Reviewer's report

Title: Extending the spectrum of Ellis van Creveld syndrome: a large family with a mild mutation in the EVC gene

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Reviewer: Bruno Dallapiccola

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Ulucan et al report an extended and interesting Turkish family in which affected individuals presented a constellation of features bridging Ellis van Creveld syndrome and Weyers or acrodental dysostosis syndrome. These are allelic disorders due to EVC genes’ mutation. Investigated patients in the reported family disclosed and homozygous c.1868T>C mutation within EVC1 gene, predicting p.L623P, which was likely a causative mutation. According to the authors, distinguishing features in these patients were rhizomelic shortening of the limbs, absent upper lip defects and hypertelorism, normal chest circumference with pectus excavatum, short non hypoplastic nails, absence of mucobuccal fold.

Major compulsory revision

The clinical and molecular data are well illustrated and sound. The only major point refers to the differential diagnosis between the reported patients and Weyers syndrome (WeS), in particular the distinguishing features illustrated in Table 1.

Based on the Table 1 legend, the symbol +++ was used to indicate a nearly invariant clinical finding, ++ a frequent finding, + an occasional finding, and – a finding not considered part of the syndrome. Postaxial polydactyly was classified as +++ in WeS, while it is known that this abnormality can shows wide interindividual variability, including only postminimus digits in some cases (+) (Gorlin). Septal defects have not been considered part of WeS (-), while it is known that a number of patients display single atrium, atrioventricular canal defect (+) (Digilio). Short stature was considered a frequent feature (++), while growth retardation is in general mild and not grossly different compared to the stature reported in patients 1 and 2 (+) by Ulucan. Hypotelorism (++) in WeS is likely anecdotal, since “no facial dysmorphism” was clearly stated in a number of these patients (Digilio), and Gorlin has reported that “the facies...is not unusual”. Similarly, the only consistent mandible anomaly in WeS is the delay in fusion of the mandibular symphisis in patients under 1 year of age. Based on the Ulucan’s patients’ ages it is hard to conclude if this feature was really a distinguishing feature in respect to the WeS individuals. Also the nails’ features are probably oversimplified in Table 1. In fact, a number of reported WeS cases have only short non dysplastic nails. Thus, a revision of criteria used in Table 1 to classify the clinical features in patients assigned to different syndromes is
recommended

Minor essential revision

Please, check the location of Table 1 within the text.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.