**Supplemental Material**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Phenotype** | rs2272017 | rs144452294 | rs3832109 | rs2385404 | rs2385402 | rs3731904 | rs3731905 | rs878437 | rs2002892 | rs878437 | rs2271456 | rs11352428 | rs2271457 | rs1040009 | rs13018645 | rs58721028 | rs2070927 | rs1318299 | rs2017800 | **p.L115I** | rs111828114 | rs907677 | rs12991025 | rs1058261 | rs12920 | rs1058284 | rs4674398 | rs4674399 | rs1567488 | rs73991563 |
| **Reference** |  | G | C | A | C | C | G | C | C | C | C | G | AG | T | T | A | C | C | A | T | **C** | C | T | C | C | G | G | G | C | C | C |
| **Alteration** |  | C | T | AATT | A | G | A | G | A | T | A | A | A | C | C | G | CAT | T | G | C | **A** | T | G | T | T | C | A | T | T | T | T |
| **Position** |  | 2-220046349 | 2-220162129 | 2-220194247 | 2-220197388 | 2-220197492 | 2-220239534 | 2-220239561 | 2-220250322 | 2-220249329 | 2-220250322 | 2-220250826 | 2-220250897 | 2-220251178 | 2-220251208 | 2-220264412 | 2-220264543 | 2-220282955 | 2-220283259 | 2-220283277 | **2-220283527** | 2-220283592 | 2-220283826 | 2-220284779 | 2-220285309 | 2-220285666 | 2-220286142 | 2-220306413 | 2-220316579 | 2-220330724 | 2-220336517 |
|  **MAF** |  | 0.46 (C) | < 0.01 (T) | 0.4122(AATT) | 0.47 (A) | 0.47 (G) | 0.24 (G) | 0.24 (C) | 0.13(C) | 0.12 (C) | 0.13(C) | 0.16(G) | 0.082(GGG) | 0.12(T) | 0.49(T) | 0.49(G) | 0.020(C) | 0.46(C) | 0.11(A) | 0.13(T) | **0** | 0.01(T) | 0(T) | 0.47(C) | 0.34(T) | 0.34(C) | 0.33(A) | 0.14(G) | 0.04 (C) | 0.42 (T) | 0.31(T) |
| B-II-2 | Affected | GC | CT | AATT | AA | GG | AA | GG | AA | TT | AA | AA | AA | CC | TT | AA | CAT | CC | GG | CC | **CA** | CC | GG | CC | TT | CC | AA | TT | TT | TT | CT |
| B-I-2 | Affected | CC |  |  | AA |  |  | GG |  |  |  | AA |  |  | TT | AA | CAT |  |  |  | **CA** | CC | GG |  |  | CC |  |  | TT |  | CT |
| A-III-3 | Affected | CC | CT | A/AATT | CA | CG | AA | GG | AA | TT | AA | AA | AA | CC | TC | AG | CAT | CC | GG | CC | **CA** | CC | GG | CC | CT | GC | GA | TT | TT | TT | CT |
| A-III-5 | Affected | CC | CT | A/AATT | CA | CG | AA | GG | AA | TT | AA | AA | AA | CC | TC | AG | CAT | CT | GG | CC | **CA** | CC | GG | CT | CT | GC | GA | TT | TT | TT | CT |
| A-II-2 | Affected | GC | CT | A/AATT | CA | CG | AA | GG | AA | TT | AA | AA | AA | CC | TC | AG | CAT | CC | GG | CC | **CA** | CT | GG | CT | CT | GC | GA | TT | TT | CT | CT |
| A-III-4 | Affected | CC | CT | A/AATT | CA | CG | AA | GG | AA | TT | AA | AA | AA | CC | TC | AG | CAT | CC | GG | CC | **CA** | CC | GG | CC | CT | GC | GA | TT | TT | TT | CC |
| C-II-1 | Affected | CC |  |  | CA |  |  | GG |  |  |  | AA |  |  | TC | AG | CAT |  | GG | CC | **CA** | CC | GG | CT | CT | GC | GA |  | TT |  | CT |
| C-I-1 | Affected | CC |  |  | AA |  |  | GG |  |  |  | AA |  |  | TT | AA | CAT |  |  |  | **CA** | CC | GG |  |  | CC |  |  | TT |  | TT |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C-I-2 | Unaffected | CC |  |  | CA |  |  | GG |  |  |  | AA |  |  | TC | AG | CAT |  |  |  | **CC** | CC | GG |  |  | GC |  |  | TT |  | CC |
| A-IV-1 | Unaffected | CC | CC | AA | CC | CC | GA | CG | AA | TT | AA | AA | AA | CC | CC | GG | CAT | TT | GG | CC | **CC** | CC | GG | TT | CC | GG | GG | TT | TT | TT | CC |
| A-III-2 | Unaffected | CC |  |  | CC |  |  | GG |  |  |  | AA |  |  | TC | AG | CAT |  |  |  | **CC** | CC | GG |  |  | GC |  |  | TT |  | CC |

**Supplementary Table S1:** Haplotype analysis data of genotyped individuals from families A, B and C are presented. The position of the p.Leu115Ile variant has been marked with red fonts. Twenty-nine polymorphic markers were studied from whole exome data that were available from the individuals A-II-2, A-II-3, A-II-4, A-II-5, B-II-2 and A-IV-1. The individuals B-I-2, C-I-1, C-II-1, A-III-2 and C-I-2 were genotyped only for specific single nucleotide polymorphisms around p.Leu115Ile. MAF shows the frequency of the second most frequent allele in the 1000 Genomes Phase 3 combined population. Variant positions according to the Human Genome assembly GRCh37.p13.