Subset of Bone Cancers Have Mutations Affecting IGF Signaling, Suggesting Possible Treatment

Jun 23, 2017 | staff reporter

NEW YORK (GenomeWeb) – A portion of bone cancers may respond to existing insulin-like growth factor 1 receptor inhibitors because they carry mutations in IGF signaling genes, a new study suggests.

Researchers from the Wellcome Trust Sanger Institute and elsewhere sequenced the genomes of 112 osteosarcomas from both children and adults, which included all major histological subtypes. As they reported in *Nature Communications* today, they found that nearly 10 percent of the tumors had mutations in IGF signaling genes. This suggested to the researchers that IGF1R inhibitors could be re-visited as an osteosarcoma treatment.

"The mutations of patients' tumors may enable clinicians to predict who will and will not respond to these drugs, resulting in more efficient clinical trials," Peter Campbell, lead author from the Sanger Institute, said in a statement.

The researchers also reported that chromothripsis, in which chromosomes are shattered and stitched back together in different configurations, in combination with amplification might contribute to osteosarcoma development.

Campbell and his colleagues sequenced tumor and paired normal tissue from 112 osteosarcoma patients. Seventy-five samples underwent exome sequencing, while the remaining 37 underwent whole-genome sequencing. Tumor tissue was sequenced to at least 40X coverage and normal tissue to at least 30X coverage on either the Illumina HiSeq 2000 or 2500 platform.

The tumors each contained between three and 316 mutations. In particular, the researchers uncovered mutations in 67 known cancer-linked genes. Commonly affected genes included TP53, CDK4, and RB1, but they also uncovered mutations in a dozen other cancer genes, such as DNM2, ERBB4, and TERT, that hadn't before been observed in osteosarcoma.

But a number of samples had mutations affecting IGF signaling genes. IGF has previously been considered as a factor in osteosarcoma as it is involved in bone growth and development.

The researchers reported four mutations in eight patients that would lead to IGF1R signaling activation at the receptor level. They also noted additional mutations further downstream of IGF1R that would also affect the PI3K or Ras/Raf/mitogen-activated protein kinase signaling pathway. If those are included, the researchers said that IGF1R signaling could be a key factor in up to 27

percent of tumors in their set.

This suggested to the them that targeting IGF signaling genes with IGF1R inhibitors could help treat a portion of osteosarcoma patients, though they noted that their study was small and would need to be repeated with additional samples.

A number of tumors also had large amounts of rearrangements. Eleven of the 37 tumor genomes had chromothripsis affecting at least one chromosome, and 22 of them were affected by chromothripsis combined with amplification.

Three chromosomes — 5, 12, and 17 — were recurrently affected by chromothripsis. In six cases, chromothripsis amplification of chromosome 12 led to the co-amplification of CDK4 and MDM2, which drives some cancers, including osteosarcoma.

This and other amplifications of oncogenes they found in their samples indicated to the researchers that chromothripsis amplification might be a mechanism for the development of multiple driver mutations.

"By sequencing the whole genome of the tumors, we have unpicked the mechanism behind osteosarcoma for the first time," Adrienne Flanagan, senior author from the Royal National Orthopedic Hospital NHS Trust and University College London Cancer Institute, said in a statement. "We discovered a new process — chromothripsis amplification — in which the chromosome is shattered, multiplied, and rejigged to generate multiple cancerdriving mutations at the same time."

Filed Under Sequencing Cancer osteosarcoma Sanger Institute University College London Wellcome Trust

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