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Molecular genetics and racial disparities of uterine leiomyomas

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Abstract

Uterine leiomyomas (ULMs) are benign oestrogen-dependent tumours of the myometrium. They are the most common tumours of the female genital tract, affecting around 77% of the female population. ULMs are more common in Black women than White women. These tumours tend to develop earlier and be more numerous, larger in size and more symptomatic in Black women than other ethnic groups. The molecular mechanism underlying this ethnic disparity is not fully understood. Polymorphism of genes involved in oestrogen synthesis and/or metabolism (*COMT*, *CYP17*), variation in the expression levels or function of oestrogen and progesterone receptors or retinoic acid nuclear receptors (retinoid acid receptor-α, retinoid X receptor-α), or aberrant expression of micro-RNAs are some of the molecular mechanisms that may be involved.

Keywords

molecular genetics; race; leiomyoma

Uterine leiomyomas (ULMs) are benign, monoclonal tumours of the smooth muscle cells of the myometrium. They are composed of large amounts of extracellular matrix containing collagen, fibronectin and proteoglycan.[1] ULMs may cause significant morbidity through their presence in the uterus and pelvic cavity. These benign tumours are a significant cause of pelvic pain, abnormal uterine bleeding, infertility and pregnancy complications.[2]

ULMs are the most common tumours of the female genital tract. Serial sectioning at 2-mm intervals of 100 consecutive total hysterectomy specimens revealed the presence of leiomyomas in 77% of cases.[3] The rate of hospitalization of women for ULMs is 3.0 per 1000 women-years in the USA. Around 200 000 hysterectomies and 30 000 myomectomies

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are performed each year to treat women with ULMs,[4,5] and the overall costs for inpatient surgeries for ULMs are US$ 2.1 billion per year.[1]

OESTROGEN DEPENDENCY OF ULMS

There is plenty of clinical and research evidence that ULMs are oestrogen-dependent tumours. The risk of developing ULMs increases with age during the premenopausal years; however, tumours typically regress and/or become asymptomatic with the onset of menopause.[6] Obesity, age at menarche and unopposed oestrogen exposure have been linked to an increased risk of ULMs, and cigarette smoking, use of oral contraceptives and parity have been identified as protective factors.[7] Moreover, using gonadotrophin-releasing hormone agonists leads to shrinkage of ULMs through the suppression of ovarian oestrogen production to postmenopausal levels.[8] At the molecular level, primary ULM cells express oestrogen receptors (OR) and progesterone receptors (PR). Rodent leiomyoma cells derived from the Eker rat model for this disease proliferate in response to oestrogen in culture, and this response can be inhibited by oestrogen antagonists such as ICI 182780, tamoxifen and raloxifene.[9] In addition, an elevated transcriptional response to oestrogen in leiomyoma cells suggests that these tumours may have increased responsiveness or be hypersensitive to oestrogen stimulation.[10]

EPIDEMIOLOGICAL STUDIES OF RACIAL DIFFERENCES IN THE INCIDENCE OF ULMS AND OTHER OESTROGEN-RELATED DISORDERS

ULMs do not affect all races equally. Increased prevalence of ULMs in African-American women was observed more than 100 years ago. A report published in 1894 on the prevalence of fibrosis processes in the dark-skinned races identified leiomyomas as one of the diseases considered as peculiar to the dark-skinned races. The author attributed this to ‘something in the blood of the dark-skinned people that predisposes to the development of fibrous growth’.[11]

Recent data have confirmed the racial differences in ULMs. Marshall et al prospectively studied a large cohort of premenopausal women with intact uteri and no history of ULMs for 4 years. They found that the age-standardized rates of ultrasound- or hysterectomy-confirmed leiomyoma were significantly higher in Black women compared with White women. Similarly, Baird et al[12] demonstrated that the incidence of myomas was 60% among African-American women by 35 years of age, and the incidence increased to over 80% by 50 years of age. Caucasian women had an incidence of 40% by 35 years of age and almost 70% by 50 years of age (Figure 1).

The ethnic differences in the incidence of ULMs were reflected in the hysterectomy rates in different ethnic groups. Kjerulff et al[13] found that the annual age-adjusted hysterectomy rate was significantly higher in Black women compared with White women. ULMs were the primary diagnosis for 65.4% of hysterectomies in Black women, compared with only 28.5% in White women. Also, Myers et al[14] reported a three-fold increase in hysterectomy rates in Black women compared with White or Hispanic women. Black women had a lifetime risk of hysterectomy approaching 22% (Figure 2).

Kjerulff et al[13] found that the average ages at ULM diagnosis and hysterectomy were younger for Black women than White women. The average uterine weight was heavier for Black women compared with White women. Black women were more likely to have seven or more ULMs than White women, and a higher proportion of Black women reported severe symptoms in the form of anaemia or severe pelvic pain. The molecular background behind the ethnic disparity in ULMs is not fully understood.

Epidemiological studies have shown that, in addition to ULMs, several other oestrogen-dependent disorders show ethnic/racial disparity in their incidence and biological behaviours. White women have higher incidence rates of endometrial and breast cancers than African-American women.[15] In contrast, African-Americans have higher mortality rates from breast and endometrial cancer than White women.[16] This is related to a greater frequency of adverse clinicopathological features in African-American women, including advanced tumours, high-grade tumours and more aggressive histology, compared with White women.[17–19]

Moreover, Black women have a lower risk for osteoporosis compared with White women. Age-adjusted estimates of osteoporosis of the hip are significantly higher for postmenopausal White women than Black women.[20] In addition, Black race appears to be protective against the development of pelvic floor disorders such as urinary stress incontinence and pelvic organ prolapse, which are more common in White women.[21] Figure 3 summarizes the ethnic disparities in the incidence of oestrogen-dependent diseases.

The racial/ethnic disparity in the incidence and biological behaviours of ULMs in addition to other oestrogen-dependent diseases suggests that different races may exhibit differences in oestrogen biosynthesis and/or metabolism. This concept appears more plausible as racial differences in the exposure to risk factors associated with ULMs could not explain the differences in their incidence between races. In the work by Marshall et al, even after adjustment for factors such as marital status, body mass index, age at first birth, years since last birth, history of infertility, age at first oral contraceptive use and current alcohol consumption, ULM incidence rates in Black women were still significantly higher than those in White women.

POLYMORPHISM OF GENES INVOLVED IN OESTROGEN SYNTHESIS AND/OR METABOLISM (*CYP17* AND *COMT*)

CYP17

Polymorphism of genes coding for different enzymes involved in oestrogen biosynthesis and/or metabolism have been investigated in different studies as a possible mechanism. One of these genes is *CYP17* which codes for the cytochrome P450C17α enzyme. This enzyme mediates both steroid 17α-hydroxlyase and 17, 20-lyase activities, and functions at key branch points in human steroidogenesis.[22] The 5′ untranslated region of *CYP17* contains a single base pair polymorphism, a T (designated as A1) to a C (designated as A2), 34 base pairs upstream from the initiation of translation and 27 base pairs downstream from the transcription start site.[23] Among premenopausal women, there appears to be a steady increase in serum oestradiol and progesterone concentrations depending on the number of

A2 alleles that a woman carries, with the A2/A2 genotype corresponding to the highest concentrations.[24]

Amant et al[25] studied 89 Black South African and 56 Caucasian women who underwent hysterectomy. Blood samples were withdrawn from these women, and the hysterectomy specimens were examined pathologically for the presence (study group) or absence (control group) of ULMs. DNA was isolated from the blood cells and was used in a polymerase chain reaction to determine the *CYP17* genotype of the patient. To determine the impact on the incidence of ULMs, *CYP17* genotype in addition to other risk factors associated with ULMs (age, parity, age at last birth, weight, body mass index, menopausal status, cigarette smoking and oral contraceptive use) were put in a statistical model. Age, race and parity appeared to affect the incidence of ULMs in that model which included Caucasian and Black South African women. Logistic regression analysis in Caucasian women showed that oral contraceptives were protective against the development of ULMs regardless of *CYP17* genotype. Logistic regression applied in Black South African women showed that age and *CYP17* polymorphism were correlated positively with the presence of ULMs. Using categorical data analysis, the risk for ULM development among Black South African women with the *CYP17* A2/A2 genotype was shown to be increased, whereas the risk in Black South African women with the *CYP17* A1/A1 and A1/A2 genotypes was shown to be lower (Table 1). Also, ULMs were larger in size in women with the *CYP17* A2/A2 genotype compared with women with the A1/A2 or A1/A1 genotypes; however, the difference was not statistically significant. The authors hypothesized that higher levels of oestrogen in African women homozygous for *CYP17* A2 allele expose the myometrium to a stronger stimulatory effect, which may, in the long term, result in spontaneous mutations and uncontrolled growth; an important feature of ULMs.

COMT

Catechol-O-methyltransferase (COMT) is a ubiquitous enzyme that catalyses methyl conjugation of the hydroxyl groups of catechol oestrogens. Specifically, it catalyses the conversion of 2,4 hydroxy oestradiol to 2,4 methoxy oestradiol. Therefore, regulation of COMT activity may indirectly modulate the biological effects of oestrogen and play an aetiological role in leiomyoma formation.[26] A common genetic polymorphism, G to A transition at codon 158, resulting in a valine-to-methionine substitution, is associated with thermal instability and a four-fold decrease in enzymatic activity. The genotypes designated in relation to the predicated enzymatic activity of the protein are high (Val/Val), intermediate (Val/Met) and low (Met/Met) activity.[27]

In recent work by the authors' group, *COMT* gene polymorphism was studied in 186 women with ULMs and 142 women without ULMs. All subjects had a hysterectomy, and the presence (study group) or absence (control group) of ULMs was documented at histological level. Genotyping was performed using DNA isolated from normal myometrium, and was confirmed with DNA isolated from peripheral blood cells. The Val/Val (high activity) genotype was highly represented in ULM patients (39%) compared with the controls (21%) from all ethnic groups. However, the homozygous Met/Met (low activity) genotype was less represented in ULM patients (12%) compared with the controls (27%). The heterozygous

Val/Met genotype did not differ significantly between cases (49%) and controls (52%). Within each ethnic group, the Val/Val genotype was significantly more common in ULM cases than controls (Table 2).

Using multiple logistic models, White women had the lowest occurrence of leiomyomas. African-American and Hispanic women were 5.3 and 2.1 times more likely to have ULMs than White women, respectively. Overall, women with the Val/Val genotype were 2.5 times more likely to have ULMs compared with women with the Met/Met genotype (controlling for ethnicity). Conversely, *COMT* Val/Met and Met/Met did not mediate significantly different associations with ULMs.

The natural distribution of *COMT* genotypes in different racial groups was also addressed in the authors' study. African-American women had a high frequency of the Val/Val genotype (47%) and a low frequency of the Met/Met genotype (5%); heterozygous Val/Met was 49%. In sharp contrast, White women had a low frequency of the Val/Val genotype (19%) and a higher frequency of the Met/Met genotype (33%); heterozygous Val/Met was 48%.

Overall, these data show that the high-activity *COMT* (Val/Val) genotype is associated with ULMs in all ethnic groups. This genotype is more common in African-Americans than other races, and this may be associated with the higher incidence of ULMs in that ethnic group.

The exact relationship between *COMT* gene polymorphism and leiomyoma is not yet clear. COMT converts 2-hydroxy oestradiol to 2-methoxy oestradiol. 2-hydroxy oestradiol has been found to work as as anti-oestrogen in many tissue systems.[28,29] On the other hand, 2-methoxy oestradiol has been demonstrated to possess a mitogenic effect on different cell types.[30–32] Therefore, the high-activity *COMT* genotype (Val/Val) would derive rapid and efficient conversion of the anti-oestrogenic metabolite (2-hydroxy oestradiol) into the more mitogenic counterpart (2-methoxy oestradiol), thus creating a high oestrogenic cellular milieu. Conversely, the low-activity *COMT* genotype (Met/Met) would lead to the accumulation of 2-hydroxy oestradiol, creating a low oestrogenic environment. As ULMs are oestrogen dependent, a higher frequency of occurrence would be associated with the *COMT* Val/Val genotype than the low oestrogenic Met/Met genotype. In agreement with this hypothesis were the findings of Reddy et al,[33] who demonstrated lower levels of 2-hydroxy oestradiol in leiomyomas compared with adjacent normal myometrium and implicated this in the tumourgenesis. In the same context, two reports in American[34] and Finnish[27] populations described a significantly decreased risk of breast cancer in premenopausal women with a *COMT* Met/Met genotype.

In-vitro data have confirmed the effects of the *COMT* genotype on the phenotype of myometrial and ULM cells.[35] The Val/Val primary myometrial cells showed a significantly higher proliferation rate, greater transcriptional response to oestrogen (as evidenced by higher luciferase reporter transactivation) and a gene expression profile expressive of high oestrogenic milieu (increased expression of cyclo-oxygenase 2, cyclin D1, PR-A, PR-B and Bcl2, and decreased expression of BAX) compared with their Met/Met counterparts. This confirms the high oestrogenic drive of myometrial cells of the *COMT* Val/Val genotype.

Variations in steroid receptor expression were one of the molecular mechanisms evaluated by researchers to explain the racial differences in ULMs. Several recent reports have attempted to expose leiomyomas to gene arrays, and suggested no significant difference in OR expression levels in leiomyomas compared with adjacent normal myometrium.[36] In addition, two studies failed to show significant differences in the expression of ORs and PRs in the myometrium between Black and White women.[37,38]

DYSREGULATION OF RETINOIC ACID NUCLEAR RECEPTORS

More recently, Wei et al[39] applied immunohistochemistry with high-density tissue micro-array to identify the ethnic differences in the expression of selected gene products between Black, Asian, Hispanic and White women with ULMs. Relative protein expression was determined by normalizing the absolute immunoscores in ULMs to that of the adjacent normal myometrium. The absolute expression value of OR-α in both normal myometrium and ULMs was higher in Black women compared with other ethnic groups; however, when the relative OR-α expression was calculated, ULMs of Black women did not differ significantly from those of other ethnic groups. In ULMs of Black women, the relative expression of PR-A (upregulated in relation to normal myometrium), retinoid acid receptor-α (RAR-α; downregulated) and retinoid X receptor-α (RXR-α; no change from adjacent myometrium) differed significantly from other ethnic groups (Table 3). About one-third of ULMs from Black women subclustered together in association with a group of upregulated gene products. Many other gene products, including local growth factors, insulin-like growth factor signalling proteins and cell proliferation markers, were dysregulated in ULMs, but showed non-significant differences between the ethnic groups (Table 3).

As ULMs are hormone dependent, the differential expression of steroid hormone receptors (OR and PR) among different races would be of crucial importance to explain the ethnic differences in the incidence of these benign tumours. The downregulation of retinoic acid receptors (RAR-α and RXR-α) in ULMs of Black women in comparison with their upregulation in other ethnic groups indicates dysregulation of retinoic acid metabolism in ULMs of Black women. Other studies have shown abnormal expression of genes coding for enzymes involved in retinoic acid metabolism in ULMs.[40,41] However, the exact role of retinoic acid and its nuclear receptors in the ethnical disparity of ULMs still needs to be elucidated.

POLYMORPHISM OF OESTROGEN RECEPTOR GENES

The authors investigated whether racial differences in the incidence of ULMs may be related to variation in the function of the steroid receptors, rather than the expression level. The distribution of two common OR gene polymorphisms was assessed between Black, Hispanic and White women with or without ULMs. The polymorphisms tested were in the first intron of the OR gene and included a T/C polymorphism that is recognized by the restriction endonuclease P*vu*II, and an A/G polymorphism recognized by X*ba*I restriction enzyme. The T and C alleles correspond to the presence (p allele) or absence (P allele), respectively, of the restriction site. Similarly, the A and G alleles correspond to the presence (x allele) or

absence (X allele), respectively, of the restriction site. Genotypes for P*vu*II and X*ba*I polymorphisms were termed PP, Pp and pp, and XX, Xx and xx, respectively.

According to the authors' results, the PP genotype was associated with significantly greater risk of ULMs among Black and White women, but not among Hispanic women (Table 4). Using the logistic model, White women had the lowest incidence of leiomyomas. Black and Hispanic women were 9.7 and 2.4 times more likely, respectively, to have ULMs than White women. Overall, women with the PP genotype were 6.4 times more likely to have ULMs compared with women with the pp genotype. Furthermore, the PP genotype was significantly more common in cases with severe disease (uterine weight > 400 g) and was associated with younger age at hysterectomy compared with the pp genotype.

The authors also addressed the distribution of different OR genotypes in various ethnic groups. Black women had a significantly high frequency of the PP genotype (35%) compared with White women (13%) and Hispanic women (16%). In contrast, White and Hispanic women had a higher frequency of the pp genotype (38% and 40%, respectively) compared with Black women (27%). There was no significant difference in the Pp heterozygous genotype among the three ethnic groups

The strong association between ULMs and the PP genotype of ORs, and the in-vitro data of higher cellular proliferation in myometrial cells harbouring the same genotype detected in the authors' study, together with the results of other studies that detected more ULM-related hysterectomies and higher bone mineral densities in women with the PP genotype,[42,43] indicate the higher prevalence of the P allele in more potent local oestrogenic environments.

It is not fully understood how the polymorphism at the P*vu* II locus, which is located in the first intron of the OR gene, alters the oestrogenic response. There are a number of possibilities; the first intron may contain a regulatory site (like an enhancer) to control the gene function, this polymorphism may lead to differential mRNA splicing with different functional proteins, or this polymorphism may serve as a marker in linkage with other, as yet unidentified, regulatory regions.

ABERRANT EXPRESSION OF MICRO-RNAS

Micro-RNAs (miRNAs) are a class of small, non-coding RNAs which are transcribed by RNA polymerase II. miRNAs regulate cell proliferation, differentiation and cell death during development.[44] They are expressed aberrantly in certain types of tumour.[45,46] Many genes are dysregulated in ULMs, and some of this dysregulation may be due to abnormal expression of miRNAs.[47]

Wang et al[48] collected 55 ULMs and matched myometrium from 41 patients of different ethnic groups for micro-array-based global miRNA expression analysis. They demonstrated that ULMs from Black women showed more than two-fold overexpression in certain miRNAs, including miR-23a/b, let-7s, miR-145, miR-197, miR-411 and miR-412 (Table 2), compared with tumours from White women. The miRNA expression profile from other racial groups (Asian and Hispanic) appears to be in between that of Black and White women.

One of the predicted target genes of miR-23b is TGIF (TGFB-induced factor). TGIF plays a role in inhibiting retinoic-acid-dependent RXR-α transcription. ULMs in Black women exhibit minimal change of RXR-α expression compared with ULMs in other racial groups, in which a higher level of overexpression of RXR-α is evident.[49]

In conclusion, the incidence of ULMs in Black women is much higher than in women of other ethnicities. The molecular background of this racial difference is not fully understood. Polymorphism of genes involved in oestrogen synthesis and/or metabolism (*COMT*, *CYP17*), variation in the expression levels or function of steroid receptors (OR, PR) or retinoic acid nuclear receptors (RAR-α, RXR-α), or aberrant expression of miRNAs may be some of the molecular mechanisms involved.

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Research agenda

- the exact molecular explanation for the association between the A2/A2 genotype of *CYP17*, the Val/Val genotype of *COMT* and the PP genotype of ORs with higher incidence of ULMs
- the exact role played by retinoic acid receptors in the tumourigenesis of ULMs and the implications on explaining racial disparity in the incidence of these benign tumours
- the interaction between aberrantly expressed miRNAs and dysregulation of retinoic acid receptors in the pathogenesis of ULMs in different ethnic groups

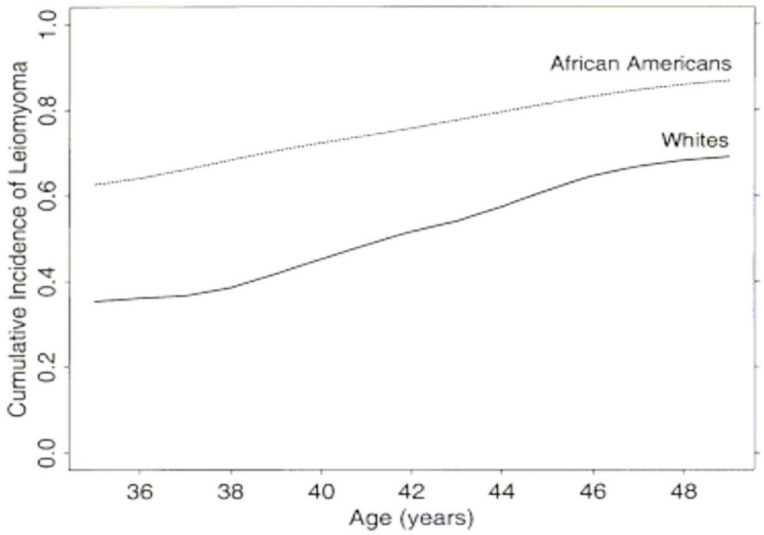

Figure 1.
Estimated age-specific cumulative incidence of uterine leiomyomas for Black and White women aged 35–49 years.[12]

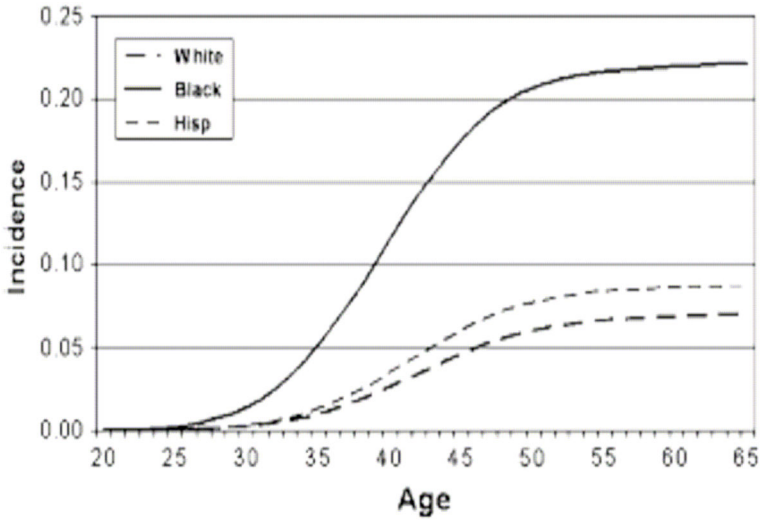

Figure 2.
Cumulative incidence of hysterectomy by race.[14]

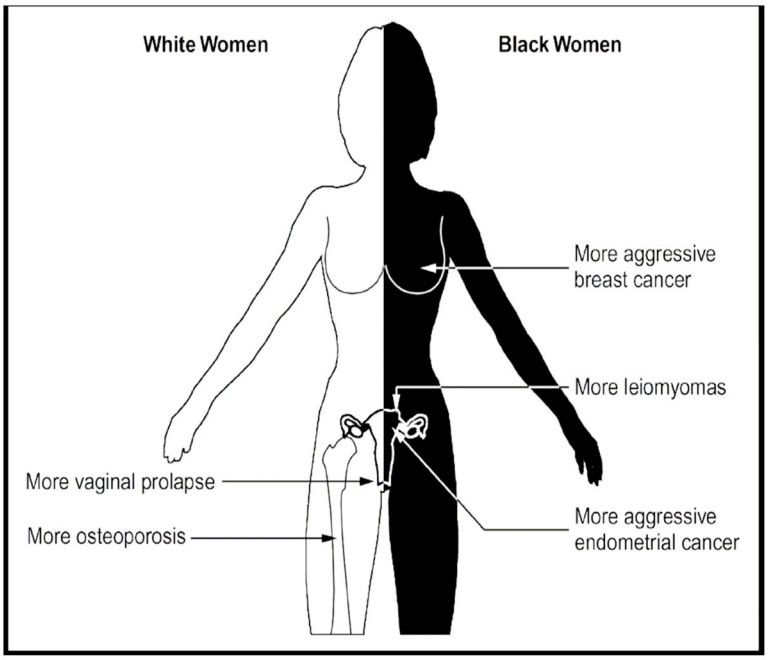

Figure 3.
Ethnic disparities in the incidence and biological behaviours of oestrogen-dependent diseases.

Table 1

Risk of Black South African women developing uterine leiomyomas based on CYP17 genotype.[25]

CYP17 genotype	Odds ratio	95% confidence interval
A1A1	3.80	0.98–14.67
A1A2	3.83	1.56–9.41
A2A2	Infinite	1.18–infinite

Table 2

Distribution of *COMT* genotypes in women with and without uterine leiomyomas by ethnic group.[49]

	African–American		White		Hispanic	
Genotype	**With leiomyoma (%)**	**Without leiomyoma (%)**	**With leiomyoma (%)**	**Without leiomyoma (%)**	**With leiomyoma (%)**	**Without leiomyoma (%)**
Val/Val	42 (52)	6 (27)	15 (25)	14 (15)	16 (35)	6 (21)
Val/Met	36 (44)	14 (64)	29 (50)	44 (48)	26 (56)	18 (64)
Met/Met	3 (4)	2 (9)	15 (25)	34 (37)	4 (9)	4 (15)

Table 3

Results of immunoscores by ethnicity status, median and range of difference between uterine leiomyomas and matched myometrium.[39]

Biomarkers	Black	Asian	Hispanic	White	p[a]	p[b]
ORα	0 (−3,5)	0.25 (−2, 5.5)	0 (−3.5, 6.5)	0 (−3, 3)	NS	
PR-A	2.8 (−7, 10)	0 (−5, 6)	0 (−5, 5.5)	1.75 (−6, 6)	0.02	< 0.02[c]
RAR-α	−0.5 (−10, 5)	1.25 (−4, 7.5)	−1 (−6, 9)	2 (−8, 10)	<0.02	0.01[d]
RXR-α	0 (−6, 2.5)	1.25 (−4, 5.5)	0.5 (−4, 10)	0.75 (−3, 5.5)	NS	0.03[e]
GCR	−1 (−4,1)	−1 (−4.5, 0.5)	−1 (−2, 1)	−1.5 (−5, 1)	NS	0.07[f]
AIB1	2 (−4, 9)	2 (−4, 10)	1 (−8.5, 8)	1.25 (−4, 6)	NS	0.08[g]
SRC1	0.5 (−1, 2)	0.5 (−0.5, 2.5)	0 (−2, 1.5)	0.75 (−1, 2)	0.03	0.01[h]
IGF2	2 (−2, 7.5)	2.5 (0, 6)	2 (−11, 6)	3 (−0.5, 6)	NS	< 0.04[i]
IGF1Rβ	0 (−0.5, 1.5)	0 (−1, 1.5)	0.5 (−1, 1)	0 (−1, 1.5)	NS	
Tuberin	−2 (−6, 3)	−2 (−5, 1.5)	−1 (−5, 4)	−1 (−6, 3)	NS	
Hamartin	0 (−1, 1)	0.5 (−1,1)	−0.3 (−1, 2)	0.5 (−1, 1.5)	NS	
BCL2	0 (−3.5, 3)	0.5 (−3, 6.5)	0.5 (−2, 4.5)	0.5 (−2.5, 3.5)	NS	< 0.07[e]
MIB1	1 (−2, 26.5)	1 (−28, 30)	2.5 (−9.5, 24	1.8 (−1, 18.5)	NS	
HMGA2	0.5 (−1, 2)	1 (0,2)	1 (−1, 3)	0.5 (−0.5, 3)	NS	
CD24	0.5 (0, 1)	0.5 (−1, 1.5)	1 (−1, 2)	0 (0, 1.5)	NS	< 0.02[i]
PDGF	0 (−1, 4)	0 (0, 6)	0 (−2, 4)	0.(0, 8)	NS	
EGFR	0 (−1.5,2)	0 (−1.5, 1.5)	0 (−2, 1.5)	0 (−1.5, 2)	NS	
Factor VIII	−5 (−20, 0)	−5 (−20, 5)	−5 (−20, 5)	−10 (−25, 10)	NS	

[a] For overall differences between ethnic groups using Kruskal-Wallis test

[b] For pair-wise differences suing Wilcoxon rank sum test

[c] Blacks versus Hispanics

[d] Blacks versus Asians

[e] Blacks versus all other groups

[f] Whites versus all other groups

[g] Whites and Hispanics versus blacks and Asians

[h] Whites versus Hispanics

[I] Hispanics versus all other groups

NS, not statistically significant.

OR, oestrogen receptor; PR, progesterone receptor; RAR-α, retinoid acid receptor-α; RXR-α, retinoid X receptor-α.

Table 4

Distribution of P*vu*II genotypes of the oestrogen receptor-α gene among women with or without uterine leiomyomas in different ethnic groups.

Genotype or allele	Black patients with leiomyoma (%)	Black control patients without leiomyoma (%)	*P*-value	White patients with leiomyoma (%)	White control patients without leiomyoma (%)	*P*-value	Hispanic patients with leiomyoma (%)	Hispanic control patients without leiomyoma (%)	*P*-value
PP	36 (39)	3 (14)	0.004	17 (28)	1 (2)	0.001	8 (18)	6 (12)	NS
Pp	34 (37)	9 (43)	NS	23 (38)	99 (62)	NS	23 (51)	18 (35)	NS
pp	22 (24)	9 (43)	NS	21 (34)	57 (36)	NS	14 (31)	27 (53)	NS

NS, not statistically significant.

Table 5

Differential expression of micro-RNAs associated with race in uterine leiomyomas.

Average fold change				
	Black	**White**	**Other**	
Number of tumours	**20**	**19**	**9**	***P*-value**
MiR21	5.0783	1.9764	2.2327	0.013
miR23b	5.0092	1.6317	1.6517	0.009
miR27a	2.2770	1.4710	1.4901	0.002
miR16-1	2.1789	1.2272	1.4181	0.021
let7e	2.0704	1.2671	1.6273	0.016
miR30a	1.7230	1.3591	1.2947	0.026
let7i	1.6203	1.2933	1.3304	0.008
let7g	1.3641	1.0398	1.2809	0.010
miR191	1.2981	0.9857	0.7997	0.003
miR25	1.1375	1.3144	0.9150	0.022
miR384	0.9919	1.2465	0.7923	0.006
miR224	0.9263	1.1381	0.8883	0.019
miR194-1	0.8659	0.8728	0.5680	0.022
miR302b*	0.7810	0.9738	0.5563	0.011
miR19a	0.7802	1.1314	0.7924	0.010
miR217	0.7507	0.9787	0.6299	0.023
miR323	0.7326	0.9496	0.6332	0.013
miR330	0.7205	1.0471	0.7552	0.008
miR141	0.6961	0.9702	0.4284	0.000
miR200a	0.6804	0.9977	0.5808	0.022
miR142	0.6216	0.9424	0.4765	0.011
miR207	0.6011	0.8764	0.4662	0.013
miR18	0.5881	0.8948	0.6798	0.004
miR345	0.5143	0.7016	0.7956	0.013
miR184	0.5128	0.6297	0.3225	0.010
miR376b	0.4237	0.6708	0.7820	0.013
miR324	0.4227	0.7202	0.2864	0.006
miR203	0.3963	0.8328	0.5984	0.001
miR412	0.3957	0.8787	0.4966	0.017
miR144	0.3785	0.6279	0.3752	0.014
miR212	0.3066	0.5654	0.7880	0.013