Table S1. Genotyping details of the studied polymorphisms.

| Polymorphism (Gene) | Primer sequences (Forward e Reverse) | Anneling temperature (°C) | Product size after amplification by PCR (bp) | Restriction enzyme (Units used per reaction) | Fragment size after digestion (bp) |
|---------------------|-------------------------------------|---------------------------|-----------------------------------------------|---------------------------------------------|----------------------------------|
| rs1052133 (OGG1)    | F5'-AGTGGATTCTCATGGCTTCCG-3'        | 57                        | 251                                           | Fnu4HI (1U)                                 | 251, 155, 96                     |
|                     | R5'-GGTGCTTTGGAAGATTTCTTT-3'        |                           |                                               |                                             |                                  |
| rs909253 (TNFR)     | F5'-TCCTGAACCTCCATCTGTCAAGTC-3'     | 62                        | 290                                           | NeoI (2U)                                   | 290, 262, 55                     |
|                     | R5'-GAAGAGACCTTCAAGGTGTCTCAT-3'     |                           |                                               |                                             |                                  |
| rs1800629 (TNFA)    | F5'-GGCAATAGGTGGGAGCCAT-3'          | 55                        | 107                                           | NeoI (2U)                                   | 107, 87, 20                      |
|                     | R5'-TCCTCTCTGCTCCAGTCC-3'           |                           |                                               |                                             |                                  |
| rs2227956 (HSPAIL)  | F5'-GGCAAACTGTTGAGTACAG-3'          | 57                        | 877                                           | NeoI (2U)                                   | 877, 553, 324                    |
|                     | R5'-TACTACAGTCATTTGGC-3'            |                           |                                               |                                             |                                  |
| rs1061581 (HSPAIR)  | F5'-CATGCACTTCTACACGTTCA-3'         | 57                        | 1146                                          | PstI (7U)                                   | 1146, 934, 183                   |
|                     | R5'-CAAAGCTCTGTGATTCCAC-3'          |                           |                                               |                                             |                                  |
| rs763780 (IL17F)    | F5'-GACCAAGGCTGCTGTTCTCTT-3'        | 55                        | 145                                           | NlaIII (3U)                                 | 145, 86, 59                      |
|                     | R5'-GTTAAGGAGTGTGATTCTACA-3'        |                           |                                               |                                             |                                  |
| rs4644 (LGALS3)     | F5'-CTCCATGATGCGTTATCTGTTCTGG-3'   | 57                        | 324                                           | NeoI (2U)                                   | 324, 171, 153                    |
|                     | R5'-CATGGGCCAAGGCGACCCAGCCTAAGG-3'  |                           |                                               |                                             |                                  |
| rs1042522 (TP53)    | F5'-GAAGACCGGCTCCAGATG-3'           | 55                        | 152                                           | BstUI (2U)                                  | 152, 102, 50                     |
|                     | R5'-CTGCCCTCTGAGTTTGGTCTTC-3'       |                           |                                               |                                             |                                  |

Polymorphisms genotyped by Real Time PCR using allelic discrimination TaqMan™ SNP Genotyping Assay

| Polymorphism (Gene) | Primer sequences and fluorescently labelled [VIC/FAM] MGB™ probes | TaqMan® assays ID |
|---------------------|---------------------------------------------------------------|-------------------|
| rs699947 (VEGFA)    | GCCAGCTGTAGGCCAGACCCTGCGCA[A/C]GATCTGCTGTTGGAATACGACTGAC     | C__8311602_10     |
| rs833061 (VEGFA)    | GAGTGTGCTGCTGTTGAGTACAG[GT/CT]GTGAGCAGGAGGAGGAAGGCCAGGGG    | C__1647381_10     |
| rs2010963 (VEGFA)   | CGCGCGGCGCGCGGAGGAGCCCTGAGGCAAGGCAAAATGTGAGTGACCTGC         | C__8311614_10     |
| rs3025039 (VEGFA)   | GCATTTTCTGAGGCGGAGGCCAGGCAAGCAGGCAAAATGTGAGTGACCTGC         | C__16198794_10    |
| rs689466 (COX-2)    | TTAGATGAAAGAGAGATTTTGCTACGAGC[CT]TGGAATTTACTTCTTTGTTT      | C__2517145_20     |
| rs5275 (COX-2)      | TGTTTTTTTGTATGAGAAAATA[A/G]ACACAAAGATTTTTAAATTTCCA          | C__7550203_10     |

Polymorphisms genotyped by Real Time PCR using allelic discrimination custom TaqMan® assays

| Polymorphism (Gene) | Primer sequences and fluoresently labelled [VIC/FAM] MGB™ probes | Product size |
|---------------------|---------------------------------------------------------------|--------------|
| rs6917 (PHB)        | F5'-TTGGTCCCCTCTGAGTTACCA-3'                                 | 131bp        |
|                     | R5'-CGGTGAGAAGGGCAGCTCCTCT-3'                                 |              |
|                     | P5'-CTGCCAAAGA[T/C]GGTT-3'                                    |              |
| p.R337H (TP53)      | F5'-CTCCCTCTGCTGCTCATGACT-3'                                  | 64bp         |
|                     | R5'-CTCCATCTCGCTCAGACAT-3'                                    |              |
|                     | P5'-CGTGAAGC[G/A]CTTCGAG-3'                                   |              |

PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism; SNP: single nucleotide polymorphism; R: reverse; F: forward; P: probe; bp: base pair; ID: identification code for the validated TaqMan® SNP Genotyping Assays.
Table S2. General characteristics of the studied sample and comparison of the sociodemographic status, smoking and alcohol consumption between controls and cases (both considering the total sample and the cases stratified for the diffuse histological subtype).

| Characteristics       | CONTROLS |                          | CASES |                          |
|-----------------------|----------|--------------------------|-------|--------------------------|
|                       | Total sample N (%) | Total sample N (%) | χ²/U  | p  | OR (95% CI) | p* | Diffuse subtype N (%) | χ²/U  | p  | OR (95% CI) | p* |
|                       | N=262    | N=178                    |       |    |              |    | N=112                   |       |    |              |    |
| **Age**               |          |                          |       |    |              |    |                        |       |    |              |    |
| Median (IQR) years old| 57 (26)  | 62 (21) 21155 0.098a    | 1.0 (1.00-1.03) 0.040* | 60.5 (21) 14396 0.773a | 1.01 (0.99-1.02) 0.53 |
| **Gender**            |          |                          |       |    |              |    |                        |       |    |              |    |
| Female                | 143 (54.6) | 69 (38.8) 10.6 0.001b*  | 1.9 (1.3-2.8) <0.001* | 42 (37.5) 9.157 0.002b* | 2.0 (1.3-3.2) 0.003* |
| Male                  | 119 (45.4) | 109 (61.2) |       |    |              |    |                        |       |    |              |    |
| **Ethnicity**         |          |                          |       |    |              |    |                        |       |    |              |    |
| White                 | 214 (82.3) | 134 (75.3) |       |    |              |    |                        |       |    |              |    |
| Brown                 | 25 (9.6)  | 25 (14.0) 6.05 0.108b    | 1.6 (0.9-2.9) 0.12 | 16 (14.3) 4.508 0.212b | 1.63 (0.8-3.2) 0.16 |
| Black                 | 18 (6.9)  | 12 (6.7)  |       |    |              |    |                        |       |    |              |    |
| Yellow                | 3 (1.2)   | 7 (3.9)  | 3.7 (0.9-14.6) 0.06 | 4 (3.6) 3.4 (0.7-15.5) 0.11 |
| **Educational level** |          |                          |       |    |              |    |                        |       |    |              |    |
| 0 to 5 years          | 56 (23.5) | 44 (26.2) 1 (Ref)       |       |    |              |    |                        |       |    |              |    |
| 6 to 9 years          | 124 (52.1) | 103 (61.3) 7.024 0.068b  | 1.0 (0.6-1.6) 0.96 | 66 (62.3) 6.119 0.106b | 1.02 (0.6-1.7) 0.96 |
| 10 to 12 years        | 42 (17.6) | 14 (8.3)  | 0.6 (0.3-1.1) 0.10 | 8 (7.5)  | 0.51 (0.2-1.2) 0.13 |
| > 12 years            | 16 (6.7)  | 7 (4.2)  | 0.3 (0.1-1.1) 0.07 | 4 (3.8)  | 0.27 (0.1-1.2) 0.09 |
| **Smoking status**    |          |                          |       |    |              |    |                        |       |    |              |    |
| Never                 | 161 (61.5) | 66 (37.1) 1 (Ref)       |       |    |              |    |                        |       |    |              |    |
| In the past           | 66 (25.2) | 66 (37.1) 26.169 <0.001b** | 2.4 (1.6-23.8) <0.001* | 38 (33.9) 24.112 <0.001b** | 2.3 (1.4-3.9) 0.002* |
| Current               | 35 (13.4) | 46 (25.8) 3.2 (1.9-5.4) <0.001* |       |    |              |    |                        |       |    |              |    |
| **Drinking status**   |          |                          |       |    |              |    |                        |       |    |              |    |
| Never                 | 213 (81.3) | 94 (52.8) 1 (Ref)       |       |    |              |    |                        |       |    |              |    |
| In the past           | 20 (7.6)  | 47 (26.4) 43.527 <0.001b** | 5.3 (3.0-9.5) <0.001* | 31 (27.7) 42.335 <0.001b** | 6.0 (3.2-11.3) <0.001* |
| Current               | 29 (11.1) | 37 (20.8) 2.9 (17-5.0) <0.001* |       |    |              |    |                        |       |    |              |    |

N: number of individuals; IQR: interquartile range; OR: Odds ratio; 95% CI: 95% Confidence Interval; Ref: reference; a Mann Whitney test (U); b Chi-Square test (χ²); c Univariate Logistic Regression analysis; *p <0.05.
Figure S1. Representation of the haplotype blocks whose polymorphisms located on chromosome 6 (TNFB, TNFA, HSP1AL, HSPA1B, and VEGFA genes) were in linkage disequilibrium (LD) in the total sample of cases (N=178) and controls (N=262). Block 1 is composed by polymorphisms of the TNFB/TNFA genes; Block 2 by polymorphisms of HSP1AL/HSPA1B genes and Block 3 by polymorphisms of VEGFA gene. The numbers in squares indicate pairwise D’ values and corresponding shade of red represents the degree of LD between the polymorphisms; LD considered when D’ ≥ 0.75. Adapted from Haploview 4.2 software.
Table S3. Polymorphisms in linkage disequilibrium and haplotype association analyses with gastric cancer susceptibility.

| Block | Polymorphisms (Genes) | Haplotypes | Frequency (%) | Cases/Controls (%) | $\chi^2$ | $p$ |
|-------|------------------------|------------|---------------|-------------------|---------|-----|
| 1     | rs909253 and rs1800629 (*TNFB/TNFα*) | AG         | 64.4          | 64.3/64.4         | 0.00    | 0.98|
|       |                        | GG         | 21.9          | 22.5/21.5         | 0.11    | 0.74|
|       |                        | GA         | 12.6          | 11.6/13.4         | 0.60    | 0.44|
|       |                        | AA         | 1.1           | 1.6/0.7           | 1.49    | 0.22|
| 2     | rs2227956 and rs1061581 (*HSPA1L/HSPA1B*) | TG         | 54.2          | 57.0/52.2         | 1.89    | 0.17|
|       |                        | TA         | 38.0          | 36.3/39.3         | 0.80    | 0.37|
|       |                        | CA         | 6.7           | 5.2/7.8           | 2.13    | 0.14|
|       |                        | CG         | 1.1           | 1.5/0.7           | 1.24    | 0.27|
| 3     | rs699947, rs833061 and rs2010963 (*VEGFA*) | ACG        | 32.8          | 33.3/32.4         | 0.08    | 0.78|
|       |                        | CTC        | 32.4          | 37.6/28.6         | 7.66    | 0.006*|
|       |                        | CTG        | 23.3          | 24.7/22.3         | 0.69    | 0.40|
|       |                        | ATG        | 4.7           | 0.3/8.0           | 26.51   | <0.001*|
|       |                        | CCG        | 3.4           | 3.1/3.7           | 0.21    | 0.65|
|       |                        | CCC        | 3.2           | 0.6/5.1           | 13.11   | <0.001*|

Haplotypes with frequency less than 1% were excluded of the analysis; * $p$ <0.05. Haploview 4.2 software.
Table S4. Clinicopathological characteristics of the cases with gastric cancer at the time of diagnosis in the total sample and stratified by Lauren’s histological subtypes and results of the comparison of these parameters between Diffuse and Intestinal subtypes.

| Clinicopathological characteristics | Cases N (%) | \( \chi^2/U \) | \( p \) | OR (95% CI) | \( p \) |
|-------------------------------------|-------------|----------------|----------|-------------|-------|
| **Total cases**                     | N=178       |                |          |             |       |
| **Clinicopathological characteristics** |            |                |          |             |       |
| **Age at diagnosis**               |             |                |          |             |       |
| Median (IQR) years old             | 62 (21)     | 60.5 (21)      | 66 (17)  | 2571.5      | 0.017*| 0.97 (0.95-0.99) | 0.026*|
| **Gender**                         |             |                |          |             |       |
| Female                             | 143 (54.6)  | 42 (37.5)      | 24 (41.7)| 0.17        | 0.685b| 1 (Ref)          |       |
| Male                               | 119 (45.4)  | 70 (62.5)      | 35 (59.3)|            |       |
| **Histological subtype**           |             |                |          |             |       |
| Intestinal                         | 59 (33.1)   | -              | 59 (100.0)|            |       |
| Diffuse                            | 112 (62.9)  | 112 (100.0)    | -        |            |       |
| Mixed                              | 7 (3.9)     | -              | -        |            |       |
| **Tumor size**                     |             |                |          |             |       |
| \( \leq 5 \text{ cm} \)            | 94 (52.8)   | 61 (54.5)      | 33 (55.9)| 0.03        | 0.854b| 1 (Ref)          |       |
| \( > 5 \text{ cm} \)              | 84 (47.2)   | 51 (45.4)      | 26 (44.1)|            |       |
| **Perineural invasion**            |             |                |          |             |       |
| No                                 | 76 (44.2)   | 38 (34.9)      | 34 (60.7)| 10.1        | 0.002b*| 1 (Ref)          |       |
| Yes                                | 96 (55.8)   | 71 (65.1)      | 22 (39.3)|            |       |
| **Lymphatic invasion**             |             |                |          |             |       |
| No                                 | 68 (39.5)   | 38 (34.5)      | 27 (49.1)| 3.2         | 0.071b| 1.8 (0.9-3.5)    | 0.073|
| Yes                                | 104 (60.5)  | 72 (65.5)      | 28 (50.9)|            |       |
| **Vascular invasion**              |             |                |          |             |       |
| No                                 | 81 (49.4)   | 44 (43.6)      | 33 (58.9)| 3.4         | 0.065b| 1.9 (0.9-3.6)    | 0.066|
| Yes                                | 83 (50.6)   | 57 (56.4)      | 23 (41.1)|            |       |
| **Inflammatory infiltration**      |             |                |          |             |       |
| none to weak                       | 50 (49.5)   | 34 (53.1)      | 15 (50.0)| 0.08        | 0.777b| 1 (Ref)          |       |
| moderate to intense                | 51 (50.5)   | 30 (46.9)      | 16 (50.0)|            |       |
| **Desmoplasia**                   |             |                |          |             |       |
| none to weak                       | 39 (37.9)   | 18 (26.9)      | 17 (58.6)| 8.8         | 0.003b*| 3.9 (1.5-9.6)    | 0.004*|
| moderate to intense                | 64 (62.1)   | 49 (73.1)      | 12 (41.4)|            |       |
| **Depth of invasion (pT)**         |             |                |          |             |       |
| t1+t2                              | 36 (20.3)   | 20 (18.0)      | 16 (27.1)| 1.9         | 0.167b| 1 (Ref)          |       |
| t3+t4                              | 141 (79.7)  | 91 (82.0)      | 43 (72.9)|            |       |
| **Lymph nodes metastasis**         |             |                |          |             |       |
| No                                 | 40 (22.6)   | 17 (15.3)      | 23 (39.0)| 12.0        | 0.001b*| 1 (Ref)          |       |
| Yes                                | 137 (77.4)  | 94 (84.7)      | 36 (61.0)|            |       |
| **Distant metastasis (pM)**        |             |                |          |             |       |
| No                                 | 152 (85.4)  | 94 (83.9)      | 52 (88.1)| 0.55        | 0.459b| 1 (Ref)          |       |
| Yes                                | 26 (14.6)   | 18 (16.1)      | 7 (11.9) |            |       |
| **TNM staging**                    |             |                |          |             |       |
| I+II                               | 54 (30.5)   | 27 (24.3)      | 26 (44.1)| 7.0         | 0.008b*| 2.5 (1.3-4.8)    | 0.009*|
| III+IV                             | 123 (69.5)  | 84 (75.7)      | 33 (55.9)|            |       |

N: number of individuals; IQR: interquartile range; TNM based on the 7th edition of UICC/AJCC, 2010; * Mann Whitney test (U); b Chi-Square test (\( \chi^2 \)); OR: Odds Ratio; 95% CI: 95% Confidence Interval; Ref: reference; * OR calculation was based on Diffuse in relation to Intestinal subtype; \( p < 0.05 \).
Figure S2. Representation of the haplotype blocks whose polymorphisms were found in linkage disequilibrium (LD) in the subgroup of cases with gastric cancer. (A) Block 1 is composed by polymorphisms of the TNFB/TNFA genes; Block 2 by polymorphisms of VEGFA gene and (B) Block 3 by polymorphisms of COX-2 gene. The numbers in squares indicate pairwise D' values and corresponding shade of red represents the degree of LD between the polymorphisms; LD considered when D' ≥ 0.75. Adapted from Haplovieview 4.2 software.
Table S5. Polymorphisms in linkage disequilibrium in the sample of cases (N=178) and haplotype association analyses with anatomopathological features of gastric cancer patients.

| Block | Polymorphisms (Genes) | Haplotypes | freq (%) | Anatomopathological characteristics | Presence/Absence (%) | χ² | p  |
|-------|------------------------|------------|----------|-------------------------------------|----------------------|----|----|
| 1     | rs909253 and rs1800629 (TNFB/TNFA) | AG         | 64.2     | -                                   | 26.0/17.0            | 4.05 | 0.044* |
|       |                        | GG         | 22.6     | Perineural invasion                 | -                    | -   | -   |
|       |                        | GA         | 11.4     | -                                   | -                    | -   | -   |
|       |                        | AA         | 1.8      | -                                   | -                    | -   | -   |
| 2     | rs699947, rs833061 and rs2010963 (VEGFA) | CTC        | 38.2     | -                                   | -                    | -   | -   |
|       |                        | ACG        | 33.6     | Vascular invasion                  | 39.8/26.7            | 6.26 | 0.012* |
|       |                        | CTG        | 24.5     | -                                   | -                    | -   | -   |
|       |                        | CCG        | 3.4      | -                                   | -                    | -   | -   |
|       |                        | CCC        | 3.2      | -                                   | -                    | -   | -   |
| 3     | rs689466 and rs5275 (COX-2) | AT         | 45.2     | -                                   | -                    | -   | -   |
|       |                        | AC         | 37.4     | -                                   | -                    | -   | -   |
|       |                        | GT         | 17.4     | Intestinal histological subtype    | 23.7/14.7            | 4.27 | 0.038* |

freq: haplotype frequency in the sample of case individuals; * p <0.05. Haplovie 4.2 and PLINK softwares.
Table S6. Overall and Disease-free survival by anatomopathological features, stratified for the cases with the diffuse histological subtype (N=112).

| Anatomopathological characteristics | Categories | Overall Survival | Disease-free Survival |
|------------------------------------|------------|-----------------|----------------------|
|                                    |            | Cases N | Events N | Mean | log-rank p | HR (95% CI) | p  | Cases N | Events N | Mean | log-rank p | HR (95% CI) | p |
| Tumor size                          | ≤ 5 cm     | 61     | 35      | 82.4 | 0.032*      | 1 (Ref) | 0.034* | 61     | 25      | 100.7 | 0.014*      | 1 (Ref) | 0.016* |
|                                    | > 5 cm     | 51     | 39      | 44.2 | 1.7 (1.0-2.6) | 1.7 (1.0-2.6) | 0.040* | 51     | 34      | 50.3 | 1.9 (1.1-3.2) | 1.9 (1.1-3.2) | 0.010* |
| Depth of invasion (pT)              | t1+t2      | 20     | 10      | 99.1 | 0.036*      | 1 (Ref) | 0.034* | 20     | 5       | 128.8 | 0.006*      | 1 (Ref) | 0.010* |
|                                    | t3+t4      | 91     | 63      | 61.1 | 2.0 (1.0-3.9) | 2.0 (1.0-3.9) | 0.040* | 91     | 53      | 70.2 | 3.3 (1.3-8.4) | 3.3 (1.3-8.4) | 0.010* |
| Perineural invasion                 | no         | 38     | 21      | 88.8 | 0.019*      | 1 (Ref) | 0.021* | 38     | 18      | 96.0  | 0.120      | 1 (Ref) | 0.123  |
|                                    | yes        | 71     | 51      | 56.2 | 1.8 (1.1-3.0) | 1.8 (1.1-3.0) | 0.021* | 71     | 39      | 71.5 | 1.6 (0.9-1.7) | 1.6 (0.9-1.7) | 0.016* |
| Lymphatic invasion                  | no         | 38     | 18      | 104.0 | <0.001*     | 1 (Ref) | <0.001* | 38     | 11      | 125.9 | <0.001*     | 1 (Ref) | <0.001* |
|                                    | yes        | 72     | 54      | 46.3 | 2.7 (1.6-4.6) | 2.7 (1.6-4.6) | <0.001* | 72     | 46      | 53.7 | 3.9 (2.0-7.5) | 3.9 (2.0-7.5) | <0.001* |
| Vascular invasion                   | no         | 44     | 23      | 95.8 | 0.001*      | 1 (Ref) | 0.001* | 44     | 16      | 113.9 | <0.001*     | 1 (Ref) | <0.001* |
|                                    | yes        | 57     | 42      | 45.7 | 2.3 (1.4-3.9) | 2.3 (1.4-3.9) | 0.001* | 57     | 36      | 53.3 | 2.9 (1.6-5.3) | 2.9 (1.6-5.3) | <0.001* |
| Inflammatory infiltration           | none to weak | 34   | 22      | 72.9 | 0.820      | 1 (Ref) | 0.820  | 34     | 20      | 77.6  | 0.734      | 1 (Ref) | 0.734  |
|                                    | moderate to strong | 30   | 19      | 74.4 | 1.1 (0.6-2.0) | 1.1 (0.6-2.0) | 0.820  | 30     | 15      | 89.3  | 0.9 (0.5-1.7) | 0.9 (0.5-1.7) | 0.734  |
| Desmoplasia                        | none to weak | 18   | 11      | 78.4 | 0.495      | 1 (Ref) | 0.496  | 18     | 11      | 79.2  | 0.947      | 1 (Ref) | 0.947  |
|                                    | moderate to strong | 49   | 33      | 68.6 | 1.3 (0.6-2.5) | 1.3 (0.6-2.5) | 0.496  | 49     | 27      | 80.6  | 1.0 (0.5-2.1) | 1.0 (0.5-2.1) | 0.947  |
| Lymph nodes metastasis             | no         | 17     | 7       | 110.8 | 0.022*     | 1 (Ref) | 0.027* | 17     | 3       | 139.0 | 0.007*     | 1 (Ref) | 0.013* |
|                                    | yes        | 94     | 66      | 59.2 | 2.4 (1.1-5.3) | 2.4 (1.1-5.3) | 0.027* | 94     | 55      | 70.9  | 4.3 (1.4-13.9)| 4.3 (1.4-13.9)| 0.013* |
| Distant metastasis (pM)            | no         | 94     | 56      | 78.4 | <0.001*     | 1 (Ref) | <0.001* | 94     | 41      | 95.7  | <0.001*     | 1 (Ref) | <0.001* |
|                                    | yes        | 18     | 18      | 17.4 | 3.4 (1.9-5.8) | 3.4 (1.9-5.8) | <0.001* | 18     | 18      | 16.4  | 4.0 (2.3-7.0) | 4.0 (2.3-7.0) | <0.001* |
| TNM staging                        | I+II       | 27     | 11      | 111.4 | 0.001*     | 1 (Ref) | 0.002* | 27     | 4       | 146.0 | <0.001*     | 1 (Ref) | <0.001* |
|                                    | III+IV     | 84     | 62      | 52.7 | 2.8 (1.4-5.3) | 2.8 (1.4-5.3) | 0.002* | 84     | 54      | 60.5  | 6.4 (2.3-17.8)| 6.4 (2.3-17.8)| <0.001* |

N: number of individuals; Mean: mean survival time in months; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; Ref: reference; * p <0.05.
Table S7. Overall and Disease-free survival by anatomopathological features in the total sample of gastric cancer patients (N=178).

| Anatomopathological characteristics | Categories | Overall Survival | Disease-free Survival |
|-------------------------------------|------------|-----------------|-----------------------|
|                                     |            | Cases N | Events N | Mean | log-rank p | HR (95% CI) | p    | Cases N | Events N | Mean | log-rank p | HR (95% CI) | p    |
| Tumor size                          | ≤ 5 cm     | 94     | 46      | 95.13 | 0.017*     | 1.0 (Ref)   | 0.018*    | 94     | 31      | 115.3 | 0.001*     | 1.0 (Ref)   | <0.001*   |
|                                     | > 5 cm     | 84     | 53      | 59.85 | 0.007*     | 1.6 (1.1-2.4) | 0.008*    | 84     | 48      | 64.2  | 2.8 (1.7-4.6) | 1.0 (Ref)   | 0.003*    |
| Depth of invasion (pT)              | t1+t2      | 36     | 14      | 112.29| <0.001*    | 1.0 (Ref)   | 0.001*    | 36     | 7       | 137.3 | 0.001*     | 1.0 (Ref)   | 0.006*    |
|                                     | t3+t4      | 141    | 84      | 74.00 | 2.1 (1.2-3.8) | 0.008*    | 141    | 71      | 83.2  | 3.6 (1.5-8.3) | 1.0 (Ref)   | 0.006*    |
| Perineural invasion                 | no         | 76     | 32      | 104.39| <0.001*    | 1.0 (Ref)   | 0.001*    | 76     | 27      | 111.7 | 0.006*     | 1.0 (Ref)   | 0.006*    |
|                                     | yes        | 96     | 64      | 63.40 | 2.1 (1.4-3.2) | <0.001*    | 96     | 50      | 78.3  | 2.0 (1.2-3.3) | 1.0 (Ref)   | <0.001*    |
| Lymphatic invasion                  | no         | 68     | 27      | 110.18| <0.001*    | 1.0 (Ref)   | <0.001*   | 68     | 17      | 129.7 | <0.001*    | 1.0 (Ref)   | <0.001*    |
|                                     | yes        | 104    | 69      | 58.13 | 2.4 (1.5-3.8) | <0.001*    | 104    | 60      | 64.7  | 2.9 (1.6-5.0) | 1.0 (Ref)   | <0.001*    |
| Vascular invasion                   | no         | 81     | 32      | 109.49| <0.001*    | 1.0 (Ref)   | <0.001*   | 81     | 24      | 121.8 | <0.001*    | 1.0 (Ref)   | <0.001*    |
|                                     | yes        | 83     | 56      | 56.39 | 2.4 (1.6-3.8) | <0.001*    | 83     | 47      | 66.5  | 3.0 (1.7-5.3) | 1.0 (Ref)   | <0.001*    |
| Inflammatory infiltration           | none to weak | 50    | 30      | 75.07 | 0.376      | 1.0 (Ref)   | 0.378    | 50     | 26      | 83.3  | 0.400      | 1.0 (Ref)   | 0.296     |
|                                     | moderate to strong | 51    | 26      | 92.52 | 0.376      | 0.9 (4.7-1.3) | 0.378    | 51     | 22      | 100.4 | 0.7 (0.4-1.3) | 1.0 (Ref)   | 0.776     |
| Desmoplasia                         | none to weak | 39    | 19      | 92.36 | 0.238      | 1.0 (Ref)   | 0.240    | 39     | 18      | 94.1  | 0.454      | 1.0 (Ref)   | <0.001*   |
|                                     | moderate to strong | 64    | 39      | 77.25 | 0.238      | 1.0 (Ref)   | 0.240    | 64     | 33      | 86.4  | 1.1 (0.6-2.1) | 1.0 (Ref)   | <0.001*   |
| Lymph nodes metastasis              | no         | 40     | 14      | 118.42| <0.002*    | 1.0 (Ref)   | 0.003*   | 40     | 4       | 153.7 | <0.001*    | 1.0 (Ref)   | <0.001*   |
|                                     | yes        | 137    | 84      | 70.25 | 0.002*     | 2.4 (1.3-4.2) | 0.003*   | 137    | 74      | 78.0  | 6.1 (2.2-17.0) | 1.0 (Ref)   | <0.001*   |
| Distant metastasis (pM)             | no         | 152    | 76      | 92.19 | <0.001*    | 1.0 (Ref)   | <0.001*   | 152    | 56      | 107.8 | <0.001*    | 1.0 (Ref)   | <0.001*   |
|                                     | yes        | 26     | 23      | 19.39 | <0.001*    | 3.9 (2.4-6.3) | <0.001*   | 26     | 23      | 18.5  | 5.0 (2.8-9.0) | 1.0 (Ref)   | <0.001*   |
| TNM staging                         | I+II       | 54     | 18      | 120.59| <0.001*    | 1.0 (Ref)   | <0.001*   | 54     | 7       | 149.1 | <0.001*    | 1.0 (Ref)   | <0.001*   |
|                                     | III+IV     | 123    | 80      | 63.08 | 2.8 (1.7-4.7) | <0.001*    | 123    | 71      | 69.8  | 5.9 (2.7-13.1) | 1.0 (Ref)   | <0.001*   |
| Lauren’s histological classification| Intestinal | 59     | 23      | 99.97 | 0.003*     | 1.0 (Ref)   | 0.005*   | 59     | 18      | 109.6 | 0.008*     | 1.0 (Ref)   | 0.009*    |
|                                     | Diffuse    | 112    | 74      | 68.16 | 2.0 (1.3-3.2) | 0.005*    | 112    | 59      | 81.1  | 2.0 (1.2-3.4) | 1.0 (Ref)   | <0.001*   |

N: number of individuals; Mean: mean survival time in months; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; Ref: reference; * p <0.05.
Table S8. In silico prediction for the functional effect in the final coded protein for the studied polymorphisms that lead to amino acid change.

| Polymorphism (Gene) | Chromosome | Amino acid change   | Polyphen2    | SIFT         |
|---------------------|------------|---------------------|--------------|--------------|
| rs1052133 (OGG1)    | 3          | Ser326Cis           | benign       | tolerated    |
| rs2227956 (HSPA1L)  | 6          | Thr493Met           | benign       | tolerated    |
| rs763780 (IL17F)    | 6          | His161Arg           | benign       | tolerated    |
| rs4644 (LGALS3)     | 14         | Pro64His            | possibly pathogenic | deleterious |
| rs1042522 (TP53)    | 17         | Arg72Pro            | benign       | tolerated    |
| p.R337H (TP53)*     | 17         | Arg337His           | possibly pathogenic | deleterious |

* genetic variation described as mutation; Polyphen-2: Polymorphism Phenotyping v2; SIFT: Sorting Intolerant From Tolerant.
**Text S1:** Discussion of the polymorphisms that did not present any relevant association in our study.

Here we discuss the selected polymorphisms included in our study that did not present any relevant association.

Among the four studied VEGFA polymorphisms, we did not find any association regarding the rs2010963 polymorphism. A previous study in breast cancer showed that this SNP was associated with several factors related to a worse progression and higher aggressiveness of the disease (increased susceptibility risk, higher VEGFA mRNA levels, tumor with bigger sizes, presence of perineural invasion, higher staging and shorter disease-free survival) [1].

Another cytokine that was selected for investigation in our study was IL17F. The rs763780 (IL17F) polymorphism was associated with gastric cancer in the Allele Model, but this significance was lost in the multivariate analysis. IL17F is part of a gene family with important involvement in tissue inflammation by inducing the expression of several other cytokines and chemokines. This polymorphism leads to a His to Arg substitution at amino acid 161 and in vitro analysis showed that the polymorphic variant loses the ability to activate the production of the mitogen-activated protein kinase pathway and certain cytokines and chemokines [2]. Our in silico analysis showed that this amino acid change is tolerated/benign for the final coded product. Although this SNP has been previously associated with risk and progression of gastric cancer [3], we did not find associations to any clinicopathological variable or prognosis in our study. The frequency of the polymorphic allele was too low (8.4% and 4.8% in cases and controls, respectively) and it also presented deviation from HWE in our sample. Therefore, this result should be reanalyzed in an independent and increased set of sample. We cannot exclude the hypothesis that this SNP has an impact on gastric cancer risk and progression because its function might be compensated by other redundant molecules inside the same pathway.

Regarding the rs1061581 (HSPA1B) polymorphism, we did not find any association neither with susceptibility, progression nor prognosis in our sample. It causes a silent substitution and has been described as able to regulate the protein expression interfering with its secondary structure and mRNA stability, affecting its anti-apoptotic effect and its function as a modulator of the immune system [4,5].

OGG1 is a DNA glycosylase that belongs to the BER (Base Excision Repair) pathway, which repairs mainly endogenous/oxidative lesions as result of the cellular metabolism [6]. We hypothesized that maybe functional polymorphisms in repair genes could influence in the capacity of the organism repair DNA damage caused by diet carcinogens, oxidative stress or inflammation induced by H. pylori, in the gastric mucosa. Also, OGG1 has been shown to be important as a modulator of the immune and inflammatory systems [7]. We selected the rs1052133 polymorphism for investigation, which is located in the exon 7 and results in a change from Ser to Cis in 326 position of the protein. The in silico analysis by Polyphen and SIFT softwares showed that this change is tolerated/benign. However, Cis variant has demonstrated to increase the genetic instability and decrease the repair rate of 8-oxoguanine in vivo [8]. Nevertheless, no association was found with this polymorphism in the present study.

Although some studies have described a functional role for the rs6917 polymorphism, located in the 3′ UTR of the PHB gene [9] and that it has been associated with an increased risk for development of some types of tumors [10,11], in the present study we did not find association with gastric cancer susceptibility. No association was found regarding progression and prognosis as well. Our group has been studying the role of PHB and we have observed that the TT genotype increased the risk for melanoma in the presence of specific host risk factor [12]. Another study from our group demonstrated a possible role for this polymorphism in the transcriptional regulation of PHB in gastric cancer once T allele was associated with reduced PHB expression levels [13]. Therefore, functional studies on prohibitin polymorphism are necessary to elucidate its functional role.

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