Multiple Cutaneous and Uterine Leiomyomas: Refinement of the Genetic Locus for Multiple Cutaneous and Uterine Leiomyomas on Chromosome 1q42.3–43

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Abstract

Cutaneous leiomyomas, rare benign tumors originating from the arrector pili muscle of the hair follicle, can be associated with the common uterine fibroids in a syndrome called multiple cutaneous and uterine leiomyomas. Multiple cutaneous and uterine leiomyomas are inherited as an autosomal dominant trait, providing an excellent opportunity for the study of the common non-Mendelian manifestation of isolated uterine fibroids. This study reports the clinical and molecular characterization of an extended family with multiple cutaneous and uterine leiomyomas. Linkage analysis has shown that the disease in this family is linked to the recently reported genetic locus for multiple cutaneous and uterine leiomyomas, with a maximum two-point LOD score of 4.453 for markers D1S2670, D1S2785, D1S547, and D1S1609. The identification of key recombination events has allowed us to refine substantially the location of the genetic locus for multiple cutaneous and uterine leiomyomas, from 14 cM to an interval of 4.55 or 7.19 cM, depending on the final phenotype of a young family member in which one of the key recombination events has occurred. In addition, we provide a description of the interesting pattern and progression of the skin phenotype in this four-generation kindred. The refinement of the genetic locus for multiple cutaneous and uterine leiomyomas and the availability of an extended multigeneration pedigree will facilitate the identification of the mutated gene responsible for multiple cutaneous and uterine leiomyomas, which, in turn, may provide key information for the understanding of the molecular basis of the common uterine fibroids.

Keywords: genetic locus for multiple cutaneous and uterine leiomyomas, leiomyoma

Abbreviations: COL4A5 and COL4A6, α5(IV) and α6(IV) collagen genes; MCL, multiple cutaneous and uterine leiomyomas; MCUL1, genetic locus for multiple cutaneous and uterine leiomyomas

Cutaneous leiomyomas are benign tumors arising from the arrector pili muscle of the hair follicle. They can range in number from a few to several hundred. Skin leiomyomas are found in association with uterine leiomyomas in an autosomal dominant syndrome called multiple cutaneous and uterine leiomyomas (MCL; MIM 150800) (Reed et al, 1973;Thyresson and Su, 1981;Valdivia et al, 1983;Garcia Muret et al, 1988;Fernandez-Pugnaire and Delgado-Florencio, 1995;Fearfield et al, 2000;Konig and Happle, 2000;Alam et al, 2001). One of the main approaches for the elucidation of the genetic components underlying a complex trait is the study of related Mendelian disorders. Such is the case for the common uterine leiomyomas (myomas or fibroids), where both genetic and nongenetic factors are thought to play a part, and MCL, a Mendelian disease.

Very recently, the locus responsible for MCL has been mapped to an ~ 14 cM region on chromosome 1q42.3–43 (Alam et al, 2001). Moreover, the same locus has been identified in a separate study as the susceptibility locus for a hereditary cancer syndrome, including renal cell cancer, as well as uterine and cutaneous leiomyomas (Kiuru et al, 2001;Launonen et al, 2001). This study reports the clinical and genetic findings in an extended pedigree with MCL. The clinical features of MCL in a new large family are described in detail, with emphasis on the particular timing of the appearance and progression of the skin lesions. Moreover, evidence is provided for a case of type II segmental manifestation of cutaneous leiomyoma within the family. The genetic analysis of this pedigree has allowed us to narrow the location of the genetic locus for multiple cutaneous and uterine leiomyomas (MCUL1) to a region of 4.55–7.19 cM on chromosome 1.

Materials and methods

Patients

Forty-three family members of a large Israeli family with MCL were interviewed and examined by two physicians. Photographs were taken during these meetings and blood samples collected following informed consent. Four family members, II-3, III-8, III-9, and IV-14 (Figure 1), were available only for the interview and examination and one member (II-1) only for blood collection. Skin and uterine involvement of the offspring of II-1 was reported anecdotally by relatives. Biopsies taken prior to this study from four affected patients confirmed the diagnosis of cutaneous (III-17, III-19, III-21, and IV-5) and uterine (III-17, III-19) leiomyomas.

Linkage analysis

Blood samples were collected from 40 family members and genomic DNA was extracted using the PureGene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). Two genomic regions were analyzed before embarking in a genome-wide scan: chromosome 18p, as monosomy for this chromosomal region has been described in a patient with mental retardation and multiple cutaneous leiomyomas, and the MCUL1 locus, on chromosome 1q. Microsatellite markers covering these regions were chosen from the genetic map at the Center for Medical Genetics, Marshfield Medical Research Foundation (Broman et al, 1998), and the sequences for their polymerase chain reaction (PCR) primers obtained from the Genome Database and the Cooperative Human Linkage Center. The (PCR) amplification products were resolved on 6% nondenaturing polyacrylamide gels and visualized by ethidium bromide staining.

Two-point, multipoint, and haplotype analyses were performed on the pedigree. For all linkage analyses, a dominant model with age-dependent penetrance was assumed. Seven liability classes were defined as follows: age 0–10, 0.001; age 11–20, 0.500; age 21–30, 0.700; age 31–40, 0.800; 41–50, 0.900; 51–60, 0.950; 61 or older, 1.000. The disease allele was assumed to have a frequency of 0.001. The marker-allele frequencies were estimated from the data using observed and reconstructed genotypes of founders within the pedigrees. To avoid computation errors due to observed allele frequencies of 0.0, marker alleles for all markers were re-coded using the RECODE program (Weeks, 2000). This re-coding program insured that alleles were numbered sequentially, and that every allele frequency was nonzero. In addition, the re-coding had no effect on any of the analyses, in terms of power of the methods.

Two-point analyses were carried out using the MLINK program of the FASTLINK suite of programs (Lathrop et al, 1984;Cottingham et al, 1993;Schaffer et al, 1994). LOD scores were computed for θ (recombination fraction) values ranging over the interval (0.0, 0.5) in increments of 0.02, as well as $\theta = 0.05$. In the interest of brevity, only a small number of LOD score values for each marker locus are reported (Table I).

Multipoint and haplotype analyses were carried out using the SIMWALK program version 2.8 (Sobel and Lange, 1996). This software was chosen because it employs a Markov chain Monte Carlo approach, which allows for both a large number of founders in a pedigree and multiple markers in the computation of LOD scores. Markers were chosen for the multipoint analysis according to the following steps: (i) all markers that showed 0.0 recombination fractions with other markers according to the Marshfield genetic map (Broman et al, 1998) were put into distinct groups, and (ii) among markers in the distinct groups, those markers with the largest heterozygosity were chosen for multipoint analysis. This procedure was followed as the method used in

SIMWALK has computational limitations for markers with 0.0 recombination distances (E. Sobel, personal communication). As a result of this procedure, two markers, D1S2670 and D1S547, were excluded from the multipoint and haplotype analyses. Recombination distances between markers were computed using the sex-averaged Marshfield genetic map (Broman et al, 1998). For haplotype analysis, we used the same set of markers as those used for multipoint analysis. Informative recombination events are discussed in Results.

Family members with cutaneous leiomyomas were classified as affected. All individuals younger than the age of onset of their affected parent were scored as unknown. Finally, although II-1 and II-5 had affected offspring, they were also classified as unknown, as they were not examined by the authors and clinical records on the skin involvement were not available.

Electronic database information

The URL for the databases used in this study are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.research.marshfieldclinic.org/genetics/

Cooperative Human Linkage Center, http://www.lpg.nci.nih.gov/CHLC

Ensembl Genome Server, http://www.usensembl.org

GeneMap'99, http://www.ncbi.nlm.nih.gov/genemap99/

Genome Database, The, http://www.gdb.org

Human Genome Project Working Draft, http://www.genome.ucsc.edu/index.html

National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov

Results

Clinical findings

The individuals in this study belong to a four-generation pedigree from Israel in which MCL is inherited in an autosomal dominant manner (Figure 1). All patients reported sensitivity to touch, and pain to cold exposure. Skin leiomyomas were found in 10 individuals (six females and four males), ranging in age from 18 to 65. In two additional family members, a history of skin leiomyoma was reported by their relatives. In six of 10 patients, the disease started at age 18–20, whereas the rest developed the disease at age 14 (V-12), 30 (IV-2), 45 (III-19), and 55 (III-21). The lesions were firm, skin colored to pinkish-red, ranged in number from few in the younger members to up to 100 in the oldest individual examined (III-17), and their diameter ranged from 0.2 cm to

1.0 cm (Figure 2). The number of lesions increased with time and became more grouped. The pattern of progression was highly consistent among the patients. In six affected members, the disease started on the left arm, where only two or three leiomyomas were found (Figure 2a). In two other members, two or three lesions first appeared on the left anteromedial thigh and then on the left arm. Following the left arm, a few lesions appeared on the left upper back in nine of 10 patients, and then on the right upper back in five patients (Figure 2b), the right lower back (Figure 2c), right arm, and right leg. The involvement of the right side in patients who had a more prolonged disease (III-17, III-19, III-21, IV-3, and IV-5) was more severe than on the left side. Patient IV-13, aged 26 y, showed only involvement of the right arm (one lesion) and the lower right abdomen (one lesion). Interestingly, the major exception was V-12, a young female aged 18. She first developed the disease at an early age, 14 y old, with multiple painful, firm, pale red skin lesions, of approximately 0.2–0.5 cm in size, on the right shin followed by the right lower thigh. On examination, at age 18, two pale painful lesions were also found on the left upper arm and two on the left upper back in accordance with the typical pattern observed in other family members.

Regarding the uterine involvement, two affected females, III-17 and III-19, underwent hysterectomy due to uterine myomas at ages 38 and 30, respectively. Individual IV-12 has myomas. Among the rest of the affected females, II-5 suffered from abdominal pains and died during labor due to suspected uterine tumor at age 34, and V-12 suffered from menometrorrhagia. Individuals III-21 and IV-2 denied having myomas or related symptoms. Finally, III-9, the daughter of an unaffected mother, had a hysterectomy at age 28. This case would be in accordance with the high prevalence of uterine leiomyoma among women (Stewart, 2001). No other diseases were reported in the family, except for patient III-17 who suffered from an undiagnosed progressive neurologic disease.

Confirmation and refinement of the MCUL1 locus

As an initial step, prior to performing a genome-wide scan, we analyzed the candidate loci on chromosomes 18p and 1q42.3–43 (MCUL1). As monosomy for 18p had been described in a patient with mental retardation and cutaneous leiomyoma (Fryns et al, 1985), we performed a cytogenetic analysis in one of the patients, III-21, and no chromosomal alterations were found. To definitively rule out this chromosomal region we performed cosegregation analysis with microsatellite markers covering chromosome 18p and found no evidence of linkage (data not shown). These results are not unexpected, asTurleau et al (1988) also excluded cytogenetic abnormalities in three cases of MCL.

Analysis of the MCUL1 locus, on the other hand, provided strong evidence in favor of linkage. To confirm these results, we typed a total of 12 markers in the region. A maximum two-point LOD

score of 4.453 was obtained for markers D1S2670, D1S2785, D1S547, and D1S1609 ($\theta = 0$) (Table I). Multipoint analysis supported linkage to this region, with a maximum multipoint LOD score of 4.453 throughout the interval D1S2785–D1S1609. Haplotype analysis revealed critical recombination events in two family members, III-17 and V-2 (Figure 1). In III-17, an affected female, a recombination event has occurred between markers D1S517 and D1S2670. This recombination event identifies the same centromeric boundary as the one established in previous reports (Alam et al, 2001;Launonen et al, 2001); however, individual V-2, an unaffected 19 y old female, provides key information to narrow the MCUL1 locus. As V-2 is too young, we need to consider two alternatives. If V-2 does carry the disease gene, the recombination event would narrow the MCUL1 locus from 14 cM (Alam et al, 2001), to a 7.19 cM interval, between markers D1S2785 (recombination in individual V-2, this study) and D1S2842 (individual 302, from family ML304, inAlam et al, 2001). If, on the contrary, V-2 does not carry the disease gene, we would have narrowed the disease locus to a 4.55 cM interval, flanked by markers D1S517 (recombination in individual III-17, this study) and D1S204 (V-II).

Discussion

The identification of the MCUL1 locus as responsible for the disease in the pedigree studied here, one of the largest MCL kindreds reported up to now, provides strong evidence for the genetic nature of the disease, inherited as an autosomal dominant trait.

Both the age of onset and the pattern of clinical symptoms appear to be consistent throughout the pedigree. Seven of 10 affected individuals developed the disease before age 20. Two patients claimed that the disease started at ages 45 (III-19) and 55 (III-21); however, the location of the first skin lesions in most of the family members (see clinical findings in Results) raises the possibility that the first lesions could go unnoticed by some patients. It is of interest that patient III-19 was diagnosed to have uterine myoma since at least age 30. This patient has eight unaffected children, aged 24–42. As this is an extremely rare situation, with a probability of 0.4%, the eight siblings were examined by two dermatologists and none was found to be affected. Furthermore, all five daughters denied any history of abdominal pain, irregular bleeding, or an enlarged uterus.

The striking finding in this family is the relatively constant pattern of progression of the skin lesions, from left to right, which does not fit any known skin patterning lines, such as Blashko's lines (Happle, 1993). To our knowledge, this phenomenon was not noticed previously, although the increased number of lesions with time has been documented in some studies. Skin leiomyomas have been classified so far as solitary, segmental, dermatomal, or disseminated; however, it is possible that this classification could be based on incomplete clinical observations. Patient V-12 is an

interesting case, as she may represent an example of type II segmental leiomyomatosis (localized loss of heterozygosity or LOH) superimposed upon familial disseminated cutaneous leiomyomatosis. Previous reports have documented the earlier appearance of segmental lesions in cutaneous leiomyoma (Happle, 1997). According toHapple (1993), when disseminated and segmental leiomyomatosis coexist, "the lesions in the segmental pattern tend to be more numerous and prominent than the other tumors present in the same patient and his family members". These observations would explain both the early onset of the first skin lesions in V-12, at age 14, and the more severe manifestation observed in the segmental involvement, compared with the rest of the affected family members.

Of special interest is that pedigrees such as those reported byAlam et al(2001),Launonen et al (2001), and this study, can provide insights into more complex diseases, such as common uterine leiomyomas, where a genetic predisposition is only suspected. The susceptibility to uterine myomas is thought to have environmental, hormonal, and genetic components (Stewart, 2001). In MCL, however, uterine leiomyomas are clearly inherited in an autosomal dominant fashion, with incomplete penetrance in some pedigrees (Thyresson and Su, 1981;Valdivia et al, 1983;Garcia Muret et al, 1988;Fernandez-Pugnaire and Delgado-Florencio, 1995;Fearfield et al, 2000;Konig and Happle, 2000;Alam et al, 2001). Both cutaneous and uterine leiomyomas have been associated with several chromosomal abnormalities. A patient with severe mental retardation and multiple cutaneous leiomyomas has been described with 9p trisomy/18p monosomy (Fryns et al, 1985). Moreover, about 40–50% of uterine leiomyomas are associated with chromosomal abnormalities in the tumors, with chromosomes 6, 7, 12, and 14 as the most frequently involved (seeLigon and Morton, 2001, for a review). In addition, deletion of both COL4A5 andCOL4A6 genes on the X chromosome have been identified in esophageal leiomyomatosis associated with Alport syndrome (Heidet et al, 1995;Ueki et al, 1998).

The most compelling evidence for a genetic basis of leiomyoma, however, is the recent identification of the MCUL1 locus on chromosome 1q42.3–43, in a group of 10 families with multiple cutaneous leiomyomas and uterine fibroids (Alam et al, 2001) and the identification of two pedigrees with the specific combination of renal cell cancer and uterine and cutaneous leiomyomas linked to the same locus (Kiuruet al, 2001; Launonen et al, 2001). In both studies, LOH at the linked locus has been found in some of the tumors, suggesting the possibility of an underlying tumor suppressor gene.

In the report by Alam et al (2001) one of 11 families with MCL was not linked to theMCUL1 locus. Although the possibility remains that the genetic susceptibility to MCL is genetically

heterogeneous, the authors point to phenocopies or a diagnostic error in the unlinked family as alternative explanations. Moreover, both pedigrees studied by Launonen et al (2001), with the combination of MCL and renal cancer are also linked to MCUL1. Assuming genetic homogeneity, our results significantly refine the MCUL1 locus. As the key recombination event has taken place in a young unaffected female, V-2, we must consider two possible scenarios based on her definitive phenotype: the refinement of the MCUL1 locus to a 7.19 cM interval, if V-2 does, indeed, carry the mutated gene; or a considerably shorter interval of 4.55 cM if V-2 does not carry a mutated MCUL1 allele. Although careful repeated clinical examination of V-2 did not reveal any sign of the disease, she is still too young to draw any conclusion. Her affected mother and brother developed the disease at ages 30 and 18, respectively. The age of onset in the family studied ranged from 14 to 55; however, six of 10 family members developed the disease before age 18, and seven of 10 before age 20.

Ten of the 14 individuals carrying the disease-associated haplotype were already affected at the time of the study (Figure 1). Two of the remaining individuals with this haplotype (II-1 and II-5) were scored as unknown for linkage analysis purposes even though they had affected offspring, because they were not examined. Moreover, II-5 suffered from abdominal pains and died from a suspected uterine tumor during labor, at age 34. Finally, V-2 and V-17 are 19 and 18 y old, respectively, thus they are still too young to draw any definitive conclusion. The rest of family members classified as unknown (IV-15 through IV-21), ranging in age from 24 to 42 y old and coded as unknown because their mother developed the cutaneous disease at age 45, as well as the children in the last generation, all under age 21, have inherited the wild-type chromosome from their affected parent (Figure 1).

The data presented in this study show that MCUL1 is inherited as an autosomal dominant gene with high penetrance, in accordance withAlam et al (2001). In their pedigrees, seven unaffected individuals, aged 28–67, carry the disease-associated haplotype. The results reported byLaunonen et al (2001), on the other hand, show a more complex scenario. Although they have identified one single unaffected carrier (unspecified age), only 14 of 16, seven of 16, and six of 16 carriers have developed uterine leiomyoma/leiomyosarcoma, cutaneous leiomyomas, and renal cell cancer, respectively.

The MCUL1 interval includes several known genes, as well as many unknown expressed sequence tags, although there is no obvious candidate among them (Human Genome Project Working Draft; National Center for Biotechnology Information; Ensembl Genome Server; GeneMap'99). The further refinement of the critical linkage interval will be needed to define the exact location of

the MCUL1locus, as well as to elucidate the possibility of heterogeneity on the genetic predisposition to MCL. It is of interest that both LOH (Mao et al, 1999) and balanced translocations (Mitelman et al, 1997) have been reported in uterine leiomyomas involving the chromosomal region 1q42.

The recent reports on the identification of the MCUL1 locus, together with the data presented here may provide valuable insights into the etiology and genetic causes of skin and uterine leiomyomas, the latter being a major health issue for women. Its association with the more aggressive renal cell cancer (Kiuru et al, 2001; Launonen et al, 2001) may facilitate early patient identification. Finally, the development of new drugs and treatments may be achieved once the molecular basis of these tumors is established.

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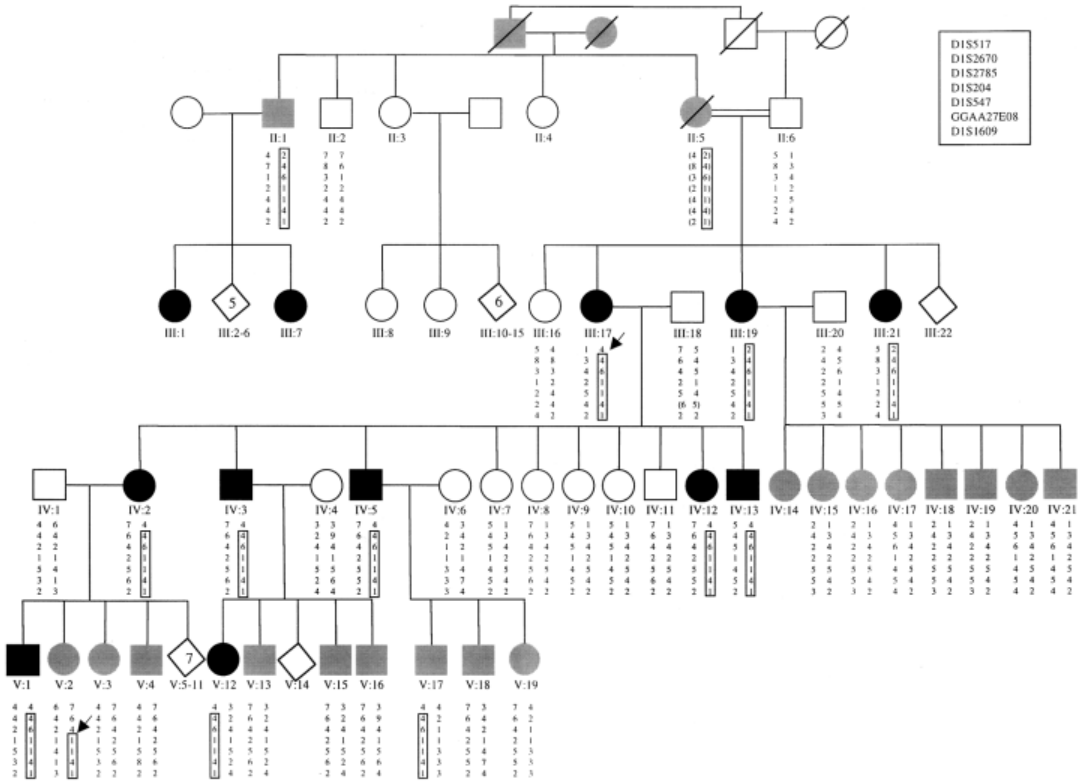
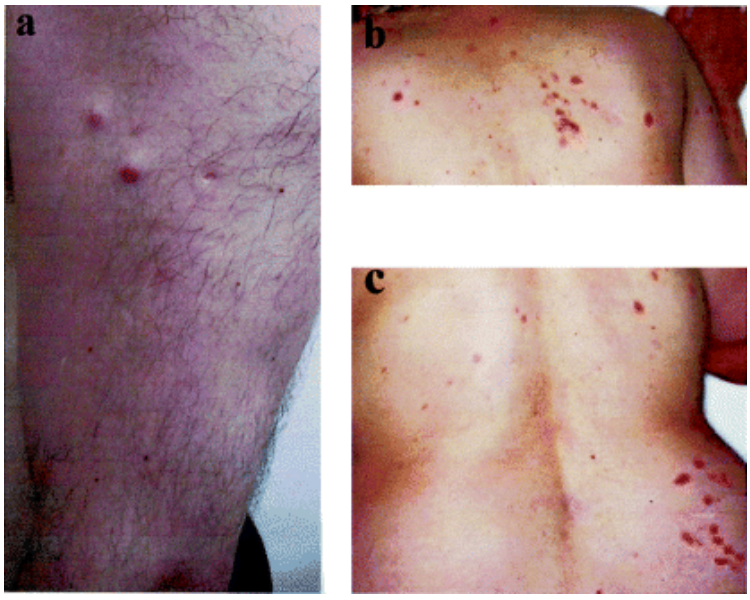
Figures

Figure I



Pedigree with MCL, showing the haplotypes for markers at 1q42.3–43. Black, gray, and empty symbols indicate family members scored as affected, unknown, and unaffected in the linkage analysis, respectively. The order of the markers is indicated in the upper right corner. The disease-associated haplotype is boxed. Genotypes in parentheses for family members II-5 and III-18 were inferred from their offspring. The genotype for marker GGAA27E08 in individual V-4 could represent a mutation affecting the length of the microsatellite. Arrows indicate the meiotic recombination events.

Figure 2



Clinical findings in the MCL pedigree. In most family members, the disease begins with leiomyomas on the left upper arm (patient IV-3:a).The disease then progresses to the left upper back and right upper back (patient III-17: b), and then to the middle and lower right back (patient III-17: c).

Tables

Table I. Two-point LOD scores for chromosome 1q42.3–43 markers in the MCL pedigree

		LOD score at θ =						
Marker	Genetic location (cM)	0.00	0.01	0.05	0.1	0.2	0.3	0.4
D1S517	262.96	- 17.24	2.38	2.80	2.73	2.26	1.61	0.85
D1S2670	262.96	4.45	4.38	4.07	3.68	2.83	1.91	0.94
D1S2785	266.27	4.45	4.38	4.07	3.68	2.83	1.91	0.94
D1S204	267.51	1.64	1.60	1.43	1.20	0.77	0.39	0.12
D1S547	267.51	4.45	4.38	4.07	3.68	2.83	1.91	0.94
GGAA27E08	272.27	0.47	0.47	0.45	0.43	0.37	0.27	0.15
D1S1609	274.53	4.45	4.38	4.07	3.68	2.83	1.91	0.94