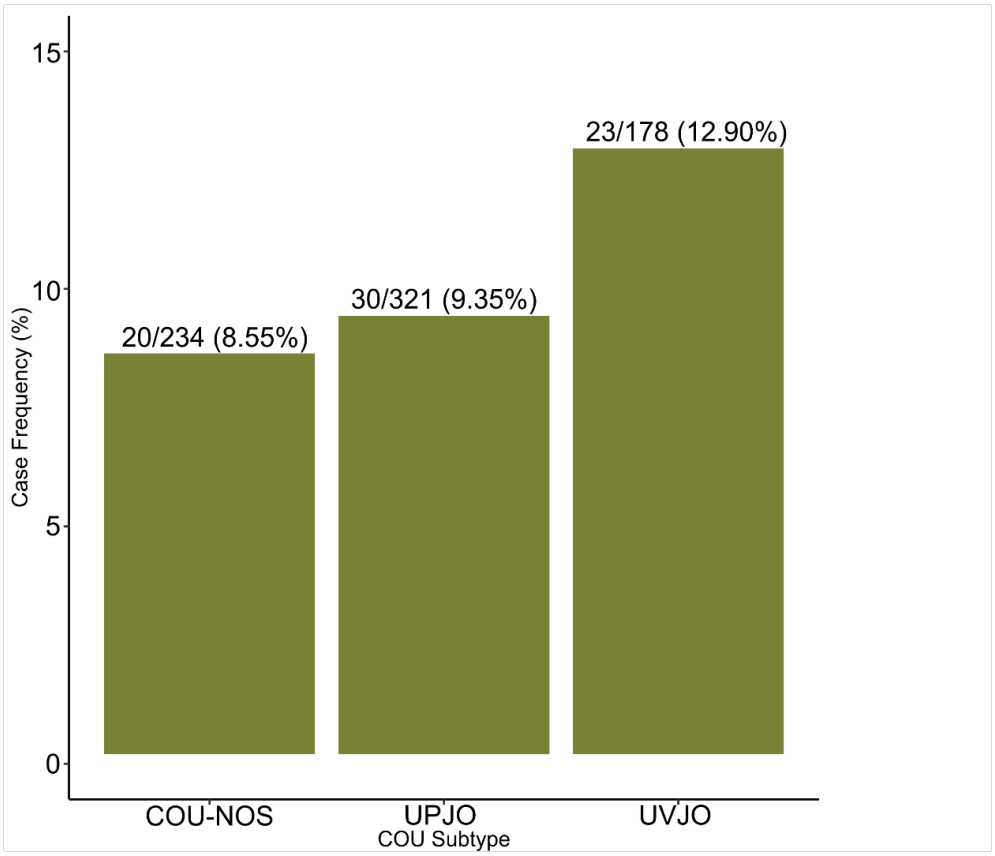
A) The COU cohort comprised 733 cases that have been subjected to exome sequencing. 434 of the 733 cases were also genotyped with DNA SNP arrays and have been used as an orthogonal method for CNV variant calling and validation in this study. Among these 434 cases with DNA array data, 162 of the were previously published (Verbitsky et al., Nat Genet 2019)[1]. **B)** Depiction of workflows to retrieve single nucleotide variants data and copy-number variant data using exome sequencing (left, orange) and chromosomal microarray (right, blue). Data on copy number variation was retrieved using exome sequencing, and compared to chromosomal microarray data which was available for a subgroup of the study cohort for internal validation. For a detailed description of our work-flow, see Methods section in the main manuscript.

Supplementary Figure S2. Genetically-determined ancestry proportions of the study cohort



The predicted probability of genetic ancestry for each of the 733 cases included in the COU cohort was computed using a set of 12,840 common, ancestry-informative, markers extracted from exome sequencing data. The ancestry probability for every sample was calculated by projecting the 12,840 common markers on principal component analysis (PCA) space and then running a previously trained ancestry classifier (multi-layer perceptron using Scikit-learn API in Python) implemented with ATAV IGM server[2]. Each column distributed on the x-axis represents the probability distribution of ancestry in a COU case. Columns with more than one color denote genetic admixture of multiple ancestries. COU= congenital obstructive uropathy.

Supplementary Figure S3. Overall diagnostic yield in each COU subcategory



There were no statistical differences between COU subcategories (Chi-square 3x2 *P*= 0.3). COU-NOS, congenital obstructive uropathy not otherwise specified, UPJO, ureteropelvic junction obstruction; UVJO, ureterovesical junction obstruction.

SUPPLEMENTARY TABLES

See attached Excel file

SUPPLEMENTARY REFERENCES

1. Verbitsky, M. *et al.* The copy number variation landscape of congenital anomalies of the kidney and urinary tract. *Nat Genet* **51**, 117-127 (2019).
2. Ren, Z. *et al.* ATAV: a comprehensive platform for population-scale genomic analyses. *BMC Bioinformatics* **22**, 149 (2021).