Novel mutations p.V220E and c.30G>T in menin gene are associated with hereditary predisposition to multiple endocrine neoplasia type 1.

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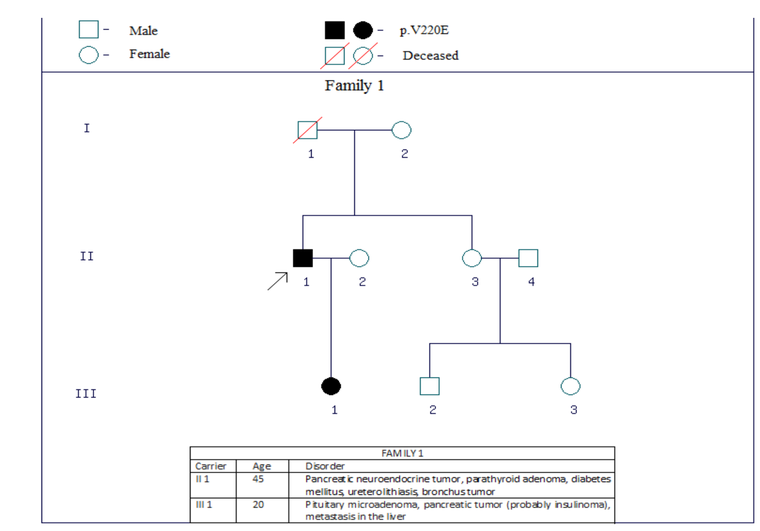
INTRODUCTION

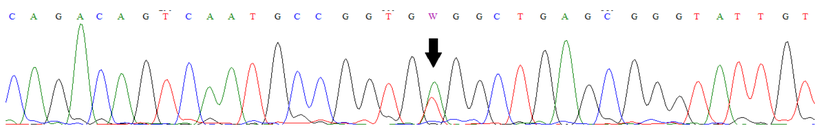
Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant condition characterized by varying combinations of endocrine tumors and commonly accompanying hyperplasia within the parathyroid gland, anterior pituitary and gastrointestinal tract (1-4). Heterozygous germline mutation of the tumor suppressor gene *MEN1* (menin) is the most common cause of the disease (5-6). Genetic testing of *MEN1*, detects pathogenic variants in approximately 80%-90% of probands with familial background and in approximately 65% of sporadically occurring cases (7). Until now over 1000 germline mutations and 200 somatic, have been identified in patients with MEN1 (7). Here we describe novel pathogenic mutations p.V220E and splite-site c.30G>T in two separate families presenting MEN1 manifestation.

RESULTS

Family 1

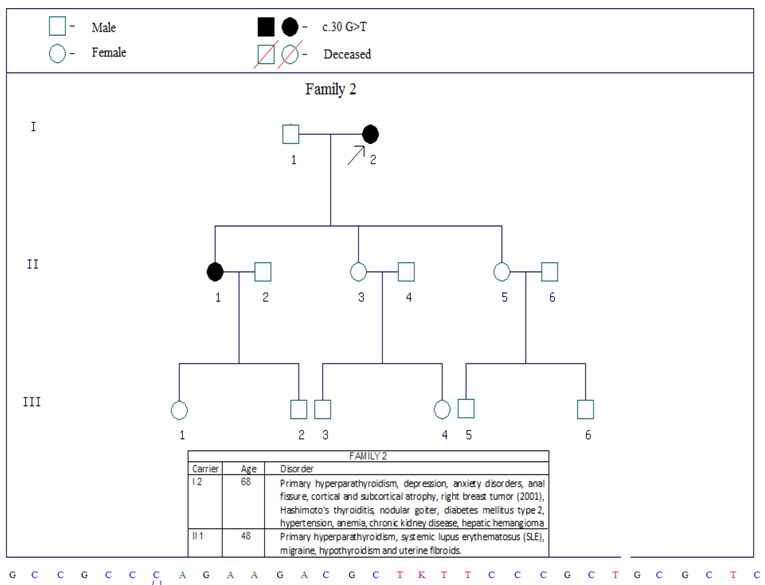


FAMILY 1		
Carrier	Age	Disorder
II 1	45	Pancreatic neuroendocrine tumor, parathyroid adenoma, diabetes mellitus, ureterolithiasis, bronchus tumor
III 1	20	Pituitary microadenoma, pancreatic tumor (probably insulinoma), metastasis in the liver

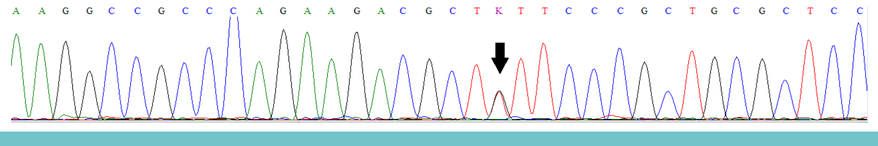


A 45 – year - old male patient suffered from pancreatic neuroendocrine tumor, parathyroid adenoma, diabetes mellitus and ureterolithiasis was referred to Department of Endocrinology, Metabolism and Internal Diseases. The proband successfully underwent pancreaticoduodenectomy (Whipple procedure 2008, 2011), parathyroidectomy (2009) and ureterorenoscopic lithotripsy (2015). During hospitalization 9 mm tumor of the segmental bronchus was detected at computed tomography. According to clinical findings, the diagnosis of MEN1 was highly suspected. Genetic testing of the patient revealed a missense mutation p.V220E (c.659T>A, g.3394T>A) in exon 3 of *MEN1* gene. Molecular analysis of the MEN1 gene was also performed on proband's daughter. The survey confirmed transmission of p.V220E mutation. Laboratory test and imaging have diagnosed pituitary microadenoma, pancreatic tumor (probably insulinoma) and metastasis in the liver in 20-year-old female patient.

Family 2



FAMILY 2		
Carrier	Age	Disorder
I 2	68	Primary hyperparathyroidism, depression, anxiety disorders, anal fissure, cortical and subcortical atrophy, right breast tumor (2001), Hashimoto's thyroiditis, nodular goiter, diabetes mellitus type 2, hypertension, anemia, chronic kidney disease, hepatic hemangioma
II 1	48	Primary hyperparathyroidism, systemic lupus erythematosus (SLE), migraine, hypothyroidism and uterine fibroids.



A 68-year old woman had been diagnosed with primary hyperparathyroidism in 2011. The proband had also history of depression, anxiety disorders, anal fissure, cortical and subcortical atrophy, right breast tumor (2001), Hashimoto's thyroiditis, nodular goiter, diabetes mellitus type 2, hypertension, anemia, chronic kidney disease, hepatic hemangioma,hysterectomy and oophorectomy. Genetic testing of the patient, revealed heterozygous substitution c.30G>T (p.Leu=), which may predispose to MEN1. Her 48 - year old daughter also suffered of PHPT. Parathyroidectomy had been performed in 2012. Patient medical history revealed systemic lupus erythematosus (SLE), migraine, hypothyroidism and uterine fibroids. Woman reported arthralgia, walking difficulty, hemiparesis headaches and decreased vision. After surgery, patient's serum calcium level and PTH normalized. During hospitalization abdominal sonography was performed, revealing three hepatic hemangiomas and left kidney cyst (1,4 cm diameter). Genetic studies confirmed the presence of inherited c.30G>T substitution.

CONCLUSIONS

In both families, novel pathogenic mutations were identified. Mutations and locations were searched in the literature and genomic databases but so far no such abnormalities were reported. Missense mutations represent 20% of *MEN1* changes while splice site mutations accounts only for 9%. Others, such as frameshift deletions, insertions and nonsense mutations are more common (7). Studies have shown that more than 10% mutation arise de novo and can be passed to the next generation (7,8). Since now, no clear genotype-phenotype correlation in this gene has been established (9). Patients presenting solid components of MEN1 syndrome should be routinely screened for mutations in a coding sequence of menin gene. There is limited understanding of tumor biology, behavior, and heterogeneous clinical presentation in MEN1. Abundance of genetic alterations in menin as well as lack of mutational hot spots, prompt the usage of wider genetic analysis including *MEN1* interacting genes. This work also indicate the necessity of thorough analysis of synonymous alterations as potentially pathogenic splice site mutations that are commonly overlooked.

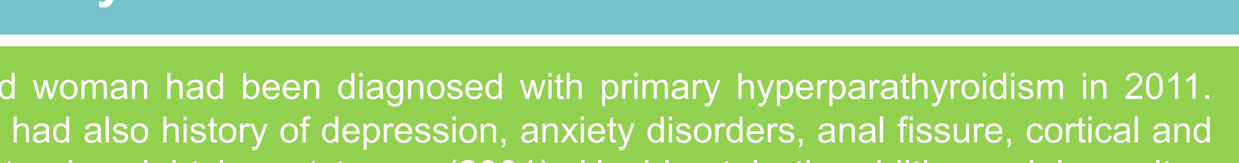


Fig. 1 MEN1 gene structure and identified mutations

Bibliography:

1. Wermer P. Genetic aspects of adenomatosis of endocrine glands. Am J Med. 1954;16:363-371.
2. Trump D, Farren B, Wooding C, Pang JT, Besser GM, Buchanan KD, Edwards CR, Heath DA, Jackson CE, Jansen S, Lips K, Monson JP, O'Halloran D, Sampson J, Shalet SM, Wheeler MH, Zink A, Thakker RV. Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM 1996;89:653-69
3. Thakker RV. Multiple endocrine neoplasia type 1. In: DeGroot LJ, Jameson JL, eds. Endocrinology. 6th ed. Philadelphia, PA: Elsevier, 2010: 2719-2741.
4. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G,Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001; 86: 5658-5671
5. Larsson C., Skogseid B., Oberg K., Nakamura Y., Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma.Nature. 1988;332:85–87
6. Friedman E., Sakaguchi K., Bale A.E., Falchetti A., Streeten E., Zimering M.B. Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. N. Engl. J. Med. 1989;321:213–218.
7. Benson L., Ljunghall S., Akerstrom G., Oberg K. Hyperparathyroidism presenting as the first lesion in multiple endocrine neoplasia type 1. Am. J. Med.1987;82:731–737.
8. Bassett J.H., Forbes S.A., Pannett A.A., Lloyd S.E., Christie P.T., Wooding C. Characterization of mutations in patients with multiple endocrine neoplasia type 1.Am. J. Hum. Genet. 1998;62:232–244.
.9. Kouvaraki MA, Lee JE, Shapiro SE, Gagel RF, Sherman SI, Sellin RV, Cote GJ&Evans DB. Genotype-phenotype analysis in multiple endocrine neoplasia type 1. Archives of Surgery 2002 137 641–647.

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