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The role of *STK 11* gene testing in individuals with oral pigmentation.

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Abstract

Importance: Peutz-Jeghers Syndrome (PJS) is a rare, autosomal dominant condition characterised by mucocutaneous pigmented lesions, gastrointestinal polyposis and a significant risk of cancer. Laugier-Hunziker Syndrome (LHS) is a benign condition with similar dermatological features, but with no systemic complications. STK 11 gene testing allows clinicians to differentiate between these two disorders. This case report compares the dermatological similarities seen in four individuals with PJS or LHS and illustrates the potential benefit of genetic testing.

Observations: There is greater than 90% likelihood of identifying a mutation in STK 11 if a patient fulfils the diagnostic criteria for PJS. Lifelong risk management is advised for these individuals with confirmed PJS. Diagnostic confirmation is important to provide rational management, in particular, endoscopic cancer surveillance, and psychological support.

Conclusions and Relevance: STK 11 testing can confirm those at risk of PJS, who require lifelong surveillance, and possibly release those with a simple dermatosis, such as LHS, from invasive and thus potentially harmful surveillance.

Key words: Peutz-Jeghers Syndrome (PJS), Laugier-Hunziker Syndrome (LHS), STK

11 Introduction

Peutz-Jeghers Syndrome (PJS) (OMIM 175200) is rare, autosomal dominant condition caused by mutations in the Serine/Threonine Kinase 11 (STK11) gene. The syndrome is characterised by mucocutaneous pigmentation, gastrointestinal hamartomatous polyps, which can cause intussusception and an increased risk of cancer of multiple sites, including gastrointestinal and breast. The lifetime risk of cancer is estimated to be 76-85% .^{1,2} PJS affects approximately 1 in 8300 individuals.

A clinical diagnosis of PJS is made if any **one** of the following is present: two or more histologically confirmed Peutz-Jeghers (PJ) polyps; any number of PJ polyps in an individual who has a family history of PJS; characteristic mucocutaneous pigmentation in an individual who has a family history of PJS; or any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation.³ The PJS diagnostic criteria was established in 2007 following a consensus statement by European experts who had previously published guidelines on Lynch syndrome and Familial Adenomatous Polyposis. ³

Genetic confirmation of a clinical diagnosis of PJS by STK11 testing is available in Australia, following assessment by a clinical genetic service or a familial cancer clinic. Pre-test counselling includes confirmation of personal and family history, and discussing the implications for the individual and family if a mutation is identified. STK11 testing is publically funded in Australia, although this can vary across states. Methodologically, gene sequencing and MLPA detects 58-69% and 31-42% of mutations, respectively. ^{4,5,6}

Up to 95% of individuals with PJS have pigmentation. Typically the lesions are macular, and tan, bluish black or dark brown in colour. ³ The macules range from 1-5mm in size and can affect the lips, gingiva, buccal mucosa, hand, feet and genitals. Lip pigmentation appears in childhood and may fade with age, whereas buccal pigmentation often persists in adulthood.^{1, 3, 7}

Individuals with PJS are recommended to have lifelong cancer surveillance starting from 8 years of age, including at least 3 yearly colonoscopy, gastroduodenoscopy and capsule endoscopy. If female, yearly breast Magnetic Resonance Imaging (MRI) and 2 yearly gynaecological assessment is advised, and testicular examination in males.^{3,7} The risk of pancreatic cancers is also increased in PJS; although some experts recommend frequent ultrasound, the benefit of pancreatic surveillance requires further investigation.^{3,7,8} Prior to the availability of confirmatory genetic testing, patients who had a suspected clinical diagnosis of PJS were likewise recommended to have this cancer screening. Anecdotally, patients have been diagnosed with PJS, due to the presence of mucocutaneous lesions, and have been advised surveillance, although they have not met the PJS diagnostic criteria.

The risks associated with surveillance, albeit low, can lead to significant morbidity and on rare occasions, mortality. Serious complications of screening colonoscopy, for example, occur in 2.4 per 1000 procedures⁹ and include perforation, bleeding, myocardial infarction and stroke. Long term regular surveillance can be intrusive, and can contribute to anxiety and depression, along with endorsement of an individual identifying as being at potentially high risk for a range of cancers.¹⁰ There have been few studies that have assessed the psychosocial impact of PJS. Woo et al., and van Lier et al., identified, via quality of life questionnaires, that individuals with PJS had mild depressive symptoms, and poorer health perceptions in comparison to the general population. 30-40% of respondents also reported that having PJS affected major life decisions, reproductive choices and even their desire to have children.^{10,11} The psychosocial implications, in addition to the potential iatrogenic complications of investigating such a diagnosis, should not be underestimated and hence, an accurate diagnosis is paramount.

Laugier-Hunziker syndrome (LHS) is a rare, benign condition with PJS – like mucocutaneous lesions. LHS perioral macules are also dark brown to black in colour; it is more predominant in females, and often begins in the third to fifth decade of life.¹² Approximately 180 cases have been reported since it was first described in 1970 and it is mostly a diagnosis of exclusion.¹⁶ 60% of individuals with LHS also have longitudinal melanonychia.^{14,15} In contrast to PJS, there

are no known systemic complications of LHS and no evidence of an increased cancer risk; therefore a correct diagnosis avoids the requirement for surveillance.^{16,17} There does not appear to be a consistent familial pattern of LHS and to date a genetic basis for this dermatosis has not been elucidated.

The following cases illustrate the dermatological similarities of PJS and LHS and the role of STK11 genetic testing.

Case 1

A 37 year old female, had multiple peri-oral pigmented macules from the age of 15, which are increasing in number (Fig 1a). She has no intraoral or nail pigmentation. She has intermittent abdominal pain and constipation, but is relieved on a low Fermentable, Oligo-, Di-, Mono-saccharides And Polyols (FODMAP) diet. There is no family history of pigmentation and both of her parents have had normal colonoscopies.

The patient was previously advised to have screening colonoscopies, although declined and preferred to have STK11 testing. However, soon thereafter, prior to her testing results, she required a colonoscopy for symptomatic anaemia. No polyps or cause was identified. No mutation was identified in STK11 and a diagnosis of probable LHS was made. In the absence of symptoms and family history, no further endoscopy is required.

Case 2

A 40 year old woman had lip and buccal mucosal pigmentation since the age of 12 (Fig 1b). The pigmentation initially increased but has not progressed in recent years. She has no other pigmentation and no gastrointestinal symptoms. There is no family history of significance, although her father was adopted. She had been diagnosed with clinical PJS (although the PJS

diagnostic criteria was not fulfilled) and has had regular colonoscopies since the age of 14, all of which have been normal. No mutation was identified in STK11 and further endoscopy screening has been ceased.

Case 3

This 33 year old man was first reviewed at the age of 20, when he was referred for assessment of lip and finger pigmentation that had begun in early childhood (Fig 1c). Prior to referral, he had a few episodes of rectal bleeding, associated with abdominal pain, but he did not pursue further investigations, as the symptoms had resolved. There is no family history of significance. Genetic testing identified a STK 11 mutation (frameshift in codon 27) which introduces a premature stop codon downstream.

Since PJS has been confirmed, this patient has undergone regular endoscopy screening and hamartomatous polyps have been identified throughout the gastrointestinal tract. His siblings and mother have all tested negative for the mutation.

Case 4

This 30 year old woman has had a clinical diagnosis of PJS since the age of 15 when she presented with intussusception. Polyps and characteristic lip pigmentation was identified at that time (Fig 1d). Both her father and sister have clinical features of PJS and her brother was diagnosed with metastatic cholangiocarcinoma at the age of 28, shortly after her presentation. A STK11 mutation (out of frame deletion of exons 1-3) was detected which segregated with the phenotype across the family.

Conclusion

STK 11 testing was helpful in the assessment and ongoing management of these cases who all presented with similar dermatological findings.

These cases illustrate the value of utilizing the clinical criteria in the diagnosis of PJS. They also highlight the benefit of genetic testing as an adjunct to a clinical PJS diagnosis. Lip pigmentation is suggestive, but is not diagnostic of PJS. Endoscopy, especially in young individuals may be time limited, and repeated investigations are warranted to confirm or negate a clinical diagnosis. In individuals with a clinical diagnosis of PJS based on consensus guidelines, genetic testing reveals a STK11 mutation in over 94%.⁴ To date, no alternate gene has been found to explain the missing 6% of heritability. In individuals where a mutation is not identified, the clinical diagnosis needs reviewing with a view to testing other polyp associated genes, if polyposis is present. If an individual still meets the diagnosis criteria for PJS, they should continue the risk management for PJS.

The absence of a mutation in STK 11, negated the diagnosis in Cases 1 and 2 and removed the anxiety associated with a cancer syndrome for both women (noting that although they had received a clinical diagnosis, neither case 1 nor 2 met PJS criteria). Neither individual require further surveillance and have been released from our ongoing care. Had a family history been present, these patients would have been given individualised colonoscopy screening advice based on the youngest age of diagnosis of bowel cancer or polyps in the family.

A negative STK11 result can be cost effective in a public healthcare system, through the cessation of unnecessary screening. In the future, the identification of the Laugier- Hunziker Syndrome gene locus, if indeed one exists, could confirm this alternative diagnosis.

Genetic testing in Cases 3 and 4 identified pathogenic STK 11 mutations, confirming PJS.

Although some would argue that testing of individuals with clear PJS is not necessary, detecting a STK 11 mutation allows family members to have predictive testing to decipher their own risk or facilitate pre-implantation genetic diagnosis for future children.

STK11 testing in individuals with suspected PJS, provides a confirmatory basis for lifelong surveillance for those where it is required, and provides the potential for release from surveillance for those with a simple dermatosis.

Informed consent, including permission to publish photographs has been obtained from all patients referred to in this report.

References

1. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006; 12(10): 3209-3215.
2. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010; 105(6):1258-1264.
3. Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010; 59(7):975-86.
4. Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat. 2005; 26:513-19.
5. Papp J, Kovacs ME, Solyom S, et al. High prevalence of germline STK11 mutations in Hungarian Peutz-Jeghers Syndrome patients. BMC Med Genet. 2010;11:169
6. Chow E, Meldrum CJ, Crooks R, et al. An updated mutation spectrum in an Australian series of PJS patients provides further evidence for only one gene locus. Clin Genet. 2006;70(5):409-414
7. Giardiello FM, Trimpath JD. Peutz-Jeghers Syndrome and Management Recommendations. Clin Gastroenterol Hepatol. 2006; 4(4): 408 – 415

8. Korsse SE, Harinck F, van Lier MG, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. *J Med Genet.* 2013; 50(1):59-64.
9. Stock C, Ihle P, Sieg A, et al. Adverse events requiring hospitalization within 30 days after outpatient screening and nonscreening colonoscopies. *Gastrointestinal Endoscopy.* 2013; 77(3):419-429
10. Woo A, Sadana A, Mauger DT, et al. Psychosocial impact of Peutz-Jeghers Syndrome. *Fam Cancer.* 2009; 8(1):59-65.
11. van Lier MG, Mathus-Vliegen EM, van Leerdam ME, et al. Quality of life and psychological distress in patients with Peutz–Jeghers syndrome. *Clin Genet.* 2010; 78(3):219-26.
12. Laugier P, Hunziker N. Essential lenticular melanic pigmentation of the lip and cheek mucosa. *Arch Belg Dermatol Syphiligr.* 1970; 26(3):391-9.
13. Wang WM, Wang X, Duan N, et al. Laugier–Hunziker syndrome: a report of three cases and literature review. *Int J Oral Sci.* 2012; 4(4): 226–230.
14. Baran R. Longitudinal melanotic streaks as a clue to Laugier-Hunziker syndrome. *Arch Dermatol.* 1979; 115(12):1448–1449.
15. Kanwar AJ, Kaur S, Kaur C, et al. Laugier-Hunziker syndrome. *J Dermatol.* 2001; 28(1):54–57.
16. Yago K, Tanaka Y, Asanami S. Laugier-Hunziker-Baran syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008; 106(2):e20–25.
17. Nayak RS, Kotrashetti VS, Hosmani JV. Laugier-Hunziker syndrome. *J Oral Maxillofac Pathol.* 2012; 16(2):245-50.

Figure Legends

Fig 1. Mucocutaneous Pigmentation of the lips 1a. Benign dermatosis 1b. Benign dermatosis 1c. PJS 1d. PJS

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