Genetic Links

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Uterine leiomyomata (UL), also called fibroids, are the most common pelvic tumors in females. Although benign neoplasms, UL constitute a major public health problem as 20-25% of affected women experience debilitating symptoms including excessive menstrual bleeding, pelvic discomfort, and reproductive failure. Medical treatment options for UL are limited, and surgery is the mainstay of therapy. In fact, UL are the most common indication for hysterectomy accounting for over 200,000 procedures annually in the United States. Although it is well recognized that UL are steroid-dependent tumors, much remains to be known about their growth and development. Compelling evidence suggests a genetic liability to develop UL. These tumors are at least three times more frequent in black than in white women [Faerstein et al., 2001; Marshall et al., 1997], and twin-pair correlations for hysterectomy in monozygotic twins are about twice that observed in dizygous twins [Treloar et al., 1992]. Studies of familial aggregation indicate a 2.5-fold increased risk for UL among first-degree relatives of affected probands compared to relatives of unaffected probands; this odds ratio increases to 5.7 after stratifying cases by age of proband (< 45 years) and of relatives (≤ 40 years) [Schwartz et al., 2000]. About 25-40% of UL are karyotypically abnormal, and several genes involved in the pathobiology of the tumors have been identified using positional cloning approaches based on chromosome rearrangements [Schoenberg Fejzo et al., 1996; Schoenmakers et al., 1995; Williams et al., 1997]. Genetic linkage analysis in two rare Mendelian disorders, Reed syndrome (MIM150800), characterized by UL in association with multiple cutaneous leiomyomata, and hereditary leiomyomatosis and renal cell cancer (HLRCC, MIM605839), a cancer syndrome characterized by uterine leiomyomas and papillary renal cell carcinoma, resulted in the surprising finding of mutations in the gene for fumarate hydratase [Alam et al., 2001; Tomlinson et al., 2002; Toro et al., 2003]. Despite these important findings, we remain ignorant of the major genes that predispose millions of women to develop these tumors. Studies are clearly warranted that focus on identification, isolation and characterization of genes involved in the pathogenesis of UL. Underway in my laboratory is an effort to identify genes that predispose women to develop UL through a genome-wide scan (www.fibroids.net: "Finding Genes for Fibroids"). Ultimately, understanding genetic pathways involved in the formation of UL may lead to improved treatment options for affected women and lifestyle changes for at risk individuals.

References

Alam NA, Bevan S, Churchman M, Barclay E, Barker K, Jaeger EE, Nelson HM, Healy E, Pembroke AC, Friedmann PS and others. 2001. Localization of a gene (MCUL1) for multiple cutaneous leiomyomata and uterine fibroids to chromosome 1q42.3-q43. Am J Hum Genet 68(5):1264-9.

Faerstein E, Szklo M, Rosenshein NB. 2001. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. Am J Epidemiol 153(1):11-9.

Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. 1997. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 90(6):967-73.

Schoenberg Fejzo M, Ashar HR, Krauter KS, Powell WL, Rein MS, Weremowicz S, Yoon S-J, Kucherlapati RS, Chada K, Morton CC. 1996. Translocation breakpoints upstream of the

HMGIC gene in uterine leiomyomata suggest dysregulation of this gene by a mechanism different from that in lipomas. Genes, Chromosomes and Cancer 17:1-6.

Schoenmakers EFPM, Wanschura S, Mols R, Bullerdiek J, Van den Berghe H, Van de Ven WJM. 1995. Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumours. Nature Genetics 10:436-443.

Schwartz S, Voigt L, Tickman E, Yarbro P, Daling J, Scholes D. 2000. Familial aggregation of uterine leiomyomata. Presented at the annual meeting of the Society for Epidemiological Research, Seattle, WA (June 2000).

Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, Leigh I, Gorman P, Lamlum H, Rahman S and others. 2002. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 30(4):406-10.

Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, Stewart L, Duray P, Tourre O, Sharma N and others. 2003. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in north america. Am J Hum Genet 73(1):95-106.

Treloar SA, Martin NG, Dennerstein L, Raphael B, Heath AC. 1992. Pathways to hysterectomy: Insights from longitudinal twin research. American Journal of Obstetrics and Gynecology 167(1):82-88.

Williams AJ, Powell WL, Collins T, Morton CC. 1997. HMGI(Y) expression in human uterine leiomyomata: Involvement of another HMG architectural factor in a benign neoplasm. American Journal of Pathology 150:911-918.