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Amplification and gain of MDM4, a p53 regulator in urothelial cell carcinoma

A Veerakumarasivam[1], H E Scott[1], M J Wallard[1], H C Whitaker[1], I G Mills[1], K Ichimura[2], H Y Leung[3], V P Collins[2], D E Neal[1], J D Kelly[1]

[1]Hutchison-MRC Research Centre, Department of Oncology, University of Cambridge, Cambridge, United Kingdom; [2]Division of Histopathology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom; [3]Department of Surgery, The Medical School, University of Newcastle upon Tyne, Newcastle, United Kingdom

Introduction: DNA copy number alterations detected by array Comparative Genomic Hybridisation (aCGH) can identify novel oncogenes and tumour suppressor genes. We performed a genome wide survey of copy number changes in urothelial cell carcinomas (UCCs) using a high resolution aCGH platform.

Materials & Methods: DNA was extracted from 100 snap-frozen UCCs and hybridised to a whole genome array at <1Mb resolution. Boundaries of amplification and gains were delineated using tiled-path arrays and fluorescence in situ hybridisation (FISH). Gene and protein expression were evaluated by rtPCR and immunodetection.

Results: We identified the region 1q32 to be a frequently gained (1 amplification,16 gains) in high grade tumours. A chromosome 1 tiled array and FISH identified MDM4 as the candidate gene within 1q32. Elevated mRNA and protein expression of MDM4 was associated with amplification and copy number gain, as well as a subset of high-grade tumours with two copies.

Conclusion: We have identified MDM4 as the amplification target in the 1q32 region in UCC. MDM4 is a critical regulator of p53, and not previously reported in UCC. The overexpression of MDM4 in high grade tumours supports its role as a putative oncogene in bladder tumourogenesis.