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Abstract

Peutz-Jeghers syndrome (PJS) is a well-described inherited syndrome, characterized by the development of gastrointestinal polyps, and characteristic mucocutaneous freckling. PJS, an autosomal prevailing disease due to genetic mutation on chromosome 19p, manifested by restricted mucocutaneous melanosis in association with gastrointestinal (GI) polyposis. The gene for PJS has recently been shown to be a serine/threonine kinase, known as LKB1 or STK11, which maps to chromosome subband 19p13.3. This gene has a putative coding region of 1302

bp, divided into nine exons, and acts as a tumour suppressor in the hamartomatous polyps of PJS patients and in the other neoplasms which develop in PJS patients. It is probable that these neoplasms develop from hamartomas, but remains possible that the LKB1 or STK11 locus plays a role in a different genetic pathway of tumour growth in the cancers of PJS patients. This article has focused on role of LKB1 or STK11 gene expression in PJS and related cancers.

Keywords: Peutz-Jeghers syndrome; LKB1; STK11; gastrointestinal polyps; gene expression

Introduction

Peutz-Jeghers syndrome (PJS) is characterized by a specific type of hamartomatous polyp of the gastrointestinal tract, and by freckling of the lips, buccal mucosa, and other sites. PJS often presents in the first decade of life with pigmentation (usually in a familial context) or with complications of small bowel polyps, such as obstruction or intussusception. Older PJS patients have an increased risk of neoplasia of multiple sites, predominantly the colon, breast, stomach, ovary, uterus, and pancreas. This risk may approach a 20-fold increase over the general population if all organs are considered, although the increased risk for any particular site is necessarily more modest. About three quarters of PJS cases occur in families, with the remainder resulting from new mutations or low penetrance variants [1, 2].

The gene for PJS has recently been shown to be a serine/threonine kinase, known as LKB1 or STK11, which maps to chromosome subband 19p13.3. This gene has a putative coding region of 1302 bp, divided into nine exons, and acts as a tumour suppressor in the hamartomatous polyps of PJS patients and in the other neoplasms which develop in PJS patients. It is probable that these

neoplasms develop from hamartomas, but remains possible that the LKB1 locus plays a role in a different genetic pathway of tumour growth in the cancers of PJS patients [3, 4].

Previous studies have found germline LKB1 mutations in 50-75% of Peutz-Jeghers patients using genomic DNA or cDNA sequencing as a primary screen. Most of these mutations are frameshifts or nonsense changes and thus result in a truncated protein. In frame deletions or missense mutations occur less frequently, generally at conserved amino acids in the kinase core (codons 50-337). Although data are currently insufficient for a formal analysis, the germline mutations of Peutz-Jeghers patients appear to occur throughout the gene, but with a possible bias towards exons 1 and 6. Most studies have reported few somatic LKB1 mutations in sporadic cancers, despite screening tumours from most of the sites (colon, breast, testis, ovary, and pancreas) at which PJS patients have an excess of cancers. One study has, however, found a high frequency of missense LKB1 mutations in left sided sporadic colon cancers. In addition, one somatic mutation with convincing pathogenic effects has been reported in a sporadic testicular cancer and two mutations have been found in malignant melanoma. There is some evidence of a second, minor PJS locus not on 19p13.3 and, although its existence remains unproven, it may explain why mutation screening does not detect a higher frequency of LKB1 mutations in PJS patients [5-8].

Genetic defects in Peutz-Jeghers syndrome

Mucocutaneous melanosis associated with PJS is autosomal disorder and in 1997 it was discovered that expression of it related to chromosome 19p13.3. However, further research findings by two-research groups revealed the involvement of LKB1 (liver kinase B1) gene mutation (also recognised as STK11 [serine/threonine kinase 11] gene) on expression of mucocutaneous melanosis. A 30%–70% of PJS sporadic cases associated with STK11/LKB1

gene mutation, however, the rate of spontaneous mutation in mucocutaneous melanosis is under investigation [9, 10]. The main setback in identification of STK11/LKB1 gene in mucocutaneous melanosis patients is genetic mosaicism, lack of effective molecular techniques PJS loci, etc.. Later some studies on PJS revealed the link of loci on chromosome 16q and19q for expression of mucocutaneous melanosis. These mutations on PJS leads to null alleles by nonsense insertion, deletion and rearrangement [11, 12].

Additionally, Hemminki and team revealed the involvement of STK11 gene mutation in almost 90% of PJS patients by DNA and mRNA direct sequencing method. On the other hand, germline mutations were simultaneously investigated by multiplex ligation dependent probe amplification and direct sequencing method, where the results detects 80 to 94% of germline mutations in PJS patients. PJS polyps showed loss of heterozygosity at 19p13.3. SKT11 also act as a tumor suppressor gene, which is almost 23 kb in length along with 433 amino acid and nine-axon. Further investigation on function and activity of SKT11 is still ongoing. The expression of serine-threonine kinase is wide in fetal tissue and adult. In short, G1 cell-cycle arrest, p53 mediated apoptosis and WAF1 signalling is mediated by STK11 and plays important role in regulation of Wnt signalling pathway and cell polarity. Moreover, it is also take part in cell homeostasis and metabolism, and also act as a upstream regulator of adenosine monophosphate activated protein kinase and control tuberous sclerosis complex pathway along with negative regulation of mammalian target of rapamycin pathway [13-15]. Mammalian target of rapamycin pathway is final common pathway and also can be downregulated by other hamartomatous polyposis syndromes triggered by SMAD4, germline PTEN and BMPR1A mutations.

Abundance of COX-2 also noticed in case of cancer and PJS polyps, can target for modulation of PJS. Additionally, role of MYH11 gene mutation in 25 STK11mutation negative patients having PJS phenotype were examined [16-18]. One patient was found with MYH11 mutation; however, this mutation was modest relevance. Until now, no confirmed gene was found for mucocutaneous melanosis cases without detectable STK11 mutation [19, 20].

Correlation between genotype and phenotype

Various researchers around the world investigated correlation between phenotype and genotype in PJS. Amos *et al* found out that persons with other mutation in STK11 have early onset of PJS symptoms compared to person with missense mutations. On the other hand, Schumacher *et al* proposed that in-frame mutation in ATP binding, catalysis (IeVIA) and encoding protein domain were hardly related to cancer; however, missense mutation in the part of encoding protein domain gene and C terminus were more likely associated with malignancies. They also suggested that truncating mutations predominantly found in breast carcinoma. Moreover, Mehenni *et al* proposed mutations in exon 6 of the STK11 associated with the higher risk of cancer following investigating on 49 PJS family with mutations [21, 22]. Although, it is difficult to draw final conclusion from these studies with small numbers of patients. Majority of these studies was carried out in western European populations, whereas, in one of the studies in American PJS patients illustrated the involvement of exon 6 (c.811_813delAG) and exon 2 (c.350_351insT) mutation of STK11gene in PJS [17, 23, 24]. STK11 mutation were analysed in 240 PJS patients and families and no difference was observed neither in truncating and missense mutations in individual, nor in sporadic and familial cases. However, mutation in exon 3 of the gene was found to cause higher risk of cancer in individual. Continuation of this study, Hearle *et*

al analysed 419 patient in which 297 patients were document for mutations and concluded that site and type of mutation did not affect the cancer risk in individual. In summary, no significant differences was observed in PJS patients without mutation and patients with STK11 mutation. Moreover, no correlation has been observed in genotype and phenotype of the patients [25-27].

Clinical Characteristics of PJS

A disease resembling PJS was described by Peutz in 1921 and by Jeghers et al in 1949. The pathology of PJS is considered to be hamartomatous, since PJS polyps are not cancerous and their histology is similar to the normal mucosal structure. A more accurate description of the lesions is hyperplasia of the lacunar epithelium. However, the morphology differs from that of a general hyperplastic polyp. The gland opening is dilated toward the outer side due to the hyperplastic mucoepithelium and muscular fibers overgrow in a dendritic pattern along the epithelium. These changes are preceded by epithelial hyperplasia. Adjacent lamina muscularis mucosae are believed to bend and fuse to give the characteristic appearance and small lesions undergo hyperplastic changes [28, 29].

Clinically, PJS is characterized by the development of abdominal symptoms, including pain, ileus and gastrointestinal hemorrhage, which occur with an increase in the number and size of the gastrointestinal polyps. The incidence of PJS is secondary to that of familial adenomatous polyposis among the types of hereditary gastrointestinal polyposis. Malignant and benign tumor complications may occur in PJS, with studies indicating that malignant tumors develop in approximately half of patients by the age of 57 years [30-32]. The incidence of digestive organ malignant tumors is highest in the colorectum, followed by the stomach, small intestine, duodenum and pancreas. In regions other than the digestive organs, the incidence is reported to

be highest in the uterine cervix, followed by the lung and ovary in female PJS patient. Associations with ovarian SCTAT and uterine cervical LEGH and MDA have been highlighted in the field of gynecology, and an association with endometrial cancer has recently gained interest based on case reports and genetic studies [33-36].

Associated cancer risk with PJS

PJS association with cancer and involvement of PJS polyp in cancer development is still controversial. Hypothesis of hamartoma adenoma carcinoma pathway was supported by presence of adenomatous foci in polyp of PJS and also describe possible rising of cancer from polyp. Some researchers proposed that PJS polyp is not having malignant potency and thus, cancer transformation of polyp is rarely ensued [37-39]. Moreover, PJS polyp found to be polyclonal and actually a form of abnormal mucosal prolapse arises due mutation in STK11 gene leads to change in cellular polarity, it is not a type of true hamartoma. As there is no involvement of PJS polyp in cancer, so background of cancer development may have associated with mucosal instability, through neoplastic pathways [40-42]. On the basis of several molecular genetics and epidemiological studies, it was suggested the PJS patients have higher risk of many cancer. It was evident from the literature that multiple studies have been performed on individual groups, however, it is difficult to conclude the cancer risk association with PJS due to publication bias and ascertainment of these studies [43-45]. In this regard, meta-analysis was performed by Giardiello *et al* on six studies with total 210 patients. Similarly, as stated above 419 patients with PJS was assessed by Hearle and team to generate comprehensive data for cancer risk association with PJS. As per findings, out of 419, 297 patients were documented to have STK11 mutations and 23% of them developed cancer. From these studies, it was proposed that breast cancer and luminal GI cancers is most common cancer associated with it, followed by pancreatic cancer [46-

[48]. Hearle and team reported the higher risk of cancer after the age of 50. Recently, Mehenni *et al* investigated 76 males and 73 females with STK11 mutation and on contrary to the above study report, they reported only one breast cancer. Although the reason of this discrepancy in observation in these studies are still in question. Else the luminal GI cancer predominance and more risk after age of 50 was established by these study [49-51]. Alternately, Young *et al* investigated occurrence of rare sex cord tumour in PJS. They found that out of 74 patients with sex cord ovarian tumors with annular tubules, 27 were documented with PJS and all were benign, calcified and multifocal. Four affected patients had adenoma malignum and twelve have hyper-oestrogen syndrome [52-54]. Additionally, Dozois and team reviewed 115 female PJS cases from literature and found 16 cases of ovarian tumors at the age from 4.5 to 60 years. Moreover, five cystadenomas, five granulosa cell tumours, four non-neoplastic cysts, one dysgerminoma and one Brenner tumor were diagnosed. A case of broncho-alveolar cancer was reported by Von Herbay to show association of cancer with PJS [55-57]. Obtained reports in this field demonstrated several controversial theories relating development of PJS and cancer, however majority of incidences are focusing on hamartoma polyposis in the GI tract, no correlation evidenced on mucocutaneous melanosis with any incidence of cancer. Connecting section of the article will bring available possibilities in the management of these mucocutaneous melanosis in PJS [58-60].

STK11/LKB1 and PJS

The gene that is responsible for causing PJS is the tumor suppressor gene, STK11/LKB1, which is located on the short arm of chromosome 19 (19p13.3). The gene is 23 kb in size and is comprised of nine coding exons and one non-coding exon. The gene encodes a serine threonine kinase containing 433 amino acids. The mRNA is 3.0–3.3 kb in size and is expressed in almost all human tissues. Germline mutations of STK11/LKB1 are observed in more than half of PJS

patients. However, the somatic development of PJS in patients with no familial medical history and cases without a mutation in STK11/LKB1 have also been described [61-63].

In 1997, Hemminki et al identified the responsible gene region in PJS to be near the chromosome 19 short arm marker using a linkage analysis of families with PJS. Amos et al confirmed this finding. The STK11 gene was known to be present on chromosome 19 and Yoon et al subsequently identified a number of mutation types in this gene, including missense, frame shift, nonsense and splicing site mutations, in 10 PJS patients using polymerase chain reaction-single strand conformation polymorphism [57, 64, 65]. Germline mutations were present in five of these patients. Tseng et al analyzed STK11 mRNA expression in twin sisters with PJS with the same allele using PCR and revealed that STK11 gene expression was absent in the two subjects. These results suggest that STK11 on chromosome 19 is responsible for PJS and that a mutation or decreased expression of STK11 is the cause of the disease [66-68].

The protein product of STK11 is involved in cellular energy metabolism, cell proliferation, cell polarity, p53-dependent apoptosis, the regulation of VEGF and Wnt signal transduction. LOH due to a mutation, including a deletion in the normal allele, in addition to the germline STK11 mutation, results in gastrointestinal polyposis and cancerization of other organs, which are common clinical features of PSJ [69, 70].

As noted previously, Yoon et al identified germline mutations in five of 10 PJS patients, which suggests other developmental mechanisms in the remaining five patients, based on STK11 gene mutation-induced development (somatic case) and the association with other genes. Several studies have suggested the presence of a gene that is associated with PJS other than STK11. In an investigation of 21 PJS patients from 13 families, Papp et al identified that 8 (62%) of the 13 cases of PJS had familial medical histories and that the remaining five cases (38%) were due

to de novo mutations. Germline mutations were screened in the 21 patients and 13 pathogenic mutations of STK11 were identified [71-73]. Three of these were frameshift mutations, three were nonsense mutations, two were mutations of the splicing sequence and five were deletions of exons 1–7. This deletion was noted in five of the 13 families, showing a high frequency, and was also shown to affect two genes that were located upstream of the STK11 gene, SBNO2 and GPX4, which are considered to modify STK11. This finding suggests that an abnormality in the genes that modify STK11 function may promote the development of PJS, even in the absence of a mutation in STK11 itself [74-77].

Souza et al initially reported a contiguous genetic syndrome in which a developmental disorder, heart malformation and facial dysplasia appear as phenotypes, in addition to the symptoms of PSJ. This syndrome is caused by a 19p13.3 chromosomal deletion of a region of ~1.1 Mb that includes STK11. Scollon et al also reported a syndrome with a similar gene deletion at a similar site, but the development of a cleft lip and gastrointestinal polyposis differed between the syndromes, suggesting that the phenotypes may vary, despite a common STK11 deletion between the two syndromes [78-80].

Conclusion

The frequency and type of SKT11/LKB1 gene inactivation unequivocally attests to its tumor-suppressor role in lung tumorigenesis and demonstrates its significance in cancer development in other circumstances that merely the cancer-prone PJS. In addition to PJS, the use of highly sensitive screenings for mutations and large deletions may reveal that SKT11/LKB1 gene alterations occur in a broad range of tumor types. Finally, the critical involvement of SKT11/LKB1 in energetic control checkpoints highlights the importance of these processes in

PJS, carcinogenesis and provides novel potential targets for gene screening in tumors and for therapeutic intervention.

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