Increased Support for Linkage of a Novel Locus on Chromosome 5q13 for Essential Hypertension in the British Genetics of Hypertension Study

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Abstract—Human hypertension arises from a combination of genetic factors and lifestyle influences. With cardiovascular disease set to become the number 1 cause of death worldwide, it is important to understand the etiologic mechanisms for hypertension, because these might provide new routes to improved treatment. The British Genetics of Hypertension Study has recently published a primary genome screen that identified 4 chromosomal regions of interest. We have now genotyped additional markers to confirm the most promising regions for follow-up studies. Thirty-four additional microsatellites were genotyped in our severely hypertensive affected sibling pair resource (now 1635 families with 2142 affected sibling pairs), leading to a substantial increase in information content in the regions of interest. We found increased support for linkage of chromosome 5q13 to human hypertension (multipoint logarithm of odds = 2.50) with 3 adjacent markers yielding single point logarithm of odds scores of 3.22, 2.84, and 2.51. The placement of additional markers on 2q, 6q, and 9q diminished support for linkage in these regions. However, the addition of new data and families identified novel regions of interest on chromosomes 1q and 11q. The 3 positive markers in the chromosome 5 region were also genotyped in 712 distinct parent–offspring trios with the same severe phenotype to replicate linkage and association. Borderline support for replication was found (P = 0.07). We found increased evidence for linkage and borderline-significant evidence for association for a hypertension susceptibility locus on chromosome 5q13 that is worthy of detailed fine mapping and assessment of candidate genes. (Hypertension. 2006;48:105-111.)

Key Words: genetics ■ hypertension, essential ■ polymorphism

H uman hypertension affects >1 billion people worldwide and contributes to an estimated 50% of all cardiovascular disease (http://www.who.int/en/index.html).1 This disorder originates from an interaction of lifestyle exposures, such as dietary sodium, excess weight, and alcohol consumption with multiple genetic factors.2,3 The study of simpler Mendelian forms of hypertension has highlighted several causative genes, which affect sodium regulation.4 It has proved more difficult to define the genetic architecture of the common human essential hypertension phenotype.4 One approach to identify novel candidate pathways for human hypertension has been to undertake a genome scan using evenly spaced genetic markers in large family resources based on affected sibling (sib) pairs. A number of these studies using diverse phenotyping strategies in different ethnic groups and some meta-analyses have been published, but no consistent candidate locus has emerged.3,5,6

A “first pass” genome scan from the BRItish Genetics of HyperTension (BRIGHT) Study in 2010 severely affected, white European sib pairs indicated 4 regions that attained genome-wide significance using a locus counting method.7 In any such experiment, the results of an initial sparse genome scan (markers every 10 cM) requires further validation by placement of an additional dense “grid” of genetic markers
across the region of interest to assess support for linkage (markers every 2 CM for the most promising signals or 5 CM for regions with lesser support). This process, known as “grid tightening,” is a key stage in defining linkage peaks worthy of detailed interrogation. In the event that additional support for linkage accrues, it would be ideal to replicate these findings in a second separate resource with the same white European ancestry and phenotyped using the same strategy. The BRIGHT Study is able to do this in 712 parent–offspring trios, where the proband meets the same phenotypic criteria and has the same ancestry as our affected sib pairs. This distinct family-based resource offers the opportunity to corroborate findings from the affected sib pairs by using a family-based test of linkage and association known as the Transmission Disequilibrium Test (TDT). The BRIGHT consortium now reports results from the grid tightening analysis in 2142 hypertensive sib pairs and follow-up of a linked region in 712 distinct TDT trios.

Methods

Patient Resources

The ascertainment criteria for the BRIGHT Study sib-pair resource has been described previously. Briefly, this resource is now composed of 1635 families of white European origin with ≥2 severely affected hypertensive sibs. Both affected sibs had onset of hypertension before 60 years of age and blood pressure (BP) recordings of 150/100 mm Hg using 1 reading or 145/95 mm Hg, the mean of 3 readings, while seated. BPs were recorded with the Omron HEM-705CP portable semiautomated oscillometric device (Omron Healthcare). Individuals who were diabetic, had intrinsic renal disease, and those with a history of secondary hypertension or coexisting illness were excluded from the study.

As part of the BRIGHT Study strategy to characterize complimentary resources for replication and association studies, we have recruited 712 distinct hypertensive families of white European ancestry (ascertained as for affected sib pairs to the level of grandparental ancestry) to allow transmission disequilibrium testing. These families consist of 371 standard trios (affected proband and both parents) and 341 trios of single parent, affected proband, and a sibling. The ascertainment and phenotyping of the proband was the same as for the sib-pair recruitment. Ethics committee approval was obtained from multi-center resources for replication and association studies, we have recruited 712 distinct hypertensive families of white European ancestry (ascertained

Genotyping

The BRIGHT investigators have reported previously a 10 CM genome scan using Linkage Marker set MD10 (Applied Biosystems). Thirty-four additional microsatellite markers were genotyped in the sib-pair resource to tighten the grid on regions of interest with the highest multipoint or single point logarithm of odds (LOD) scores. Markers spaced, on average, every 2 CM were genotyped in primary regions of interest from the first-pass genome screen on chromosomes 2 (D2S2275, D2S2241, D2S2299, D2S306, D2S354, D2S3245, and D2S2284), 5 (D5S398, D5S427, D5S1359, D5S2019, D5S1988, D5S1977, D5S646, and D5S672), 6 (D6S503 and D6S2522), and 9 (D9S1881, D9S1821, D9S1795, D9S1863, D9S1818, and D9S312). In addition, markers spaced every 5 CM were genotyped on chromosome 8p (D8S1706), chromosome 11q (D11S1974), chromosome 13q (D13S1812), chromosome 15q (D15S986, D15S1019, D15S1023, D15S979, D15S652, D15S657, and D15S212), and chromosome 21q (D21S1256). These regions were selected for further analysis if LOD scores were either >1.0 in the first-pass genome scan using Cooperative Human Linkage Center (CHLC) or deCODE Genetics maps (http://www.decode.com) or if quality control checks had revealed that additional markers were required. In our primary screen of chromosome 5, we had not maximized data capture for all of the markers; additional genotyping data are provided here so that a comprehensive analysis is presented. The majority of markers were selected from the Sequence Tag Site database at the National Centre of Biotechnology Information (http://www.ncbi.nlm.nih.gov/dbSTS/).

Genotype Quality Assurance

After genotyping we performed extensive additional quality control checks on all of the markers (the original 400 plus 34 new markers). Allele frequency distributions were compared between phases of the project to detect differences in allele binning over time. Furthermore, we identified alleles outside of the expected range and tested for deviations from Mendelian inheritance (using the Pedcheck program) and from Hardy–Weinberg equilibrium.

A further novel approach that we took was to search for “sudden death” (or “birth”) markers, which is analogous to identification of outliers that have excessive leverage on results in a regression analysis. We reanalyzed the data for each chromosome, in turn dropping the data for a single marker to establish any markers that exert a large influence on the LOD score. The rationale being that identity by descent estimates should change smoothly along the chromosome and that a single marker with a large influence on the multipoint LOD score could suggest either genotyping or map errors.

For any markers highlighted by these tests, the raw genotype data were re-examined manually to identify errors in genotype calling. Any markers exhibiting unequivocal evidence of genotyping error that could be resolved were rescoped; those that showed clear errors but could not reliably be scored were removed from further analysis. Once these additional quality checks were completed, kinship analysis was repeated to identify any misreported relationships.

Statistical Analysis of Affected Sib Pairs

As for our primary genome screen, we estimated allele frequencies by maximum likelihood using the SPLINK computer program, version 1.9. We used marker map positions given in the Rutgers combined linkage-physical map and estimated by identity by descent probabilities for all of the affected full- and half-sib pairs using Merlin. From these, we computed single and multipoint LOD scores using MLSix, which maximizes the likelihood of the observed data as a function of the sib recurrence risk ratio, \( \lambda_s \). We computed confidence intervals for the associated \( \lambda_s \) estimates by bootstrap resampling of the identity by descent vectors.

To evaluate the genomewide significance of our previous results, we applied a locus-counting approach. This compares the number of distinct regions showing evidence for linkage at different thresholds to that expected if no hypertension locus existed. The latter is calculated by simulation using gene dropping, which preserves family structure and missing data patterns. Although some new genotype data have been included, we have used thresholds from our primary scan that remain broadly applicable to our current results.

Linkage and Association Analysis Using the Transmission Disequilibrium Test

To replicate our linkage findings, we genotyped 3 markers, which yielded the strongest evidence for linkage in 712 distinct TDT trios. When an allele is associated with disease, it is expected to be inherited more frequently by affected offspring than the alternate allele carried by a heterozygous parent. The TDT approach tests for preferential transmission of particular alleles to affected children from their parents. The untransmitted allele acts as a matched control, so this test is robust to problems caused by population stratification. We used TRANSMIT (version 2.5.4) to conduct the analysis, which allows for missing parental genotypes to be reconstructed from unaffected siblings of the affected proband. Significance was calculated by 2 methods. First, the score statistic was assumed to asymptotically follow a \( \chi^2 \) distribution and, second, by comparison to its empirical distribution estimated using 10,000
bootstrap replicates. The \( \chi^2 \) approximation may not hold for rare alleles, and so the bootstrap \( P \) values are favored in this instance.

**Results**

**Demographics From Affected Sib Pairs and TDT Families**

We present summary statistics indicating that the 2142 affected sib pairs and our 712 TDT probands are similarly hypertensive at diagnosis and remain hypertensive at phenotyping when many are on treatment. Application of stringent recruitment criteria shows both the cases and probands of the parent–offspring trios to be generally not obese; however, the TDT probands do have an earlier age of diagnosis of hypertension from the sib pairs, because their parents had to be available for analysis (see Table 1).

**Grid Tightening Analysis in Affected Sib Pairs**

The maximum LOD scores are presented in Figure 1. No chromosomal region reached genome-wide significance according to the multipoint LOD score. The maximum multipoint LOD score genewide is 2.50 at marker DSS2019 on chromosome 5q13. This maximum LOD score reflects an increase from the LOD score of 1.85 found in the first pass genome scan and includes 3 neighboring markers with single point LOD scores >2.5, 1 of which was >3 (see Figure 2). However, the LOD score fell in the other 3 regions of primary interest from the first pass genome scan (see Table 2). LOD scores were augmented by additional data on chromosomes 1 and 11, both achieving multipoint LOD scores >1.5, with 2 markers under the chromosome 11 peak (D11S1974 and D11S4175) achieving single-point LOD scores >2. We present the “top 10” maximum multipoint LOD scores >1.1 and the associated estimate of the recurrence risk (\( \lambda_s \)) for all of the regions in Table 2.

No single locus achieves genomewide significance, and a locus-counting analysis of the linked regions with the largest scores also suggests that we do not reach a genomewide significance level of 5%. However, more regions achieve modest LODs than expected (eg, 9 exceed 1.16 when only 8 would be expected to reach this threshold), suggesting that there seem to be too many modest LOD scores for them all to be attributable to chance.

**Effect of Different Marker Maps on LOD Scores**

Genetic maps of the markers used in linkage analysis continue to improve in accuracy as markers are typed in more families and different maps are merged. Multipoint LOD scores can depend heavily on the marker map when parents are not available for genotyping, which is common in studies of late-onset diseases, such as hypertension. Results must, therefore, be interpreted against an evolving genetic marker map. Our initial study used the CHLC genetic map. Since then, further information has been used to create more precise genetic maps, and the current analysis was conducted under the more recently published Rutger’s map, which incorporates sequence data to ensure the correct ordering of markers. We detected several differences between these maps. The most marked difference was in the telomeric region of 6q, where 2 markers originally placed 16 cM apart by CHLC were, in fact, in very close proximity and their positions reversed in Rutger’s. When analyzed under the 2 maps, the evidence for linkage differed considerably (LOD = 3.2, CHLC map; LOD = 0.7, Rutger’s map). Further exploration of the 6q locus with additional microsatellites reduced support for linkage.

Between the CHLC and Rutger’s maps there were 3 further map order differences between pairs of markers used in our study (D1S2896 and D1S2076, DSS1977 and DSS424, and D19S894 and D19S209). Whereas the changes at the first 2 pairs of markers had a minimal effect on the LOD score, the maximum multipoint LOD score on chromosome 19 increased from 0.9 using the CHLC map to 1.4 using Rutger’s. This highlights the need to recognize that genetic maps are still in evolution as marker positions are revalidated.

Analysis using the sudden death approach found 2 points of interest. The first was an inversion of a 12 cM region on chromosome 8 in the genetic marker map, which has since been published, and 1 marker, DSS1359, which led to a change in the maximum multipoint LOD score on chromosome 5 (LOD = 2.12 with DSS1359 included; LOD = 2.50 with DSS1359 excluded). This marker is not in the Rutger’s map, and had been selected according to position at Southampton (http://cedar.genetics.soton.ac.uk/public_html/LDB2000/release.html), which we have not been able to further validate. Because of its uncertain position and effect on the LOD score, we removed it from further analysis.

**Transmission Disequilibrium Testing**

Of the 3 chromosome 5 markers displaying single-point LOD scores >3, which were genotyped in the TDT resource, DSS2019 showed borderline evidence for linkage and association (\( P < 0.07 \); see Table 3).

**Discussion**

The BRIGHT Study grid tightening analysis has found enhanced support for a hypertension locus on human chromosome 5q13. It is of particular interest that single-point

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**TABLE 1. Demographic Characteristics of the BRIGHT Study Sib-Pair and Transmission Disequilibrium Families Summarized as Mean±SD or Median and Interquartile Range**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sib-Pair Families</th>
<th>TDT Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pedigrees</td>
<td>1635</td>
<td>712</td>
</tr>
<tr>
<td>No. hypertensive offspring</td>
<td>3512</td>
<td>728</td>
</tr>
<tr>
<td>Gender: male/female</td>
<td>1426/2086</td>
<td>329/399</td>
</tr>
<tr>
<td>Mean age at diagnosis, BP</td>
<td>49 (9.6)</td>
<td>39 (9.8)</td>
</tr>
<tr>
<td>Mean diastolic at phenotyping, mm Hg</td>
<td>171.2 (17)</td>
<td>164.2 (15.8)</td>
</tr>
<tr>
<td>Mean diastolic at phenotype, mm Hg</td>
<td>103.6 (8)</td>
<td>103.3 (8.7)</td>
</tr>
<tr>
<td>Mean systolic at phenotype, mm Hg</td>
<td>155.8 (21.1)</td>
<td>146.7 (17.7)</td>
</tr>
<tr>
<td>Mean diastolic at phenotype, mm Hg</td>
<td>93.5 (11.4)</td>
<td>94 (10.4)</td>
</tr>
<tr>
<td>Median body mass index, kg/m²</td>
<td>27 (25 to 30)</td>
<td>27 (25 to 30)</td>
</tr>
</tbody>
</table>
support for this locus accrues from several microsatellite markers exhibiting single-point LOD scores >2.5 (and ≥3). Further evidence that chromosome 5 harbors ≥1 susceptibility gene arises from our borderline support for linkage and association of 1 of these markers in a complimentary but distinct parent–offspring trio resource. The use of multiallelic markers with higher degrees of freedom causes a marked loss of power compared with biallelic markers. Under these circumstances, this borderline result is very encouraging. TDT replication of linkage has been used to extend support for loci on chromosomes 2q, 6q, and 9q. The locus at the telomere of 6q exhibited the strongest support for linkage in our first-pass genome scan based on marker positions derived from the Genethon and Marshfield Maps (CHLC map). All of the genomic maps, linkage and sequence based, have undergone revisions and improvements as new data have accumulated, and the CHLC map has now been superseded by deCODE and Rutger’s map. The Rutger’s maps fixes marker

Figure 1. Maximum LOD scores for the BRIGHT genomewide scan. The top and bottom panels show multipoint and single-point results, respectively. The number of each chromosome is given in the middle line.
order on the basis of physical sequence data and includes a substantial increase in the number of informative meioses, which allows more precise estimates of intermarker genetic distances. As recombination increases toward the ends of chromosomes, we have always been cautious about the 6q linkage peak. Multipoint linkage analysis is very sensitive to intermarker distance and order when parents are unavailable. Therefore, evidence for linkage can be inflated by tightly juxtaposed markers being assigned an inaccurate position.21 Our observation that the order and position of several markers has changed with appreciable effects on the resulting linkage statistics suggests that other complex trait researchers should consider reanalyzing their genome scan data using the most accurate contemporary map.

Recent data evaluating the behavior of LOD scores during a grid tightening process implies that false-negative results, as well as false-positive results, can arise in these studies.22 In the BRIGHT Study, the contribution of multiple markers with positive single-point LOD scores and augmentation of the multipoint LOD score on chromosome 5q13 makes this unlikely to be a false-positive linkage produced by genotyping or map errors. In addition, the evidence of simultaneous borderline support for association in our TDT resource increases the chance of it being a true positive locus.

The chromosome 5q13 interval (D5S398-D5S672) spans \( \approx 22 \) Mb of DNA, and there is no other genome scan with significant linkage to this region; however, there is 1 report of suggestive linkage with BP in Mexican Americans.23 Human chromosome 5q13 has syntenic with rat chromosome 2 (23 to 41 Mb) and mouse chromosome 13 (90 to 170 Mb; http://nar.oupjournals.org/cgi/content/full/30/1/38). A number of BP quantitative trait loci have been mapped to rat chromosome 2. Although a congenic mapping approach has been used to narrow some of these regions, none have been shown to be syntenic with human 5q13.24,25 Bioinformatic analysis of the region reveals: 131 reference sequence genes, 1001 messenger ribonucleic acids, 34 386 expressed sequence tags, and nearly 7000 HapMap ([SNPs] http://genome.ucsc.edu/ and http://www.hapmap.org). There are several potential candidate genes within this interval (phosphatidylinositol 3-kinase regulatory \( \alpha \) subunit, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and 5-hydroxytryptamine 1A receptor), which could be investigated in case–control studies.

Figure 2. Chromosome 5 maximum LOD scores from the BRIGHT Study. The dotted line is the LOD score from our primary genome scan, and the solid line is the LOD score for the current data with an additional dense grid of markers analyzed under the Rutger’s map.
using SNPs, which tag the combined genotypes or haplotypes.\textsuperscript{26,27} Although this is a reasonable strategy, it is somewhat constrained by our current understanding of the biological plausibility of candidates. A complementary strategy that we will use is the interrogation of the entire interval under our linkage peak with a dense group of tag SNPs derived from the evolving public domain HapMap data set that enable definition of the genetic architecture of this locus in a case–control design.\textsuperscript{26,27} For the other loci where LOD scores have diminished, we cannot make a compelling case for extensive survey using dense SNP maps of these intervals.

**Perspectives**

Despite many genome scans and candidate gene studies, the genetic factors underpinning hypertension remain elusive. In 2003, we reported linkage between loci on chromosomes 2, 5, 6, and 9, and hypertension in the BRIGHT Study affected sib-pair resource. After analysis of further families and markers, we now present enhanced support for a locus on chromosome 5q13, which achieves genomewide significance according to the single-point LOD score. Additional credibility comes from the rise in the multipoint LOD score with increasing information content in the region and borderline significant evidence for replication from our distinct resource of parent–offspring trios. These data provide an important step forward in the identification of a hypertension susceptibility locus in the BRIGHT Study. We are undertaking detailed fine mapping of this locus using >3000 SNPs selected from HapMap and which we are genotyping in 1600 hypertensive cases and normotensive controls to expedite localization and gene discovery. We also expect further loci of interest to arise from gene–gene interaction studies and analysis of covariate phenotypes within the sib-pair resource.

**Acknowledgments**

We thank the BRIGHT nurses for all of their help with recruitment and phenotyping and the British Public for their participation in this study.

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**Disclosures**

None.

**References**


**TABLE 2. Maximum LOD Scores in Rank Order With Chromosome Location and Estimated Effect Size, \(\lambda_{Sib} (95\% \text{ CI Limits})\)**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Nearest Marker</th>
<th>Max LOD</th>
<th>(\lambda_{Sib} (95% \text{ CI}))</th>
<th>Max LOD (2006)</th>
<th>(\lambda_{Sib} (95% \text{ CI})) 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top 4 regions*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>D6S281</td>
<td>3.21‡</td>
<td>1.09 (1.04 to 1.16)</td>
<td>0.38</td>
<td>1.05 (1.00 to 1.22)</td>
</tr>
<tr>
<td>9</td>
<td>D9S290</td>
<td>2.24‡</td>
<td>1.15 (1.04 to 1.26)</td>
<td>0.20</td>
<td>1.03 (1.00 to 1.11)</td>
</tr>
<tr>
<td>5</td>
<td>D5S2019</td>
<td>1.85‡</td>
<td>1.05 (1.02 to 1.13)</td>
<td>2.50</td>
<td>1.04 (1.01 to 1.15)</td>
</tr>
<tr>
<td>2</td>
<td>D2S142</td>
<td>1.76‡</td>
<td>1.05 (1.01 to 1.10)</td>
<td>0.23</td>
<td>1.01 (1.00 to 1.05)</td>
</tr>
<tr>
<td>Top 10 regions†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>D5S2019</td>
<td>2.50</td>
<td>1.044 (1.014 to 1.145)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>D11S898</td>
<td>1.76</td>
<td>1.046 (1.013 to 1.094)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>D1S2797</td>
<td>1.51</td>
<td>1.043 (1.021 to 1.130)</td>
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<td></td>
</tr>
<tr>
<td>19</td>
<td>D19S209</td>
<td>1.44</td>
<td>1.039 (1.012 to 1.122)</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>D15S1012</td>
<td>1.31</td>
<td>1.099 (1.015 to 1.192)</td>
<td></td>
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<tr>
<td>15</td>
<td>D15S657</td>
<td>1.28</td>
<td>1.054 (1.013 to 1.146)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>D6S289</td>
<td>1.20</td>
<td>1.104 (1.016 to 1.194)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>D3S1304</td>
<td>1.19</td>
<td>1.038 (1.006 to 1.126)</td>
<td></td>
<td></td>
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<tr>
<td>22</td>
<td>D22S315</td>
<td>1.16</td>
<td>1.092 (1.009 to 1.180)</td>
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<tr>
<td>13</td>
<td>D13S170</td>
<td>1.15</td>
<td>1.082 (1.01 to 1.161)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Top 4 regions from primary genome scan by Caulfield et al\textsuperscript{2} and grid-tightening analysis results.†Top 10 regions, from grid-tightening analysis.‡2003.

**TABLE 3. Results From Transmission Disequilibrium Testing of Chromosome 5 Markers in 712 Parent–Offspring Trios**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Single-Point LOD</th>
<th>(\chi^2)</th>
<th>df</th>
<th>P</th>
<th>Bootstrap P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5S2089</td>
<td>3.22</td>
<td>7.953</td>
<td>10</td>
<td>0.633</td>
<td>0.585</td>
</tr>
<tr>
<td>D5S2019</td>
<td>2.84</td>
<td>15.648</td>
<td>9</td>
<td>0.075</td>
<td>0.067</td>
</tr>
<tr>
<td>D5S1988</td>
<td>2.51</td>
<td>12.888</td>
<td>11</td>
<td>0.301</td>
<td>0.392</td>
</tr>
</tbody>
</table>

\(df\) indicates degrees of freedom.


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