

Letter regarding “Distal Limb Defects and Aplasia Cutis: Adams-Oliver Syndrome”

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To the Editor,

I read with interest the recent case report by Drs Renfree and Dell (1).

The specific limb and scalp defects observed in Adams-Oliver syndrome (AOS) cover a wide range of clinical severity such that the disorder is often not diagnosed on first presentation. Elucidating the underlying molecular mechanisms is therefore critical to our understanding of the manifestation and progression of this disorder, in turn providing an opportunity for improved patient diagnosis and clinical management.

The article stated that no gene has been identified for this disorder. On the contrary, there has been considerable progress in our understanding of the biological pathways important in this condition after the identification of six genes since 2011 (2). Of the genes reported to date, *ARHGAP31* and *DOCK6* are regulators of the Rho GTPases Cdc42 and Rac1, while *RBPJ*, *EOGT*, *NOTCH* and *DLL4* are involved in the Notch signalling pathway. The mode of inheritance may be either autosomal dominant or autosomal recessive, although a number of cases have been shown to be caused by *de novo* mutation (3). Through assessment of specific clinical features, some genotype-phenotype correlations are starting to emerge, but these are limited by small sample size. Of note, autosomal recessive mutations in *DOCK6* are associated with an increased risk of neurological and ophthalmological defects (4), and our recent findings indicate a higher proportion of cardiovascular defects in AOS patients harbouring autosomal dominant *NOTCH1* mutations (5).

In conclusion, we and others have identified four autosomal dominant and two autosomal recessive genes, which highlight Rho dysregulation and aberrant Notch signalling as consistent risk factors in AOS pathogenesis. These genes account for ~50% of AOS cases, providing the option of genetic counselling and improved clinical care for a considerable proportion of patients affected with this condition, while also indicating there are likely to be a considerable number of genes yet to be found.

References

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