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SUCCINATE DEHYDROGENASE DEFICIENT GASTROINTESTINAL STROMAL TUMORS (GISTs) – A REVIEW

Markku Miettinen and Jerzy Lasota

Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland, USA

Abstract

Loss of function of the succinate dehydrogenase complex characterizes a rare group of human tumors including some gastrointestinal stromal tumors, paragangliomas, renal carcinomas, and pituitary adenomas, and these can all be characterized as SDH-deficient tumors. Approximately 7.5% of gastric gastrointestinal stromal tumors are SDH-deficient and not driven by KIT/PDGFRA mutations, as are most other GISTs. The occurrence of SDH-deficient GISTs is restricted to stomach, and they typically occur in children and young adults representing a spectrum of clinical behavior from indolent to progressive. Slow progression is a common feature even after metastatic spread has taken place, and many patients live years with metastases. SDH-deficient GISTs have characteristic morphologic features including multinodular gastric wall involvement, often multiple separate tumors, common lymphovascular invasion, and occasional lymph node metastases. Diagnostic is the loss of succinate dehydrogenase subunit B (SDHB) from the tumor cells and this can be practically assessed by immunohistochemistry. SDHA is lost in cases associated with SDHA mutations. Approximately half of the patients have SDH subunit gene mutations, often germline and most commonly A (30%), and B, C or D (together 20%), with both alleles inactivated in the tumor cells according to the classic tumor suppressor gene model. Half of the cases are not associated with SDH-mutations and epigenetic silencing of the SDH complex is the possible pathogenesis. Extensive genomic methylation has been observed in these tumors, which is in contrast with other GISTs. SDH-loss causes succinate accumulation and activation of pseudohypoxia signaling via overexpression of HIF-proteins. Activation of insulin-like growth factor 1-signaling is also typical of these tumors. SDH-deficient GISTs are a unique group of GISTs with an energy metabolism defect as the key oncogenic mechanism.

Keywords

Gastrointestinal stromal tumor; GIST; SDH-complex; SDHA; SDHB; SDHC; SDHD; mutation; pseudohypoxia

Address for correspondence: Markku Miettinen, M.D., National Cancer Institute, Laboratory of Surgical Pathology, 9000 Rockville Pike, Bldg. 10, Rm. 2B50, Bethesda, Maryland, 20892, miettinenmm@mail.nih.gov.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Although GISTs occur most frequently in the stomach and small intestine, they can present anywhere in the gastrointestinal tract with a lower frequency. Epidemiologic studies suggest that GISTs have an annual incidence of at least 14-20 per million people. However, minimal clinically indolent tumors are probably much more common based on studies on surgical excisions for unrelated tumors and autopsy studies, in which as many as 10-25% study subjects harbored an incidental minimal GIST. GISTs show phenotypic similarity with gastrointestinal Cajal cells. These mesenchymal cells are the functional intermediaries between autonomic nervous system and smooth muscle cells. Like Cajal cells, GISTs are almost uniformly KIT-expressing, and KIT receptor tyrosine kinase is a centrally important signaling molecule regulating cell proliferation and apoptosis (Corless et al., 2011, Miettinen & Lasota, 2013).

Most GISTs are driven by oncogenic KIT or PDGFRA receptor tyrosine kinase activating mutations. This mechanism has been successfully countered by tyrosine kinase inhibitor treatment as the first example of targeted therapy for a solid tumor. Approximately 10-15% of all GISTs lack KIT or PDGFRA mutations and are therefore called wild type GISTs in reference to KIT and PDGFRA mutation status (Lasota & Miettinen 2008, Corless et al., 2011) SDH-deficient GISTs are the largest group of KIT/PDGFRA wild type GISTs (Janeway et al., Miettinen et al., 2011). Neurofibromatosis 1-associated GISTs are also KIT/PDGFRA wild type, but they are not SDH-deficient (Wang et al. 2011)

Deficiencies in the succinate dehydrogenase complex characterize subsets of certain types of human tumors, most importantly gastrointestinal stromal tumors, paragangliomas, renal cell carcinomas, and pituitary adenomas (Barletta & Hornick 2012, Gill 2012, Hoekstra & Bayley 2013). In these tumors that we call “succinate dehydrogenase deficient” the succinate dehydrogenase complex is inactivated in the tumor cells. In many cases, this happens via combination of a loss-of-function germ line mutations in one of the SDH subunit genes and somatic loss-of-function mutations in the tumor cells, leading into inactivation of both alleles according to the principle of classic tumor suppressor genes. In some cases the mechanism of inactivation is unclear and possibly related to epigenetic silencing. Although SDH-complex is essential for life, haploinsufficiency is tolerated and compensated. However, disruption of both alleles by compound heterozygotic germline SDHA mutations causes a severe neurodegenerative syndrome, Leigh syndrome (Parfait et al., 2000) and a homozygous loss-of-function SDHB mutation a leukodystrophy (Alston et al., 2012).

Succinate dehydrogenase (SDH) is a heterotetrameric enzyme complex located in the inner mitochondrial membrane and is entirely encoded by chromosomal DNA. The SDH-complex participates in the Krebs cycle with subunit A (SDHA) being the catalytic unit responsible for conversion of succinate to fumarate. Subunit B (SDHB) is an iron sulphur protein that participates in the electron transport chain for the oxidation of ubiquinone to ubiquinol, and subunits C and D (SDHC and SDHD) are membrane-anchoring subunits (Rutter et al., 2010).

Studies on paragangliomas and GISTs indicate that loss of any SDH-subunit renders the complex inactive, and it has been found that any paraganglioma associated with an SDH-mutation (usually germline syndrome) lacks SDHB subunit. Therefore, loss of SDHB, as tested by immunohistochemistry, is the most practical way to identify SDH-deficient tumors (van Nederveen et al., 2009, Gill et al., 2010, Gill et al., 2011).

In this paper, we review the epidemiology, clinical features, histopathology, and molecular pathology of SDH-deficient gastrointestinal stromal tumors (GISTs).

TERMINOLOGY, EPIDEMIOLOGY AND CLINICAL FEATURES OF SDH-DEFICIENT GISTS

SDH-deficient GIST implies a gastrointestinal stromal tumor that has a loss of succinate dehydrogenase complex function as the oncogenic mechanism, instead of KIT or PDGFRA-activating mutations, as seen in a great majority of GISTs in general. This group encompasses most pediatric GISTs and two previously described syndromes: Carney-Stratakis syndrome and Carney triad.

Carney-Stratakis syndrome includes occurrence of GIST and paraganglioma in the context of SDH-germline mutation and is hereditary (Carney & Stratakis, 2002, Pasini et al., 2008). Carney triad includes the combination GIST and pulmonary chondroma, paraganglioma, or both without SDH mutations or hereditary basis (Carney 1999, Matyakhina et al., 2007). Because both of these syndromes require additional manifestations for the diagnosis, their definition is fulfilled only by a small minority of SDH-deficient GISTs (15-20%). One of the reasons is highly asynchronous occurrence of the different tumor components in these syndromes. For example, paragangliomas can occur in a span of 25 years or more apart from a GIST. However, systematic radiologic screening that reveals subclinical paragangliomas will probably enhance detection of these syndromes (Jasperson et al., 2013).

Based on current experience, SDH-deficient GISTs occur exclusively in the stomach and not in the intestines. Our screening of >500 gastric GISTs shows their frequency as 7.5% of all gastric GISTs, but no cases were found among 265 small intestinal GISTs (Miettinen et al., 2011). We are not aware of well-documented intestinal examples ever being reported in the literature.

SDH-deficient GISTs are typically of early onset and most of them manifest before the age of 40 years, whereas other GISTs only rarely affect young people. Great majority of pediatric GISTs are SDH-deficient, and approximately 2/3 of gastric GISTs at the age of 20-29 are SDH-deficient, while approximately half of gastric GISTs at the age 30-39 years belong to this group. Still SDH-deficient GISTs occur in older age groups but at a very low frequency. Pediatric SDH-deficient GISTs have a great predilection to girls, whereas SDH-deficient GISTs at older age groups have a less marked female predominance (Janeway et al., 2011, Miettinen et al., 2011).

Even if SDH-deficient GISTs, like SDH-deficient paragangliomas, are associated with germline mutations of the SDH-subunit genes, SDH-deficient GISTs do not seem to have a

marked tendency for familial occurrence, as compared with SDH mutation syndrome-associated paragangliomas that show familial occurrence. The reason for this is unknown, but one could suspect that this might be related to the lower risk of simultaneous loss of the other copy of SDH subunit in the ancestral cells of GIST, Cajal cells or their stem cell-like precursors, than the risk of the same event in paraganglial cells. However, there are isolated reports of multiple family members involved with SDH-deficient GISTs (Wagner et al. 2013).

Clinical manifestations that lead to the detection of SDH-deficient GIST most commonly include gastrointestinal bleeding and vague epigastric complaints. Occasional patients present by symptoms related to metastatic tumors in the abdomen or liver.

PATHOLOGY OF SDH-DEFICIENT GISTS

Characteristic of SDH-deficient GISTs is a relatively high frequency of tumor multiplicity with many patients showing coalescent or separate tumor nodules involving the gastric wall. Although SDH-deficient GISTs can involve any part of the stomach, there is some predilection to distal stomach and antrum. Occurrence of lymph node metastases is a feature almost restricted to SDH-deficient GISTs among all GISTs, although this is still seen in a minority of patients, 10% or less (Miettinen et al., 2011). A similar clinicopathological profile has emerged from the studies of Carney triad-associated GISTs (Zhang et al., 2010).

Histologically SDH-deficient GISTs are distinctive in their multinodular gastric wall involvement with interspersed tracts of gastric wall smooth muscle; in pathology terminology this is often referred to a “plexiform” pattern (Fig. 1A). The tumor cells typically have an epithelioid morphology with variably eosinophilic cytoplasm (Fig. 1B), whereas KIT-mutant GISTs more often are composed of spindle-shaped cells with a paler cytoplasm. Lympho-vascular invasion is relatively common, seen in up to 50% of cases, and its presence may explain not only some propensity to lymph node metastases but also the multinodular gastric involvement and high local recurrence rate following apparently curative surgery (Miettinen et al., 2011). On the other, field effect based on a systemic SDH-subunit mutation could also explain tumor multiplicity and multifocality.

SDH-deficient GISTs lack SDHB expression in the tumor cells, but stromal and vascular elements should be positive to verify adequate immunohistochemical detection (Fig.1). Cases that do not have SDHA mutation are SDHA-positive demonstrating a strong contrast between SDHB staining (Fig. 1). These GISTs express KIT equally strong as KIT mutant GISTs in general. They are uniformly immunohistochemically positive for DOG1/Ano1 (Anoctamin-1) and usually also for CD34. However, they rarely if ever express smooth muscle actin, which is present in 30% of GISTs in general (Miettinen et al. 2013b).

CLINICAL ASPECTS OF SDH-DEFICIENT GISTS

Clinically SDH-deficient GISTs are a heterogeneous group ranging from indolent tumors that never recur or metastasize to those that are metastatic at presentation and some of these are fatal in a few years. These tumors do not follow well the predictions of behavior made

for GISTs based on mitotic activity and tumor size and therefore a separate set of criteria should be developed for them in the future.

While SDH-deficient GISTs that are relatively small and contain low mitotic activity (< 5 mitoses/ 5 mm^2) are usually indolent, a small proportion of them metastasize to liver, often after a long delay 10 years or more after presentation. The longest delay we have so far observed is 42 years from primary tumor to liver metastasis (Miettinen et al, 2011). Based on this, lifelong follow-up is necessary. Yet if liver metastasis occurs, many patients live with metastases, and 10-year survival in this context is not unusual as would be with a KIT mutant GIST. Higher mitotic rates often relate to earlier development of metastases. Perhaps the apparent slow growth of the SDH-deficient GISTs is related to the metabolic handicap provided by the succinate dehydrogenase deficiency in the tumor. Overall tumor mortality seems to be at least 15% but probably higher after longer observation than has been so far available. Long-term follow-up comparison between all SDH-deficient GISTs and SDHA-mutant SDH-deficient GISTs have not shown any clear clinicopathological differences, except that the latter tend to occur at an older age (Miettinen et al., 2011, Miettinen et al., 2013b). Similar clinicopathologic features and overall mortality has also been reported on pediatric GISTs associated with paragangliomas, pulmonary chondromas, or both in Carney triad (Zhang 2010).

Occurrence of other SDH-deficient tumors can be highly asynchronous. In some cases, paragangliomas have been detected 25 years before or after the detection of GIST. In one case, SDH deficient renal cell carcinoma was diagnosed 40 years after the GIST (Miettinen et al, 2011).

GENETIC BACKGROUND AND ITS CLINICAL CORRELATION

At least half of SDH-deficient GISTs contain loss-of-function SDH subunit germline and somatic mutations. These mutations include frame shift deletions leading to premature stop codons, missense, and nonsense mutations and occasionally splice site mutations. SDH-complex mutations reported in non-syndromic GISTs are listed in Table 1.

SDHA mutation-associated GISTs

While SDHA mutations have been associated with very few paragangliomas (Burnichon et al, 2010), the most commonly mutated SDH subunit in SDH-deficient GISTs is SDHA, with an estimated frequency of 28% of all SDH-deficient GISTs. In most cases, these are germline mutations (Miettinen et al., 2013b). SDHA mutation has an excellent correlation with immunohistochemical loss of SDHA expression, so that this loss is an superb screening tool and surrogate marker for SDHA mutation analysis (Italiano et al., 2012, Belisnky et al., 2013, Dwight et al., 2013, Oudjik et al., 2013, Wagner et al., 2013, Miettinen et al., 2013b, Pantaleo et al., 2014). Based on these studies, the most common recurrent SDHA mutation translates to protein abrogation R31X. Simultaneous allelic loss at the SDHA locus at 5p15 has been detected with comparative genomic hybridization. Therefore, the biallelic SDHA loss seems to follow a classic tumor suppressor gene model. SDHA mutation-associated GISTs occur at an older age than other SDH-deficient GISTs and are rare in children with the median age of presentation in the largest series being 34 years. (Miettinen et al., 2013b).

Because the information on germline SDHA mutations is very recent and is essentially based on study of patients with detected tumors, it is difficult to give precise guidelines for possible clinical surveillance. Routine search for asymptomatic carriers does not seem to necessary because the disease penetrance is low. Nevertheless, studies of carrier families on trial basis could shed light into natural history of these tumors in the future.

SDHB, SDHC, and SDHD mutation-associated GISTs

Even if these mutations are regularly associated with SDH-deficient paragangliomas, they seem to occur only in a minority of SDH-deficient GISTs, estimated here as 20-30%. Most of these SDH-mutations have also been germline. A number of patients, perhaps 20% of those showing these SDH subunit mutations, also have paragangliomas (McWhinney et al., 2007, Janeway et al., 2011, Miettinen et al., 2013b).

SDH DEFICIENCY WITHOUT SDH SUBUNIT MUTATION

Up to half of SDH-deficient GIST appears to lack SDH-subunit mutations. However, this number may be too high as the number of cases comprehensively analyzed for mutation remains relatively small and also because some larger deletions may have remained undetected in the used analytical systems more geared toward detection of single nucleotide changes or small deletions.

METHYLATION IN SDH-DEFICIENT GISTS

Independent of SDH gene status, all SDH-deficient GISTs have a high frequency of gene methylation, in comparison with KIT or PDGFRA mutant GIST. Markedly higher number of hyper- than hypomethylations were detected in a screening for a large number of genes via Golden Gate® Assay for Methylation (Illumina, Inc.) Similar methylation patterns were also detected in IDH1-mutant gliomas, tumors with another Krebs cycle deficiency (Killian et al., 2013). Therefore, Krebs cycle enzyme deficiency may well be the unifying factor related to abnormal genome methylation. Hypermethylation may be related to disruption of DNA demethylation machinery by downregulated TET enzyme (Killian et al., 2013, Mason et al., 2013).

BIOCHEMICAL CONSEQUENCES OF SDH-DEFICIENT STATUS

Most of this work is based on in-vitro studies and studies of paraganglioma cells or cells artificially rendered SDH-deficient. Unfortunately, no cell line exists yet to allow dynamic experimental studies on SDH-deficient GIST cells.

SDH-deficient cells accumulate succinate and this inhibits processing of HIF1- α by prolyl hydroxylase, which leads to HIF1- α overexpression and HIF transport (translocation) into nuclei (Brière et al., 2005, Selak et al., 2005). Overexpressed HIF proteins then act as aberrant transcription factors leading to expression hypoxia-associated tumorigenic responses and angiogenesis. This is referred to hypoxic drive or pseudohypoxia signaling, as this occur in normo-oxic conditions in SDH-deficient cells. Similar observations have also been made in paraganglioma cells (Pollard et al., 2005). Experimental silencing of SDHB also seems to lead into tumor-like phenotype with

increased adherence to matrix and expression of proliferation-associated genes, which also highlights the tumorigenic role of SDH-loss (Cervera et al., 2008).

Typical of SDH-deficient GISTs (originally often designated “pediatric GISTs”), is overexpression of insulin-like growth factor 1 receptor (IGF1R) gene, possibly by gene amplification. As a result, IGF1R signaling is activated, and this has been identified as a new potential therapeutic target (Tarn et al., 2008, Pantaleo et al., 2009). High expression of IGF1R protein has been demonstrated in SDH-deficient GISTs (Janeway et al., 2010), and immunohistochemically detected high expression of IGF1R seems indeed quite specific for these GISTs among all GISTs (Chou et al., 2012, Lasota et al., 2013).

TREATMENT OF SDH-DEFICIENT GISTS

Due to the rarity of SDH-deficient GISTs, treatment experience is limited to a very small number of patients. Complete surgical removal of the primary tumor and locoregional (omental or nodal) metastases should be performed whenever possible. The adjuvant treatment of patients with SDH-deficient GISTs is evolving and to date there is no uniform standard or recommendations for treating these patients. One of the complicating factors is difficulty of clinically determining what constitutes progressive disease or treatment response, because the disease may remain clinically stable even long after metastases have developed.

Traditional cytotoxic chemotherapy is generally ineffective for SDH-deficient GISTs, as it is for KIT/PDGFR α mutant GISTs. SDH-deficient GISTs (that are KIT/PDGFR α wildtype) do not respond well to tyrosine kinase inhibitor drugs, neither the first line inhibitor imatinib mesylate or a second line multikinase inhibitor sunitinib malate, although stable disease has been observed in some cases. It has been suggested that kinase inhibitor treatment should be reserved to cases that show disease progression and not routinely used after complete surgery. For postoperative surveillance, chest X-rays and CT-scans of the abdomen have been recommended every 3 months for two years and for every 6 months thereafter (Pappo et al., 2011) or every 6 weeks, as more recently suggested (Janeway and Pappo 2012).

Newer tyrosine kinase inhibitor drugs potentially usable in SDH-deficient GISTs include regorafenib, nilotinib, and sorafenib. Experimental agents that are based on biology of SDH-deficient GISTs and could be useful in the future but are not yet available except on trial basis, include insulin-like growth factor 1-receptor inhibitor OSI-906 (Linsitinib), and heat shock protein inhibitors (Vadakara and van Mehren 2013).

CONCLUSION

SDH-deficient GISTs comprise a subgroup of a relatively rare tumor type and show a number of clinically and biologically unique features. Tumor cells have the loss of the SDH-complex, either by the combination of germline and somatic mutations in the SDH-subunit genes, or unknown possibly epigenetic mechanisms. Mutation of any subunit, most commonly SDHA, leads to loss of the complex that can be reliably detected by immunohistochemistry for SDHB. SDH-deficient GISTs have an increased genomic methylation different from conventional KIT/PDGFR α -mutant GISTs and there may be an

epigenetic factor. SDH-deficient GISTs are restricted to stomach and occur predominantly at a young age and are clinically heterogeneous, with some patients having other SDH-deficient tumors, especially paragangliomas. In clinical series, tumor mortality has been around 15% although the behavior is unpredictable with metastases sometimes developing long time after primary tumor. New treatment strategies may include novel tyrosine kinase inhibitors or inhibitors of insulin-like growth factor 1 signaling, a pathway specifically activated in SDH-deficient GISTs.

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Fig. 1.

A. Histologically SDH-deficient GISTs are typically multinodular forming tumor nodules between strands of gastrointestinal smooth muscle. B. The tumor cells show usually epithelioid histology and variably eosinophilic cytoplasm. They lack cytoplasmic SDHB granular immunolabeling in the tumor cells, but this is present in the non-neoplastic components, such as blood vessels and pericytes. This SDHB-negative tumor is SDHA-positive showing strong granular cytoplasmic staining.

Table. 1

SDHA, –B, –C and –D mutations reported in SDH-deficient GISTs.

Gene	Intron	Exon	Mutation	Predicted protein sequence	No. of cases	Reference
SDHA		2	c.91C>T	p.R31*	15	Italiano et al., 2012, Belinsky et al., 2013, Miettinen et al., 2013, Oudijk et al., 2013, Wagner et al., 2013, Pantaleo et al., 2014
		2	c.113A>T	p.D38V	1	Italiano et al., 2012
		3	c.160C>T	p.Q54*	1	Dwight et al., 2013
	4	5	c.457-3 457-1delCAG	fs*	1	Pantaleo et al., 2014
	4	5	c.457-2 c457delAGC	p.L153Kfs*71	1	Belinsky et al., 2013
		5	c.511C>T	p.R171C	1	Pantaleo et al., 2014
		5	c.553C>T	p.Q185*	1	Wagner et al., 2013
		5	c.562C>T	p.R188W	1	Miettinen et al., 2013
		6	c.688delG	fs	1	Wagner et al., 2013
		6	c.767C>T	p.T256I	1	Miettinen et al., 2013
		7	c.800C>T	p.Y267M	1	Dwight et al., 2013
		7	c.818C>T	p.T273I		Belinsky et al., 2013, Miettinen et al., 2013
		8	c.985C>T	p.R329X	1	Wagner et al., 2013
		8	c.1043 1055del	p.T348Kfs* 108	1	Wagner et al., 2013
		8	c.1046 1047delTG	p.L349R fs*11	1	Pantaleo et al., 2014
		9	c.1151C>G	p.S384*	1	Pantaleo et al., 2014
		9	c.1255G>A	p.G419R	1	Pantaleo et al., 2014
		10	c.1334C>T	p.S445L	1	Miettinen et al., 2013
		10	c.1357G>A	p.G453R	1	Belinsky et al., 2013
		10	c.1361C>A	p.A454E	1	Miettinen et al. 2013
		11	c.1471G > T	p.E491*	1	Belinsky et al., 2013
		11	c.1534C>T	p.R512*	1	Wagner et al., 2013
		13	c.1690G>A	p.E564K	1	Pantaleo et al., 2014
		13	c.1765C>T	p.E564K		Wagner et al., 2013, Pantaleo et al., 2014
		13	c.1766G>A	p.R589Q	1	Pantaleo et al., 2014
		13	c.1794G>C	p.K598N	1	Miettinen et al., 2013
	13	14	c.1795-1G>T	splice site	1	Miettinen et al., 2013
		14	c.1969G>A (polymorphism)	p.V657I	1	Dwight et al., 2013
SDHB		1	c.17 42dup	p.A15Hfs*4	1	Miettinen et al., 2013
		2	c.137G>A	p.R46Q	1	Miettinen et al., 2013
		3	c.274T>A	p.S92T		Janeway et al., 2010 Miettinen et al., 2013

Gene	Intron	Exon	Mutation	Predicted protein sequence	No. of cases	Reference
		4	c.380T>G	p.I127S	1	Miettinen et al., 2013
	4		c.423+1G>A		1	Gill et al. 2011
	4		c.423+20T>A		1	Pantaleo et al., 2014
		6	c.600G>T	p.W200C	2	Janeway et al., 2010 Miettinen et al., 2013
		7	c.725G>A	p.R242H	1	Janeway et al., 2010
SDHC		1	c.1A>G	p.M1V	1	Miettinen et al., 2013
		1	c.6delT	p.A2fs	1	Miettinen et al., 2013
		4	c.224G>A	p.G75D	2	Belinsky et al., 2013, Miettinen et al., 2013
		4	c.301delT	p.C101V fs*3	1	Pantaleo et al., 2014
		4	c.380A>G	p.H127R	2	Gill et al., 2013 Miettinen et al., 2013
		5	c.397C>T	p.R133*	1	Miettinen et al., 2013
	5		c. 405+1G > A	splice site	1	Janeway et al., 2010
		6	c.455G>C	p.E144Q	1	Pantaleo et al., 2014
SDHD		1	c.34G>A (polymorphism)	p. G12S	2	Janeway et al., 2010
		4	c.352delG	p.D118Mfs*17	1	Miettinen et al., 2013
		4	c.416T>C	p.L139P	1	Oudijk et al., 2013