C-59

Presacral Neuroendocrine Tumors Associated with the Currarino Syndrome

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BACKGROUND: Currarino Syndrome (CS) is an autosomal dominant syndrome caused by mutations in MNX1 and characterized by anorectal abnormalities, partial sacral agenesis and presacral masses. The presacral masses are typically benign, however malignant degeneration can occur, and presacral neuroendocrine tumors (NETs) have been reported in three cases. We report two families affected by CS in which two individuals developed presacral NETs.

METHODS: Exome sequencing was performed on genomic DNA, and tumor DNA in patients with presacral NETs and MNX1 mutations. Sequencing reads were aligned using Burrows Wheeler Aligner. Variants were generated using the Genome Analysis Toolkit, Varscan, and annotated using Variant Effect Predictor. Consistency of variant candidates was assessed using the Integrative Genomics Viewer. Mutations in MNX1 were confirmed by commercial testing.

RESULTS: Family 491 had 6 members with features of CS including two siblings who presented with presacral, grade 2 NETs, one of which had metastasized to bone and lymph nodes. A germline c.874C>T (p.Arg292Trp) mutation was found in a highly conserved region of MNX1 in three affected members who underwent sequencing (Table 1). A second somatic variant/deletion in MNX1 was not detected in either patient's tumor. In family 342, two patients had presacral NETs, and sequencing did not reveal an MNX1 mutation or copy number variants.

CONCLUSION: We describe four new patients with CS and NETs, highlighting the variable presentation of CS, and the potential for malignancy in these patients. MNX1 is a transcription factor which is important for caudal embryogenesis. Mutations in this gene lead to CS, which in rare cases has been associated with presacral NETs. The lack of a second, somatic mutation in the tumor argues against MNX1 acting as a tumor suppressor, and the absence of a germline MNX1 mutation in family 342 suggests that other genetic and anatomic factors contribute to the development of presacral NETs.

Table 1: Family members from two families with Currarino Syndrome and presacral NETs. Presacral mass indicates final surgical pathology. CS manifestations indicates all other signs of CS aside from the presacral mass.

Pt ID	Presacral Mass	CS Manifestations	MNX1 Mutation
494-1 - Proband	G2 NET associated with rectrorectal cystic hamartoma	Asymptomatic	c.874C>T
491-2 - Mother	None	Unaffected	None
491-3 - Sibling	G2 NET ssociated with rectrorectal cystic hamartoma	Asymptomatic sacral dysraphism	c.874C>T
491-5 - Great nephew	Mature cystic teratoma	Anal stenosis, partial sacral agenesis	c.874C>T
342-1 - Proband	G1 NET associated with mature cystic teratoma	None	None
342-2 - Father	NET associated with teratoma	None	Not performed