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Title: High success in molecular diagnosis of skeletal dysplasias using a customized NGS panel and the identification of a gene related to Beemer-Langer syndrome

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Objectives: Skeletal dysplasias (SD) are rare diseases whose diagnosis is usually a challenge because of the phenotypic heterogeneity of most conditions. The molecular investigation is fundamental for both, to get the final diagnosis and to providing a precise genetic counseling. Although next-generation sequencing (NGS) techniques have been used to promote large-scale sequencing of several individuals in an easier and less expensive way, most of the reported results so far have shown a detection rate of mutation around or less than 50%. Here we present the results of a cohort of 36 patients with SD analyzed by NGS.
Methods: The sequencing was performed on MiSeq sequencer using a customized NGS panel (TruSeq Custom Amplicon - Illumina) with 39 genes related to SD. Sanger sequencing confirmed all pathogenic variants.
Results: All patients, except one, had a previous precise clinical-radiological diagnosis. Pathogenic mutations were found in 25 (69,4%) of the patients, however, for ten patients regions of bad coverage of the respective genes are still being investigated. Regarding the severity of the conditions, for 14 lethal and 23 non-lethal SD, the detection rates of mutations were 78.6% and 63,6%, respectively. For the whole group, we identified 32 different pathogenic variants, being 25 novel mutations and one recurrent mutation (*DYNC2H1*- p.Met2671Thr) in 3 patients. One mutation (*PCYT1A* gene) was found only by Sanger sequencing during the investigation of a region insufficiently covered of the gene. Another interesting and novel result was the identification of a cilia-related gene associated with Beemer-Langer syndrome.

Conclusion: Our results confirm the advantage of NGS in the diagnosis of the SD, showing a high detection rate (69.4%) of mutations. We also identified for the first time a cilia-related gene associated with the Beemer-Langer syndrome. Finally, we put in evidence the importance to analyze by Sanger sequencing the regions with insufficient coverage by NGS.

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