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Somatic Alterations of *CDKN1B* are Associated with Small Bowel and Pancreas Neuroendocrine Tumors

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Introduction: *CDKN1B*, a cyclin-dependent kinase inhibitor associated with G1 arrest, was recently proposed as an important tumor suppressor gene in small bowel neuroendocrine tumors (SBNETs). Two groups found exonic somatic mutations of the gene in SBNET primary tumors at a combined rate of 7.4% (95% C.I.: 4.4-10.3%); hemizygous deletions were seen in 6.7%. Alterations of this gene have not been investigated in pancreatic neuroendocrine tumors (PNETs). We set out to confirm the role of mutations and copy number variants (CNVs) of *CDKN1B* in another large cohort of SBNET patients and also examined the importance of these changes in PNETs.

Methods: Genomic DNA was isolated from 86 primary SBNETs and 67 PNETs. Each exon and intron-exon boundary of *CDKN1B* was amplified by PCR, then bidirectionally sequenced. CNV analysis was performed by quantitative PCR using CDKN1B-specific probes at the 5'and 3' ends of the gene. Results were evaluated using sequencing, CNV, and mutational analysis software. p27 expression was evaluated using immunohistochemistry.

Results: Three frameshifts, and 1 hemizygous deletion were observed in SBNETs, giving a total rate of *CDKN1B* alterations of 4.7% (95% C.I.: 0.2-9.1%; Table). The rate of frameshift mutations was 3.5% (95% C.I: 1.2-9.8%). p27 expression was reduced or lost in SBNETs with frameshift mutations. One likely deleterious missense mutation, and 4 CNVs were observed in PNETs, giving a total rate of *CDKN1B* alterations of 7.5% (95% C.I.: 1.2-13.8%). There were no frameshift mutations in the PNETs.

Conclusion: This study confirms that *CDKN1B* plays a role in SBNETs, with frameshift rates statistically similar to the previous reports. Conversely, frameshifts were not seen in PNETs, but a few had losses or duplications of unknown significance. Depression or loss of p27 expression in SBNETs with frameshift mutations suggests that these mutations may lead to cell cycle dysregulation and eventual tumor initiation.

Table 1. Somatic mutations found in CDKN1B in a set of 86 primary SBNETs.

Tumor Type	Mutation	Location	Protein Change
SBNET	Frameshift	c.127delCinsTAA	p.R43fs
SBNET	Frameshift	c.279_280insT	p.P94fs
SBNET	Frameshift	c.334delA	p.S112fs
PNET	Missense	c.125C>T	p.T42I
SBNET	*CDKN1B* deletion	c.?56_1590?dup	Loss of 1 copy
PNET	*CDKN1B* deletion and duplication	c.?56_1590?del	Loss of 3' end
			Gain of 5' end
PNET	*CDKN1B* deletion	c.?56_1590?del	Loss of 1 copy
PNET	*CDKN1B* duplication	c.?56_1590?del	Gain of 1 copy
PNET	*CDKN1B* duplication	c.?56_1590?del	Gain of 1 copy