

Alessandro Perez and Daniele Fanale*

Department of Surgical, Oncological and Oral Sciences,
Section of Medical Oncology, University of Palermo, 90127
Palermo, Italy

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*Corresponding author: Daniele Fanale, Section
of Medical Oncology, Department of Surgical,
Oncological and Oral Sciences, University of
Palermo, Via del Vespro 129, 90127 Palermo, Italy,
E-mail: fandand@libero.it

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Review Article

Heredo-Familial and Pediatric GISTs: Spot the Differences

Abstract

Gastrointestinal stromal tumors (GISTs) are rare sporadic tumors that typically occur late in life, although they are the most common mesenchymal neoplasms of the gastrointestinal tract. GISTs are believed to originate from the Interstitial Cells of Cajal (ICC), a group of cells identified in the wall of the organs of the gastrointestinal tract, which act as a pace-maker for peristalsis and gut movements. However, familial and pediatric cases have also been reported. These rare subsets of GISTs have clinicopathological and molecular features different from their sporadic counterparts. Pediatric GISTs account for only 1% of all the identified cases of GISTs. Most of them lack the gain-of-function mutation in *c-KIT* or *PDGFRA* commonly found in adult cases, and may harbor mutations in other genes such as *SDH*. Gene expression profiling studies of pediatric GISTs show distinct molecular signatures, suggesting a unique origin as compared with adult GISTs. The review discusses also familial GISTs with germline *c-KIT* or *PDGFRA* gene mutations and variants harbouring no mutations in these genes such as Carney triad, Carney-Stratakis syndrome, and neurofibromatosis type 1. However, the initial phases of familial GISTs appear biologically similar to those of sporadic GISTs, with similar cytogenetic progression mechanisms and genic expression profiles.

Introduction

Gastrointestinal stromal tumors (GISTs) are rare tumors whose incidence has been recently clarified after the redefinition of the diagnostic criteria following the recognition of the peculiar immunohistochemical profile of these tumors [1]. These tumors were initially considered exceptional with an estimated incidence in the past of about 1.5 cases per 100.000 per year, but now this assumption is no longer accepted given a new estimated incidence more than ten times higher than that previously assumed; approximately 1,000 cases per year in Italy and almost 4500-5000 cases in USA [2,3]. GISTs represent less than 1% of all malignancies, but are the most common mesenchymal tumors of the gastrointestinal tract (0.1-3%) [4]. Their identification is relatively recent, since as a result of their myogen or neurogen pattern they were previously classified as leiomyomas, leiomyosarcomas, neurofibromas, and schwannomas [5]. GISTs are believed to originate from the Interstitial Cells of Cajal, a group of cells identified in the wall of the organs of the gastrointestinal tract, which act as a pace-maker for peristalsis and gut movements [6]. Data proving this relationship are based on similar histological profiles and above all on the common expression of certain antigens such as CD117, the product of the oncogene *c-KIT*, and myoid antigens. Although GISTs are well characterized histochemically, the data reported in literature until now are not much consistent at molecular level [7]. They may originate from any part of the gastrointestinal tract, but are more frequently found in the stomach (40-70%) followed by the small intestine (20-40%) [8]. Other sites are considered rare. Moreover, GISTs usually present as friable, non-capsulated masses ranging from 1-2 to more than 20cm wide and may present areas of necrosis and hemorrhage [9]. Histological findings usually showed a spindle cell pattern, resembling smooth muscle cells, an epithelioid pattern and occasionally a mixture of these. However, this distinction has no prognostic relevance [10].

In over 99% of cases they occur in the sporadic form, but there is a small percentage of heredo-familial GISTs characterized by germline mutations in different susceptibility genes. Specifically, these GISTs can be distinguished in two different forms: the familial form occurring when within the same family most subjects are affected by the same type of cancer and the hereditary form whenever it's demonstrated that susceptibility to the development of cancer is genetically transmitted from parents to children [11]. Familial tumors are due to a combination of risk factors such as inherited susceptibility genes and environmental factors, whereas hereditary tumors, which represent a subgroup of the familial forms, are caused exclusively by inherited genetic changes.

Biomolecular features of GISTs: c-KIT and PDGFRA

Molecular genetics has not only revealed the mechanism involved in the genesis of GIST but, also, gave us an immunophenotypic marker, the c-KIT protein [12]. The majority of GISTs (90-95%) show activating mutations of *c-KIT* with KIT/CD117 immunopositivity of approximately 95%. This marker allows then to deliver a very reliable diagnosis in 90-95% of cases [13,14]. *c-KIT* is an oncogene mapping on chromosome 4q12 and is composed of 21 coding exons [15]. The codifying sequence presents 4 mutational "hot spot" falling, in frequency order, in exons 11, 9, 13 and 17 [16]. KIT is a 145KD transmembrane glycoprotein with tyrosine kinase activity, a pivotal enzyme involved in development (differentiation) and cell growth (proliferation) [17]. In non-pathological conditions c-KIT is a receptor with TK activity that acts as a "cellular switch". Indeed, if activated from the interaction of its ligand (stem cell factor, SCF) with the extracellular portion of the receptor via dimerization, triggers the activation of an intracellular pathway that initiates a cascade of signals whose final aim is to increase proliferation, differentiation and inhibition of apoptosis [18]. More in detail, the binding of a SCF molecule with each of the c-KIT monomers gives rise to the

formation of a c-KIT dimer. The interaction of two adjacent receptors (homodimer) is specifically mediated by two molecules of SCF [19]. The homodimerization involves structural changes in the receptor with the activation of the intracellular tyrosine kinase that, firstly, catalyzes the auto-phosphorylation of specific tyrosine residues, which antagonizes the self-inhibition and is necessary for the transduction of the downstream signal triggered by the initial ligand-receptor interaction. The main activated pathways are PI3-kinase/AKT, RAS/RAF/MAPK and JAK/STAT [20-22]. In pathological conditions most of the mutations on this gene are responsible of spontaneous homodimerization that, ultimately, causes an uncontrolled activation with advantages in terms of proliferative and anti-apoptotic effects. To date, it has been well recognised that mutations in *c-KIT* are mainly responsible of the pathogenetic event (90% of cases), but they do not are the only cause [23,24]. Indeed, a percentage of GIST cases that show no mutations in *c-KIT* exhibits alterations in *PDGFRA* gene (platelet-derived growth factor receptor), with a mutually exclusive relationship. The codifying sequence contains 23 exons and preferred mutational “hot spot” falling in exons 12, 18 and 14 [25]. The gene sequence encodes for a molecule with tyrosine kinase activity with similar function to *c-KIT* [26,27]. Structurally, the receptor consists of three main portions:

1. An extracellular portion with the ligand binding sites, consisting of 5 Ig-like domains. In this region it is possible to recognize:
 - The ligand binding domain (consisting of 4 Ig-like domains) through which the ligand or growth factor specifically binds the receptor;
 - The dimerization domain, which is fundamental for the receptor activation.
2. A transmembrane portion.
3. A portion containing the intracellular tyrosine kinase activity, divided in two domains:
 - The juxtamembrane domain or autoinhibitory loop (encoded by the exon 11 and able to autoinhibit the kinase activity in the absence of the specific ligand) below the cell membrane;
 - The kinase domain (catalytic), which represents the active part of the receptor and has the biochemical properties required for transferring a phosphate group from ATP to a substrate. In particular, the TK1 domain contains the ATP binding site, while the TK2 domain contains the phosphotransferase activity [24,28,29].

A schematic representation of *c-KIT* and *PDGFRA* protein domains and the respective coding exons is showed in Figure 1.

Mutational “hot spots” in *c-KIT* and *PDGFRA*

More than 90% of GISTs carry activating mutations in the *c-KIT* gene (approximately 90-95% of cases) or less commonly in the *PDGFRA* gene (about 5-10% of cases) [30,31]. In *c-KIT* four mutational “hot spots” in exons 9, 11, 13 and 17 were identified. It exists a hierarchy for the mutations involved in GIST [32]. The most interested exon is the exon 11, in approximately 70-80% of new

cases, which encodes the “autoinhibitory loop”. This domain plays its autoinhibitory effect against the tyrosine kinase receptor [33,34]. Moreover, exon 9 is mutated in 10-20% of GIST. The exon 9 encodes for the fifth immunoglobulin-like domain of the receptor extracellular region. Unlike the aforementioned exons, point mutations in the exons 13 and 17 codifying for the tyrosine kinase domains of the receptor intracytoplasmic portion are detected with significant lower frequency (about 1.5%) [35,36]. The *PDGFRA* gene encodes for the platelet-derived growth factor receptor and shares with *c-KIT* about 35% of the amino acid sequence. This is a molecule with also a tyrosine kinase activity. The pathway that follows the activation of the receptor is basically similar to that of *c-KIT* [23,25]. The most frequent genetic alterations in *c-KIT* and *PDGFRA* including missense mutations as well as insertions and deletions are summarized in Tables 1, 2,

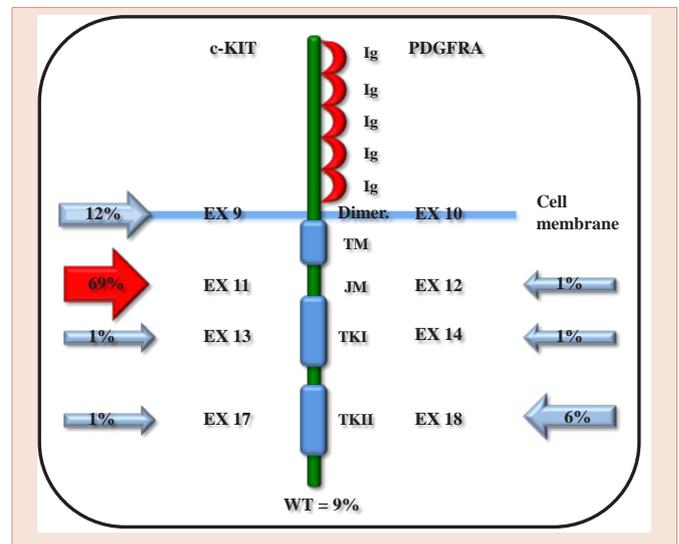


Figure 1: A schematic representation of *c-KIT* and *PDGFRA* protein domains and the respective coding exons.

| Table 1: The most frequent genetic alterations in <i>c-KIT</i> . | |
|--|---|
| <i>c-KIT</i> | Type of mutation |
| Exon 9 (transmembrane domain) | Insertion: p.Y503_F504insAY |
| | Missense: several |
| | Deletion: several |
| Exon 11 (juxtamembrane domain) | Deletion: W557del, V559del |
| | Missense: W557, K558, V559, V560, L576P |
| | Insertion: several |
| Exon 13 (TK1 domain) | Missense: K642E, V654A, T670I |
| | Deletion: S715del |
| Exon 17 (TK2 domain) | Missense: D816V, D820Y, N822K |

| Table 2: The most frequent genetic alterations in <i>PDGFRA</i> . | |
|---|------------------------------------|
| <i>PDGFRA</i> | Type of mutation |
| Exon 12 (juxtamembrane domain) | Insertion: several |
| | Missense: V561D |
| | Deletion: several |
| Exon 14 (TK1 domain) | Missense: K646E, N659K |
| Exon 18 (TK2 domain) | Missense: D842V |
| | Deletion: several at low frequency |

respectively. Moreover, since *PDGFRA* and *c-KIT* genes share a high amino acid sequence homology, the functional consequences of their alterations are similar. Indeed, in both cases the mutations can generate autophosphorylation, which triggers the activation of two main signaling pathways, the RAS-RAF-MEK-ERK and the PI3K-AKT-mTOR cascades, which leads to uncontrolled cell growth [25].

Tumor progression model in GIST

Activating mutations in *c-KIT* or *PDGFRA* are observed almost in the whole GIST cell population, while chromosome alterations are observed only in a percentage of neoplastic cells [37]. This suggests that mutations of *c-KIT* represent an early event, presumably, having a role in the initiation of the neoplastic transformation process, while subsequent cytogenetic abnormalities are involved in the neoplastic progression process [38]. Low grade GISTs have often a normal karyotype or only loss of chromosome 1p or 14 or 22 (50% of cases). High-grade GISTs are often accompanied by loss of at least 3 chromosomal portions (1p, 9p, 11p or 22p). Metastatic GISTs are characterized by loss in chromosome 9p often accompanied by gain in 5q, 8q, 17q and 20q. Loss of heterozygosity (LOH) of *c-KIT* and *TP53* and MSI downregulation are also frequent [39,23]. However, it must be emphasized that this sequence of events represents a simplification and that not all GISTs acquire genetic alterations in the aforementioned order [33].

About 10-15% of adult and pediatric gastrointestinal stromal tumors (GIST) do not show any activating mutation in *c-KIT* or *PDGFRA*. Indeed, it has been demonstrated that about 4% of wild-type GISTs show BRAF exon 15 mutation (V600E) [40]. It is widely reported that GISTs harboring activating *c-KIT* or *PDGFRA* mutations well respond to imatinib administration. This selective tyrosine kinase inhibitor is able to interfere with receptor activity by binding its ATP-binding pocket. However 80-85% of the cases seem to overcome drug efficacy becoming resistant to the treatment mainly due to the onset of secondary resistance. Indeed, an *in vitro* approach recently showed that imatinib-sensitive *c-KIT* mutated cells no longer respond to imatinib administration if *KRAS* or *BRAF* mutants are transfected [41].

Pediatric GISTs

Any GIST case diagnosed before the age of eighteen is defined as pediatric. The pediatric GISTs described until now represent between 1 and 2% of all cases of GISTs, and then represent rarely diagnosed tumors in youth. Basic research on GIST biology has been hampered by the rarity of this disease and by the lack of reliable experimental models [42]. Despite these limitations, the knowledge acquired through the study conducted in adults and other tumor types associated with them (eg. paragangliomas), in addition to the emergence of new methods (eg. microarrays techniques), allowed significant advances in the understanding of rare pediatric forms [43]. These pediatric forms may have a different pathogenesis than those seen in adult GISTs, since they may be lacking of mutations in *c-KIT* or *PDGFRA* genes (GIST wild-type) [44]. This feature could suggest that other mechanisms of activation of *c-KIT*, or oncogenic pathways not related to it, are active within cells. In most of the examined pediatric GIST, there was no indication of any cytogenetic

abnormality or alterations in *c-KIT* exons 9, 11 or 13. Among the few pediatric GIST underwent to a mutational analysis, and reported in the literature, only 11% of cases highlighted mutations in *c-KIT* or *PDGFRA*, equally distributed [45]. These evidences are different from those seen in adults sporadic GISTs where mutations in *c-KIT* are 10 times more common than mutations in *PDGFRA* [46]. In the pediatric forms these mutations are identified mainly in males. Indeed, only a single case of female patient it has been reported to carry a mutation in *PDGFRA*. Probably these mutations are random molecular events. It could be assumed the presence of mutations on other *c-KIT* and *PDGFRA* exons, different from those found in adults, but when analyzed through direct sequencing no new mutations in *c-KIT* were identified [47]. Although no *KIT* mutations are usually found in GIST pediatric forms, such gene is often expressed and its pathway activated [46]. In relation to the small number of cases identified to date, the genetic basis of the onset of a pediatric GIST are still little known and probably are also involved epigenetic changes or hypomorphic mutations in genomic portions that regulate the involved gene. Indeed, the degree of activation measured through the phosphorylation in the corresponding protein in these patients appears to be similar to that found in *c-KIT*-mutated adult GISTs [48]. Moreover, other *c-KIT* downstream genes, such as MAPK, Akt, S6 and mTOR, are also activated. These data support the hypothesis that *c-KIT* and the downstream genes may play a fundamental role as therapeutic targets also in pediatric patients [49]. The majority of pediatric GISTs that show no mutations in *c-KIT* or *PDGFRA* are characterized by few chromosomal rearrangements on a large scale [44]. Using microarray technology through SNP analysis, it was observed that almost all the wild-type pediatric GISTs preserve heterozygosity and diploid copy number along the entire genome. This finding agrees with previously evaluated pediatric GISTs by classical cytogenetics, which showed a diploid karyotype [50]. Through subsequent CGH (comparative genomic hybridization) analysis, 60% of the 13 pediatric wild type GISTs showed no chromosomal alterations. In the remaining 40% of tumors with chromosome variations, the most common identified aberration was the deletion 1q, observed in 3 cases. The gene expression profiles of pediatric GISTs are different from those of adult wild type GISTs and are characterized from the upregulation of the following genes: BAALC, IGF1R, FGF4, CRLF1, PLAG1 and NELL1 [45]. Moreover, in a study conducted in 2005, Prakash et al. [51] analyzed the gene expression of GIST tumor samples from children, young adults (under 30 years) and adults. The authors found a higher expression in the *PHKA1*, *FZD2*, *NLGN4*, *IGF1R* and *ANK3* genes in the first two groups of patients. Young adult GISTs, with similar characteristics to those observed in the pediatric forms, showed gene expression profiles similar to those of wild-type pediatric GISTs. However, the described gene expression experiments were carried out using a small number of tumor samples and the results were not confirmed later because of the difficulty to obtain tissue samples for RNA analysis [51]. The expression of IGF1R (insulin-like growth factor 1 receptor) is 5 times higher in wild-type pediatric GISTs than in wild-type adults. IGF1 and its receptor (IGF1R) play a key role in cell growth, proliferation and development. The analysis of IGF1R protein expression in GISTs, performed by western blotting and

immunohistochemistry, showed that the protein is expressed in all GISTs, but the expression levels are much higher than in the wild type GISTs [52]. IGF1R is activated in many GISTs, but its activation levels are not related to its expression. Moreover, it was observed that during stimulation with IGF1, the inhibition of IGF1R by small molecules reduced proliferation of a *c-KIT*-mutated GIST cell line. These data support the role of IGF1R as a potential therapeutic target in pediatric GISTs [53,54]. As in adult GISTs, the most common clinical manifestations, at the time of diagnosis, include gastrointestinal bleeding and anemia, related to it, and sometimes there is a palpable and bulky abdominal mass that often determine intestinal compression [55]. To the pediatric GISTs are often associated other forms of cancer as osteosarcoma and neuroblastoma. About 10% of pediatric GISTs occur in the context of the Carney triad or dyad, hence other suggestive features of the complex, in particular hyperpigmentation and the syndrome of inappropriate secretion of catecholamines associated to paragangliomas must be carefully sought at the initial evaluation of a pediatric patient suffering from GIST. The most common histological type is associated with an epithelioid cell or mixed fusiform/epithelioid morphology [56]. The clinical course, generally indolent, however, is usually less predictable than in adults, while considering commonly used prognostic factors (size, mitotic index and tumor site) [44]. Another common feature is the multifocality in the context of the anatomical region site of the localization that affects the onset of local recidives after several years from surgery. Before the introduction of targeted agents (primarily imatinib) in the treatment of GIST, surgery was the only possible treatment and is still the standard when the cancer is radically unresectable [42]. Although lymph nodes dissection is not recommended in adults, in pediatric GISTs, for the relatively higher incidence of lymph node metastases, suspicious nodes are surgically removed [43]. The interval between checks subsequent to surgery should include, beyond physical examination, the use of periodic imaging tests such as ultrasound, CT, MRI and PET, which should be carried out for the first 2 years every 3 months and every 6 months in the following two years, lastly annually as in adults. Before the introduction of mesylate imatinib, radical surgery was offered also to patients with locally advanced disease as well as non totally resectable or metastatic [57]. However, available data showed that complete resection of secondary injuries is not followed by healing and further relapse of disease occurs in almost all cases (90-100%). The framework in pediatric GISTs is similar [55]. The extensive surgery for debulking purpose, particularly used in the past, in the absence of other effective medical therapies, is no longer a viable option in the era of imatinib. GISTs, similar to mesenchymal tumors, are poorly responsive to chemotherapy. Randomized studies with anthracyclines, taxanes, ifosfamide and other various combinations showed response rates below 10%. Imatinib mesylate permitted to have better results than any type of chemotherapy or other treatment [58]. The optimal dose of imatinib in pediatric patients, as initial therapy, ranges from 230 to 400 mg/day and can be increased to 600-800 mg/day at disease progression. Sunitinib or nilotinib can be alternatively used [59].

Heredo-familial GISTs

Hereditary-familial gastrointestinal stromal tumors (GIST), together, represent less than 1% of all GISTs and are characterized

by inherited mutations in different susceptibility genes. They can be mainly distinguished in GISTs with *c-KIT* or *PDGFRA* mutations, which represent the main pathogenetic events in 90% of sporadic GISTs, and GISTs with mutations in other genes [60].

Heredo-familial GISTs with mutations in *c-KIT* and *PDGFRA*

Any activating germline mutation in *c-KIT* and *PDGFRA* genes shows autosomal dominant transmission and have been already reported in a small number of families [61]. The clinical manifestations in individuals carrying germline mutations in *c-KIT* vary in relation to the involved exon. The exon encoding for the membrane receptor juxtamembrane domain in *c-KIT* is a key and very early event in GIST oncogenesis [62]. When inherited in a germline way, it determine hyperplasia of ICCs that early evolves in the formation of multiple GISTs [63]. It includes also mastocytosis and skin hyperpigmentation, especially at perineum, axillary, hands and face (pigmentary urticaria) level. The presence of pigmentation disorders and mastocytosis are justified by the fact that c-KIT is involved in melanogenesis and in the development of mast cells [58,64]. The association of GIST and ICC generalized hyperplasia supports the origin of these tumors from CD34+ mesenchymal stem cells during ICC differentiation (Figure 2). The *c-KIT* activation is sufficient to determine an ICC hyperplasia (proliferative stimulus to GIST progenitor cells), but need additional oncogenic events to generate a GIST. Mutations in the tyrosine kinase domain of the receptor determine multiple stomach and small intestine GISTs in the absence of clear skin disorders [61,63] (Figure 2). Also GISTs involving no skin pigmentation or mastocytosis can be associated with abnormalities in the esophageal peristalsis. The onset average age of this group of heredo-familial GISTs is 46 years, slightly lower than the onset average age of sporadic adult GISTs (about 50 years) and out from the indicated range for pediatric GIST [49]. Their initial stages appear biologically similar to those of sporadic GISTs, with similar mechanisms of cytogenetic progression and comparable gene expression profiles. The germline mutations in *c-KIT* and *PDGFRA* are mostly similar to those found in sporadic GISTs [11]. However, two families with hereditary GIST showed two mutations never seen in sporadic GISTs, respectively in *c-KIT* and *PDGFRA* (Asp419del and Tyr555Cys) [65]. These two missense

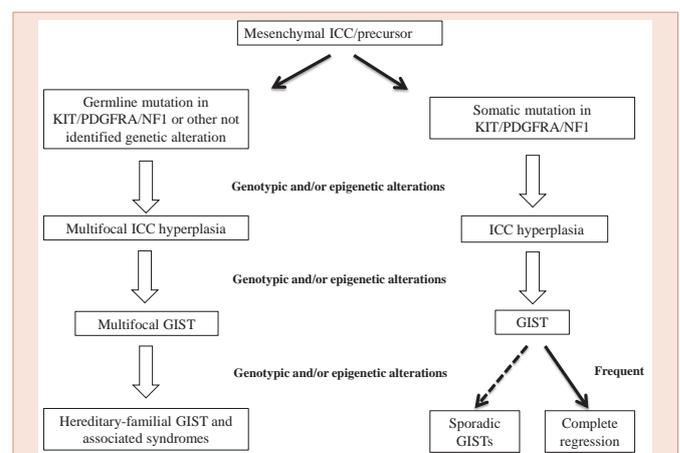


Figure 2: The oncogenetic mechanism in heredo-familial and sporadic GISTs.

mutations are located on the extramembrane and juxtamembrane domain, respectively, and are both responsible of the receptor autophosphorylation also in absence of a specific signal. In addition, another study reported the case of a patient who developed lipomas and GIST and showed a germline mutation (Asp561Val) in *PDGFRA* [66]. The main genotype-phenotype correlations in this heredo-familial GIST group are summarized in **Table 3**.

Heredo-familial GISTs with mutations in other genes

The Carney complex (from the name of the Majo Clinic’s famous anatomist who devoted his activity to the study of these diseases) includes the Triad Carney, described for the first time in 1977, and the Carney/Stratakis Dyad [67]. The Carney triad is an earlier onset syndrome (mean age 20 years) characterized by multiple gastric GISTs with multifocal onset that occurs in association to other tumors: extra-adrenal paragangliomas and pulmonary chondromas [68,69]. A careful follow-up of these patients also showed an increased risk of cortico-adrenal adenomas. The female population is the most affected (85% of all cases) and the disease course is usually slow and indolent (80% of patients alive at 20 years) [68,70]. Local recurrence, as well as liver and peritoneal lymph nodes metastases, are not frequent. In this context *c-KIT*, *PDGFRA* and *SDH* genes are wild-type [71]. The Carney-Stratakis Dyad is characterized by gastric GISTs and multiple paragangliomas. The onset average age is 19 years, and some patients may show, along with GIST, anemia and gastrointestinal haemorrhage, in the absence of evidente paraganglioma. In most patients with the Carney-Stratakis syndrome there is no evidence of mutations in *c-KIT* and *PDGFRA*, but germline mutations or deletions in *SDH B, C* or *D* genes, coding for the subunit B, C and D of the succinate dehydrogenase (SDH, mitochondrial complex II) were detected [70,72]. The predisposition to the development of these tumors is inherited in an autosomal dominant way with an incomplete penetrance. The succinate dehydrogenase is an enzyme system which has a dual role in the Krebs cycle and in the electrons transport chain in mitochondria [73]. The SDH complex consists of 4 subunits encoded by the genes *SDHA*, *SDHB*, *SDHC* and *SDHD*, made up of 15, 8, 6 and 4 exons, respectively [74]. The first two genes, located on chromosome 5p15 and on chromosome 1p35, encode for the two catalytic subunits, while the last two for the two transmembrane hydrophilic subunits. Germline mutations in the tumor-suppressor gene *SDH* were previously associated with hereditary paraganglioma (PGL1) and pheochromocytoma and should be sought in familial GISTs and paragangliomas [69,75] (**Table 4**). Although no SDH defects have been so far highlighted in Carney Tryad syndrome, the study conducted by Szarek et al. [76], provided new insights into mitochondrial ultrastructure in Carney Tryad tissues and GIST and Paragangliomas from SDH-deficient mice. Indeed, by comparing three different models, the study showed similar abnormalities in mitochondrial structure and function confirming the contribution of the abnormal mitochondria also in Carney Tryad pathogenesis [77]. Moreover, Carney Tryad seems to be also related to the CpG island methylation pattern of SDH subunit loci. Indeed, hypermethylation of SDH subunit C promoter, because of its transcription inactivation, seem to be characteristic of Carney Tryad tumor patients in comparison with Carney-Stratakis Dyad and Paragangliomas [78].

Table 3: Heredo-familial GISTs with mutations in c-KIT: main genotype-phenotype correlations.

| | |
|-------------------------------------|---|
| KIT exon 11 (V559A, delV559, W557R) | Pigmentary urticaria; mastocytosis |
| KIT exon 13 (K642E) | No skin pigmentation or mastocytosis |
| KIT exon 17 (D820Y) | No skin pigmentation or mastocytosis; anomalies in esophageal peristalsis |

Table 4: Carney Triad and Dyad differences.

| Variables | Carney Triad | Carney-Stratakis Dyad |
|---------------------------|--------------|-----------------------|
| GISTs | YES | YES |
| Paragangliomas | YES | YES |
| Pulmonary chondromas | YES | NO |
| Hereditary | NO | YES |
| Sex | >F (M:F=1:6) | F and M |
| KIT or PDGFRA mutations | NO | NO |
| Mutations in SDH subunits | NO | YES in 9/11 families |
| Chromosome loss in SDH | NOT in all | NOT in all |

An increased incidence (about 200 times) of GIST in patients affected by type 1 neurofibromatosis (NF1) it has been reported [56,79]. NF1 is one of the most common autosomal dominant disease, and it affects 1/2500-3000 births in the world, with a prevalence of about 1/4000-5000 individuals within the general population. The disease is transmitted in an autosomal dominant way, with a penetrance of 100% at variable expressivity, as segmental or mosaic forms may be detected [80]. The patients’ genetic background influences instead the manifestation of the related phenotypes. The *NF1* gene encodes a 220-250 kDa protein, called neurofibromin, which acts by inducing the GTPase function (GAP) of the Ras family proteins. Its action determines the stimulation of the Ras GTPase activity, with the consequent conversion of the mitogenic Ras-GTP complex in the inactive Ras-GDP form [81]. Therefore, the loss of this protein determines the permanent activation of Ras, typical condition of many sporadic tumors in which Ras activating mutations eliminate the catalytic activity [82]. To support this function, it has been shown that NF1-deficient human and mouse cell lines showing a hyperproliferative phenotype can be reverted to wild type with the inhibition of Ras [83,84]. The Ras protein is also involved in signal transduction pathways activated by *c-KIT*. GIST incidence in this subset of patients is about 5-25%. Even in these cases, these tumors arise in the absence of *c-KIT* and *PDGFRA* mutations, mainly in females, and show an indolent clinical course.

The oncogenetic counselling in heredo-familial GISTs

The identification of susceptibility genes involved in various hereditary cancer syndromes provided the molecular basis of genetic tests that allow to identify, among high risk individuals, germline mutation carriers considered for the “high risk” of developing a specific cancer. This new acquisition of molecular genetics has revealed the need to employ the oncogenetic counselling to meet the needs of all those cancer or healthy individuals, who want to understand the risk of recurrence of a genetic disease within the family for planning a proper clinical management [85]. The number of research laboratories and experts in the field which dedicate their activities to oncogenetic counselling is growing tremendously. This is mainly due to the increased demand from oncologists and other physicians who

daily see patients with high risk factors for heredo-familial tumors, which are consequently directed to genetic counseling. The first risk factor for an hereditary cancer is the early age of onset, even without a family history [86]. In the case of heredo-familial GISTs, the reference age is about 45 years. The presence of the same type of tumor in different members from a side of the family (paternal or maternal) or the association of a group of various cancers caused by mutations in *c-KIT*, *PDGFRA* and *SDH* (e.g. paragangliomas and chondromas) represent high risk factors for identifying family candidates for the genetic counseling [87]. The oncogenetic counseling (CGO) takes place within specialized centers and provides a multidisciplinary and integrated approach among various specialists such as medical oncologists, geneticists and psychologists. Each of these figures plays a well-established role and acts at a different level of the various phases of a counseling (pre-test phase, the genetic test phase, post-test, follow-up) [88]. The multidisciplinary approach takes account of the different aspects and needs of the subject at risk of an hereditary cancer. Individuals at risk of developing a tumor are subjected to analysis of the personal and family history through the reconstruction of a pedigree during the pre-test. The main features of the personal history that suggest hereditary GIST include early age GIST diagnosis, primitive multiple GISTs, or GIST associated with another tumor (eg paragangliomas, adenomas, chondromas, neurofibromas) [69]. The reconstruction of the family history of a proband represents a fundamental step, since the detailed description of the pedigree allows specialists to make a correct diagnosis, predict prognosis more accurately and, thus, help the experts in making decisions. It should be fundamental to collect personal and clinical information for at least three generations for the family members of first (children, siblings, parents), second (grandparents, uncles, grandchildren) and third degree (cousins, great-uncles) of the proband to facilitate the identification of the hereditary pattern possibly present in the family [89]. For the correct construction of a pedigree you need to collect as many information as possible, considering:

- a) either the paternal or the maternal side;
- b) Parenthood, consanguinity, the use of assisted reproductive technologies.

It is important to gather information on family members both suffering or unaffected from tumors. For each family member with cancer is necessary to evaluate:

- a) the type and the primary tumor site;
- b) the age of primary tumor onset to the first diagnosis;
- c) the current age if the individual is still alive, or the age of death and the cause of death;
- d) the exposure to carcinogens (e.g., tobacco, exposure to radiation);
- e) other significant health problems (e.g., presence of known genetic diseases which can predispose to the development of tumors);

For each family member unaffected from cancer is necessary to examine:

- a) the current age or age death;
- b) the cause of death (if applicable);
- c) surgical interventions that can have reduced the risk of developing cancer;
- d) screening performed for early detection of cancer;
- e) the exposure to carcinogens;
- f) other diseases;

In particular, the characteristics that may suggest the genetic predisposition for the GIST onset include the presence of:

- Two or more relatives with first degree familiarity with GIST;
- A family member who has been diagnosed with GIST and another member with an another rare primary tumor;
- A family member with GIST who have a personal or family history for the typical cutaneous manifestations, multifocality or results a carrier of the *NF1* gene mutations.

The **Figure 3** shows the pedigree of a family affected by Carney-Stratakis Dyad, characterized by the verticality of the hereditary transmission for 4 generations and by the association of GIST cases with paragangliomas. Moreover, noteworthy, the early onset age of the disease respect the sporadic cases. After the evaluation of the personal and family history follows the phase of the genetic test. The identification of a genetic mutation may allow, thanks to the genotype-phenotype correlations associated with the syndrome, to frame the clinical manifestations of the syndromes previously described. The post-test involves the delivery of the report, and for mutation carriers, contemplate the follow-up in order to adopt individualized surveillance programs [90,91].

Conclusions

GIST represent the most common mesenchymal tumors of the gastrointestinal tract. In adulthood, they mainly occur in the

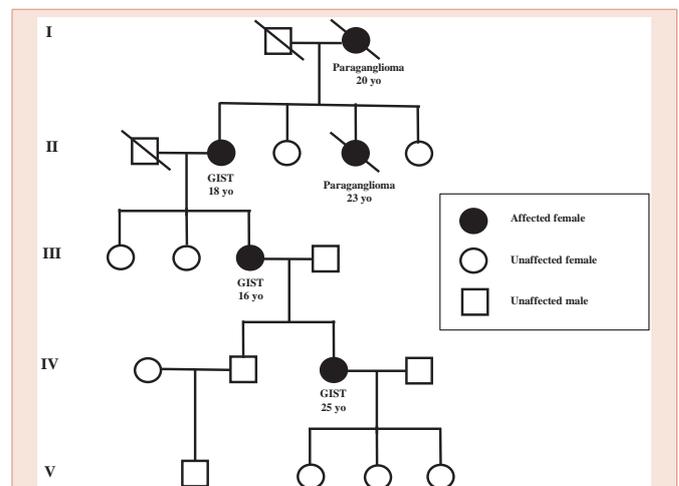


Figure 3: Pedigree of a family with Carney-Stratakis Dyad.

sporadic form but there is a small percentage of heredo-familial GISTs characterized by germline mutations in different susceptibility genes. In fact, the majority of sporadic GISTs show high frequency of activating mutations of the *c-KIT* oncogene. Moreover, a smaller percentage of GIST cases present mutually exclusive alterations in *PDGFRA* oncogene. Both gene sequences encode for a molecule with tyrosine kinase activity with a pivotal role in many pathways such as PI3K/AKT, RAS/RAF/MAPK and JAK/STAT. Genetic alterations in *c-KIT* and *PDGFRA* represent both the main pathogenetic events responsible of 90% of sporadic GISTs [92]. Moreover, the GIST pediatric variant is described only in 1 and 2% of all studied cases and they probably have a different pathogenesis if compared to adult GISTs. Indeed, they often did not show any mutations in *c-KIT* or *PDGFRA* as demonstrated in the examined pediatric GISTs where only 11% of all cases highlighted mutations in *c-KIT* or *PDGFRA*. Furthermore, heredo-familial GIST, represent less than 1% of all GISTs and are characterized by inherited mutations in different susceptibility genes. Their initial stages appear biologically similar to those of sporadic GIST as well as the germline mutations in *c-KIT* and *PDGFRA* are mostly similar to those found in sporadic GISTs. In individuals carrying germline mutations in *c-KIT*, the clinical manifestations tightly depend on the involved exon as the one encoding for the juxtamembrane domain which is implicated in the early stage oncogenesis. Indeed, it determine hyperplasia of ICC that early evolves in the formation of multiple GISTs as also mastocytosis and skin hyperpigmentation. However, not all GIST variants, although they appear hereditary, show detectable mutations in susceptibility genes. Indeed, the Carney Triad is characterized by multiple gastric GISTs and occurs often in association to other tumors: extra-adrenal paragangliomas and pulmonary chondromas. In this context, *c-KIT*, *PDGFRA* and *SDH* genes are often wild type. On the contrary, in the Carney-Stratakis Dyad, characterized by gastric GISTs and multiple paragangliomas even if there is not apparently evidence of mutations in *c-KIT* and *PDGFRA*, germline mutations or deletions in *SDHB*, *C* or *D* genes were found. Moreover, an increased GIST incidence has been also reported in patients affected by type 1 neurofibromatosis with no mutations in *c-KIT* and *PDGFRA* [93]. Indeed, these patients often show multifocal GISTs in the small intestine as well as in stomach even if at lower frequency. The interest in studying the role of susceptibility genes involved in several hereditary cancer syndromes has dramatically risen in the last decade. Indeed, the genetic counseling appear to be fundamental in order to meet the needs of cancer patients as well as healthy subjects in understanding the risk of recurrence of a genetic disease within their family. It provides a multidisciplinary and integrated approach among various specialists such as medical oncologists, geneticists and psychologists, each of them playing a well-established role at the different levels of a counseling. The reconstruction of the family history of a proband represents a fundamental step, since the detailed description of the pedigree allows to specialists to make a correct diagnosis, predict prognosis more accurately and, thus, plan a proper and personalized clinical management.

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