



Patient Report

Unsolved Mysteries

A Report by
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A letter from a group member about PJS genetic testing got me thinking about PJS unsolved mysteries. One of them is whether all PJS folks have the STK11/LKB1 mutation on chromosome 19p13.3. When that mutation site was found in 1998, nearly all the PJS patients had a mutation there. Not the same mutation, in fact by 2003 nearly 80 distinct mutations were described. (Boudeau, 2003). But, five years ago most researchers agreed on the genetic cause of PJS. Since then it is clear that there is more than one mutation site (genetic heterogeneity) for PJS. The end of this report lists many research findings on the frequency of this mutation in PJS patients.

After analyzing PJS patients for the mutation, many researchers began analyzing the cancers of people who don't have PJS to find out whether it is mutated in "sporadic" cancers. This is a fairly common practice -- to identify a hereditary cancer syndrome, find the genetic locus for that syndrome, find that locus in affected patients, then explore whether that locus is mutated in cancers of people who don't have the syndrome. The most "famous" of these cancer-predisposing syndromes is Li-Fraumeni syndrome which affects something like 300 people worldwide and confers a tremendously high risk of multiple cancers. People with Li-Fraumeni have a p53 mutation at birth and undergo "second hits" during life which lead to cancer. Researchers found that p53 is mutated in many cancers of people who don't have Li-Fraumeni; and that PJS is associated with p53.¹

When researchers found few STK11/LKB1 mutations in cancers of people who don't have PJS, they stopped that line of investigation and went on to develop mouse and fly models with STK11/LKB mutations. I've written about these developments in PJS genetics advances for this group during the past three years. But I've not reported much on "genetic heterogeneity" in PJS. Genetic heterogeneity (hetero=different, geneity=gene) means that different mutation sites can lead to a genetic condition.

Although early reports indicated that most PJS folks had a mutation of STK11/LKB1 at chromosome 19p13.3, later reports didn't confirm that finding. What follows are different reports of the frequency of this mutation in PJS patients. I've included quotes from a couple of the articles to provide more detail.

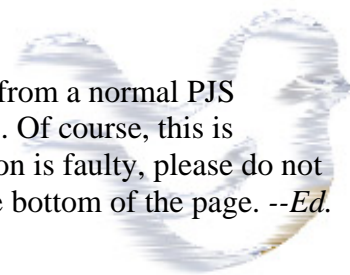
If a PJS person doesn't have a mutation at the known site, other family members cannot get genetic testing. If a patient's genetic screening is negative or inconclusive for the mutation, then their children must be treated as if they have PJS and undergo screening for polyps including scopes and x-rays - expensive, traumatic procedures with risk of complications. If a patient's mutation can be found, then offspring can be tested for that mutation and those with the mutation will undergo screening for polyps, while those without the mutation won't need to do it. Finding another PJS site or locus would benefit families whose mutation isn't at the known site. Researchers have begun to search for a second PJS locus.² And a possibility on chromosome 2q36 was suggested in an earlier article by Smith et al.³

Hopefully researchers will continue to explore possible alternate mutation sites for PJS. Finding other sites will, at minimum, help those families who don't have a mutation at the known site. It may also lead to understanding and treatment of people with PJS. And finally, it may contribute to prevention, treatment and cure of cancer in the general population.

There is much more to be written about this interesting topic. Hopefully some of you will look at the references in this article. The numbers of PJS folks with and without the mutation and also the authors, titles and dates of the articles give an emerging picture of genetics research into PJS.

Number of patients with mutation	Location, if noted	Reference Article
11 of 12	n/a	Hemminki et al ⁴
5 of 6	n/a	Jenne et al ⁵
6 of 6	n/a	Gruber et al ⁶
7 of 9	n/a	Mehenni et al ⁷
5 of 9	Italy	Resta et al ⁸
9 of 15	Japan	Nakagawa et al ⁹
4 of 4	Germany	Kruse et al ¹⁰
16 of 33	n/a	Ylikorkala et al ¹¹
12 of 19	Holland	Westerman et al ¹²
7 of 12	n/a	Wang et al ¹³
1 of 10	Canada	Jiang et al ¹⁴
2 of 8	China	Li et al ¹⁵
6 of 33	n/a	Boardman et al ¹⁶
5 of 10	Korea	Yoon et al ¹⁷
6 of 18	China	Li et al ¹⁸
7 of 14	Australia	Scott et al ¹⁹
6 of 6	n/a	Boudeau et al ²⁰
115 of 224	(51.3%)	

Note: Statistically, it is likely that the above samples were taken from a normal PJS population. The results are not unexpected, from a statistics view. Of course, this is coming from a very amateur statistician. If you find my conclusion is faulty, please do not hesitate to let me know by using the Email Webmaster link at the bottom of the page. --Ed.



¹Karuman P, Gozani O, Odze RD, Zhou XC, Zhu H, Shaw R, Brien TP, Bozzuto CD, Ooi D, Cantley LC, Yuan J. *The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death*. Mol Cell. 2001 Jun;7(6):1307-19.

PMID: 11430832 [PubMed - indexed for MEDLINE]

²Buchet-Poyau K, Mehenni H, Radhakrishna U, Antonarakis SE. *Search for the second Peutz-Jeghers syndrome locus: exclusion of the STK13, PRKCG, KLK10, and PSCD2 genes on chromosome 19 and the STK11IP gene on chromosome 2*. Cytogenet Genome Res. 2002;97(3-4):171-8.

PMID: 12438709 [PubMed - indexed for MEDLINE]

³Smith DP, Rayter SI, Niederlander C, Spicer J, Jones CM, Ashworth A. *LIP1, a cytoplasmic protein functionally linked to the Peutz-Jeghers syndrome kinase LKB1*. Hum Mol Genet. 2001 Dec 1;10(25):2869-77.

PMID: 11741830 [PubMed - indexed for MEDLINE]

⁴Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, Warren W, Aminoff M, Hoglund P, Jarvinen H, Kristo P, Pelin K, Ridanpaa M, Salovaara R, Toro T, Bodmer W, Olschwang S, Olsen AS, Stratton MR, de la Chapelle A, Aaltonen LA. *A serine/threonine kinase gene defective in Peutz-Jeghers syndrome*. Nature. 1998 Jan 8;391(6663):184-7.

PMID: 9428765 [PubMed - indexed for MEDLINE]

⁵Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Muller O, Back W, Zimmer M. *Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase*. Nat Genet. 1998 Jan;18(1):38-43.

PMID: 9425897 [PubMed - indexed for MEDLINE]

PMID: 9425897 [PubMed - indexed for MEDLINE]

⁶Gruber SB, Entius MM, Petersen GM, Laken SJ, Longo PA, Boyer R, Levin AM, Mujumdar UJ, Trent JM, Kinzler KW, Vogelstein B, Hamilton SR, Polymeropoulos MH, Offerhaus GJ, Giardiello FM. *Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome*. Cancer Res. 1998 Dec 1;58(23):5267-70.

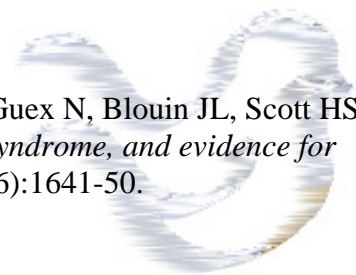
PMID: 9850045 [PubMed - indexed for MEDLINE]

⁷Mehenni H, Gehrig C, Nezu J, Oku A, Shimane M, Rossier C, Guex N, Blouin JL, Scott HS, Antonarakis SE. *Loss of LKB1 kinase activity in Peutz-Jeghers syndrome, and evidence for allelic and locus heterogeneity*. Am J Hum Genet. 1998 Dec;63(6):1641-50.

PMID: 9837816 [PubMed - indexed for MEDLINE]

⁸Resta N, Simone C, Marenzi C, Montera M, Gentile M, Susca F, Gristina R, Pozzi S, Bertario L, Bufo P, Carlomagno N, Ingrosso M, Rossini FP, Tenconi R, Guanti G. *STK11 mutations in Peutz-Jeghers syndrome and sporadic colon cancer*. Cancer Res. 1998 Nov 1;58(21):4799-801.

PMID: 9809980 [PubMed - indexed for MEDLINE]



⁹Nakagawa H, Koyama K, Miyoshi Y, Ando H, Baba S, Watatani M, Yasutomi M, Matsuura N, Monden M, Nakamura Y. *Nine novel germline mutations of STK11 in ten families with Peutz-Jeghers syndrome*. Hum Genet. 1998 Aug;103(2):168-72.
PMID: 9760200 [PubMed - indexed for MEDLINE]

¹⁰Kruse R, Uhlhaas S, Lamberti C, Keller KM, Jackisch C, Steinhard J, Knopfle G, Loff S, Back W, Stolte M, Jungck M, Propping P, Friedl W, Jenne DE. *Peutz-Jeghers syndrome: four novel inactivating germline mutations in the STK11 gene. Mutations in brief no. 227. Online*. Hum Mutat. 1999;13(3):257-8.
PMID: 10090485 [PubMed - indexed for MEDLINE]

¹¹"...we studied samples from 33 unrelated PJS patients including eight non-familial sporadic patients, 20 familial patients and five patients with unknown family history. Nineteen germline mutations were identified, 12 (60%) in familial and four (50%) in sporadic cases. LKB1 mutations were not detected in 14 (42%) patients, indicating that the existence of additional minor PJS loci cannot be excluded."

Ylikorkala A, Avizienyte E, Tomlinson IP, Tiainen M, Roth S, Loukola A, Hemminki A, Johansson M, Sistonen P, Markie D, Neale K, Phillips R, Zauber P, Twama T, Sampson J, Jarvinen H, Makela TP, Aaltonen LA. *Mutations and impaired function of LKB1 in familial and non-familial Peutz-Jeghers syndrome and a sporadic testicular cancer*. Hum Mol Genet. 1999 Jan;8(1):45-51.
PMID: 9887330 [PubMed - indexed for MEDLINE]

¹²Westerman AM, Entius MM, Boor PP, Koole R, de Baar E, Offerhaus GJ, Lubinski J, Lindhout D, Halley DJ, de Rooij FW, Wilson JH. *Novel mutations in the LKB1/STK11 gene in Dutch Peutz-Jeghers families*. Hum Mutat. 1999;13(6):476-81.
PMID: 10408777 [PubMed - indexed for MEDLINE]

¹³Wang ZJ, Churchman M, Avizienyte E, McKeown C, Davies S, Evans DG, Ferguson A, Ellis I, Xu WH, Yan ZY, Aaltonen LA, Tomlinson IP. *Germline mutations of the LKB1 (STK11) gene in Peutz-Jeghers patients*. J Med Genet. 1999 May;36(5):365-8.
PMID: 10353780 [PubMed - indexed for MEDLINE]

¹⁴Jiang CY, Esufali S, Berk T, Gallinger S, Cohen Z, Tobi M, Redston M, Bapat B. *STK11/LKB1 germline mutations are not identified in most Peutz-Jeghers syndrome patients*. Clin Genet. 1999 Aug;56(2):136-41.
PMID: 10517250 [PubMed - indexed for MEDLINE]

¹⁵Li Y, Lu X, Xia J. *[STK11 gene mutation in Chinese with PJS]* Zhonghua Yi Xue Za Zhi. 1999 Jun;79(6):425-7. Chinese.
PMID: 11715436 [PubMed - indexed for MEDLINE]

¹⁶Boardman LA, Couch FJ, Burgart LJ, Schwartz D, Berry R, McDonnell SK, Schaid DJ, Hartmann LC, Schroeder JJ, Stratakis CA, Thibodeau SN. *Genetic heterogeneity in Peutz-Jeghers syndrome*. Hum Mutat. 2000;16(1):23-30.
PMID: 10874301 [PubMed - indexed for MEDLINE]

¹⁷Yoon KA, Ku JL, Choi HS, Heo SC, Jeong SY, Park YJ, Kim NK, Kim JC, Jung PM, Park JG. *Germline mutations of the STK11 gene in Korean Peutz-Jeghers syndrome patients*. Br J Cancer. 2000 Apr;82(8):1403-6.

PMID: 10780518 [PubMed - indexed for MEDLINE]

¹⁸"Mutation frequency is 66.7% in the family suffering PJS in two or more generations, and 16.7% in the disseminated cases."

Li Y, Lu X, Xia J, Tang X, Xia K, He Y, Zhang G. *[Mutation characteristic of STK]* Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2001 Feb;18(1):4-7. Chinese.

PMID: 11172631 [PubMed - indexed for MEDLINE]

¹⁹Scott RJ, Crooks R, Meldrum CJ, Thomas L, Smith CJ, Mowat D, McPhillips M, Spigelman AD. *Mutation analysis of the STK11/LKB1 gene and clinical characteristics of an Australian series of Peutz-Jeghers syndrome patients*. Clin Genet. 2002 Oct;62(4):282-7.

PMID: 12372054 [PubMed - indexed for MEDLINE]

²⁰Boudeau J, Kieloch A, Alessi DR, Stella A, Guanti G, Resta N. *Functional analysis of LKB1/STK11 mutants and two aberrant isoforms found in Peutz-Jeghers Syndrome patients*. Hum Mutat. 2003 Feb;21(2):172.

PMID: 12552571 [PubMed - indexed for MEDLINE]

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