Regarding cancer predisposition detected by CHG arrays

To the Editor:

We read with interest the article by Adams et al.[1] summarizing microdeletions and microduplication syndromes with cancer predisposition detected by array-based comparative genomic hybridization. We would like to add an additional, potentially recognizable microdeletion to this list, 2p16.2 p21.

This deletion was first described by Sanders et al.[2] in a child with developmental delay and mild facial dysmorphism including microcephaly and hypotelorism. Retrospectively, these facial features are possibly due to deletion of *SIX3* (2p21) mutations which are responsible for holoprosencephaly 2, which has an extremely variable phenotype even within the same family.[3] Patients with loss of *SIX3* may have a severe central nervous system defect that precludes survival, while others may survive into adult life and be at risk for the Lynch syndrome, due to deletion of one or two mismatch repair genes, *MSH2* and *MSH6*. For example, Lucci-Cordisco et al.[4] described a 37-year-old woman with a history of developmental delay and mild dysmorphic features who developed cancer. A routine peripheral blood karyotype was normal. However, the colon tumor exhibited microsatellite instability, and more detailed study revealed microdeletion 2p16.21 including the *MSH2* gene.

We recently evaluated a 21-year-old man with developmental delay, mental retardation, short stature, microcephaly, and hypotelorism. Peripheral blood chromosome analysis performed in infancy as well as a head computed tomography scan were reportedly normal. Because of concern about heritability evoked by his two normal sibs, an array-based comparative genomic hybridization was performed (CMDX, Irvine, CA), which showed deletion of 2p16.3p21, including all three relevant genes, *SIX3*, *MSH2*, and *MSH6*. Both parents were normal.

Most patients with the Lynch syndrome do not develop colon cancer or any of the other tumors within the Lynch syndrome spectrum until the third decade. Our patient had a history of unexplained bouts of diarrhea. A colonoscopy was performed, fortunately revealing only an inflammatory pseudopolyp. We provided a screening protocol for the Lynch syndrome to the parents and referring physician.

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Response to the letter by Collins and Schimke

To the Editor:

We thank Collins and Schimke for their letter adding to the discussion of loci that predispose to cancer that can be detected by microarray analysis with the addition of the deletion of 2p16.2p21 that includes *SIX3*, *MSH2*, and *MSH6*. At the time of our publication,[1] we had not yet identified any patients with *MSH2* or *MSH6* deletions. Since then, we have encountered three patients with deletions including one or both of these Lynch syndrome genes. One case involved a fetus with holoprosencephaly, in whom microarray analysis identified a 17.6 Mb deletion encompassing *SIX3*, *MSH2*, and *MSH6*. The other two patients had smaller deletions (192 kb and 537 kb) encompassing only *MSH6* and a neighboring gene, *FBXO11*. Both patients with smaller deletions had developmental delay and dysmorphic features; so while testing identified cancer predisposition in both, it is unclear if these deletions are the cause of their developmental features.

The Collins and Schimke case is another valuable example of a condition that can be identified by microarray analysis that requires specialist involvement beyond the neurologist, geneticist, or perinatologist who may have referred the case for testing. Their case nicely illustrates that a specific clinical action or decision may be dictated by the particular alteration identified. Microarray analysis can also detect conditions in addition to cancer predisposition that require specific clinical actions. These conditions include, among others, some forms of inherited cardiac arrhythmia[2] (e.g., OMIM# 613688); renal anomalies and diabetes[3] (OMIM# 137920); a form of thrombocytopenia[4] (OMIM# 188025); and deafness[5] (OMIM# 193500). As microarray testing becomes increasingly used in assessing patients with developmental abnormalities, its ability to alert physicians to unanticipated and actionable clinical problems is becoming more evident. The end results are more appropriate medical management and improved patient outcomes.

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