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## Title

Did Cro-Magnon 1 have neurofibromatosis type 2? – Authors' reply

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## Keywords

Retrospective diagnosis; phenotype; subclassifications; genetics.

## Text

We read with interest the letter of Ruggieri et al. regarding our retrospective diagnosis of the Cro Magnon I skull.<sup>1</sup> We are pleased that the diagnosis of neurofibromatosis is not in question, but its sub-classification and clinical presentation.

First, the ambiguity of any retrospective diagnosis on old skeletal elements is due to the fact that researchers are forced to base their conclusions on traces only (here: the negative of pathological processes having since disappeared).<sup>2</sup> In addition, the absence of DNA preserved in this individual prevents from any genetic verification of the diagnosis.

Second, the case cited by Ruggieri et al. is that of an Inca child's mummy from the 17<sup>th</sup> century, with perfectly preserved organic tissues, authorizing a diagnosis of multiple neurofibromas present in the soft tissues:<sup>3</sup> it cannot reasonably serve as a comparison case with the dry skull of a fossil man.

Third, our diagnostic proposal was mainly based on comparison with cases present in anatomical reference collections, and we stress that neurofibromatosis type 1 remains the preferred diagnosis for Cro Magnon I. In this type of disease, the patient's skin is covered with tumors of dermal origin (neurofibromas) which will progressively grow and erode the bone in depth: in the case of Cro Magnon I, these lesions are at the level of the right frontal bone, the root of the nose, the left brow bone, the maxillary bone, etc. As stated by Ruggieri et al, it is true that the acoustic neuroma (or schwannoma of the *nervis vestibularis*) is one of the major signs of neurofibromatosis type 2 (it is generally bilateral, or unilateral but associated with brain tumors such as meningioma, glioma, schwannoma, posterior subcapsular lenticular opacities... which is obviously not the case in Cro Magnon I). Therefore, unilateral erosion of the internal auditory canal is absolutely not pathognomonic of neurofibromatosis 2 disease. It has to be said that further micro-CT-scan analyses will take place to detect any sphenoid wing dysplasia on Cro Magnon I, despite severe post-mortem damages, an anomaly particularly related to neurofibromatosis type 1.<sup>4</sup>

Lastly, we insist on the fact that skin lesions in neurofibromatosis type 2 are very minor, and would not have left lesions as severe as those diagnosed on the face of this patient nearly 28,000 years old.<sup>5</sup>

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