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LETTER TO THE EDITORS

HOXA11 is another monogenic cause of congenital anomalies of the kidney and urinary tract—Reply

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Dear Editors,

We wish to thank Professor Ozaltin for his letter to the editor and to express our gratitude for his interest in our review [1]. Professor Ozaltin suggests to include *HOXA11* as a CAKUT-causing gene [2].

As the research field of monogenic CAKUT expands, it has been realized that many published variants suspected to cause monogenic CAKUT have conflicting interpretations of disease causality—as we have also noted in the review. For this reason, in the manuscript [1], we attempted to exclusively include genes with variant alternations that are relatively established based on multiple lines of evidence, such as reports of more than one disease causing allele, biological conservation, segregation analysis, and functional studies (in vitro and/or in vivo). We were cautious regarding the inclusion of the reported CAKUT-causing genes that are based on a single family. In line with that and given the significant challenges in CAKUT genetics, in terms of false attribution of pathogenicity of certain genes, endeavors such as The Gene Curation Working Groups under the Clinical Genome Resource (ClinGen) initiative (https://clinicalgenome.org/) are currently working on clinical validity of CAKUT genes (among many other kidney-related genes) and establishing a framework for assessing the evidence necessary to determine if a gene causes a particular disease. During the review preparation, we indeed encountered the paper by Saygili et al., while the case report by Sezer et al. [3] was yet to be published. The former paper suggested a causal link between *HOXA11* c.775G>A (p.Glu259Lys) and CAKUT based on a single family. However, it also possesses major concerns in terms of causality. First, this variant is classified as a variant of uncertain significance (VUS) according to the ACMG standards and guidelines (PM1, PM2, and PP3). Second, the genetic analysis did not include copy number variation (CNV) analysis which can also lead to CAKUT in many cases as we noted in the review. Third, the report is lacking any functional studies to support causality. The report by Sezer et al. [3] notes a de novo heterozygous variant which is also classified as VUS as per ACMG criteria. Moreover, the paper lacks functional studies and speculates on a dominant negative effect without any evidence to support it. In summary, *HOXA11* is an example of a gene that does not yet have sufficient evidence supporting it as a monogenic cause of CAKUT in humans. We believe that any generalizations regarding its direct causal role must await the description and characterization of mutations in additional patients.

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