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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for juvenile polyposis syndrome, CS, Bannayan-Riley-Ruvalcaba syndrome, and autoimmune lymphoproliferative syndrome)
UCSC Genome Browser (May 2004), http://genome.ucsc.edu/

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Reply to Salviati et al.

To the Editor: In this issue, Salviati and colleagues report the case of an 8-year-old girl whose mild developmental delay and dysmorphic features led them to perform a high-resolution karyotype.[1] A 12-Mb deletion located in 10q23 and encompassing the *PTEN* and *BMPR1A* loci was detected. The child presented with rectal bleeding at age 5 years. Colonoscopy at age 6 years uncovered >15 hamartomatous polyps throughout the entire colon, allowing the diagnosis of juvenile polyposis (JP). By operational definition, JP in patients younger than 6 years may be classified as "JP of infancy." Thus, the rectal bleeding in this child at age 5 years was almost certainly due to the juvenile polyps uncovered only the following year; therefore, this case corroborates our report.[2] However, the presentation and the disease course of the patient reported by Salviati et al.[1] were not as severe as those of the four patients reported in our recent study[2] and about which we hypothesize that the cooperation of the deletions of both tumor-suppressor genes *PTEN* and *BMPR1A* leads to severe JP and, hence, to cases of JP of infancy. The report by Salviati and colleagues[1] is very interesting, illustrating that a very large deletion (12 Mb, compared with 2 Mb in patients 1 and 2 in our report[2] and ~4.8 Mb in the patient reported by Tsuchiya et al.[3]) may be, paradoxically, associated with a less severe disease course than a small deletion or a point mutation. As proposed by Salviati and colleagues,[1] the protective effect of a modifier allele of a gene unlinked to the *PTEN* and *BMPR1A* genes may explain this phenomenon even if, at the present time, no candidate gene is suggested. Another explanation for this milder phenotype may be the increased expression level of the *PTEN* and *BMPR1A* genes by the remaining allele, which thus allows correction of the haploinsufficiency. Indeed, evidence is accumulating that allelic-specific expression is relatively common among nonimprinted autosomal genes and may be due to *cis*-acting, genetically inherited variations.[4] Because of the very large size of the 10q22.3-q23 deletion in the patient reported by Salviati and colleagues,[1] we speculate that, without the increased expression level by the remaining chromosome of some critical genes other than *PTEN* and *BMPR1A* located in the deleted region, this condition would have been lethal. Thus, we suggest that the affected child may have some *cis*-acting–specific sequences in the remaining allele that correct the haploinsufficiency in the 10q22.3-q23 region and lead, paradoxically, to an attenuated phenotype. The study by Salviati et al.[1] illustrates how meticulous analyses of cases presenting with a similar disease are useful. Together with our original publication, this study should spur the international community to cooperatively and systematically study all JP syndrome diagnoses, the frequency of deletion of either or both genes, and their pre-

cise phenotypic manifestations, including age at onset and severity.

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