GATA3 and kidney development: why case reports are still important

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Introduction

The recent discovery that GATA3 haplo-insufficiency in man is responsible for hypoparathyroidism, sensorineural deafness, and renal anomalies (HDR) syndrome [1], has provided new insights into the genetic control of renal development. This is a salutary lesson of how a clinical case report can lead to important advances in the understanding of normal and abnormal embryonic development.

From Di George syndrome to HDR syndrome

The discovery of the gene responsible for the HDR syndrome occurred as part of a detailed study of individuals with the Di George syndrome (Mendelian Inheritance in Man (MIM) number 188400). These patients present abnormalities in organs derived from the 3rd and 4th branchial arches, including the parathyroid glands, thymus and outflow tract of the heart. In the majority of Di George patients a microdeletion in chromosome 22q11 is present, however, in a small
group of patients there is evidence of deletion or aberration in chromosome 10p [2]. Molecular deletion analyses of these patients have defined two non-overlapping regions on chromosome 10p that contribute to this phenotype. Terminal 10p deletions (10p14-10pter) are associated with hypoparathyroidism, renal anomalies and sensorineural deafness, whereas interstitial deletions (10p13-14) are associated with heart malformations and immune deficiency [3].

In 1992, one of us reported a family with autosomal dominant hypoparathyroidism, sensorineural deafness and renal dysplasia (later termed the HDR syndrome MIM 146255) [4]. Analysis of stored DNA and immortalized cell lines from this family showed the presence of a submicroscopic deletion on chromosome 10p15 in all four individuals with the full HDR syndrome. A search for candidates in the terminal 10p region revealed that the GATA3 gene was located in the critical interval, and mutation analysis in HDR patients without cytogenetic abnormalities confirmed the involvement of GATA3 in the human HDR syndrome [1].

GATA3 role in embryonic development

GATA3 is one of six members of a family of transcription factors that bind the consensus motif A/TGATAA/G and which regulates critical steps of differentiation during embryonic development [5–7]. GATA 1, 2 and 3 are critically involved in myeloid differentiation whereas GATA 4, 5 and 6 are implicated in cardiac and intestinal development [8]. GATA3 is the only member to be expressed in T-lymphocytes. The binding element comprises two C4 zinc finger motifs shared with the steroid hormone receptor superfamily, and is highly conserved among different vertebrate and invertebrate species [9].

In situ hybridization studies in developing human and mouse embryos demonstrate a widespread and conserved expression pattern of GATA3. In mice, expression is high 8.5 days post coitus (dpc) and continues for several days thereafter. Embryos deficient in GATA3 do not survive beyond 11.5 dpc, probably secondary to heart failure as a result of noradrenaline deficiency [10]. These animals also show no evidence of metanephric differentiation. In human embryos, GATA3 transcripts are found from the beginning of the 4th week of gestation (equivalent to 8.5 dpc in the mouse) in the neural tube, foregut endoderm and the Wolffian duct. Over the next 7 days, it can be detected in the otic vesicle, parathyroids, second and third branchial arches, thymus, and the mesonephros [11]. Normal kidney development results from metanephric differentiation that occurs as a result of reciprocal interactions between the ureteric bud from the Wolffian duct and the metanephric blastema. GATA3 labelling is intense at the interface of these two structures at about 7 weeks gestational age and remains high in the developing collecting ducts, but is absent in the loop of Henle and developing glomeruli. There is little or no expression of GATA3 in the kidney in postnatal life [12]. GATA3 expression has also been observed in the developing inner ear and parathyroid glands, consistent with the HDR phenotype. Downstream or interacting target proteins have not yet been identified. Recently, another family of transcription factors, named glial cell missing or Gcm, has been found to play an essential role during parathyroid development [13]. It would be of interest to investigate if both transcription factors are involved in the same developmental pathway.

GATA3 and kidney development

The renal abnormalities that have been observed in patients with chromosome 10p abnormalities, including GATA3 mutations, are vesico-ureteric reflux, renal dysplasia and unilateral agenesis [2]. This observation raises the possibility of involvement of GATA3 in some of these more common renal tract malformations. In addition, one child from the original HDR family had Potter’s sequence with bilateral severe renal dysplasias at birth [4], suggesting that this abnormality may also belong to the spectrum of GATA3-associated renal malformations. However, it should be noted that one other family member had isolated renal dysplasia with no detectable abnormalities on chromosome 10p. Moreover, renal malformations are also observed in a minority of patients with the classical Di George syndrome (del(22q11)), confirming the multiplicity of genes controlling normal kidney development [2]. As yet, no potential target genes for GATA3 are known, so the precise molecular consequences of GATA3 haploinsufficiency are unclear.

Implications for future research in renal tract abnormalities

What does all this mean? First, detailed study of chromosome 10p should be undertaken in patients with well-defined phenotypes of renal tract abnormalities such as kidney dysplasia and agenesis, especially when there is associated hypoparathyroidism or deafness. Second, unravelling the molecular consequences of GATA3 activation will advance our understanding of normal renal development and is an urgent priority. Finally, reports of careful studies of isolated families or individuals with an unusual aggregation of clinical features can lead to important breakthroughs in understanding of disease many years later. Editors and reviewers please take note.

References


