Syndromic gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal tract. They feature heterogeneous triggering mechanisms, implying relevant clinical differences. The vast majority of GISTs are sporadic tumors. Rarely, however, GIST-prone syndromes occur, mostly depending on heritable GIST predisposing molecular defects involving the entire organism. These conditions need to be properly identified in order to plan appropriate diagnostic, prognostic and therapeutic procedures.

Clinically, GIST-prone syndromes must be thought of whenever GISTs are multiple and/or associated with accompanying signs peculiar to the background tumorigenic trigger, either in single individuals or in kindreds. Moreover, syndromic GISTs, individually considered, tend to show distinctive features depending on the underlying condition. When applicable, genotyping is usually confirmatory.

In GIST-prone conditions, the prognostic features of each GIST, defined according to the criteria routinely applied to sporadic GISTs, combine with the characters proper to the background syndromes, defining peculiar clinical settings which challenge physicians to undertake complex decisions. The latter concern preventive therapy and single tumor therapy, implying possible surgical and molecularly targeted options.

In the absence of specific comprehensive guidelines, this review will highlight the traits characteristic of GIST-predisposing syndromes, with particular emphasis on diagnostic, prognostic and therapeutic implications, which can help the clinical management of these rare diseases.

Keywords: Syndromic GIST, Hereditary GIST, Familial GIST, PDGFRA-mutant syndrome, Carney’s triad, Carney-Stratakis syndrome, Succinate dehydrogenase, germline mutations

Background

Gastrointestinal (GI) stromal tumors (GISTs) are the most common GI mesenchymal neoplasms [1, 2]. They generally express KIT (CD117) and DOG1, similar to interstitial cells of Cajal (ICC) [3, 4].

GISTs have been a paradigm of molecular targeted therapy since they revealed activating KIT mutations [5], leading to the successful employment of the tyrosin kinase (TK) inhibitor (TKI) imatinib [6]. Since then, besides KIT mutations (~% of cases), GISTs have revealed other possible triggers: platelet-derived growth factor (PDGF) receptor α (PDGFA) mutations (~7 %), succinate dehydrogenase (SDH) complex deficiency (~5 %, half of which depending on mutations of SDH subunits), and mutations of BRAF (2 %) or neurofibromatosis type 1 (NFI) (1, 5 %). This heterogeneity implies different pathogenic, diagnostic and prognostic features characterizing distinct GIST subgroups, entailing diverse therapeutic approaches [1].

All of these pathogenic mechanisms but BRAF mutations have been rarely described to involve the entire organism, causing syndromes featuring multiple GISTs and peculiar associated signs. The resulting repertoire of syndromic GISTs constitute ~3-4 % of GISTs. Within them, NF1-associated GISTs prevail [1]. Much rarer are GISTs hinging upon germline KIT or PDGFA mutations, with <50 kindreds/individuals described [7–48].

An overall favorable prognosis has been attributed to GISTs when multiple (including syndromic ones), no matter their number/phenotype [27]. However, despite the relatively high fraction of indolent GISTs due to NF1 or SDH-deficiency, “multiple GISTs” is a crucible where heterogeneous conditions merge in, differing in pathogenesis, prognosis and therapy. The approach to syndromic GISTs must therefore be personalized, considering the characters of both individual tumors,
influencing their own natural history, and of the background syndrome, defining peculiar clinical settings.

GIST-predisposing syndromes will be herein reviewed, emphasizing inherent diagnostic, prognostic and therapeutic implications. Additionally, pertinent fundamentals of GIST pathogenesis will be recalled.

Features of GIST-predisposing syndromes

**KIT mutant syndrome**

KIT is a transmembrane type III TK receptor (TKR), whose gene is mapped to 4q12. Physiologically, KIT activation follows homodimerization upon stem cell factor (SCF) binding. Mutated KIT homodimerizes in a ligand-independent way. Activated KIT initiates RAS/MAPK, PI3K/AKT/mTOR and JAK/STAT3 signaling [49–51] (Fig. 1).

At the best of my knowledge, germline KIT-mutant GISTs have been described in 31 kindreds and 6 individuals without familial history [7–44]. Additionally, ungenotyped kindreds with signs coherent with KIT-dependent familial GISTs have been described prior to the discovery of KIT role in GISTs [52–55].

Average age-at-diagnosis of germline KIT-mutant GISTs anticipates that of sporadic cases of ~10 years: late forties/early fifties versus early/middle sixties [20, 29, 56–58]. This is true also if, in case of KIT-mutant kindreds, only the first individuals diagnosed with GIST (or GIST-compatible tumors in “pre-KIT era”) are considered, resulting in a 48-year mean, not influenced by familial screening. This anticipation likely parallels the early GIST trigger intrinsic to the connatal KIT mutation. The probability of GIST diagnosis in germline KIT-mutants increases with age, raising from 0.077 before the age of 40 to 0.462 by the age of 50 [29]. The age-at-diagnosis decrease reported in successive generations [17] is possibly due to subclinical GISTs diagnosed at screening.

**KIT**-mutant syndrome features no sex predilection, as expected given its autosomal dominant inheritance. Penetrance for GISTs is high [13, 20], unlike that for altered skin pigmentation [29].

Familial KIT-mutant GISTs occur along the whole GI tract (especially in small bowel/stomach), featuring a spindle, epithelioid or spindle-and-epithelioid citology (with the former prevailing), commonly expressing CD117 and DOG1 (Table 1), similar to their sporadic counterparts.

As shown in Table 1, other features of germline KIT mutants include: diffuse ICC hyperplasia (ICCH) (with related peristalsis disturbances), skin pigmentation alterations and mast-cell disorders. Sporadically, melanoma, non-GIST stromal tumors and breast cancer have been

![Fig. 1](image.png)

**Fig. 1** Molecular triggers and intracellular pathways involved in syndromic GIST arousal. Syndromic GISTs reported so far hinge upon alterations of one of the following (evidenced with a halo): KIT, PDGFRA, neurofibromin or SDH. KIT and PDGFRA activation initiates a downstream signaling involving multiple pathways: RAS/RAF/MEK/ERK (MAPK) (left, green hue); JAK/STAT3 (centre, blue hue); and PI3K/AKT/mTOR (top right, yellow/brown hue), stimulating oncogenic gene transcription or protein synthesis. In NF1-associated GISTs, tumoral inactivation of the WT neurofibromin impairs its RAS inhibiting effect, resulting in the activation of MAPK cascade downstream to KIT and PDGFRA. Impairment of the SDH enzymatic complex prevents succinate conversion to fumarate. Accumulated succinate inhibits prolyl-hydroxylase; the missed hydroxylation of HIF1-α prevents the degradation of this molecule which, consequently, heterodimerizes with HIF1-β and translocates into the nucleus acting as an oncogenic transcription factor. Furthermore, succinate accumulation inhibits TET DNA hydroxylases resulting in impaired conversion of 5-methylcytosine to 5-hydroxymethylcytosine, required for DNA demethylation, thereby influencing gene expression.
| Reference | Type of report | Mutant exon (mutation) | GIST | Other manifestations |
|-----------|----------------|------------------------|------|----------------------|
| Nishida et al. [7] | family | 11 (p.V560del) | SI, M | Perineal hyperpigmentation |
| O’Brien et al. [8]; Hirota et al. [9]; Chen et al. [10] | family | 11 (p.W557R) | SI, M | yes yes |
| Isozaki et al. [11]; Handra-Luca et al. [12]; Bachet et al. [13] | family | 13 (p.K642E) | ST, SI, M | yes yes |
| Maeyama et al. [14] | family | 11 (p.V559A) | ST, SI, S, E, M | yes yes |
| Beghini et al. [15] | family | 11 (p.V559A) | ST, SI, S, M | yes yes |
| Hirota et al. [16] | family | 17 (p.D820Y) | ST, SI, M | yes |
| Robson et al. [17] | family | 11 (p.W557R) | ST, SI, S, M | yes yes |
| Antonescu et al. [18] | individual | 11 (p.W557R) | ST, SI, S | yes |
| Carballo et al. [19] | family | 11 (p.L756_P577InsQL) | ST, SI, S | yes |
| Li et al. [20] | family | 11 (p.V559A) | ST, SI, S | yes |
| Tarn et al. [21] | family | 11 (p.D579del) | ST, M | yes |
| Hartmann et al. [22] | family | 8 (p.D419del) | SI, M | yes |
| Kim et al. [23] | individual | 11 (p.V559A) | SI, S, M | yes |
| O’Riain et al. [24] | family | 17 (p.D820Y) | ST, SI, ICV, M | yes yes |
| Miettinen et al. [25]; Lasota and Miettinen [26] | family | 11 (p.D579del) | SI, A, C, NS | | |
| Kang et al. [27] | family | 11 (p.V560G) | SI, NS | yes |
| Kang et al. [27] | individual | 11 (p.V559A) | SI, NS | yes |
| Graham et al. [28] | individual | 13 (p.K642E) | NS | yes |
| Ricci Hereditary Cancer in Clinical Practice (2016) 14:15 | | | | |
| Kindreds and individuals affected by gastrointestinal stromal tumors associated with germline KIT mutations (Continued) |
|---|
| Kleinbaum et al. [29] family 11 (c.D579del) | E, ST, SI, R | S | yes | yes | Hyperpigmentation, nevi |
| Woźniak et al. [30] family 11 (p.Q575_577delinsH) | R | S, M | yes | Constipation |
| Thalheimer et al. [31] family 17 (p. N822Y) | ST, SI, A, R | S | yes | yes |
| Campbell et al. [32] family 11 (NS) | ST, SI, C | NS | yes | yes | Dysplastic nevi, lentigines, darkening of labia minora pudendi |
| Veiga et al. [33] family 17 (p.D820Y) | ST, SI, R | NS | yes | 1 endometrial stromal sarcoma |
| Kuroda et al. [34] family 11 (p. V559A) | ST, SI, C | S | yes | Hyperpigmentation of external genitalia and axilla |
| Vilain et al. [35] family 13 (p. K642E) | ST, SI | S' | yes | Hyperpigmentation (multiple nevi in the axillae and trunk and spontaneously resolving childhood facial hyperpigmentation) and hypopigmentation consistent with WS type 2 |
| Nakai et al. [36] family 11 (p. Y553K) | ST, SI, C | NS | yes |
| Wadt et al. [37] family 13 (p.K642E) | ST, SI | NS | yes | yes | 1 breast cancer |
| Speight et al. [38] individual 9 (p.K509I) | SI | S | yes | yes | Mastocytosis |
| Bachet et al. [13] family 13 (p.K642E) | ST, SI, C, R | S | yes | Lentigines and nevi |
| Bachet et al. [13] family 13 (p.K642E) | ST, SI | S | yes | Multiple lentigines on face, neck, chest, back, axillae, legs |
| Neuhann et al. [39] family 11 (p.L576P) | ST, SI, C | S | yes | Achalasia, dysphagia |
| Yamanoi et al. [40] individual 13 (p.K642T) | ST, SI | S | yes | Dysphagia |
| Kindreds and individuals affected by gastrointestinal stromal tumors associated with germline *KIT* mutations (Continued) |
|---|
| Adela Avila et al. [41] | family | 11 (p.V559A) | SI | S | Diffuse melanosis, generalized lentiginosis, palmar crease hyperpigmentation | Dysphagia |
| | Jones et al. [42] | family | 11 (p.D579del) | ST, SI | S |
| | Jones et al. [42] | family | 11 (p.D579del) | ST, SI | S |
| | Bamba et al. [43] | family | 11 (p.V560del) | ST, SI | S |
| | Forde et al. [44] | family | 11 (p.D579del) | ST, SI | NS | Skin hyperpigmentation | Dysphagia |

* a Esophagus, ST stomach, SI small intestine, ICV ileocecal valve, A appendix, C colon, R rectum, NS not specified
* b S spindle cell, E epithelioid, M mixed spindle cell and epithelioid, NS not specified
* c M, GIST metastases
* d Diffuse Intersitial cell of Cajal hyperplasia
* e inferred from the mention of intestinal obstruction
* f inferred from published microphotographs
* g not specified in the referred paper; inferred from the diagnosis of "neurofibromatosis" previously made in several of the family members
* h café-au-lait macules were reported in one of the individuals originally thought to have neurofibromatosis; this could have influenced the term used
* i NS, not specified
* j Waardenburg syndrome
signaled. KIT mutations could be implied in the arousal of the former [49]; the latter two are likely incidental. Sometimes, non-GIST signs are the first reason for patients to seek medical help [15, 32, 35, 41, 44].

Skin pigmentation defects mostly occur in excess; nevertheless, hypopigmentation has been reported [28, 35]. Of note, lentigines and vitiligo can coexist [20]. Finally, pigmentation alterations consistent with Waardenburg syndrome type 2 have also been reported in the absence of pathognomonic mutations, candidating the detected KIT variant among the possible causes of this disease [35].

The role of KIT in ICC development and gut motility regulation, and in the development and neoplastic transformation of melanocytes and mast cells [49], explains some of the germline KIT-mutants’ features. Conversely, the variable manifestations of these signs have not been satisfactorily justified. In particular, the suggested association between dysphagia and KIT TK II domain mutations and the inability of KIT TK I domain mutations to affect skin pigmentation [11, 16] proved wrong [13, 28, 35]. Acute myeloid leukemia, seminoma/dysgerminoma and sino nasal NK/T-cell lymphoma, neoplasms related to KIT mutations (often in exon 17) [49], at the best of my knowledge have never been described in germline KIT-mutants (curiously, some familial germ-cell tumors revealed somatic KIT mutations [59]). K559I and D816V KIT mutations, found in GISTs, can cause familial mastocytosis without detectable GISTs [38, 60–63]. Thus, genotype-phenotype correlation appears loose [39].

KIT mutations in sporadic GISTs cluster in exons 11, 9, 13, 17 and 8, with a frequency of ~65%, ~8%, ~1%, ~1% and <1%, respectively [2, 64]. In germline mutants, however, the KIT mutational spectrum differs (Table 1). In fact, focusing each single GIST oncogenic mutation arousal (counting each KIT-mutant kindred as one): 1) mutations involve exon 9 in 1/37 (3%) and exon 17 in 4/37 (11%) cases; 2) among exon-11 mutations, substitutions (61%) prevail over deletions and insertion/deletions (29%) (reversing the 31% of proportion found in sporadic GISTs); 3) KIT exon-11 mutations appear enriched in p.V559A, p.W557R and p.L576P substitutions (48%, versus 10% of sporadic GISTs) [58]. These differences suggest a selection of favorable genotypes in germline mutants, possibly less life-threatening, because: 1) exon-9 mutations proved aggressive in imatinib-naive GISTs; 2) exon-17 mutations appear more favorable than exon-11 ones [65]; 3) 5’-end exon-11 mutations, especially deletions, are likely biologically severe [30]; 4) sporadic GISTs with exon-11 substitutions or duplications revealed smaller than those with exon-11 deletions, and the former featured lower mitotic rates, supporting a lower biological impact of exon-11 substitutions; 5) GISTs bearing p.V559A, p.W557R and p.L576P mutations tend to feature better relapse-free survivals [58].

The first step of GIST tumoral progression in germline KIT-mutants is ICCH. “ICCH” and “micro-GIST” are terms applied to a variety of microscopic/tiny CD117+ cell lesions. Despite gross dimensional criteria have been proposed for separating them [66], a distinction between diffuse (ICCH) and nodular/focal (micro-GISTs) lesions prevails [2, 50]. Thus defined, ICCH is a non-neoplastic polyclonal lesion [10], constituting the only known GIST precursor. Subsequent events leading to overt tumors follow those found in sporadic GISTs: chromosomes 14 and 22 deletions [20], and loss of heterozigosity (LOH) involving the KIT wild-type (WT) allele at progression to malignancy [29]. The oncological impact of individual syndromic KIT-mutant GISTS is estimated using the parameters adopted for their sporadic counterparts [67]. Besides, germline KIT-mutant subjects may suffer frequent/severe gut occlusion/hemorrhage, due to the tumor numerosness.

KIT mutations alter KIT structure simulating SCF-binding induced activation (if in exons 8 and 9, coding for the extracellular, ligand-binding domain), or allowing the kinase activation loop to switch to activation (exon 11, juxtamembrane regulatory domain), or directly imparting an active conformation to TK domains (exons 13 and 17, intracellular ATP-binding region and activation loop, respectively). This explains the differences in imatinib sensitivity depending on the KIT-mutant exon [50], either germline or not. Relatively better results are achieved when mutations occur “upstream” to the imatinib targeted site (i.e. in KIT exons 8, 9 and 11; for the rare exon 8 mutations evidences are limited [22, 64]), while the highest resistance rates are found in exon-13 and 17 mutations [50].

Table 1 details the features of the published germline KIT mutant kindreds/individuals manifesting GISTs.

**PDGFRA-mutant syndrome**

PDGFRA is a type III TKR whose gene is mapped to 4q12 [51], probably sharing with KIT a common ancestor [68]. PDGFRA is physiologically activated through binding to all PDGFs except PDGF-DD [69], triggering the same pathways elicited by KIT [50] (Fig. 1), albeit differentially activating PI3K/AKT/mTOR over RAS/MAPK [70]. Coherently, activating mutations of PDGFRA and KIT can raise similar tumors and are usually mutually exclusive.

At the best of my knowledge, germline PDGFRA-mutant GISTS have been signaled in two kindreds and in an individual without familial history [45–48]. A PDGFRA-mutant family bearing intestinal tumors defined as GISTS, but lacking GIST hallmarks except PDGFRA status, has also been reported [71]; these tumors are probably fibrous tumors, possible variants of another GI
**Table 2** Kindreds and individuals affected by PDGFRAR-mutant syndrome

| Reference          | Type of report (family vs. single individual) | Mutant exon (mutation) | Associated signs | GIST | Site | Histology | IFP | GI fibrous tumors | GI lipomas | Large hands | Other manifestations |
|--------------------|----------------------------------------------|------------------------|------------------|------|------|-----------|-----|------------------|------------|-------------|----------------------|
| Chompret et al. [45]| family                                       | 18 (p.D846F)           | ST               | M    | (mainly E) | yes       | ST F | yes              | yes        | yes         | Broad wrists, glaucoma |
| de Raedt et al. [71]; Heimann et al. [78] | family                                       | 12 (p.Y555C)          | ST               | M    | (mainly E) | yes       | ST F | yes              | yes        | yes         | yes                  |
| Pasini et al. [46]; Carney and Stratakis [47] | individual                                   | 12 (p.V561D)          | ST               | M    | (mainly E) | yes       | ST F | yes              | yes        | yes         | yes                  |
| Ricci et al. [48] | family                                       | 14 (p.P653L)          | ST               | E, M | (mainly E) | yes       | ST F | yes              | yes        | yes         | ref                 |
| Ricci et al. [72] | Individual (mother and grandmother suffered a gut occlusion) (likely related to the above mentioned kindred [48]) | 14 (p.P653L)         | SI               | S    | yes       | (bearing a concomitant somatic KIT mutation) | yes | yes              | yes        | yes         | ref                  |

*SI: Small intestine, ST: Stomach
*E: Epithelioid, M: Mixed spindle cell and epithelioid, S: Spindle cell
*ST: Stomach
*IFP: Inflammatory fibroid polyp
*Math: Mutation may be a variant of IFP [48]
*Ref: When a germline PDGFRAR mutation was found in the referred kindred, these tumors were considered GISTs since GISTs were the only PDGFRAR-mutant GI tumors known at that time
intermediate risk (exon 14) and another probably at high risk (exon 18-non-p.D842V) [65]. Besides, PDGFRA exon-14 mutations proved prognostically favorable in another work [81]. Similarly to KIT-mutant GISTs (counting each kindred as one, and considering the recently reported p.P653L individual [72] as a member of a previously published PDGFRA-mutant family [48] given the identity of both genetic defect and geographical origin), with the caveats of the limited sample, PDGFRA mutation distribution differs in germline mutations with respect to sporadic GISTs, with exon 18 involved in 25 % (Table 2) and 82 % [65] of cases, respectively. Germline-mutants appear enriched in presumably low-biological-impact mutations [65], with low molecular risk exon-12 ones found in 50 % of cases.

Germline PDGFRA-mutant GISTs feature 14q LOH [46], similar to sporadic, germline KIT-mutant and NF1-associated ones.

In PDGFRA-mutant kindreds, small bowel occlusions due to IFP can be life-threatening. Of note, only one individual died of malignancy possibly related to GIST described as “gastric cancer” in the absence of pathological records [48], coherently with the relative indolence of PDGFRA-mutant GISTs [82]. In need of treatment, however, TKI use must be pondered, evaluating the specific mutation present. In fact, although never reported in germline-mutants, p.D842V, the most common PDGFRA mutation of sporadic GISTs, confers resistance to both imatinib and the second-line TKI sunitinib, justifying alternative approaches using dasatinib and crenilanib [83–85].

Table 2 details the features of published PDGFRA-mutants syndrome cases.

**NF1-associated GISTs**

Neurofibromin, encoded by NF1 gene on 17q11.2 [51], accelerates the conversion from active GTP-bound to inactive GDP-bound RAS. NF1 inactivation stimulates MAPK cascade through increasing RAS activity [50], promoting tumorigenesis (Fig. 1).

NF1 is relatively common, with a ~13,000 birth incidence and a 1:4–5,000 prevalence [86]. NF1 transmission is autosomal dominant with complete penetrance and variable expression. ~50 % of NF1 lack familial history due to the high human NF1 mutation rate. In NF1, one NF1 allele is germline-mutant, the other displays tumoral somatic inactivation.

National Institutes of Health NF1 diagnostic criteria consist of ≥2 among: ≥2 café-au-lait macules >5 mm or >15 mm in pre-pubertal or post-pubertal subjects, respectively; ≥2 neurofibromas (one if plexiform); axillary/inguinal freckles; optic glioma; ≥2 iris hamartomas; bony dysplasia; and a NF1-affected first-degree relative [87]. 0.1-6 % of NF1 feature parangangiomas [88].

Clues of a possible association between NF1 and GIST have been known for decades [89]. As differential diagnosis between neurofibroma (NF) and GIST was made reliable [90], this association became evident. GISTS are the most frequent GI NF1 manifestation with a 7 % prevalence in NF1 patients, increasing to 25 % at autopsy. NF1 is >45-fold overrepresented among GIST patients. Coherently, NF1-mutated GISTS account for ~1.5 % of all GISTS. Average age-at-diagnosis of NF1-associated GISTS is ~49 years [1, 86, 91, 92].

NF1-associated GISTS are often multiple and small intestinal, with possible gastric exceptions (NF1 frequency is 6 %, 4 % and 0.06 % among patients with duodenal, jejunal/ileal and gastric GISTs, respectively); singly considered, they do not differ from sporadic intestinal GISTS, mostly featuring spindle cells, collagen globules (skeinoid fibers) and CD117 positivity [91]. Other NF1 GI lesions include: ICCH, with related GI motility disorders, and neuroendocrine tumors (especially periampullary somatostatinomas) [86]. The awareness of these GI signs can help to avoid diagnostic omissions caused by the variable clinical presentation and frequent non-familial form of NF1 (the lack of NF1 mutational hotspots makes genotyping an unpractical diagnostic tool) [86].

The discovery of NF1 second-hit in NF1 GISTS, already revealed peculiar because of their usually WT KIT/PDGFRα [91, 93], disclosed their pathogenesis and molecular link with NF1 [94]. KIT/PDGFRα mutations in NF1-associated GISTS are nevertheless possible, although probably incidental [95], globally accounting for ~8 % of cases [96].

NF1 GIST tumoral progression resembles that of germline KIT mutants, featuring peneplasticic ICCH followed by 14q and 22q LOH [97].

Although mostly indolent, ≤15-20 % of NF1 GISTS behave aggressively [91, 93]. NF1 GISTS are poorly responsive to imatinib, since NF1 trigger occurs downstream to imatinib targets KIT/PDGFRα; coherently, NF1 GISTS should not be treated with adjuvant imatinib, whatever their risk [98–100].

**Syndromic SDH-deficient GISTS**

SDH is a 4-subunit (A/B/C/D) Krebs cycle enzymatic complex, located in the inner mitochondrial membrane, but encoded by chromosomal DNA. SDHA/B/C/D (collectively, SDHx) are mapped to 5p15.33, 1p36.13, 1q23.3 and 11q23.1, respectively [51]. Whatever subunit is damaged, the entire complex is hampered, impairing succinate-to-fumarate conversion; succinate accumulation inhibits prolyl-hydroxylase, decreasing the hydroxylation of hypoxia-inducible factor (HIF)-1α (HIF-1α) and its consequent degradation; HIF heterodimers can thus translocate into the nucleus initiating tumorigenic transcription. Furthermore, succinate accumulation
inhibits TET DNA-hydroxylases, compromising the 5-methylcytosine conversion to 5-hydroxymethylcytosine, required for DNA demethylation; coherently, SDHx-deficient GISTs feature pervasive DNA hypermethylation, likely implied in oncogenesis [101–105] (Fig. 1).

SDH-deficiency characterizes the largest KIT/PDGFRA-WT GIST subgroup (accounting for ~5 % of GISTs) [1]. SDH deficiency is also a feature of paragangliomas, renal cell carcinomas and pituitary adenomas [106, 107]. SDH-deficient GISTs arise either in germline SDHx-mutant and/or manifest syndromic settings or not [105, 108]. Thus, not surprisingly, in case of constitutive predisposition to SHD-deficiency, GISTs can associate with paragangliomas producing two syndromes: Carney's triad (CT) and Carney-Stratakis Syndrome (CSS), both affecting young people (mean ages-at-diagnosis 22 and 19 years –22 and 24 years concerning GIST only-, respectively) [109–111]. CT and CSS are separated by the presence of pulmonary chondromas and of a striking female predilection in the former, and of an autosomal-dominant inheritance pattern in the latter, with incomplete penetrance [111]. Additionally, CT may feature esophageal leiomyoma and adrenal cortical adenoma [110]. SDH-deficient GISTs are restricted to stomach (especially antrum) and show a multinodular pattern (referred to as “plexiform” by pathologists) [103, 110]. ±50 % and ≤10 % of SDH-deficient GISTs manifest lymph-vascular invasion and lymph node metastases, respectively [112], explaining the frequent relapses despite apparently radical surgery.

SDH-deficient GIST are mostly at least-in-part epithelioid, and express DOG1, CD34 (≥75 % of cases) and CD117 (strongly/diffusely, unlike PDGFRα-driven GISTs) [103, 110]. They are peculiarly SDHB-, whatever the damaged SDH subunit (unlike SDHA positivity, lost only in SDHA-mutations), and overexpress insulin-like growth factor 1 receptor (IGF1R) [103, 113–115]. Only micro GISTs have been found to precede overt SDH-deficient syndromic GIST [116]. ICCH is not a feature of CT [110], nor has ever been described in SDH deficiencies.

The basis of SDH impairment in CSS is mutational, with a typical second-hit mechanism involving SDHβ/C/D [117, 118]. Significantly, germline SDHA mutations, described in patients bearing GISTs or paragangliomas and in paraganglioma/pituitary adenoma familial associations, are unreported in CSS, possibly due to their low penetrance [106, 108, 115, 118–125]. Of note, at the best of my knowledge, the only SDHD-mutant CSS with a reported pedigree hinged on a paternally inherited defective allele [126], coherently with the parent-of-origin effect of SDHD depending hereditary paraganglioma syndrome PGL1, simulating maternal imprinting. However, SDHD lacks physical imprinting and PGL1 is exceptionally maternally transmitted, invoking the involvement of a second, paternally imprinted, tumor suppressor gene (TSG) (possibly H19) located on 11p15, i.e. the same chromosome of SDHD. Both WT SDHD and functional 11p15 TSG can thus be inactivated by non-disjunctional loss of the maternal chromosome 11, justifying the paternal disease transmission. More complex events, such as mitotic recombination of 11p15 TSG followed by loss of the paternal chromosome, would explain the exceptional maternal transmission [127–129].

Unlike CSS, CT tumorigenesis depends on epigenetic tumoral SDHC inactivation through SDHC hypermethylation [130]. This phenomenon, distinct from the global DNA hypermethylation of SDH-deficient GISTs as a whole, is common to most SDH-deficient, SDHx-WT GISTs, irrespective of CT presence; however, “non-CT” cases could be formes frustes of CT, as suggested by the mosaic constitutional SDHC promoter hypermethylation, implying a risk for metachronous paraganglioma/pulmonary chondroma [105].

Another oncogenic stimulus of SDH deficient GISTs is the hyperactivation of the IGF1R pathway, physiologically involved in cell survival/proliferation [113, 131]. ≥50 % CT GISTs do not bear chromosomal imbalances; their rare LOHs preferentially involve 1p; 14q or 22q losses occur infrequently [132]. SDH-deficient GISTs often behave indolently, even in case of metastases, probably due to the metabolic disadvantage caused by SDH deficiency. They can nevertheless be aggressive (the SDH-deficient GIST overall mortality approaches 15 %). Of note, current risk classifications do not fit SDH-deficient GISTs [110, 112].

TKI imatinib and sunitinib proved ineffective or only partially effective, respectively, in SDH-deficient GISTs, coherently with SHD deficiency constituting a pathway independent of KIT/PDGFRα. Therefore, in the absence of guidelines specific for these tumors, TKI treatment is suggested for progressive disease but not after complete surgical resection [98–100, 112]. Inhibitors of IGF1R are being evaluated: testing of linsitinib in adult and pediatric WT GISTs (enriched in SDH-deficient GISTs), although without evidence of RECIST response, indicates a 45 % clinical benefit/52 % progression-free survival at 9 months [133]. When compared to KIT-mutant GISTs, a higher fraction of KIT/PDGFRA-WT (and PDGFRα-mutant) GISTs displayed activation of the mTOR pathway [70]; Therefore, CT/CSS GISTs can potentially benefit of PI3K/AKT/mTOR inhibitors [131]. Regorafenib, nilotinib, sorafenib and heat-shock protein inhibitors are other drugs potentially usable; finally, targeting of HIF-1α, α-ketoglutarate, and demethylating agents such as decitabine are theoretically attractive approaches [104, 105, 134–136].
CSS should be readily distinguishable from CT based on the presence or not of pulmonary chondromas, germline SDHB/C/D mutations and inheritance; female predilection of CT is another helping feature [137]. However, the arousal of tumors in SDH-deficient syndromes, including CT and CSS, can span over dozens of years [112]. Thus, if the “missing” tumor of a CT is pulmonary chondroma, CT/CSS morphologic differential diagnosis is impossible. Under these circumstances, in the absence of familial history, genotyping becomes pivotal. But recent findings have eroded also this cornerstone, evidencing germline SDHA/B/C variants, at least part of which pathogenic, in 6/63 (9.5 %) CT patients “certified” by pulmonary chondromas. On top of that, unlike typical CT, these patients were equally distributed between sexes [138]. Additionally, three males diagnosed with CT (one with a lesion “consistent with pulmonary chondroma”) were subsequently found to bear germline SDHx mutations [105, 139]. Noticeably, CT diagnosis in these cases appears questionable, with genotype and sex distribution rather supporting CSS.

GISTs could be also considered an infrequent component of SDH-deficient paraganglioma syndromes PGL1/3/4/5 [140], depending on SDHD/C/B/A germline mutations, respectively [141]. A risk of WT SDHx allele loss lower in GIST precursor cells than in paraganglial ones could explain the relative GIST rarity [112]. Noticeably, associations between GIST and renal cell carcinoma, another SDH-deficient tumor reported in paraganglioma syndromes, has been found in germline SDHA/B/C mutants [141–144].

Perhaps CT, CSS and PGL1-5 will be reconsidered in the future as different aspects of a single SDH-deficient disease.

Practical approach to GIST-predisposing syndromes
GIST-prone syndromes must be suspected in the presence of GISTs either multiple or associated with the peculiar manifestations previously described (which can raise suspicions even by themselves) (Table 3). Genotyping, if applicable, is confirmatory. NCCN guidelines suggest to investigate every KIT/PDGFRA-WT GIST patient for germline SDHx mutations [84]. Multiple GISTs sharing a phenotype not found in the germline favor a metastatic condition.

Comprehensive guidelines specific for the management of GIST-prone syndromes are lacking. Existing recommendations, dealing with adjuvant therapy of NF1-associated and SDH-deficient GISTs [99], have been treated in the pertaining chapters of this review.

Once a patient is diagnosed with a GIST-predisposing condition depending on a germline DNA defect, predictive genetic testing in family members should be considered. The latter is indicated for the highly penetrant germline KIT/PDGFRA/SDHB/SDHD mutations; conversely, the opportunity of genetic evaluation is controversial for the low penetrance SDHC and, especially, SDHA variants [141]. It is worth recalling the parent-of-origin effect of familial SDHD mutations, herein previously discussed.

Periodic computed-tomography-scan or 18F-FDG PET-computed-tomography have been suggested for the surveillance of syndromic GISTs [145]. Endoscopic ultrasound joined to fine needle tissue acquisition allowing histological assessment [146, 147] appear valid complements. Colonoscopy is expectedly of limited utility in familial KIT-dependent GISTs [29] (mostly gastric/small intestinal) and useless in SDH-deficient ones (strictly stomach restricted), while can detect colonic/ileal IFPs in PDGFRA-mutant syndrome [48]. In case of SDH-deficient GISTs, chest X-ray is indicated to look for pulmonary chondromas (especially if SDHx-WT), and plasma/urine determination of metanephrines/catecholamines and PET-tracers 68Ga-DOTATATE, 18F-DOPA and 18F-FDA can be used for investigating paragangliomas [141].

Intracellular signaling machineries and gene expressions are common to homologous syndromic and sporadic GISTs [20]. Coherently, no differences in imatinib sensitivity exist between GISTs sharing the same genotype, no matters whether somatic or germline [98]. Thus, the approach to individual syndromic GISTs in need of treatment does not differ from that to their sporadic counterparts.

There is no evidence that GIST hereditary predispositions constitute an independent prognostic factor warranting a differential GIST treatment [145]. Nevertheless, the frequent multiplicity of GI tumors constitutes a problem peculiar to GIST-syndromes deserving a special attention, commonly causing acute complications such as hemorrhage and, especially in germline KIT/PDGFRA mutations and NF1 (where the small bowel can be involved), occlusion/perforation which can be life-threatening [13, 43, 48]. Although surgery is frequently necessary as affected patients are often symptomatic [13], no agreement exists as to whether preventive therapy, either surgical or molecularly targeted, is indicated in asymptomatic subjects [145]. It has been suggested to postpone surgery based on the frequent indolence of germline-mutant GISTs [148]; however, the latter’s possible aggressiveness recommends to remove GISTs at presumable significant risk, based on size/site/genotype. Similarly, lesions at risk of occlusion/hemorrhage should be removed too. Surgery should focus on resecting the outstanding tumor(s) disregarding possible tiny nodules if numerous and involving extended areas, since their removal would sacrifice substantial portions of functional GI tissue without proven benefit in terms of tumor recurrence risk; this is particularly true in
| Syndrome                        | Trigger                      | Inheritance                                  | Sex predilection | Average age at diagnosis (years) | Site Morphology | Immunohistochemistry | Other manifestations                                      |
|--------------------------------|------------------------------|----------------------------------------------|------------------|---------------------------------|----------------|----------------------|----------------------------------------------------------|
| KIT-mutant                     | germline KIT mutation        | Autosomal dominant, high penetrance          | None             | 48                              | SI, ST > C, R > E | S > M > E            | CD117+ DOG1+ Skin hyperpigmentation, mast cell disorders, ICCH, dysphagia |
| PDGFRA-mutant                  | germline PDGFRA mutation     | Autosomal dominant, high penetrance          | None             | 48 (GIST), 41 (inflammatory fibroid polyp) | ST             | E, M                 | CD117+/− DOG1+/− Inflammatory fibroid polyps (including GI, “fibrous tumors”), GI lipomas, large hands |
| Neurofibromatosis type 1       | Germline NF1 mutation + tumor 2nd hit in WT allele | Autosomal dominant, complete penetrance and variable expression | None             | 49                              | SI > ST          | S > M                 | CD117+ DOG1+ Neurofibromas and other signs of Neurofibromatosis type 1, ICCH, dysphagia |
| SDH-deficient syndromes        | epigenetic SDHC promoter hypermethylation in tumors | None<sup>1</sup>                              | F > M            | 22 (either whatever tumor type or GIST) | ST             | E > M, S, plexiform | CD117 + DOG1+ Parangliomas/pheocromocytomas, pulmonary chondromas, esophageal leiomyoma, adrenal cortical adenoma  |
| CSS<sup>2</sup>                | Germline SDH8, C or D mutation + tumor 2nd hit in WT allele | Autosomal dominant, incomplete penetrance. Parent-of-origin if SDHD-mutant | None             | 19 (whatever tumor type), 24 (GIST) | ST             | E > M, S, plexiform | CD117 + DOG1+ Parangliomas/pheocromocytomas          |

<sup>a</sup> E esophagus, ST stomach, SI small intestine, C colon, R rectum
<sup>b</sup> S spindle cell, E epithelioid, M mixed spindle cell and epithelioid
<sup>c</sup> Diffuse Intestinal cell of Cajal hyperplasia
<sup>d</sup> GI, gastrointestinal
<sup>e</sup> Carney's triad
<sup>f</sup> Recently reported 6 germline SDHx-mutant cases, one of which with inherited parangliomas
<sup>g</sup> Carney-Stratakis syndrome
CT and CSS patients, given their frequently young age [109]. Preventive molecular therapy poses several problems. In fact, although theoretically attractive, it is presently not evidence-based. Prospective clinical trials will be hardly achieved, given the rarity of syndromic GISTs. Moreover, the risks of lifelong exposures to GIST-targeted drugs are presently unknown. Thus, active surveillance has been adopted after surgery [44]. Alternatively, a long term preventive treatment with TKI in patients bearing a sensitive mutation has been proposed [13]. A compromise has been adopted by employing half-dose imatinib in a KIT exon-11 germline mutant with multiple GISTs, obtaining marked tumor reductions after one-year [43]. Interestingly, imatinib therapy has been reported to reduce cutaneous melanosis in germline KIT-mutants [32, 41].

Exceptionally, GISTs in syndromic contexts can reveal superimposed triggers [96, 149]. Anomalous GIST site and/or morphology with respect to a given hosting syndrome can help in suspecting these “divergent” GISTs, whose pathogenesis can hinge mainly or even exclusively upon the “extra-syndromic” molecular defect, with relevant clinical implications [72]. In any event, to be on the safe side it is advisable to fully genotype whatever apparently syndromic GIST to be molecularly treated, independently of its morphology and site.

Conclusions
The correct approach to syndromic GISTs results from the integration between congruent diagnostic strategies, including familial screening, and treatment of individual tumors and background syndromic manifestations. Protein signs prompt to undertake complex choices involving the treatment of asymptomatic lesions and the prevention of future complications. Specific comprehensive guidelines are lacking, primarily due to the rarity of syndromic GISTs. However, these diseases have been the subject of an increasing number of publications, resulting in a conspicuous amount of data with relevant clinical implications. The latter allowed the draft of the present review, which hopefully will help physicians facing GIST-prone syndromes, waiting for the development of dedicated guidelines.

Abbreviations
CSS, Carney-Stratakis syndrome; CT, Carney’s triad; GIST, gastrointestinal stromal tumor; ICC, interstitial cell of Cajal hyperplasia; IFP, inflammatory fibroid polyp; NF1, neurofibromatosis type 1; PDGF, platelet-derived growth factor; SCF, stem cell factor; SDH, succinate dehydrogenase

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Author’s note
During the review process and after acceptance of this manuscript, data relevant with respect to SDH-deficient GISTs, one of the main topics of the present review, have been published: 1) Ben-Ami et al. (Ben-Ami E, Barysuzkas CM, von Mehren M, Heinrich MC, Corless CL, Butynsiki JE, et al. Long-term follow-up of the multicenter phase II trial of regorafenib in patients with metastatic and/or unseetable GI stromal tumor after failure of standard tyrosin kinase inhibitor therapy. Ann Oncol. 2016; doi: 10.1093/annonc/mdw228) reported that regorafenib induced objective responses and durable benefit in SDH-deficient GISTs; 2) Boikos et al. (Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors. A report from the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol. 2016; doi: 10.1093/annonc/mdw228) propose genotype rather than presence or absence of chondromas as the discriminating factor between CT and CSS.

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