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GENETICS

IDH mosaicism in enchondromatosis syndromes

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Mutation of certain hotspot arginine residues in the isocitrate dehydrogenases IDH1 and IDH2 has been found in cartilaginous tumours, gliomas and acute myeloid leukaemia (AML). These tumour types also occur in patients with Maffucci syndrome and Ollier disease, and two groups have investigated whether mutations in *IDH1* and *IDH2* are evident in these patients.

Ollier disease and Maffucci syndrome are non-familial diseases that are characterized by the development of multiple benign cartilaginous tumours (enchondromas), which progress to chondrosarcomas in about one-third of patients. Amary and colleagues found that ~90% of the 74 tumours analysed from 40 patients with either of these conditions had hotspot mutations in *IDH1* (affecting arginine 132) and rarely had mutations in *IDH2* (affecting arginine 172). Interestingly, when multiple tumours from 19 patients with either Ollier disease or Maffucci syndrome were analysed, the same mutation was identified in all but one patient. In two patients, the mutations were also found in non-neoplastic tissue (the blood and bone marrow), indicating that these mutations are acquired as a post-zygotic event, which leads to somatic mosaicism. These hotspot mutations result in neomorphic activity that produces the metabolite 2-hydroxyglutarate (2HG). Consistently, patient samples with IDH mutations had increased levels of 2HG. However, a few tumours with wild-type IDH also had high levels of 2HG, indicating that alterations of other genes that result in the production of 2HG might also be associated with these conditions.

Pansuriya and colleagues found heterozygous $IDH1^{R132}$ and $IDH2^{R172}$ mutations in tumours from ~80% of patients with Ollier disease or Maffucci syndrome. Using a more sensitive sequencing approach, they found eight tumours with low-frequency $IDH1^{R132}$ mutations. Immunohistochemical analyses showed IDH mosaicism within individual tumours, which has previously been reported for other types of benign bone tumours. They also found a low frequency of IDH mutations in some normal cells surrounding the tumours but not in other cell types, which is consistent with a model of somatic mosaicism. 2HG production is associated with hypermethylation, and unsupervised clustering of variable CpG methylation sites from tumours with or without *IDH1* mutations revealed that hypermethylation was associated with *IDH1* mutation. One of the most differentially methylated genes was distal-less homeobox 5 (*DLX5*), which encodes a transcription factor that regulates chondrocyte differentiation. Whether the altered methylation of *DLX5* contributes to enchondromagenesis requires further investigation.

These two papers further emphasize that mutant IDH pathways can substantially contribute to tumorigenesis. Understanding the mechanisms by which these proteins promote tumorigenesis in so many different cell types is eagerly awaited.

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ORIGINAL RESEARCH PAPERS Amary, M. F. *et al.* Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of *IDH1* and *IDH2*. *Nature Genet.* 6 Nov 2011 (doi:10.1038/ng.994) | Pansuriya, T. C. *et al.* Somatic mosaic *IDH1* and *IDH2* mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. *Nature Genet.* 6 Nov 2011 (doi:10.1038/ng.1004)