Japanese Journal of Gastroenterology and Hepatology

Review Article

ISSN: 2435-1210 | Volume 9

Inflammatory Fibroid Polyps: A Systematic Review Focusing on Genetics

Pang Y[1], He X[1], Xia Z[2] and Sun L[1*]

[1]Department of Gastroenterology, Zhejiang University School of Medicine Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China

[2]Department of Gastroenterology, The Fourth Affiliated Hospital Zhejiang University School of Medicine, School of Medicine, Zhejiang University, China

***Corresponding author:**

Leimin Sun,

Department of Gastroenterology, Zhejiang University School of Medicine Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, NO. 3 Qingchun East Road, Shangcheng District, Hangzhou, China, Tel: 86090073; E-mail: sunlm@zju.edu.cn

Received: 20 Dec 2022

Accepted: 17 Jan 2023

Published: 27 Jan 2023

J Short Name: JJGH

Keywords:

Inflammatory fibroid polyp; Vanek; PDGFRA; Gene mutation; Review

Citation:

Sun L. Inflammatory Fibroid Polyps: A Systematic Review Focusing on Genetics. J Gstro Hepato. 2023; V9(15): 1-10

Abbreviations:

IFP: Inflammatory fibroid polyp; GI: gastrointestinal; IHC: immunochemistry; PDGFRA: platelet-derived growth factor alpha; GISTs: gastrointestinal stromal tumors; INF: intestinal neurofibromatosis; NF3b: neurofibromatosis 3b; RTK: receptor tyrosine kinase; TKI: tyrosine kinase inhibitor; UKN: unknown

1. Abstract

1.1. Background: This study will review IFP (inflammatory fibroid polyp) by analyzing both sporadic and familial cases with a genetics-focused approach.

1.2. Methods: PubMed and CNKI were searched on 18 December 2021. Sporadic cases had to be diagnosed as sporadic IFP by pathology with/without IHC, reported for the first time, and tested for PDGFRA mutations. Familial cases had to meet the following condition: ≥2 fibrous tumors whose pathology was consistent with IFP were found in a single individual or family. The data were manually extracted and recorded using two standardized forms and were summarized by descriptive statistics.

1.3. Results: A total of 28 studies were included, of which 18 reported sporadic cases and 10 reported familial cases. There are currently 18 different PDGFRA mutation types for sporadic IFP; the majority occur in exon 12 (59.2%), followed by exon 18 (35.9%), with a detection rate of 56.6% overall. Patients with IFPs in the stomach were older (average 67.5 ± 11.1 years) than those with IFPs in the small intestine (average 55.8 ± 14.6 years) ($P<0.001$). The IFPs in the small intestine (median 3.8 cm, interquartile 2 cm) were larger than those in the stomach (median 1.6 cm, interquartile 1.6 cm) ($P<0.001$). The detection rate of PDGFRA mutation was higher in females (67.1%) than in males (40.7%) ($P=0.017$). PDGFRA exon 12 mutations predominated in the small intestine (58.6%), whereas PDGFRA exon 18 mutations predominated in the stomach (83.3%) ($P<0.001$). Four PDGFRA mutation types are present in familial IFP: 555Y>C, 561V>D, 653P>L, and 846D>V. The patient who suffered the most had germline 846D>V.

1.4. Conclusions: The "localization-specific mutational pattern" was demonstrated again. Further research is necessary to determine whether there is a connection between the type of mutation and the severity of familial IFP, as well as the potential therapeutic benefit of TKIs for IFPs. The pathogenesis may be sex-related.

2. Introduction

IFP, or Vanek's tumor, is recognized as a rare benign tumor occurring throughout the Gastrointestinal (GI) tract. IFPs originate from mesenchymal cells in the submucosal layer and often extend to the mucosa. They consist of bland spindle cells admixed within a loose collagenous stroma and perivascular edema and are frequently associated with inflammation and eosinophilic infiltration. They may grow in a typical onion-like pattern or exhibit different growth patterns. Most IFPs are CD34 positive, whereas almost all have negative staining for CD117, S100, and DOG1 [1-4]. The traditional diagnostic standards for IFP have been histological features and Immunochemistry (IHC).

Vanek first reported this lesion in 1949 [5]. Helwig and Rainer developed the term "inflammatory fibroid polyp" in 1953, which received widespread acceptance [6]. It has long been unclear whether IFP is neoplastic or reacts to certain irritants, such as trauma, bacteria, allergens, and foreign substances. IFP was not acknowledged as a tumor entity with somatically acquired alterations until H-U Schildhaus et al. discovered widespread Platelet-Derived Growth Factor Alpha (PDGFRA) expression and frequent activating mutations in the PDGFRA gene in IFPs in 2008 [7].

In addition to sporadic conditions, familial cases—though very rare—have also been reported. In 1984, Anthony et al. reported the first family with three women affected by recurring and multiple IFPs over three generations [8]. In 2015, Ricci et al. described a patient with a genetic germline PDGFRA mutation (653P>L in exon 14) who had many different gastrointestinal mesenchymal tumors, including IFPs, Gastrointestinal Stromal Tumors (GISTs), fibrous tumors, and lipomas. They suggested this syndrome, traditionally known as "INF/NF3b (intestinal neurofibromatosis/neurofibromatosis 3b)" and "familial GISTs," which had a heredity tendency and was characterized by various GI tumors, be more accurately named "PDGFRA-mutant syndrome" [9].

PDGF receptors, members of the Receptor Tyrosine Kinase (RTK) class III family, are mainly expressed by cells of mesenchymal origin [10]. Animal studies have shown that PDGFRα, a subtype of the PDGF receptor, and its corresponding gene, PDGFRA, play critical roles in the development of the GI tract [11], the central nervous system, the lungs, the skeleton, the testis, and the kidneys [12]. To date, activating PDGFRA mutations affect a minority of GISTs and approximately 55% of IFPs [13]. Imatinib, a type II Tyrosine Kinase Inhibitor (TKI), has been approved as a first-line therapy for metastatic GISTs [14], including those with PDGFRA mutations.

Although IFP has been reviewed previously, no studies have reviewed sporadic and familial IFP. PDGFRA mutations in IFP have been described in four studies [2,7,13,15], but the genetic characteristics have not been thoroughly explored. We will enroll both sporadic and familial cases in this analysis to provide a comprehensive overview of this disease, particularly from a genetic standpoint.

3. Methods

This systematic review was conducted according to the Cochrane and Preferred Reporting Items for Systematic Review and Meta-analysis 2020 guidelines [16].

3.1. Search Strategy

An extensive search of the US National Library of Medicine (MEDLINE, via PubMed) and the China National Knowledge Infrastructure (CNKI) was performed. PubMed was searched for articles whose titles or abstracts contained the term "inflammatory fibroid polyp" with or without "Vanek." The Chinese term "inflammatory fibroid polyp" was used to search CNKI. The search was performed from inception to 18 December 2021. We manually examined the bibliographies of relevant studies for any additional relevant studies to include.

3.2. Eligibility Criteria

For sporadic IFP, cases had to be diagnosed as IFP by pathology with or without IHC, reported as sporadic cases for the first time, and tested for PDGFRA mutations. For familial IFP, individuals or families had to meet the following condition: ≥2 fibrous tumors whose pathology was consistent with IFP were found in a single individual or family [9].

3.3. Selection Process

Two researchers made this progress (Y.P. and X.H.). All the studies returned by the search terms and identified through citation searching were exported to an Endnote 2020 library (X9), and all duplicates were removed. A manual check was performed to identify and remove any remaining duplicates. The titles and abstracts were reviewed. The full texts of studies not excluded at this point were obtained and reviewed to determine if they met the inclusion criteria. The selected studies were categorized as 'studies for sporadic IFP' and 'studies for familial IFP' according to the inclusion criteria. The senior author (L.S.) arbitrated disagreements on study inclusion.

3.4. Data Collection and Synthesis

Data extraction and collection were recorded using two standardized forms. Both forms contained the paper's author and year, the patient's age, sex, and race, the clinical and histological characteristics of IFP, the gene mutation characteristics of IFP, and the treatments for IFP. The clinical and histological characteristics of IFP included localization, diameter, layer involvement, inflammatory infiltrate, onion-skin pattern, and IHC (CD34, Ki-67, CD117, DOG1, and S100). The genetic characteristics included mutations in PDGFRA exons 10, 12, 14 and 18. Localization throughout the GI tract was recorded in the stomach, small intestine, colon, cecum, and rectum. In addition, the form for familial IFP included the sex distribution of patients within each family, the patient's age of onset, past medical history, clinical manifestations, GI wall thickening, diffuse polyps, other tumors, and chromosomal abnormalities. Because all patients with familial cases received repeated operations, the number of operations, the number of polyps, and the time span were recorded. An additional description was required when the patient had an extra treatment approach. This progress was made by two researchers (Y.P. and X.H.).

3.5. Statistical Analysis

Descriptive statistics were used to summarize the data in this article. Frequencies and percentages were used for dichotomous data, means ± standard deviations (SDs) were used for continuous variables with normal distributions, and medians with interquartile ranges were used for those with abnormal distributions. We performed all analyses using SPSS version 26.0 software (IBM, Armonk, NY, USA). Student's t test, one-way ANOVA, the Mann−Whitney U test, the Kruskal−Wallis test, Spearman's correlation, Pearson's correlation, and the chi-square test were calculated if appropriate. A value of P<0.05 was considered significant.

4. Results

4.1. Study Selection

A preliminary database search using the keywords yielded 485 articles, of which only two studies were duplicates. After the initial title and abstract screening, one hundred sixty-three studies were further excluded. A full-text review was conducted for the remaining 249 articles. In addition, these articles were searched for citations, and 14 studies were extracted. Two of the fourteen articles were excluded after the full texts were reviewed. Finally, a total of 28 studies that met the eligibility criteria were included in our systematic analysis (Figure 1). Among the 28 studies, 18 reported sporadic cases, whereas 10 reported familial cases.

4.2. Sporadic IFP

4.2.1. Characteristics of the publications included: Eighteen publications, including 182 cases of sporadic IFP, were included for further analysis. All 18 studies used PCR amplification and DNA sequencing to identify mutations in PDGFRA exons 10, 12, 14, and 18. However, not all of the research examined them equally. Five studies tested four exons [7,17-20]. Seven studies tested exons 12, 14, and 18 [2,3,13,15,21-23]. Five studies tested exons 12 and 18 [24-28]. One case showed only the detection results [29]. Exon 12 mutations were reported in ten articles, exon 18 mutations were reported in eight articles, and exon 10 and exon 14 mutations were reported in one article each. Five articles showed negative results (Table 1).

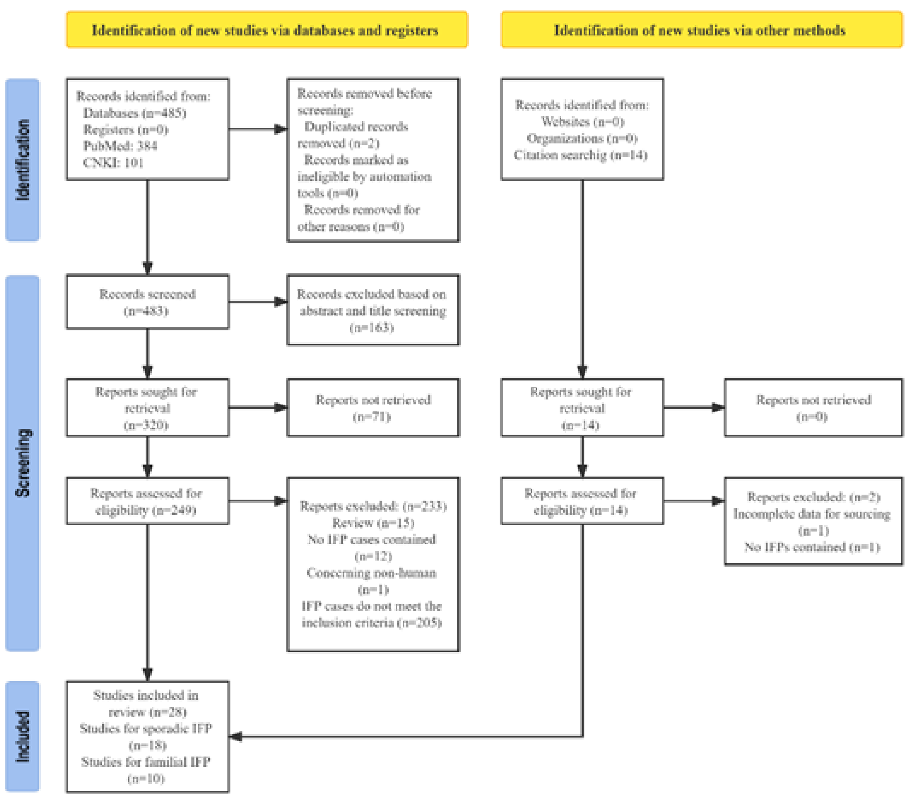

Figure 1: PRISMA flow diagram for the current review. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1: Eighteen articles reported sporadic IFP cases with PDGFRA mutation detection results, the numbers of cases, and the mutant PDGFRA exons.

Order	Year	Study	Number	Mutant PDGFRA exons
1	2008	Schildhaus H.U. et al.[7]	23	Exon 10, Exon 12, Exon18
2	2009	Lasota J. et al.[15]	60	Exon 12, Exon 18
3	2009	Calabuig-Farinas S. et al.[24]	1	Exon 12
4	2010	Daum O. et al.[2]	24	Exon 12, Exon 18
5	2012	Huss S. et al.[13]	38	Exon 12, Exon 14, Exon 18
6	2013	Bjerkehagen B. et al.[25]	2	Exon 12
7	2013	Liu T. C. et al.[3]	1	Exon 12

8	2013	Martini M. et al.[21]	1	Exon 18
9	2015	BAE JUN SANG et al.[26]	1	None
10	2015	Mitsui Y. et al.[17]	1	None
11	2016	Liu D. et al.[27]	18	Exon 12, Exon 18
12	2017	Zhao Y. et al.[29]	1	Exon 18
13	2018	Harima H. et al.[18]	1	None
14	2018	Sugawara T. et al.[22]	1	None
15	2018	Tajima S. et al.[19]	1	Exon 18
16	2018	Niu Z.R. and Li D.M.[28]	6	Exon 12
17	2019	Cunningham A. S. et al.[23]	1	None
18	2021	Nova L. M. et al.[20]	1	Exon 12

4.2.2 Characteristics of the cases included: Women comprised most of the 182 IFP patients (100/157, 63.7%). The patients were 63.7 ± 13.2 years old on average. Most patients (83/97, 85.6%) were between 40 and 79 years old. The stomach accounted for the majority of localization (69/168, 41.1%), followed by the small intestine (30/168, 17.9%) and the colon and cecum (6/168, 3.6%). The esophagus, rectum, and gallbladder accounted for only a minor proportion (1/168, 0.5% each). Notably, J Lasota et al. only studied IFPs from the small intestine, so we did not include the cases from their study here [15]. The range of IFP size was between 0.1 and 10.0 centimeters, with a median size of 2.0 centimeters (interquartile 3.0 cm). Most IFPs had a typical onion skin pattern (83/95, 87.4%) and positive CD34 expression (126/182, 69.2%). To date, PDGFRA mutations have been found in 56.6% of all sporadic cases. Most PDGFRA mutations occurred in exon 12 (61/103, 59.2%), followed by exon 18 (37/103, 35.9%). In contrast, mutations in exon 14 were uncommon. Only a nonsensical mutation existed in exon 10 (Table 2).

Table 2: The baseline information of the 182 cases.

Characteristic	Number	Percent (%)
Total cases	182	100
Sex		
Women	100	54.9
Men	57	31.3
Missing	25	13.7
Age, year		
Average (SD)	63.7 (13.2)	
<40	6	3.3
40-59	28	15.4
60-79	55	30.2
≥80	8	4.4
Missing	85	46.7
Localization		
Esophagus	1	0.5
Stomach	69	37.9
Small intestine	90	49.5
Colon and cecum	6	3.3
Rectum	1	0.5
Gallbladder	1	0.5
UKN	14	7.7
Diameter, cm		
Median (interquartile)	2.0 (3.0)	
<1	18	9.9
≥1	73	40.1
UKN	91	50

Onion-skin pattern		
YES	83	45.6
NO	12	6.6
UKN	87	47.8
CD34 expression		
YES	126	69.2
NO	56	30.8
UKN	0	0
Mutations		
Exon 10	3	1.6
Exon 12	61	33.5
Exon 14	2	1.1
Exon 18	37	20.3
None	79	43.4

UKN, unknown

4.2.3 Types, frequencies, and potential biological reactions to TKIs of PDGFRA mutations: There were 18 mutation types in sporadic IFP, including 9 in exon 12, 2 in exon 14, and 7 in exon 18. There were more deletion/deletion-insertion mutations than duplications or substitutions in exon 12 (55/61, 90.2% vs. 4/61, 6.6%). However, there were more substitutions than deletions in exon 18 (26/34, 76.5% vs. 7/34, 20.6%). Exon 14 contained exclusively substitutional mutations. In general, S566_E571delinsR was the most common mutation (45/97, 46.4%), resulting from 1696_1713delinsCGC, 1837_1851 del, 1835_1852delinsCGC, or 1698_1712del in the DNA sequence of exon 12 [2,15,19,25]. A substitution in exon 18, 842D>V, was the second most common mutation (25/97, 25.8%), followed by S566_E571delinsK in exon 12 (5/97, 5.2%), 561V>D in exon 12 (3/97, 3.1%), D842_H845del in exon 18 (3/97, 3.1%), P567_E571del in exon 12 (2/97, 2.1%), D842del in exon 18 (2/97, 2.1%), and other mutations rarely reported (1/97, 1.0% each). Three nonsense mutations, 478S>P in exon 10, 572Y>Y in exon 12, and 824V>V in exon 18, were not analyzed. Regarding potential biological reactions to TKIs, 561V>D and S566_E571delinsR in exon 12, 659N>K in exon 14, and 842D>V and D842_H845del in exon 18 were tested both in vitro and in vivo [30-32]. GISTs with mutations 561V>D, S566_E571delinsR, 659N>K, and D842_H845del have been confirmed to be sensitive to imatinib and possibly sensitive to the other TKIs mentioned above. GISTs harboring the 842D>V mutation exhibited resistance to imatinib, sunitinib, and regorafenib but sensitivity to ripretinib and high sensitivity to avapritinib [30-33] (Table 3).

Table 3: Summary of the type, frequency, and biological potential of PDGFRA mutations identified in sporadic IFPs.

PDGFRA mutations*	IFP							PDGFRA		Studies on PDGFRA mutations in GIST					
	Stomach	Small intestine	Colon	Cecum	Gallbladder	UKN	Total number	Activated 'in vitro'	Activated 'in vivo'	Imatinib sensitivity	Sunitinib sensitivity	Regorafenib sensitivity	Avapritinib sensitivity	Ripretinib sensitivity	References
Exon 12															
I557_E563dup	0	1	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	15,33
561V>D	1	1	0	0	0	1	3	Yes	Yes	Yes	PS	PS	PS	PS	3,7,15,30,31,33
I573_F588del	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	27,33
P567_E571del	0	2	0	0	0	0	2	UKN	UKN	PS	PS	PS	PS	PS	13,33
559-561del,591D>H	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	7,33
R560-567delinsS	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	7,33
S566_E571delinsK	0	5	0	0	0	0	5	UKN	UKN	PS	PS	PS	PS	PS	2,15,25,30,33
S566_E571delinsR	8	37	0	0	0	0	45	Yes	Yes	Yes	PS	PS	PS	PS	2,7,13,15,19,24,25,27,28,30,33
S566_I573delinsRIDDL	0	1	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	15,33

Not shown	0	1	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	20,33
Exon 14															
659N>K, 665T>A	0	1	0	0	0	0	1	UKN	UKN	UKN	UKN	UKN	UKN	UKN	13,33
659N>K	1	0	0	0	0	0	1	Yes	Yes	Yes	PS	PS	PS	PS	13,30,32,33
Exon 18															
842D>I	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	7,30,33
842D>V	19	5	1	0	0	0	25	Yes	Yes	No	No	No	HS	YES	7,13,15,28, 30,31,33,34
845_848del	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	7,33
D842del	0	1	0	0	1	0	2	UKN	UKN	PS	PS	PS	PS	PS	21,30,33
D842_H845del	2	1	0	0	0	0	3	Yes	Yes	Yes	PS	PS	PS	PS	7,13,30,33
D842_M844del	1	0	0	0	0	0	1	UKN	UKN	PS	PS	PS	PS	PS	13,30,33
842D>V, I843delinsV	1	0	0	0	0	0	1	UKN	UKN	UKN	UKN	UKN	UKN	UKN	13,33
Total number	38	56	1	0	1	1	97								

*Mutations at the protein level.

UKN, unknown; GIST, gastrointestinal stromal tumors; PS, possible sensitive; IFP, inflammatory fibroid polyp.

4.2.4. Relationships between age, sex, IFP localization, size, CD34 expression, mutation detection rate, and mutant exon: The one-way ANOVA result showed a statistically significant correlation between age and IFP localization (P<0.001). Patients with IFPs in the stomach were older (average 67.5 ± 11.1 years) than those with IFPs in the small intestine (average 55.8 ± 14.6 years) (Figure 2A). The patients were then divided into four age-based groups: <40 years old, ≥40 and <60 years old, ≥60 and <80 years old, and ≥80 years old. The small intestine was the only site involved by IFP in the group younger than 40 years old, whereas the stomach was the most common location affected by IFP in the remaining three age groups, especially in those ≥60 and <80 years old (Figure 2B). The Kruskal−Wallis test revealed a statistically significant correlation between IFP diameter and localization (P<0.001). The small intestine had the largest IFP diameter (median 3.8 cm, interquartile 2 cm), followed by the stomach (median 1.6 cm, interquartile 1.6 cm), and the colon and cecum had the smallest IFP diameter (median 0.7 cm, interquartile 1.2 cm) (Figure 2C). The IFPs in the small intestine were larger than those in the stomach and colon (both P<0.001), while the difference between the stomach and the colon and cecum was not significant (P=0.204). There were statistically significant correlations between sex and the detection rate of PDGFRA mutation (P=0.017), IFP localization and mutant PDGFRA exon (P<0.001), and CD34 expression and mutant PDGFRA exon (P=0.039), as determined by the chi-square test. The detection rate of PDGFRA mutation was higher in females (67.1%) than in males (40.7%) (Figure 2D). PDGFRA exon 12 mutations predominated in the small intestine (58.6%), whereas PDGFRA exon 18 mutations predominated in the stomach (83.3%) (Figure 2E). In our study, 93% of tumors with a PDGFRA mutation expressed CD34. Exon 12 mutations had a higher proportion of negative CD34 expression (14.3%) than exon 18 mutations (0.0%) (Figure 2F). The results of Student's t test showed that there was a statistically significant correlation between age and mutant PDGFRA exon (P=0.021). Patients with PDGFRA exon 18 mutations were older (average 65.5 ± 13.6 years) than those with PDGFRA exon 12 mutations (average 56.7 ± 11.6 years old). Exon 12 mutations were predominant in the two younger groups, while exon 18 mutations were predominant in the two older groups (Figure 2G). The result of the Mann−Whitney U test showed that there was a statistically significant correlation between the IFP diameter and mutant PDGFRA exon (P<0.001). IFP with exon 12 mutation had a larger diameter (median 4.0 cm, interquartile 2.7 cm) than IFP with exon 18 mutation (median 2.0 cm, interquartile 2.0 cm).

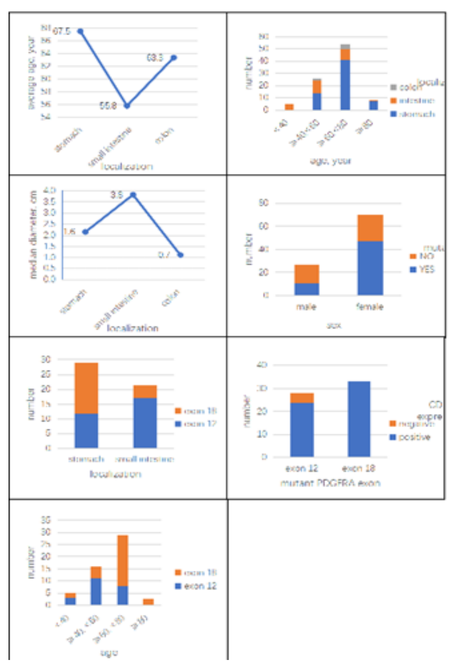

Figure 2: A, Average ages of different locations of IFP. B, Proportions of different localizations of IFP in four different age groups. C, Mean IFP diameters of different locations. D, Proportions of PDGFRA mutant and nonmutant IFPs in different sexes. E, Proportions of IFPs with exon 12 and exon 18 in different GI localizations. F, Proportions of CD34-positive and CD34-negative IFPs in PDGFRA exon 12 and exon 18 mutations. G, Proportions of IFPs with exon 12 and exon 18 mutations in different age groups.

4.3. Familial IFP

Ten papers with seven families and individuals were included for further analysis. Twenty of the twenty-two patients with familial IFP were female (90.0%), whereas only two were male (9.1%). Twenty patients had multiple IFPs in the GI tract, whereas two had a single IFP in the ileum. The tumors could be found throughout the GI tract. The age at the initial hospital visit due to GI tumor-related symptoms ranged from 16 to 67 years old, with the highest frequency among those aged 30 to 39 (Figure 3). In addition to IFPs, three families also had GISTs and fibrous and fatty tumors [9,35,36]. GI wall thickening was confirmed in three families [9,35,36]. The most common clinical manifestations were abdominal pain, vomiting, constipation, and diarrhea, but there could also be no symptoms. Three articles reported changes in appearance, including large hands and feet, broad wrists, a coarser face, coarser skin, and unexplained premature loss of teeth [36-38]. In the three families, all family members with appearance changes were confirmed to have PDGFRA mutations, and most family members with PDGFRA mutations had appearance changes at onset. However, not all of them had GI tumors. Four PDGFRA mutation types have been identified in six families and individuals. Exon 12 mutations included 555Y>C and 561V>D. Exons 14 and 18 exhibited 653P>L and 846D>V, respectively. Both families, reported by De Raedt et al. and Hodan et al., had the same PDGFRA germline mutation: 555Y>C. Only two families were affected by chromosomal abnormalities without explicit significance. Two patients from two families received imatinib and chemotherapy, respectively, in addition to surgical treatment for IFP. Most patients with GI tumors and related complications suffered recurrence following the initial surgery and underwent a total of two, three, four, five, or even more than six surgeries. A 35-year-old patient died of intestinal obstruction. The most severe manifestations occurred in a female patient with 846D>V who was affected by hundreds of GI tumors and had more than six surgeries within nine years (Table 4).

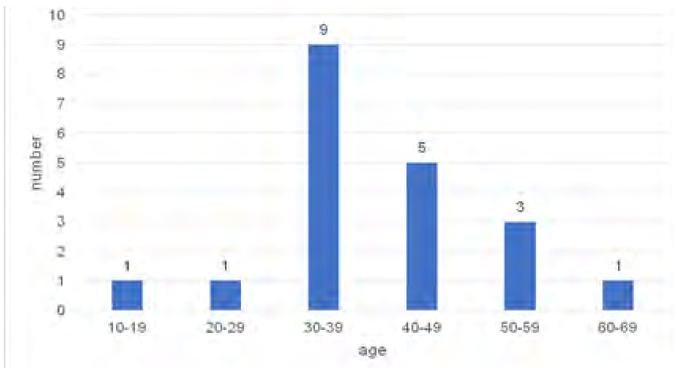

Figure 3: Numbers of patients in different age groups in familial cases.

Table 4: Summary of the 7 cases of familial IFP.

Study	Year	Country	Sex (F/M)	Age*	Localization of IFPs	Number	Other tumors	GI wall thickening	Main manifestation	Change in appearance	PDGFRA mutation	Chromosomal abnormality	Recurrence	Treatment
Anthony et al.; Allibone et al.	1984; 1992	England	May-00	34 (16-59)	Ileum, gastric antrum	Single or multiple	No	No	Intussusception	UKN	UKN	No	Yes	Surgery
De Raedt et al.	2006	Belgium	May-00	38 (35-41)	Intestine	Multiple	No	UKN	Obstruction	Large hands, broad wrists	555Y > C	t(12;14)(q13;q13)	Yes	Surgery
Pasini et al., Carney et al.	2007, 2008	USA	Jan-00	22	Stomach, small intestine, appendix	Multiple	GISTs, fibrous tumors, lipomas	Yes	Obstruction	UKN	561 V > D	Losses of chromosomal regions 1p33-36, 9q12-24, 11q13 and 16q(CGH); losses of 14q13.1 and 14q22.3(LOH)	Yes	Surgery; chemotherapy (cyclophosphamide, doxorubicin, dacarbazine, and vincristine)
Balsara et al.	2014	India	Jan-00	30	Small bowel	Multiple	No	UKN	Obstruction	UKN	UKN	UKN	Yes	Surgery
Ricci et al.	2015, 2016	Italy	2-Mar	43 (31-67)	Stomach, duodenum, ileum, ileocecal valve, colon	Multiple	GISTs, fibrous tumors, fatty tumors	Yes	Asymptomatic	No	653P > L	No	Yes	Surgery, imatinib
Manley et al.	2018	Canada	Jan-00	50	Small bowel, appendix, sigmoid colon	Multiple	GISTs	Yes	Intussusception	Coarser face, coarser skin, broader hands and feet and unexplained premature loss of teeth	846D > V	UKN	Yes	Surgery
Hodan et al.	2021	USA	Apr-00	40 (30-50)	Small bowel	Multiple	No	UKN	Intussusception	Large hands, broad wrists, coarser face	555Y > C	UKN	Yes	Surgery

*The mean age and the age range of the first hospital visit.

UKN, unknown.

5. Discussion

This review describes the epidemiological, clinical, pathological, and genetic features of sporadic and familial IFP and their interrelationships.

5.1. Characteristics of Sporadic IFP

As previously reported, IFP primarily affected women (100/157, 63.7%). The stomach had the highest percentage of IFPs (69/168, 41.1%), followed by the small intestine (30/168, 17.9%), the colon and cecum, and other parts of the GI tract. Most IFPs exhibited a typical onion skin pattern and CD34 expression (73/91, 87.4% & 126/182, 69.2%, respectively). The detection rate of PDGFRA mutation in sporadic cases was 56.6%, slightly higher than the 55.2% reported by Sebastian Huss et al [13]. PDGFRA mutations most often occurred in exon 12 (61/103, 59.2%), followed by exon 18 (37/103, 35.9%). The most common mutation type in all IFPs was S566_E571delinsR (45/97, 46.4%), followed by 842D>V (25/97, 25.8%) (Table 3). Again, we demonstrated the "localization-specific mutational pattern" that was first proposed by Sebastian Huss et al, [13]: exon 18 mutations were predominant in the stomach, and exon 12 mutations were predominant in the small intestine; IFPs in the stomach were smaller than IFPs in the small intestine; IFPs in the stomach were found in older patients, and those in the small intestine were found in younger patients. This pattern may have resulted from differences in the microenvironment of the stomach and small intestine; however, further research is required [13].

What was new was that IFP most often affected those aged 60 to 79, an older age range than previously recognized. The median diameter of IFP was 2.0 centimeters (interquartile 3.0 cm). In patients younger than 40 years old, IFP affected only the small intestine, whereas in those older than 40 years old, the stomach was most commonly affected (Figure 2B). There was no significant difference between the stomach and the colon and cecum in IFP size (Figure 2C). Only 4 cases had negative CD34 expression, and false negatives could not be ruled out, so the difference in the negative rate of CD34 expression between exon 12 and exon 18 was uncertain (Figure 2F). The ages and IFP size differences between mutations in exons 12 and 18 were consistent with the "localization-specific mutational pattern."

5.2. Characteristics of Familial IFP

The majority of the patients with familial IFP had recurrent and multiple IFPs. The preference for women was significantly higher than that for sporadic IFP (90.9% vs. 9.1%, $P<0.01$). The age group between 30 and 39 years old had the highest incidence of first hospitalization due to GI tumors (Figure 3). This syndrome was more likely to be an autosomal dominant disease because the PDGFRA mutations in three families occurred almost simultaneously with appearance changes that might have been part of the syndrome [36-38]. However, not all patients with PDGFRA mutations had IFPs, and other GI tumors were reported in some cases, displaying incomplete penetrance and variable expressivity [9,35,36]. All four types of familial IFP mutations were substitution mutations. A patient with the mutation 846D>V had the most severe manifestation, indicating that mutations occurring in the activation loop of PDGFRα may result in more severe clinical symptoms. Due to a lack of cases and data, it was challenging to explore the differences in clinical symptoms, pathological features, and prognosis between mutation types. The fact that most patients underwent surgery multiple times indicates the difficulty of treating this syndrome.

5.3. Current Status of TKIs in IFP Treatment

To date, studies have tested the biological reactions of GISTs harboring PDGFRA mutations to TKIs (Table 3). However, it remains unclear how IFPs react clinically to TKIs due to a lack of relevant studies. Only one patient with multiple IFPs, GISTs, and fibrous tumors in the context of a P653L-exon-14 PDGFRA mutation received imatinib for three years, and there was no recurrence during the 48-month follow-up period [9].

5.4. The Potential Relationship Between Sex and Pathogenesis

We found that the detection rate of PDGFRA mutation in female patients was significantly higher than that in male patients (Figure 2D). This finding did not follow the hypothesis that all IFPs were caused by mutations in PDGFRA exons 10, 12, 14, and 18. There may be mutations at other gene sites that contribute to the development of this tumor and display a sex bias that we have yet to identify. Moreover, the detection rate of PDGFRA exon 10, 12, 14, and 18 mutations in all sporadic IFPs was only 56.6%.

IFPs were more likely to affect women. As there were no significant differences in the localization and size of IFPs between male and female patients, symptom penetration and hospital admission rate were not the main factors. The familial syndrome appeared to be autosomal dominant with incomplete penetrance, so heredity was not considered. Why is there a sex difference? Zoran et al. discovered androgen receptor-positive cells in IFP tissue that corresponded with the distribution of Ki67-positive cells but no estrogen receptor-positive cells [39]. Androgen receptors, estrogen, and estrogen receptors have been found to act in various diseases, including cancer [40-43]. We hypothesized that the development and progression of IFP were associated with sex hormones and their receptors, given that IFP always affected postpubescents. The sex bias may result from differences in the serum levels of estrogen and androgen and the proportion or function of the receptors on IFP cells, just as the expression of androgen receptors was higher in male patients with gastric cancer than in female patients [44].

5.5. "Telocytes" may be the Precursor Cells of IFP

The exact pathophysiology of IFP is currently unknown. Ricci et al. proposed that "telocytes," a type of interstitial cell first described by L. M. Popescu and Maria-Simonetta in 2010, were the physiological counterpart of IFP and PDGFRA-mutant GISTs, possibly pathogenetically related to both of these tumor types, and suggested the term "telocytoma" for redefining IFP45. "Telocytes" are nucleated cells with 2-5 cell body prolongations that are very long and thin, and they can be found in the connective tissue of many organs, which could explain the single IFP found in the gallbladder (Table 2) [46]. However, the relationship between PDGFRA mutations and "telocytes" remains uncertain.

5.6. Limitations of this Systematic Review

This study had several limitations. First, we only searched two common databases to select the related cases, so many cases might have been omitted. Second, as in most systematic reviews and analyses, reporting and publication bias were present in this review. Some included publications were case reports describing unique clinical symptoms, IFP characteristics, or patient histories. Therefore, this review lacked a high degree of clinical representativeness. In addition, there was heterogeneity in the reported case data, such as patient baseline information, IHC results, and gene detection sites, which may have affected the systematic review. However, no significant heterogeneity was identified. Third, some of the findings in this review have previously been published, including the epidemiology, IFP localization, size, and specific localization differences between the stomach and small intestine. However, we presented them from a broader and more comprehensive perspective and provided a series of additional discoveries.

6. Conclusions

We reviewed IFP by studying sporadic and familial cases, emphasizing its genetic features. In conclusion, we demonstrated previously known epidemiological, clinicopathological, and genetic features, such as the "localization-specific mutational pattern" between the stomach and small intestine. We also proposed many novel results and insights. For sporadic IFP, there were 18 types of PDGFRA mutations reported in the literature, and the overall PDGFRA mutation detection rate was 56.6%. Seven families and individuals with familial IFP have been documented, and four PDGFRA mutation types have been discovered in six families. There is a potential relationship between the severity of familial IFP and the mutation type, but further study is needed. Further research is required to determine the potential therapeutic benefit of TKIs for IFPs. The sex bias in the detection rate of the PDGFRA mutation and the incidence of IFP may indicate pathophysiology related to sex at the gene and sex hormone levels that we do not yet understand.

References

1. Daum O, Hes O, Vanecek T, Benes Z, Sima R, Zamecnik M, et al. Vanek's tumor (inflammatory fibroid polyp). Report of 18 cases and comparison with three cases of original Vanek's series. Ann Diagn Pathol. 2003; 7(6): 337-347.
2. Daum O, Hatlova J, Mandys V, Grossmann P, Mukensnabl P, Benes Z, et al. Comparison of morphological, immunohistochemical, and molecular genetic features of inflammatory fibroid polyps (Vanek's tumors). Virchows Arch. 2010; 456(5): 491-497.
3. Liu TC, Lin MT, Montgomery EA, Singhi AD. Inflammatory fibroid polyps of the gastrointestinal tract: spectrum of clinical, morphologic, and immunohistochemistry features. Am J Surg Pathol. 2013; 37(4): 586-592.
4. Unal Kocabey D, Cakir E, Dirilenoglu F, Bolat Kucukzeybek B, Ekinci N, Akder Sari A. Analysis of clinical and pathological findings in inflammatory fibroid polyps of the gastrointestinal system: A series of 69 cases. Ann Diagn Pathol. 2018; 37: 47-50.
5. Vanek J. Gastric Submucosal Granuloma with Eosinophilic Infiltration. Am J Pathol. 1949; 25(3): 397-411.
6. Helwig EB, Ranier A. Inflammatory Fibroid Polyps of the Stomach. Surg Gynecol Obstet. 1953; 96(3): 355-367.
7. Schildhaus HU, Cavlar T, Binot E, Buttner R, Wardelmann E, Merkelbach-Bruse S. Inflammatory fibroid polyps harbour mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene. J Pathol. 2008; 216(2): 176-182.
8. Anthony PP, Morris DS, Vowles KD. Multiple and recurrent inflammatory fibroid polyps in three generations of a Devon family: a new syndrome. Gut. 1984; 25(8): 854-862.
9. Ricci R, Martini M, Cenci T, Carbone A, Lanza P, Biondi A, et al. PDGFRA-mutant syndrome. Mod Pathol. 2015; 28(7): 954-964.
10. Guerit E, Arts F, Dachy G, Boulouadnine B, Demoulin JB. PDGF receptor mutations in human diseases. Cell Mol Life Sci. 2021; 78(8): 3867-3881.
11. Karlsson L, Lindahl P, Heath JK, Betsholtz C. Abnormal gastrointestinal development in PDGF-A and PDGFR-(alpha) deficient mice implicates a novel mesenchymal structure with putative instructive properties in villus morphogenesis. Development. 2000; 127(16): 3457-3466.
12. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008; 22(10): 1276-1312.
13. Huss S, Wardelmann E, Goltz D, Binot E, Hartmann W, Merkelbach-Bruse S, et al. Activating PDGFRA mutations in inflammatory fibroid polyps occur in exons 12, 14 and 18 and are associated with tumour localization. Histopathology. 2012; 61(1): 59-68.
14. Al-Share B, Alloghbi A, Al Hallak MN, Uddin H, Azmi A, Mohammad RM, et al. Gastrointestinal stromal tumor: a review of current and emerging therapies. Cancer Metastasis Rev. 2021; 40(2): 625-641.
15. Lasota J, Wang ZF, Sobin LH, Miettinen M. Gain-of-function PDGFRA mutations, earlier reported in gastrointestinal stromal tumors, are common in small intestinal inflammatory fibroid polyps. A study of 60 cases. Mod Pathol. 2009; 22(8): 1049-1056.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
17. Mitsui Y, Kagemoto K, Itagaki T, Inoue S, Naruse K, Muguruma N, et al. Gastric inflammatory fibroid polyp morphologically changed by Helicobacter pylori eradication. Clin J Gastroenterol. 2015; 8(2): 77-81.
18. Harima H, Kimura T, Hamabe K, Hisano F, Matsuzaki Y, Sanuki K, et al. Invasive inflammatory fibroid polyp of the stomach: a case report and literature review. BMC Gastroenterol. 2018; 18(1): 74.
19. Tajima S, Koda K. Locally infiltrative inflammatory fibroid polyp of the ileum: report of a case showing transmural proliferation. Gastro-

enterol Rep (Oxf). 2018; 6(2): 144-148.

20. Nova LM, Lopez P, Cerezo C, Llanos C, Amat I. Ileal Intussusception in an Adult Caused by a Locally Invasive Inflammatory Fibroid Polyp: A Case Report. Rev Esp Patol. 2021; 54(1): 65-69.

21. Martini M, Santoro L, Familiari P, Costamagna G, Ricci R. Inflammatory fibroid polyp of the gallbladder bearing a platelet-derived growth factor receptor alpha mutation. Arch Pathol Lab Med. 2013; 137(5): 721-724.

22. Sugawara T, Sugita S, Tateno M, Yabutani A, Segawa K, Ito Y, et al. Colonic inflammatory fibroid polyp with PDGFRA expression. Pathol Int. 2018; 68(3): 205-206.

23. Cunningham AS, Siddique AS, Ligato S, Vignati PV. A large inflammatory fibroid polyp of the rectum removed by transanal excision. J Surg Case Rep. 2019; 2019(6): rjz164.

24. Calabuig-Farinas S, Lopez-Guerrero JA, Ribera MJ, et al. Inflammatory fibroid polyp of the small bowel with a mutation in exon 12 of PDGFR alpha. Virchows Arch. 2009; 454(3): 327-331.

25. Bjerkehagen B, Aaberg K, Steigen SE. Do Not Be Fooled by Fancy Mutations: Inflammatory Fibroid Polyps Can Harbor Mutations Similar to Those Found in GIST. Case Rep Med. 2013; 2013: 845801.

26. Bae JS, Song JS, Hong S-M, Moon WS. An unusual presentation of an inflammatory fibroid polyp of the ileum: A case report. Oncology Letters. 2015; 9(1): 327-329.

27. Li D, Wang J, Chen M, Xiao Q, Zhu CR, Jiang JX, et al. Clinicopathological observation of 37 cases of gastrointastinal inflammtory fibroid polyps. Chinese Journal of Pathology. 2016; 45(06): 381-386.

28. Niu ZR, Li DM. Inflmmatory fibroid polyp: a clinicopathologic and immunohistochemical analysis of 28 cases. The Journal of Practical Medicine. 2018; 34(02): 289-292.

29. Zhao Y, Fu YW, Wang WC, Lu T. A Case of Inflammatory Fibroid Polyp with an Elongated Shape in Cecum. Chin Med J (Engl). 2017; 130(17): 2130-2131.

30. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005; 23(23): 5357-5364.

31. Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol. 2006; 24(29): 4764-4774.

32. Heinrich MC, Jones RL, von Mehren M, Schöffski P, Serrano C, Kang YK, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. The Lancet Oncology. 2020; 21(7): 935-946.

33. Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. Nat Rev Dis Primers. 2021; 7(1): 22.

34. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003; 21(23): 4342-4349.

35. Pasini B, Matyakhina L, Bei T, Muchow M, Boikos S, Ferrando B, et al. Multiple gastrointestinal stromal and other tumors caused by platelet-derived growth factor receptor alpha gene mutations: a case associated with a germline V561D defect. J Clin Endocrinol Metab. 2007; 92(9): 3728-3732.

36. Manley PN, Abu-Abed S, Kirsch R, Hawrysh A, Perrier N, Feilotter H, et al. Familial PDGFRA-mutation syndrome: somatic and gastrointestinal phenotype. Hum Pathol. 2018; 76: 52-57.

37. de Raedt T, Cools J, Debiec-Rychter M, et al. Intestinal neurofibromatosis is a subtype of familial GIST and results from a dominant activating mutation in PDGFRA. Gastroenterology. 2006; 131(6): 1907-1912.

38. Hodan R, Charville GW, Ladabaum U. Hereditary inflammatory fibroid polyps caused by germline pathogenic variants in PDGFRA: Refining PDGFRA-mutation syndrome. Cancer Genet. 2021; 256-257: 106-109.

39. Jukic Z, Ferencic Z, Radulovic P, Mijic A, Fucic A. Estrogen and androgen receptors in inflammatory fibroid polyp (Vanek's tumor): case report. Anticancer Res. 2014; 34(12): 7203-7206.

40. Ma WL, Hsu CL, Wu MH, Wu CT, Wu CC, Lai JJ, et al. Androgen receptor is a new potential therapeutic target for the treatment of hepatocellular carcinoma. Gastroenterology. 2008; 135(3): 947-955, 955 e941-945.

41. Liang J, Shang Y. Estrogen and cancer. Annu Rev Physiol. 2013; 75: 225-240.

42. Tang WB, Liu RJ, Yan Y, Pan X, Wang M, Han X, et al. Expression of estrogen receptors and androgen receptor and their clinical significance in gastric cancer. Oncotarget. 2017; 8(25): 40765-40777.

43. Zhong Y, He K, Shi L, et al. Down-regulation of estrogen-related receptor alpha (ERRalpha) inhibits gastric cancer cell migration and invasion in vitro and in vivo. Aging (Albany NY). 2021; 13(4): 5845-5857.

44. Jukic Z, Radulovic P, Stojkovic R, Mijic A, Grah J, Kruslin B, et al. Gender Difference in Distribution of Estrogen and Androgen Receptors in Intestinal-type Gastric Cancer. Anticancer Res. 2017; 37(1): 197-202.

45. Ricci R, Giustiniani MC, Gessi M, Lanza P, Castri F, Biondi A, et al. Telocytes are the physiological counterpart of inflammatory fibroid polyps and PDGFRA-mutant GISTs. J Cell Mol Med. 2018; 22(10): 4856-4862.

46. Popescu LM, Faussone-Pellegrini MS. TELOCYTES - a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES. J Cell Mol Med. 2010; 14(4): 729-740.