**Supplementary data 1. The information of known disease-related sites of the human OPA1 protein.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Positionsa** | **Natural variantb** | **Diseasesc** | **Exons**  **(Domain)** | **Conservation**  **(grade)d** | **References** |
| 4-5 | LR→ - (del) | likely pathogenic | 1-2 | 1, 1 | ([Hayashi et al. 2017](#_ENREF_22)) |
| 8 | A→S (sub) | pathogenic | 1-2 | 1 | ([Han et al. 2006](#_ENREF_21)) |
| 15 | Q→K (sub) | likely benign | 1-2 | 1 |  |
| 24 | I→V (sub) | likely benign | 1-2 | 1 |  |
| 38-43 | RSIYHS→ - (del) | pathogenic | 1-2 | 5, 5, 1, 4, 1, 1 | ([Thiselton et al. 2002](#_ENREF_43)) |
| 80 | Y→C (sub) | pathogenic | 1-2 | 1 | ([Han et al. 2006](#_ENREF_21)) |
| 82 | Y→C (sub) | pathogenic | 1-2 | 1 |  |
| 95 | T→M (sub) | pathogenic | 1-2 | 2 | ([Ferre et al. 2009](#_ENREF_19)) |
| 102 | Y→C (sub) | pathogenic | 1-2 | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 115 | A→V (sub) | pathogenic | 1-2 | 9 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 127 | P→L (sub) | VUS | 3 | 9 |  |
| 158 | S→N (sub) | benign | 4 | 1 | ([Toomes et al. 2001](#_ENREF_44)) |
| 160 | E→Q (sub) | benign | 4 | 1 | ([Toomes et al. 2001](#_ENREF_44)) |
| 167 | P→L (sub) | benign | 4 | 9 | ([Thiselton et al. 2002](#_ENREF_43)) |
| 198 | D→N (sub) | VUS | 4b | 1 |  |
| 210 | A→V (sub) | benign | 5 | 1 | ([Pesch et al. 2001](#_ENREF_36)) |
| 247 | R→H (sub) | pathogenic | 5b | 4 | ([Cornille et al. 2008](#_ENREF_14)) |
| 256 | S→R (sub) | benign | 5b | 1 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 277 | L→P (sub) | pathogenic | 6-8 | 8 | ([Ferre et al. 2009](#_ENREF_19)) |
| 290 | R→Q (sub) | VUS | 6-8 | 9 |  |
| 315 | L→F (sub) | pathogenic | 6-8 | 3 | ([Liskova et al. 2017](#_ENREF_29)) |
| 323 | Y→C (sub) | pathogenic | 6-8 | 9 |  |
| 324 | S→F (sub) | likely pathogenic | 6-8 | 9 |  |
| 325 | E→K (sub) | pathogenic | 6-8 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 327 | L→P (sub) | pathogenic | 6-8 | 9 | ([Baris et al. 2003](#_ENREF_7)) |
| 328 | D→A (sub) | pathogenic | 6-8 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 340 | Q→R (sub) | pathogenic | 6-8 | 6 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 345 | R→Q (sub) | pathogenic | 6-8 | 9 | ([Alexander et al. 2000](#_ENREF_2); [Delettre et al. 2001](#_ENREF_16); [Pesch et al. 2001](#_ENREF_36); [Toomes et al. 2001](#_ENREF_44)) |
| 345 | R→W (sub) | pathogenic | 6-8 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 345 | R→L (sub) | pathogenic | 6-8 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 348-349 | VV→ - (del) | pathogenic | 9-16 (GTPase) | 9, 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 349 | V→ - (del) | pathogenic | 9-16 (GTPase) | 9 | ([Yu-Wai-Man et al. 2010a](#_ENREF_46)) |
| 351 | D→E (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ahmad et al. 2015](#_ENREF_1)) |
| 353 | S→N (sub) | likely pathogenic | 9-16 (GTPase) | 9 |  |
| 353 | S→G (sub) | pathogenic | 9-16 (GTPase) | 9 |  |
| 354 | A→P (sub) | pathogenic | 9-16 (GTPase) | 7 |  |
| 355 | G→E (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ban et al. 2010](#_ENREF_6); [Delettre et al. 2000](#_ENREF_17); [Toomes et al. 2001](#_ENREF_44)) |
| 357 | T→P (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 358 | S→N (sub) | likely pathogenic | 9-16 (GTPase) | 9 | ([Gaier et al. 2017](#_ENREF_20)) |
| 358 | S→G (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 365 | Q→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 368 | I→E (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Cohn et al. 2007](#_ENREF_13)) |
| 377 | M→R (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 379-381 | RSP→ - (del) | pathogenic | 9-16 (GTPase) | 9, 8, 9 | ([Puomila et al. 2005](#_ENREF_38)) |
| 384 | V→L (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Iida et al. 2016](#_ENREF_24)) |
| 385 | T→S (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2013](#_ENREF_11)) |
| 392 | H→D (sub) | likely pathogenic | 9-16 (GTPase) | 9 |  |
| 394 | A→T (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Rubegni et al. 2017](#_ENREF_39)) |
| 394 | A→D (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 395 | L→P (sub) | VUS | 9-16 (GTPase) | 1 |  |
| 397 | K→E (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Cohen et al. 2016](#_ENREF_12)) |
| 398 | D→A (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Pretegiani et al. 2017](#_ENREF_37)) |
| 412 | A→T (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Amati-Bonneau et al. 2008](#_ENREF_5); [Ferre et al. 2009](#_ENREF_19)) |
| 421 | R→Q (sub) | likely pathogenic | 9-16 (GTPase) | 9 |  |
| 431 | T→A (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Cohn et al. 2007](#_ENREF_13)) |
| 432 | V→I (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2013](#_ENREF_11)) |
| 435 | E→D (sub) | pathogenic | 9-16 (GTPase) | 8 |  |
| 436 | T→S (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Li et al. 2017](#_ENREF_27)) |
| 437 | I→M (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Carelli et al. 2015](#_ENREF_9); [Ferre et al. 2009](#_ENREF_19); [Schaaf et al. 2011](#_ENREF_40)) |
| 439 | L→F (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Toomes et al. 2001](#_ENREF_44)) |
| 450 | V→G (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Li et al. 2017](#_ENREF_27)) |
| 451 | L→P (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 451 | L→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Thiselton et al. 2002](#_ENREF_43)) |
| 455 | P→A (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Zhang et al. 2012](#_ENREF_48)) |
| 455 | P→L (sub) | pathogenic | 9-16 (GTPase) | 9 |  |
| 455 | P→S (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Yu-Wai-Man et al. 2010a](#_ENREF_46)) |
| 455 | P→T (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Li et al. 2017](#_ENREF_27)) |
| 456 | G→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 456 | G→D (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Kim et al. 2005](#_ENREF_25)) |
| 457 | V→M (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Bonneau et al. 2014](#_ENREF_8)) |
| 464 | G→D (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 476 | I→II (dup) | pathogenic | 9-16 (GTPase) | 1 | ([Chen et al. 2014](#_ENREF_10)) |
| 477 | S→R (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 481 | M→L (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 483 | N→H (sub) | pathogenic | 9-16 (GTPase) | 9 |  |
| 484-485 | PN→ - (del) | pathogenic | 9-16 (GTPase) | 9, 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 485 | N→D (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 487 | I→ - (del) | pathogenic | 9-16 (GTPase) | 9 | ([Alexander et al. 2000](#_ENREF_2); [Thiselton et al. 2002](#_ENREF_43)) |
| 488 | I→ - (del) | pathogenic | 9-16 (GTPase) | 9 | ([Alexander et al. 2000](#_ENREF_2)) |
| 489 | L→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 489 | L→P (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Li et al. 2018](#_ENREF_26)) |
| 490 | C→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Li et al. 2018](#_ENREF_26)) |
| 490 | C→Y (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 493 | D→V (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 493 | D→A (sub) | likely pathogenic | 9-16 (GTPase) | 9 | ([Almind et al. 2012](#_ENREF_3)) |
| 493 | D→G (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Dadgar et al. 2006](#_ENREF_15)) |
| 494 | G→V (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Amati-Bonneau et al. 2008](#_ENREF_5); [Ban et al. 2010](#_ENREF_6); [Liguori et al. 2008](#_ENREF_28)) |
| 498 | A→T (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 499 | E→G (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Gaier et al. 2017](#_ENREF_20)) |
| 500 | R→H (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Amati-Bonneau et al. 2005](#_ENREF_4); [Amati-Bonneau et al. 2008](#_ENREF_5); [Ban et al. 2010](#_ENREF_6); [Payne et al. 2004](#_ENREF_35); [Shimizu et al. 2003](#_ENREF_41)) |
| 501 | S→C (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 504 | T→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 504 | T→P (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Liskova et al. 2013](#_ENREF_30)) |
| 512 | P→T (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 514 | G→E (sub) | likely pathogenic | 9-16 (GTPase) | 9 | ([Almind et al. 2012](#_ENREF_3)) |
| 517 | T→I (sub) | pathogenic | 9-16 (GTPase) | 9 |  |
| 518-519 | IF→IFIF (dup) | pathogenic | 9-16 (GTPase) | 9, 9 |  |
| 519 | F→ - (del) | pathogenic | 9-16 (GTPase) | 9 |  |
| 523 | K→E (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 525 | D→G (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Baris et al. 2003](#_ENREF_7)) |
| 526 | L→P (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 537 | I→F (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 542 | E→K (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Bonneau et al. 2014](#_ENREF_8); [Ferre et al. 2009](#_ENREF_19)) |
| 543 | G→R (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 548 | M→K (sub) | VUS | 9-16 (GTPase) | 9 |  |
| 550 | A→V (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 556 | V→D (sub) | likely pathogenic | 9-16 (GTPase) | 9 |  |
| 558 | T→K (sub) | pathogenic | 9-16 (GTPase) | 9 | ([Thiselton et al. 2002](#_ENREF_43); [Toomes et al. 2001](#_ENREF_44)) |
| 560 | K→N (sub) | pathogenic | 9-16 (GTPase) | 6 | ([Toomes et al. 2001](#_ENREF_44)) |
| 576 | E→ - (del) | pathogenic | 9-16 (GTPase) | 1 | ([Ferre et al. 2009](#_ENREF_19)) |
| 589 | L→R (sub) | pathogenic | 17-18 | 9 | ([Spiegel et al. 2016](#_ENREF_42)) |
| 592-596 | HQVTT→P (del) | pathogenic | 17-18 | 8, 9, 9, 9, 9 | ([Li et al. 2017](#_ENREF_27)) |
| 600 | S→R (sub) | pathogenic | 17-18 | 9 | ([Amati-Bonneau et al. 2008](#_ENREF_5); [Ban et al. 2010](#_ENREF_6); [Ferre et al. 2009](#_ENREF_19); [Hudson et al. 2008](#_ENREF_23); [Nakamura et al. 2006](#_ENREF_32)) |
| 602 | A→AA (dup) | pathogenic | 17-18 | 9 | ([Kim et al. 2005](#_ENREF_25)) |
| 602 | A→E (sub) | pathogenic | 17-18 | 9 | ([Liskova et al. 2017](#_ENREF_29)) |
| 603 | V→I (sub) | pathogenic | 17-18 | 9 | ([Yu-Wai-Man et al. 2010b](#_ENREF_47)) |
| 605 | D→N (sub) | benign | 17-18 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 606 | C→ - (del) | pathogenic | 17-18 | 9 | ([Pesch et al. 2001](#_ENREF_36)) |
| 606 | C→Y (sub) | pathogenic | 17-18 | 9 | ([Ferre et al. 2009](#_ENREF_19); [Marelli et al. 2011](#_ENREF_31)) |
| 611 | V→E (sub) | pathogenic | 17-18 | 9 | ([Li et al. 2017](#_ENREF_27)) |
| 612 | R→P (sub) | pathogenic | 17-18 | 7 | ([Kim et al. 2005](#_ENREF_25)) |
| 626 | R→H (sub) | pathogenic | 17-18 | 9 | ([Thiselton et al. 2002](#_ENREF_43)) |
| 629 | L→P (sub) | pathogenic | 17-18 | 9 | ([Baris et al. 2003](#_ENREF_7)) |
| 637 | Y→C (sub) | pathogenic | 17-18 | 4 | ([Ferraris et al. 2008](#_ENREF_18)) |
| 641-644 | RELD→ - (del) | pathogenic | 17-18 | 9, 9, 9, 8 | ([Thiselton et al. 2002](#_ENREF_43)) |
| 645 | R→Q (sub) | pathogenic | 17-18 | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 645 | R→W (sub) | pathogenic | 17-18 | 9 | ([Puomila et al. 2005](#_ENREF_38)) |
| 648 | L→P (sub) | pathogenic | 19-22 (Middle) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 648 | L→ - (del) | pathogenic | 19-22 (Middle) | 9 | ([Yen et al. 2010](#_ENREF_45)) |
| 656 | I→V (sub) | VUS | 19-22 (Middle) | 9 |  |
| 701 | S→L (sub) | pathogenic | 19-22 (Middle) | 6 | ([Ferre et al. 2009](#_ENREF_19)) |
| 707 | T→A (sub) | pathogenic | 19-22 (Middle) | 9 |  |
| 709 | D→G (sub) | VUS | 19-22 (Middle) | 9 |  |
| 738 | R→H (sub) | VUS | 19-22 (Middle) | 4 |  |
| 755-756 | LK→ - (del) | pathogenic | 19-22 (Middle) | 9, 9 | ([Baris et al. 2003](#_ENREF_7)) |
| 771 | D→E (sub) | benign | 19-22 (Middle) | 8 |  |
| 773 | A→E (sub) | pathogenic | 19-22 (Middle) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 783 | N→K (sub) | pathogenic | 19-22 (Middle) | 9 | ([Ban et al. 2010](#_ENREF_6); [Puomila et al. 2005](#_ENREF_38)) |
| 785 | L→F (sub) | likely pathogenic | 19-22 (Middle) | 9 | ([Liskova et al. 2017](#_ENREF_29)) |
| 800 | I→M (sub) | pathogenic | 19-22 (Middle) | 9 | ([Li et al. 2018](#_ENREF_26)) |
| 823 | G→D (sub) | pathogenic | 23-25 (PH) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 825 | D→E (sub) | VUS | 23-25 (PH) | 3 |  |
| 836 | R→W (sub) | pathogenic | 23-25 (PH) | 7 | ([Ferre et al. 2009](#_ENREF_19)) |
| 838 | Q→R (sub) | pathogenic | 23-25 (PH) | 2 |  |
| 840 | Q→R (sub) | pathogenic | 23-25 (PH) | 8 | ([Ban et al. 2010](#_ENREF_6); [Delettre et al. 2001](#_ENREF_16); [Pesch et al. 2001](#_ENREF_36)) |
| 878 | S→Y (sub) | pathogenic | 23-25 (PH) | 3 | ([Ferre et al. 2009](#_ENREF_19)) |
| 886 | S→N (sub) | VUS | 23-25 (PH) | 1 |  |
| 887 | L→F (sub) | likely pathogenic | 23-25 (PH) | 4 | ([Almind et al. 2012](#_ENREF_3)) |
| 896 | Y→C (sub) | pathogenic | 23-25 (PH) | 4 | ([Han et al. 2006](#_ENREF_21)) |
| 898 | R→S (sub) | VUS | 23-25 (PH) | 7 |  |
| 933 | V→ - (del) | VUS | 26-28 (GED) | 9 |  |
| 937 | R→L (sub) | pathogenic | 26-28 (GED) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 937 | R→C (sub) | pathogenic | 26-28 (GED) | 9 | ([Rubegni et al. 2017](#_ENREF_39)) |
| 937 | R→G (sub) | VUS | 26-28 (GED) | 9 |  |
| 940 | R→H (sub) | pathogenic | 26-28 (GED) | 9 | ([Chen et al. 2014](#_ENREF_10)) |
| 942 | L→P (sub) | pathogenic | 26-28 (GED) | 9 | ([Ferre et al. 2009](#_ENREF_19)) |
| 958 | V→I (sub) | pathogenic | 26-28 (GED) | 9 | ([Li et al. 2017](#_ENREF_27)) |
| 962 | E→G (sub) | benign | 26-28 (GED) | 9 | ([Toomes et al. 2001](#_ENREF_44)) |
| 963-964 | KN→KIN (ins) | VUS | 26-28 (GED) | 9, 9 |  |
| 965 | V→ - (del) | pathogenic | 26-28 (GED) | 9 | ([Amati-Bonneau et al. 2008](#_ENREF_5); [Ban et al. 2010](#_ENREF_6)) |
| 965 | V→D (sub) | likely pathogenic | 26-28 (GED) | 9 | ([Almind et al. 2012](#_ENREF_3)) |
| 979 | K→ - (del) | pathogenic | 26-28 (GED) | 9 | ([Pretegiani et al. 2017](#_ENREF_37)) |
| 983 | L→P (sub) | pathogenic | 26-28 (GED) | 7 |  |
| 987 | R→C (sub) | pathogenic | 26-28 (GED) | 9 | ([Ferre et al. 2009](#_ENREF_19); [Nochez et al. 2009](#_ENREF_34)) |
| 987-989 | RVQ→ - (del) | pathogenic | 26-28 (GED) | 9, 9, 8 | ([Li et al. 2018](#_ENREF_26)) |
| 988 | V→F (sub) | likely pathogenic | 26-28 (GED) | 9 | ([Nasca et al. 2017](#_ENREF_33)) |
| 994 | L→P (sub) | pathogenic | 26-28 (GED) | 9 | ([Ban et al. 2010](#_ENREF_6); [Delettre et al. 2001](#_ENREF_16)) |
| 995-997 | KKV→I (del) | pathogenic | 26-28 (GED) | 1, 1, 5 | ([Zhang et al. 2014](#_ENREF_49)) |
| 1004 | L→P (sub) | pathogenic | 26-28 (GED) | 1 | ([Ferre et al. 2009](#_ENREF_19); [Yen et al. 2010](#_ENREF_45)) |
| 1004 | L→R (sub) | pathogenic | 26-28 (GED) | 1 | ([Chen et al. 2014](#_ENREF_10)) |
| 1004 | L→I (sub) | VUS | 26-28 (GED) | 1 |  |

a The positions of the amino acid sites in human OPA1 protein are in accord with those of its transcript variant 8 (NP\_570850.2).

b sub: substitution; dup: duplication; del: deletion; ins: insertion.

c pathogenic: disease associated; likely pathogenic: likely disease associated; VUS: variant of unknown significance; likely benign: likely not disease-associated; benign: not disease-associated.

d Evolutionary conservation grade of the residues, analyzed by ConSurf (9, conserved; 1, variable).

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