Genetics and Your Practice

Sara Pirzadeh-Miller, M.S., C.G.C.
Certified Genetic Counselor
Moncrief Cancer Institute/UT Southwestern Medical Center

Cowden syndrome (CS)

As everyone knows, genetic information continues to evolve and technologies change – one of the main reasons that patients should continue to stay in touch with their genetics provider! Just as importantly, oncology nurses and other clinicians need to also be aware of new information in cancer genetics, and I wanted to take this opportunity to summarize a few new articles that have been published in the last year on Cowden syndrome (CS).

CS, also known as PTEN hamartoma tumor syndrome, has been difficult to ascertain given the many benign pathognomonic features in addition to cancer risks. CS-affected female patients do have significantly higher risks for breast and endometrial cancers (as high as 50% and 15%, respectively) and all affected patients have higher risk for non-medullary thyroid cancer (as high as 10%, typically follicular). Renal and colon cancers have also been noted in this population. In addition, the major benign findings include macrocephaly, mucocutaneous lesions, hamartomatous colon polyps, and increased risk for benign diseases of the breast, thyroid and endometrium. Mutations in the PTEN gene are known to be causative of CS. Heald et al. published data reporting the Cleveland Clinic experience regarding frequency of gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers, which has not been well-understood. This group has amassed a large number of research subjects through their PTEN study, and our group is a collaborator. They had several interesting findings:

1. Colorectal cancer was diagnosed in 7% of the 127 mutation carriers, all of these were under age 50;
2. Approximately 50% of mutation carriers had colorectal polyps (which is likely an underestimate). Mixed histology was discovered in the majority of mutation carriers that underwent colonoscopy, which included hamartomatous, hyperplastic, ganglioneuromas, adenomatous and inflammatory. Several of these patients had polyps of 3 histologic types;
3. Of the 27 mutation carriers with hyperplastic polyps, at least 16 met the operational diagnosis of hyperplastic polyposis syndrome (HPS);
4. 66% of mutation carriers that underwent upper endoscopy in this study had polyps discovered. Most of the patients with upper GI polyps also had colorectal polyps.

They advise that these results need to be validated in further studies, but they suggest the need to increase the frequency of colorectal surveillance above general population screening (which is what is currently recommended). Additionally, they suggest that healthcare providers consider PTEN assessment in the presence of several nonadenomatous polyps (particularly with mixed histology) and macrocephaly, as these findings would significantly increase the probability of a PTEN mutation.

Several groups have published on a possible linkage of autism spectrum disorder (ASD)/mental retardation (MR)/developmental delay (DD) and macrocephaly to PTEN mutations. McBride et al. published a retrospective study that showed PTEN mutations in 7/99 (7.1%) of individuals with ASD and 8/100 (8%) of patients with MR/DD, all of whom had

macrocephaly. Of the combined 15 patients that were positive, only 4 had family history of cancer (included breast, uterine, renal and prostate). This confirmatory study demonstrates that PTEN assessment should be strongly considered in patients with these features. If PTEN mutation is discovered, siblings and parents would also be at up to 50% risk for the mutation and changes in cancer surveillance recommendations would be warranted.

Finally, Bennett et al. published regarding the genetic etiology of a subset of patients with clinical CS or Cowden-like syndrome (the latter patients have some but not all features of CS). PTEN mutations are found in about 80% of CS cases, while about 10% have mutations in SDHB or SDHD (genes that typically cause pheochromocytoma and paragangliomas). This paper looked to see if epigenetic changes (i.e. alteration of gene expression caused by chemical differences outside of the actual genetic code like hypermethylation) could be causative of some cases. They found that hypermethylation of a novel gene transcribed in the opposite direction of PTEN, named KILLIN, may account for the remainder of patients with clinical diagnosis of CS/ Cowden-like syndrome. Patients with germline KILLIN methylation were notes to have a 3-fold increased prevalence of breast cancer (which approaches BRCA levels of breast cancer risk) and a greater than 2-fold increase of renal cancer over the typical risks for PTEN-positive patients. These results need replication in a larger cohort; however, one important implication is a possible new gene to account for some patients with CS and the increased likelihood of breast and renal cancers related to KILLIN methylation would warrant additional diligence in surveillance for these cancers.

As always, were glad to help with any questions you might have for any cancer genetics issues. You can reach us at 817-838-4871 or 214-645-2563.

References:

1. Heald B., Mester J., Rybicki L., et al. Frequent Gastrointestinal Polyps and Colorectal Adenocarcinomas in the Prospective Series of PTEN Mutation Carriers. Gastroenterology 2010;139:1927-33.
2. McBride K., Varga E., Pastore M., et al. Confirmation Study of PTEN Mutations Among Indivifuals with Autism or Developmental Delays/Mental Retardation and Macrocephaly. Autism Research 1020;3:137-41.
3. Bennett K., Mester J., Eng C. Germline Epigenetic Regulation of KILLIN in Cowden and Cowden-like Syndrome. JAMA 2010;304(24):2724-31.