|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Additional Table1. Summary of studied according to SNP** | | | | | |
| **SNPs** | **Count of study** | **SNPs** | **Count of study** | **SNPs** | **Count of study** |
| **SLC6A4 5-HTTLPR**[1-12] | **14** | TPH1 rs211105[13, 14] | 2 | FAAH rs324420[15] | 1 |
| **TNFα rs1800629**[16-23] | **8** | ADRA1D rs1556832[24] | 1 | HTR3A rs1062613[25] | 1 |
| **IL10 rs1800896**[16, 18-20, 22, 23, 26, 27] | **7** | ADRA1D rs946188[24] | 1 | HTR3E rs56109847[28] | 1 |
| **IL23R rs11465804**[21, 23, 29, 30] | **4** | ADRA2A rs1800544[31] | 1 | IFNγ rs62559044[18] | 1 |
| **GNβ3 rs5443**[31-34] | **4** | ADRAβ2 rs1042713[24] | 1 | IL10 rs3021097[35] | 1 |
| **COMT rs4680**[24, 34, 36] | **3** | ADRAβ2 rs1042717[24] | 1 | IL1α rs1800587[35] | 1 |
| **IL10 rs1800871**[16, 18, 23, 27] | **4** | ADRAβ2 rs1432622[24] | 1 | IL1β rs1143634[35] | 1 |
| **IL6 rs1800795**[17, 21, 23, 29] | **4** | ADRAβ2 rs2400707[24] | 1 | IL2 rs2069762[37] | 1 |
| **TNFSF15 rs4263839**[21, 23, 29, 30] | **4** | ANKK1 rs1800497[24] | 1 | IL6 rs1800797[35] | 1 |
| **TNFSF15 rs6478108**[19, 21, 23] | **3** | COMT rs174697[24] | 1 | IL6 rs2069861[23] | 1 |
| HT2A rs6311[38, 39] | 2 | COMT rs6269[24] | 1 | IL8 rs2227307[23] | 1 |
| HT2A rs6313[38, 39] | 2 | CRH rs28364015[40] | 1 | SLC6A4 rs1042173[41] | 1 |
| IL10 rs1800872[18, 35] | 2 | CRHR1 rs110402[42] | 1 | SLC6A4 rs2020936[41] | 1 |
| IL1R1 rs2234650[23, 35] | 2 | CRHR1 rs242924[42] | 1 | SLC6A4 rs25531[43] | 1 |
| IL4 rs2070874[21, 23] | 2 | CRHR2 rs2190242[44] | 1 | TGFβ rs1800470[16] | 1 |
| IL4 rs2243250[21, 23] | 2 | CRHR2 rs2240403[44] | 1 | TGFβ rs1800471[16] | 1 |
| IL8 rs2227306[23, 27] | 2 | CRHR2 rs2267710[44] | 1 | TPH1 rs4537731[45] | 1 |
| IL8 rs4073[23, 27] | 2 | CRHR2 rs2284217[44] | 1 | TPH1 rs684302[45] | 1 |
| SLC6A4 rs2066713[46, 47] | 2 | CRHR2 rs2284220[44] | 1 | TPH1 rs7130929[48] | 1 |
| TNFSF15 rs6478109[19, 23] | 2 | CRHR2 rs3779250[44] | 1 | TPH2 rs4570625[45] | 1 |
| TNFSF15 rs7848647[19, 23] | 2 | CRHR2 rs4722999[44] | 1 | TRPV1 945G>C[31] | 1 |
| TNFα rs361525[17, 23, 43] | 2 | DRD3 rs6280[49] | 1 | SCN5A rs7430407[50] | 1 |

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**Additional Table2. Study characteristics analysis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Country | Ethnicity | DNA  source | SNP detection methods | IBS  (M/F) | Dignostic criteria | IBS-C  (M/F) | IBS-D  (M/F) | IBS-A  (M/F) | IBS-M  (M/F) | Control  (M/F) | Control source | NOS | SNP rs. | HWE in controls |
| sVanderV et al;2005 | Netherland | Caucasian | Blood | PCR | 111  (35/76) | Rome II | 17 | 35 | 34 | / | 162 (101/61) | CC | 7 | IL10 rs1800896 | 0.71 |
| TNFα rs1800629 | 0.40 |
| ParkJM et al;2006 | Korea | Mongoloid | Blood | PCR | 190  (96/94) | Rome II | 54 | 97 | 39 | / | 437 (210/227) | CC | 6 | SLC6A45-HTTLPR | 0.20 |
| LiY et al;2007 | China | Mongoloid | Blood | PCR | 87  (32/55) | Rome II | 44 | 26 | 17 | / | 96 (39/57) | CC | 7 | SLC6A45-HTTLPR | 0.59 |
| KohenR et al;2009 | USA | Caucasian | Blood | PCR | 186  (27/159) | Rome II | / | / | / | / | 50 (15/35) | CC | 6 | SLC6A45-HTTLPR | 0.15 |
| SikanderA et al;2009 | India | Caucasian | Blood | PCR | 151  (113/38) | Rome II | 44 | 92 | / | 15 | 100 (64/36) | NM | 5 | SLC6A45-HTTLPR | 0.43 |
| Santhosh et al;2010 | India | Caucasian | Blood | PCR-SSP | 23 | Rome II | / | / | / | / | 20 | NM | 5 | IL10 rs1800871 | 0.66 |
| IL10 rs1800896 | 0.72 |
| TNFα rs1800629 | 0.52 |
| NieslerB et al;2010 | UK | Caucasian | Blood | PCR | 195  (34/161) | Rome II | 98 | 97 | / | / | 92 (32/60) | CC | 7 | SLC6A45-HTTLPR | 0.55 |
| Barkhordari et al;2010 | Iran | Iranian | Blood | PCR | 71  (22/49) | Rome **III** | / | / | / | / | 140 (70/70) | CC | 6 | IL10 rs1800871 | 0.91 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.05 |
| Lee et al;2010 | Korea | Mongoloid | Buccal epithelial cell | PCR-RFLP | 94  (58/36) | Rome **III** | / | / | / | / | 88  (44/44) | CC | 6 | IL10 rs1800896 | 0.98 |
|  |  |  |  |  |  | TNFα rs1800629 | 0.38 |
| MarkoutsakiT et al;2011 | Greece | Caucasian | Blood | PCR-RFLP | 124  (30/94) | Rome **III** | / | / | / | / | 238  (96/142) | CC | 7 | GNβ3 rs5443 | 0.83 |
|  |  |  |  |  |  |  | SLC6A45-HTTLPR | 0.70 |
| Camilleri et al;2011 | USA | Caucasian, Hispanicor, Latino, Asian | Blood | PCR-TaqMan | 415 | Rome II | 156 | 175 | / | 84 | 231 | CC | 7 | IL23R rs11465804 | 0.61 |
|  |  |  |  |  |  | IL6 rs1800795 | 0.66 |
|  |  |  |  |  |  | TNFSF15 rs4263839 | 0.38 |
| JimenezG et al;2012 | Mexico | Mexican | Blood | PCR | 45  (9/36) | Rome **III** | 29 | 11 | / | 5 | 45  (15/30) | HC | 6 | IL6 rs1800795 | 0.44 |
|  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.81 |
| KumarS et al;2012 | India | Caucasian | Blood | PCR | 150  (114/36) | Rome **III** | / | / | / | / | 252  (197/55) | NM | 5 | SLC6A45-HTTLPR | 0.31 |
| Zucchelli et al;2012 | Sweden | Caucasian | Blood | EMSA | 427 | Rome II | 104 | 144 | / | 179 | 900 | CC | 7 | IL23R rs11465804 | 0.63 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs4263839 | 0.54 |
| SaitoYA et al;2012 | USA | Caucasian | Blood | PCR | 385  (65/320) | Rome I/II | 40 | 102 | / | 125 | 262  (75/178) | CC | 7 | GNβ3 rs5443 | 1.00 |
|  |  |  |  |  |  |  |  |  |  |  | SLC6A45-HTTLPR | 0.98 |
| Swan et al;2012 | UK | Caucasian | Blood | PCR-TaqMan | 301 | Rome II | 122 | 179 | / | / | 179 | CC | 6 | IL10 rs1800896 | 0.82 |
|  |  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.74 |
|  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs6478108 | 0.17 |
| Wouters et al;2013 | UK | Caucasian | Blood | PCR | 895 | Rome II | 325 | 430 | / | 140 | 639 | CC | 6 | IL23R rs11465804 | 0.89 |
|  |  |  |  |  |  |  |  |  |  |  |  | IL6 rs1800795 | 0.24 |
|  |  |  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.19 |
|  |  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs4263839 | 0.67 |
|  |  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs6478108 | 0.85 |
| ColucciR et al;2013 | USA | Caucasian | Blood | PCR | 204  (45/159) | Rome **III** | 106 | 98 | / | / | 200  (46/154) | NM | 6 | SLC6A45-HTTLPR | 0.65 |
| FarjadianS et al;2013 | Iran | Caucasian | Blood | PCR | 50  (16/34) | Rome **III** | 15 | 25 | 10 | / | 100 | CC | 5 | SLC6A45-HTTLPR | 0.23 |
| SchmulsonM et al;2013 | Mexico | Mexican | Blood | PCR | 45  (11/34) | Rome II | 13(5/8) | 10(2/8) | / | 22(8/14) | 92  (36/56) | CC | 7 | IL10 rs1800896 | 0.14 |
| Shiotani et al;2013 | Japan | Mongoloid | Blood | PCR-RFLP | 50  (39/11) | Rome **III** | / | 50 | / | / | 50  (34/16) | HC | 6 | IL10 rs1800896 | 0.89 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  | SLC6A45-HTTLPR | 0.58 |
| RomeroV et al;2014 | Mexico | Mexican | Blood | PCR | 45  (7/38) | Rome **III** | / | / | / | / | 137  (41/96) | NM | 5 | IL10 rs1800871 | 0.92 |
| WangY et al;2014 | China | Mongoloid | Blood | PCR | 66  (56/10) | Rome **III** | 7 | 46 | / | 13 | 115  (89/26) | HC | 6 | GNβ3 rs5443 | 0.54 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  | COMT rs4680 |  |
| ChoiYJ et al;2014 | Korea | Mongoloid | Blood | PCR-TaqMan | 99  (38/61) | Rome **III** | 13 | 51 | / | 35 | 171  (85/86) | CC | 6 | GNβ3 rs5443 | 0.52 |
| CzogallaB et al;2015 | UK | Caucasian | Blood | PCR | 194  (36/158) | Rome II | 98 | 96 | / | / | 92  (32/60) | CC | 7 | IL10 rs1800871 | 0.51 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | IL10 rs1800896 | 0.44 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | IL23R rs11465804 | 0.70 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | IL6 rs1800795 | 0.36 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.96 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs4263839 | 0.14 |
|  |  |  |  |  |  |  |  |  |  |  |  |  | TNFSF15 rs6478108 | 0.14 |
| CzogallaB et al;2015 | USA | Caucasian | Sputum and/or Blood samples | PCR | 137  (27/110) | Rome **III** | 21 | 39 | / | 77 | 96  (46/50) | HC | 7 | IL10 rs1800871 | 0.56 |
|  |  |  |  |  |  |  |  |  |  | IL10 rs1800896 | 0.67 |
|  |  |  |  |  |  |  |  |  |  | IL23R rs11465804 | 0.37 |
|  |  |  |  |  |  |  |  |  |  | IL6 rs1800795 | 0.28 |
|  |  |  |  |  |  |  |  |  |  | TNFα rs1800629 | 0.62 |
|  |  |  |  |  |  |  |  |  |  | TNFSF15 rs4263839 | 0.25 |
|  |  |  |  |  |  |  |  |  |  | TNFSF15 rs6478108 | 0.75 |
| OrandA et al;2015 | USA | Caucasian, Asian, African American, Other/Mixed | salivary | PCR-TaqMan | 278 (68/209) | Rome **III** | 62 | 65 | 138 |  | 381  (102/279) | HC | 6 | COMT rs4680 |  |
| KarlingP et al;2011 | Sweden | Caucasian |  | PCR | 70 | Rome **III** |  |  |  |  | 867  (422/445) | CC | 5 | COMT rs4680 |  |
| KatsumataR et al;2018 | Japan | Mongoloid | Blood | PCR | 62 (40/22) | Rome **III** | / | / | / | / | 64 (42/22) | HC | 6 | SLC6A45-HTTLPR | 0.66 |

Note: IBS: irritable bowel syndrome; IBS-C: constipation predominant IBS; IBS-D: diarrhea predominant IBS; IBS-M: mixture of diarrhea and constipation IBS (Rome III); IBS-A: alternating of diarrhea and constipation (Rome II); M/F: male/female; NOS: Newcastle-Ottawa Quality Assessment Scale; HWE: Hardy-Weinberg equilibrium test;

CC: community control; HC: Hospital control; NM: not mentioned but with clear healthy control inclusion criteria;

Blood including "venous blood", "whole blood", "peripheral blood cells", "peripheral leukocytes";

Mongoloid including “Chinese”, “Japanese”, “Korean”;

EMSA: Electrophoretic Mobility Shift Assay;

PCR-SSP: Polymerase Chain Reaction- Sequence Specific Primers;

PCR-RFLP: Polymerase Chain Reaction-based restriction fragment length polymorphism;