Complex interactions between p.His558Arg and linked variants in the Sodium Voltage-Gated Channel Alpha Subunit 5 (Na\textsubscript{V}1.5)

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Table S1. Summary of the collected data from 14 studies regarding the functional impact in patch clamp assays of p.His558Arg. Exp: expression system used in the functional characterization, cis- both deleterious and polymorphic variants are localized in the same construct, trans- deleterious variant and polymorphism are localized in distinct constructs and co-expressed, * Not deleterious variants - A572D, is considered a polymorphism and is found in the general population; also Q1077 and Q1077del corresponds to alternative splice isoform of SCN5A. ● AC1377587 sequence associated to this accession number is not available in NCBI.

| Mutations    | Exp. Background | Observations                                                                 | Outcome                      | Ref         |
|--------------|-----------------|------------------------------------------------------------------------------|------------------------------|-------------|
| H E161K      | cis M77235      | Loss of function (incomplete penetrance)                                     | Aggravate                    | PMID: 20384651 |
| R H558R      | cis M77235      | Steady state inactivation shifted towards hyperpolarizing potentials         | -                            |             |
| H S216L      | cis M77235 (hH1)| Decrease in $I_{Na}$ and misfolding and reduced membrane localization        | Ameliorate                   | PMID: 21705349 |
| R S216L      | cis M77235 (hH1)| Recovery of $I_{Na}$, delayed inactivation recovery                         | -                            |             |
| H R222Q+Q1007del | cis AY148488 | $I_{Na}$ density normal, alterations in the activation and inactivation negative shift | -                            | PMID: 21167004  |
| R R222Q+Q1007del | cis AY148488 | 35% reduction in $I_{Na}$ density, alterations in the activation and inactivation negative shift, slower recovery from inactivation | Aggravate in the Q1077 del |             |
| H R222Q      | cis AC1377587* | $I_{Na}$ density normal, alterations in the activation and inactivation negative shift | -                            |             |
| R R222Q      | cis AC1377587* | $I_{Na}$ density normal, alterations in the activation and inactivation negative shift | -                            |             |
| H R282H      | trans NM 198056| Reduced ~58% whole cell currents                                             | -                            | PMID: 16864729 |
| H Wt         | NM 198056       | Normal current                                                               | Full rescue through trafficking |             |
| R Wt         | NM 198056       | Reduced ~48% whole cell currents                                             | -                            |             |
| H Wt         | trans NM 198056| Normal current                                                               | Normal                       |             |
| R Wt         | NM 198056       | No current                                                                   | -                            |             |
| R R282H      | cis NM 198056  | No current                                                                   | Normal                       |             |
| R R282H      | cis NM 198056  | Reduced ~48% whole cell currents                                             | -                            |             |
| H G400A      | cis hH1a        | Reduced peak current                                                         | Aggravate                    | PMID: 17675083 |
| R G400A      | cis hH1a        | Further reduced peak current                                                  | -                            |             |
| H T512I      | cis M77235 (hH1)| Increased development of slow inactivation                                  | Ameliorate                   | PMID: 12569159 |
| R T512I      | cis M77235 (hH1)| Enhanced slow activation                                                     | -                            |             |
| H *A572+Q1077del | hH1C normal    | Not significant lower peak current, increase in late persistent current, significant negative shift in the steady states inactivation | Aggravate Double hit mutation linked to R558 |             |
| R *A572+Q1077del | hH1C normal    | Not significant lower peak current, increase in late persistent current, significant negative shift in the steady states inactivation | Aggravate Double hit mutation linked to R558 |             |
| H *Q1077     | cis AC1377587● | Reduced current (not significant)                                            | Normal                       |             |
| R *Q1077     | AC1377587●     | Little or No $I_{Na}$ density??                                              | Aggravate                    |             |
| H *Q1077del  | cis AC1377587● | Normal currents                                                              | Normal                       |             |
| R *Q1077del  | cis AC1377587● | Normal currents                                                              | Normal                       |             |
| H D1275N     | cis M77235 (hH1)| Reduced peak current                                                         | Ameliorate Through intracellular trafficking | PMID: 20384651 |
| R D1275N     | cis M77235 (hH1)| 2 fold peak increase in peak current comparable to Wt, Hyperpolarizing potential, negative shifts of the midinactivation | Ameliorate Through intracellular trafficking |             |
| H D1632H     | cis M77235 (hH1)| Hyperpolarizing potential, negative shifts of the mid inactivation           | Aggravate                    |             |
| R D1632H     | cis M77235 (hH1)| Loss of function                                                             | -                            |             |
| H558R | Mutation | Exp. | Background | Observations | Outcome | Ref |
|-------|----------|------|------------|--------------|---------|-----|
| H     | P1298L   | cis  | M77235 (hH1) | Hyperpolarizing potential, negative shifts of the mid inactivation | Aggravate | PMID: 20384651 |
| R     | P1298L   | cis  | M77235 (hH1) | Normal peak currents | | |
| H     | D1690N   | cis  | M77235 (hH1) | Reduced peak currents, defective trafficking to the membrane | | PMID: 23085483 |
| H     | G1748D   | cis  | M77235 (hH1) | Very low peak currents, defective trafficking to the membrane | | |
| H     | cis      | cis  | M77235 (hH1) | 30% reduced peak current | | |
| H     | cis      | cis  | M77235 (hH1) | 15% reduced peak current | | |
| H     | D1690N   | cis  | M77235 (hH1) | Reduced Current | | |
| R     | D1690N   | cis  | M77235 (hH1) | Restoration of Wt currents, correct trafficking to the membrane | Ameliorate | |
| R     | D1690N   | cis  | M77235 (hH1) | Very low peak currents | | |
| R     | M1766L   | hH1b | Normal currents and cell trafficking | Ameliorate | PMID: 12454206 |
| H     | M1766L   | cis  | M77235 (hH1) | Reduced currents | | |
| H     | M1766L   | cis  | hH1a | Reduced currents | | |
| R     | M1766L   | cis  | hH1a | Normal currents and cell trafficking restores | ameliorate | |
| H     | cis      | cis  | M77235 (hH1) | Normal peak currents | | |
| H     | I1835T   | trans | hH1c | Reduced currents | | PMID: 27381756 |
| R     | I1835T   | trans | hH1c | More prominent reduced currents | Aggravate | |
| H     | I1835T   | AC1377587● | hH1c | Reduced currents | | |
| R     | I1835T   | AC1377587● | hH1c | Normal currents and cell trafficking restores | ameliorate | |
| H     | I1835T+Q1007del | AC1377587● | hH1c | Reduced currents | | |
| R     | I1835T+Q1007del | AC1377587● | hH1c | Normal currents and cell trafficking restores | ameliorate | |
| H     | I1835T+Q1007del | AC1377587● | hH1c | Reduced currents | | |
| R     | I1835T+Q1007del | AC1377587● | hH1c | Normal currents and cell trafficking restores | ameliorate | |
| H     | P2006A   | NM 198056 | Normal peak currents, and +10mV shift in voltage dependence of steady state inactivation, faster recovery from inactivation | | PMID: 21109022 |
| R     | P2006A   | NM 198056 | Sodium currents recovered values comparable with Wt | Ameliorate | |
| H     | P2006A   | trans | NM 198056 | Sodium currents recovered values comparable with Wt | Ameliorate | |
| R     | P2006A   | trans | NM 198056 | Sodium currents recovered values comparable with Wt | Ameliorate | |
| R     | P2006A   | trans | NM 198056 | Sodium currents recovered values comparable with Wt | Ameliorate | |
| H     | cis      | trans | NM 198056 | +9mV shift in steady state inactivation | | |
| R     | V1951L   | cis  | NM 198056 | Recovery to Wt values | Ameliorate | |
Table S2. Accession numbers of SCN5A sequences for species with no annotated SCN5A. Gene manual annotation was performed and scaffold numbers where SCN5A was identified are provided. In the case of species with no SCN5A annotation and no genome assembly, SRA projects were searched and project numbers are indicated in Table S3.

| Species | Order | Accession number SCN5A Neonatal | Allele |
|---------|-------|---------------------------------|--------|
| 1       | HSA   | Primate-Homoioideae             | NM_198056.2 | H/R |
| 2       | PPA   | Primate-Homoioideae             | XM_008951545.1 | R |
| 3       | PTR   | Primate-Homoioideae             | XM_016940745.2 | R |
| 4       | GBE   | Primate-Homoioideae             | SRA     |     |
| 5       | GGO   | Primate-Homoioideae             | XM_019024737.2 | R |
| 6       | PAB   | Primate-Homoioideae             | XM_024245225.1 | H/Q |
| 7       | PYY   | Primate-Homoioideae             | SRA     | H/Q |
| 8       | HMO   | Primate-Homoioideae             | XM_032162037.1 | R |
| 9       | NLE   | Primate-Homoioideae             | XM_030812100.1 | R |
| 10      | RBI   | Primate-Haplorrhini-Cercopithecoidae | XM_017849653.1 | H |
| 11      | RRO   | Primate-Haplorrhini-Cercopithecoidae | XM_010371496.2 | H |
| 12      | NLA   | Primate-Haplorrhini-Cercopithecoidae | SRA     |     |
| 13      | SEM   | Primate-Haplorrhini-Cercopithecoidae | SRA     |     |
| 14      | TFR   | Primate-Haplorrhini-Cercopithecoidae | XM_033212073.1 | H |
| 15      | PTE   | Primate-Haplorrhini-Cercopithecoidae | XM_023231462.1 | H |
| 16      | CAN   | Primate-Haplorrhini-Cercopithecoidae | XM_011953304.1 | H |
| 17      | PAN   | Primate-Haplorrhini-Cercopithecoidae | XM_009201170.3 | H |
| 18      | TGE   | Primate-Haplorrhini-Cercopithecoidae | XM_025375222.1 | H |
| 19      | MLE   | Primate-Haplorrhini-Cercopithecoidae | XM_011999484.1 | H |
| 20      | MSP   | Primate-Haplorrhini-Cercopithecoidae | SRA     |     |
| 21      | CAT   | Primate-Haplorrhini-Cercopithecoidae | XM_012034251.1 | H |
| 22      | MFU   | Primate-Haplorrhini-Cercopithecoidae | SRA     |     |
| 23      | MMUL  | Primate-Haplorrhini-Cercopithecoidae | XM_015131334.1 | H |
| 24      | MNE   | Primate-Haplorrhini-Cercopithecoidae | XM_011738773.2 | H |
| 25      | MFA   | Primate-Haplorrhini-Cercopithecoidae | XM_005546682.3 | H |
| 26      | CSA   | Primate-Haplorrhini-Cercopithecoidae | XM_007971735.1 | H |
| 27      | SIM   | Primate-Haplorrhini-Platyrrhini | SRA     |     |
| 28      | CIA   | Primate-Haplorrhini-Platyrrhini | XM_017965958.1 | H |
| 29      | ANA   | Primate-Haplorrhini-Platyrrhini | XM_021666656.9 | H |
| 30      | SBO   | Primate-Haplorrhini-Platyrrhini | XM_010341492.1 | H |
| 31      | CCA   | Primate-Haplorrhini-Platyrrhini | XM_017508376.1 | H |
| 32      | APA   | Primate-Haplorrhini-Platyrrhini | PNVK010013273.1 | H |
| 33      | AGE   | Primate-Haplorrhini-Platyrrhini | PNVK010001690.1 | H |
| 34      | PPI   | Primate-Haplorrhini-Platyrrhini | PNVK010012057.1 | H |
| 35      | CSY   | Primate-Haplorrhini-Platyrrhini | PNVK01040726.1 | H |
| 36      | OGA   | Primate-Haplorrhini-Platyrrhini | XM_008053200.2 | R |
| 37      | MMUR  | Primate-Haplorrhini-Platyrrhini | XM_023515919.1 | R |
| 38      | MMUR  | Primate-Haplorrhini-Platyrrhini | XM_012753939.1 | R |
| 39      | NGM   | Rodentia-Myomorphia             | XM_008836179.1 | R |
| 40      | MMU   | Rodentia-Myomorphia             | XM_001253860.1 | R |
| 41      | RNO   | Rodentia-Myomorphia             | XM_013125.2 | H/R |
| 42      | CRG   | Rodentia-Myomorphia             | XM_035440051.1 | R |
| 43      | MOC   | Rodentia-Myomorphia             | XM_005348090.9 | R |
| 44      | PMA   | Rodentia-Myomorphia             | XM_006986726.2 | R |
| 45      | MDA   | Rodentia-Sciurophoideae         | XM_015489475.1 | R |
| 46      | ITR   | Rodentia-Sciurophoideae         | XM_005317377.2 | R |
| 47      | CPO   | Rodentia-Hysticomorphida        | XM_005001107.2 | R |
| 48      | HGL   | Rodentia-Hysticomorphida        | XM_004835238.2 | R |
| 49      | ODE   | Rodentia-Hysticomorphida        | XM_004621523.2 | R |
| 50      | CLA   | Rodentia-Hysticomorphida        | XM_005386578.2 | R |
| 51      | OCU   | Lagomorpha                      | XM_017340134.1 | R |
| 52      | OPR   | Lagomorpha                      | XM_017340134.1 | R |
| 53      | SSC   | Lagomorpha                      | XM_021071676.1 | R |
| 54      | CDR   | Lagomorpha                      | XM_010974813.1 | R |
| 55      | CFE   | Lagomorpha                      | XM_032459195.1 | R |
| 56      | BTA   | Lagomorpha                      | XM_174458.2 | R |
| 57      | BMU   | Lagomorpha                      | XM_005901131.1 | R |
| 58      | OAR   | Lagomorpha                      | XM_012140142.2 | R |
| 59      | CHI   | Lagomorpha                      | XM_018038398.1 | R |
|   |   |   |   |
|---|---|---|---|
|60| OOR | Orcinus orca | Cetartiodactyla-Cetacea-Odontoceti | XM_004277836.1 |
|61| LVE | Lipotes vexillifer | Cetartiodactyla-Cetacea-Odontoceti | XM_007468130.1 |
|62| PCA | Physeter catodon | Cetartiodactyla-Cetacea-Mysticeti | XM_007110496.2 |
|63| BAC | Balaenoptera acutorostrata | Cetartiodactyla-Cetacea-Mysticeti | XM_007191459.1 |
|64| CSI | Ceratotherium simum simum | Perissodactyla-Rhinoceratidae | XM_014790663.1 |
|65| ECA | Equus caballus | Perissodactyla-Equidea | XM_023619740.1 |
|66| ORO | Odobenus rosmarus divergens | Carnivora-Carniformia | XM_012566600.1 |
|67| CLU | Canis lupus familiaris | Carnivora-Carniformia | NM_001002994.1 |
|68| MFU | Mustela putorius furo | Carnivora-Carniformia | XM_004759336.2 |
|69| AME | Ailuropoda melanoleuca | Carnivora-Carniformia | XM_034662224.1 |
|70| UMA | Ursus maritimus | Carnivora-Carniformia | XM_008710149.1 |
|71| AJU | Acinonyx jubatus | Carnivora-Feliformia | XM_027040708.1 |
|72| PPAR | Panthera pardus | Carnivora-Feliformia | XM_019418729.1 |
|73| FCA | Felis catus | Carnivora-Feliformia | XM_023260721.1 |
|74| DRO | Desmodus rotundus | Chiroptera | XM_024565669.1 |
|75| HAR | Hipposideros armiger | Chiroptera | XM_019662785.1 |
|76| MNA | Miniopterus natalensis | Chiroptera | XM_016196168.1 |
|77| TCH | Tupaia chinensis | Scandentia | XM_006161350.2 |
|78| GVA | Galeopterus variegatus | Dermoptera | XM_008567166.1 |
|79| LAF | Loxodonta africana | Afrotheria-Proboscidea | XM_023554825.1 |
|80| CAS | Chrysoglossus asiaticus | Afrotheria-Afrosoricida | XM_006869133.1 |
|81| OAF | Orycteropus afer afer | Afrotheria-Tubulidentata | XM_007945712.1 |
|82| CCR | Condylura cristata | Insectivora-Talpidae | XM_004676302.2 |
|83| EEU | Erinaceus europaeus | Insectivora-Erinaceomorpha | XM_007517226.2 |
|84| MDO | Monodelphis domestica | Marsupialia | NM_001246327.1 |
Table S3. SRA projects searched to determine the polymorphic status at position 558 of the SCN5A gene in other primate species. * indicates that project was searched and no hit overlapping the H558R region was retrieved.

| Species                  | Project          | SRX               | Sample         | Origin          | Observations | Allele |
|--------------------------|------------------|-------------------|----------------|-----------------|--------------|--------|
| *Pan troglodytes*        | PRJNA189439      | SRX237524         | Bwanbale       | Wild Born       | Eastern      | R      |
| *                         |                  | SRX237527         | Kidongo        | Wild Born       | Eastern      | R      |
| *                         |                  | SRX237541         | Nakuu          | Wild Born       | Eastern      | R      |
| *                        | PRJEB2482        | ERX012404         | Cindy          | Chimpanzee Sanctuary | R     |        |
| *                         |                  | ERX012403         | Sally          | Chimpanzee Sanctuary | R     |        |
| *                         |                  | ERX012402         | Nakuu          | Chimpanzee Sanctuary | *    |        |
| *                         |                  | ERX012398         | Katie          | Chimpanzee Sanctuary | *    |        |
| *                         |                  | ERX012395         | Kidogo         | Chimpanzee Sanctuary | R     |        |
| *                         |                  | ERX012394         | Kazakuhire     | Chimpanzee Sanctuary | *    |        |
| *                        |                  | ERX012393         | Becky          | Chimpanzee Sanctuary | R     |        |
| *Pan troglodytes*        | PRJNA189439      | SRX243446         | Donald         | Captive Born    | Hybrid       | R      |
| *                         |                  | SRX243487         | Jimmie         | Wild Born       | Western      | R      |
| *                         |                  | SRX243489         | Vaillant       | Wild Born       | Central      | R      |
| *                         |                  | SRX243491         | Doris          | Wild Born       | Central      | *      |
| *                        | PRJEB2482        | SRX243493         | Julie          | Wild Born       | Central      | R      |
| *                         |                  | SRX243499         | Koby           | Wild Born       | Western      | R      |
| *                         |                  | SRX243495         | Clara          | Wild Born       | Central      | R      |
| *                         |                  | SRX243448         | Bosco          | Wild Born       | Western      | R      |
| *                        |                  | SRX243449         | Marcelle       | Tchimpounga Chimp rehabilitation center | R     |        |
| *                         | PRJEB2482        | ERX012401         | Bayokele       | Tchimpounga Chimp rehabilitation center | R     |        |
| *                         |                  | ERX012397         | Gofi           | Tchimpounga Chimp rehabilitation center | *    |        |
| *                         |                  | ERX012392         | Gao            | Tchimpounga Chimp rehabilitation center | R     |        |
| *                         |                  | ERX012390         | FanTuke        | Tchimpounga Chimp rehabilitation center | R     |        |
| *                         |                  | ERX012389         | Botsomi        | Tchimpounga Chimp rehabilitation center | R     |        |
| *                        |                  | ERX012388         | Agnagui        | Tchimpounga Chimp rehabilitation center | R     |        |
| *Pan troglodytes*        | PRJNA189439      | SRX360475         | Akwaya-Jean    | Wild Born       | Nigerian     | R      |
| *                         |                  | SRX360476         | Damian         | Wild Born       | Nigerian     | R      |
| *                         |                  | SRX360477         | Julie_LWC21    | Wild Born       | Nigerian     | R      |
| *                         |                  | SRX360478         | Koto           | Wild Born       | Nigerian     | R      |
| *                         |                  | SRX360479         | Taweh          | Wild Born       | Nigerian     | R      |

Continues next page
| Species          | Project | SRX     | Sample  | Origin     | Observations | H558R |
|------------------|---------|---------|---------|------------|--------------|-------|
| *Pan paniscus*   | PRJNA189439 | SRX242682 | Kumbuka | Captive Born |               | R     |
|                  |         | SRX242681 | Salonga | Captive Born |               | R     |
|                  |         | SRX241545 | Salonga | Captive Born |               | R     |
|                  |         | SRX241481 | Salonga | Captive Born |               | R     |
|                  |         | SRX241477 | Salonga | Captive Born |               | R     |
|                  |         | SRX241461 | Salonga | Captive Born |               | R     |
|                  |         | SRX241441 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241378 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241367 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241358 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241352 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241312 | Natalie | Wild Born   |               | R     |
|                  |         | SRX241311 | Chipita  | Wild Born   |               | R     |
|                  |         | SRX241308 | Chipita  | Wild Born   |               | R     |
|                  |         | SRX241307 | Chipita  | Wild Born   |               | R     |
|                  |         | SRX241305 | Chipita  | Wild Born   |               | R     |
|                  |         | SRX241304 | Kombate  | Wild Born   |               | R     |
|                  |         | SRX241303 | Catherine| Wild Born   |               | R     |
|                  |         | SRX241302 | Catherine| Wild Born   |               | R     |
|                  |         | SRX241295 | Desmond  | Wild Born   |               | R     |
|                  |         | SRX241294 | Desmond  | Wild Born   |               | R     |
|                  |         | SRX241293 | Hermien  | Wild Born   |               | R     |
|                  |         | SRX241291 | Dzeeta   | Wild Born   |               | R     |
|                  |         | SRX241289 | Dzeeta   | Wild Born   |               | R     |
|                  |         | SRX241288 | Kosana   | Wild Born   |               | R     |
|                  |         | SRX237623 | Hortense | Wild Born   |               | R     |
|                  |         | SRX243437 | LB502    | Captive Born| Lymphoblastoid| R     |
|                  | PRJNA189439 | SRX243504 | Akiba   | Wild Born   |               | R     |
|                  |         | SRX243505 | Akiba   | Wild Born   |               | R     |
|                  |         | SRX243506 | Paki    | Wild Born   |               | R     |
|                  |         | SRX243508 | Paki    | Wild Born   |               | R     |
|                  |         | SRX243509 | Paki    | Wild Born   |               | R     |
|                  |         | SRX243438 | Kowali  | Captive Born|               | R     |
|                  |         | SRX243440 | Bulera  | Captive Born|               | R     |
|                  |         | SRX243442 | Azizi   | Captive Born|               | R     |
|                  |         | SRX243444 | Suzie   | Wild Born   |               | R     |
|                  |         | SRX243455 | Banjo   | Wild Born   |               | R     |
|                  |         | SRX243457 | Banjo   | Wild Born   |               | R     |
|                  |         | SRX243461 | Delphi  | Wild Born   |               | R     |
|                  |         | SRX243466 | Kolo    | Captive Born|               | R     |
|                  |         | SRX243463 | Coco    | Wild Born   |               | R     |

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| Species                     | Project     | SRX          | Sample | Origin      | Observations | H558R |
|-----------------------------|-------------|--------------|--------|-------------|--------------|-------|
| *Gorilla gorilla diehli*    | PRJNA189439 | SRX2343507   | Nyango | Wild Born   |              |       |
|                             |             | SRX243529    |        |             |              |       |
|                             |             | SRX243528    |        |             |              |       |
|                             |             | SRX243532    |        |             |              |       |
|                             |             | SRX243531    |        |             |              |       |
| **Gorilla beringei graueri**| PRJNA189439 | SRX243530    | Victoria | Captive Born | Eastern lowland gorilla | R     |
|                             |             | SRX242688    |        |             |              |       |
|                             |             | SRX242687    |        |             |              |       |
|                             |             | SRX242686    |        |             |              |       |
|                             |             | SRX242685    |        | Wild born   | Eastern lowland gorilla | R     |
|                             |             | SRX243453    |        | Wild born   | Eastern lowland gorilla | R     |
| **Pongo pygmaeus**          | PRJNA189439 | SRX243476    | Napoleon | Wild Born   | Bornean orangutan | H     |
|                             |             | SRX243475    |        |             |              |       |
|                             |             | SRX243474    |        |             |              |       |
|                             |             | SRX243473    |        |             |              |       |
|                             |             | SRX243472    | Sari   | Captive Born | Bornean orangutan | H     |
|                             |             | SRX243471    |        |             |              |       |
|                             |             | SRX243469    | Temmy  | Captive Born | Bornean orangutan | H     |
|                             |             | SRX243468    | Nonja  | Captive Born | Bornean orangutan | H/Q   |
|                             |             | SRX243467    |        |             |              |       |
| **Pongo abelii**            | PRJNA189439 | SRX243486    | Buschi | Wild born   | Sumatran orangutan | H     |
|                             |             | SRX243485    |        |             |              |       |
|                             |             | SRX243484    | Babu   | Wild born   | Sumatran orangutan | H     |
|                             |             | SRX243483    |        |             |              |       |
|                             |             | SRX243482    |        |             |              |       |
|                             |             | SRX243481    | Dunja  | Captive Born | Sumatran orangutan | H/Q   |
|                             |             | SRX243480    |        |             |              |       |
|                             |             | SRX243479    | Kiki   | Wild born   | Sumatran orangutan | H     |
|                             |             | SRX243478    |        |             |              |       |
|                             |             | SRX243477    | Elsi   | Wild born   | Sumatran orangutan | H     |
| **Nomascus leucogenys**     | PRJNA232723 | SRX590192    | NLE-Asteriks | Captive born | female blood | R     |
|                             |             | SRX590181    | NLE-Vok | Captive born | male blood   | R     |
|                             | PRJNA13975  | SRX119997    | NLEU_NLL-600 | Captive born | male blood   | R     |
|                             |             | SRX119996    | NLEU_NLL-607 | Captive born | female blood | R     |
| **Hylabates moloch**        | PRJNA232723 | SRX120003    | HMOL_HMO | Captive born | female blood | R     |
|                             |             | SRX590190    | HMO-Madena | _ | male blood | R     |
|                             |             | SRX590198    | HLE-Drew | captive born | female blood | R     |
|                             |             | SRX590196    | HLE-Maung | captive born | male blood | R     |

Continues next page
| Species                  | Project          | SRX       | Sample  | Origin                                                                 | Observations | H558R |
|--------------------------|------------------|-----------|---------|------------------------------------------------------------------------|--------------|-------|
| *Rhinopithecus roxellana* | PRJNA28338       | SRX1024236| RR11    | Centre of Experimental Primates at Kunming Institute, China            | blood adult  | H     |
|                          |                  | SRX1024227| RR1     |                                                                        | blood adult  | H     |
|                          |                  | SRX1024247| RR22    |                                                                        | blood adult  | H     |
|                          |                  | SRX1024246| RR21    |                                                                        | blood adult  | H     |
|                          |                  | SRX1024229| RR4     |                                                                        | blood adult  | H     |
|                          |                  | SRX1024237| RR12    |                                                                        | blood adult  | H     |
| *Colobus angolensis*     | PRJNA251421      | SRX792356 | CANG.PA-37697 | San Diego Zoo | adult female heart | H       |
|                          |                  | SRX792360 |         |                                                                        |              |       |
|                          | SRP005434        | SRX039392 | Colobus monkey PR00099    | Coriell DNA Male |                      | H       |
| *Papio anubis*           | PRJNA433868      | SRX5516791| 1X1125  |                                                                        | female       | H     |
|                          |                  | SRX6809758| 9045    |                                                                        | blood        | H     |
|                          |                  | SRX6809725| 13951   |                                                                        | blood        | H     |
|                          |                  | SRX6809762| 1X3321  |                                                                        | blood        | H     |
|                          |                  | SRX6809746| 1X4080  |                                                                        | blood        | H     |
|                          |                  | SRX5516802| 9841    |                                                                        | female       | H     |
|                          |                  | SRX5516820| 12242   |                                                                        | female       | H     |
|                          |                  | SRX5516816| 26988   |                                                                        | female       | H     |
| *Macaca mullata*         | PRJNA251548      | SRX8532765| 38158   | Wisconsin National Primate Research Center | female blood | H     |
|                          |                  | SRX8532767| 38160   |                                                                        | female blood | H     |
|                          |                  | SRX8532764| 38157   |                                                                        | female blood | H     |
|                          |                  | SRX8532766| 38159   |                                                                        | female blood | H     |
|                          | PRJNA382404      | SRX7133280| m05200  |                                                                        | female blood | H     |
|                          |                  | SRX7133282| m05014  |                                                                        | male blood Indian Breed | H |
| *Chlorocebus sabaeus*    | PRJNA368714      | SRX3306491| VRV1723 |                                                                        | male blood    | H     |
|                          |                  | SRX3306490| VRV1719 |                                                                        | male blood    | H     |
|                          |                  | SRX3306492| VRV1722 |                                                                        | male blood    | H     |
|                          | PRJNA240242      | SRX497144 | VCAC-2000043-VRV0491 |                                                                         | male acd-blood | H     |
|                          |                  | SRX497168 | VCAC-2000080-VRV0501 |                                                                         | female acd-blood | H     |
|                          |                  | SRX497142 | VCAC-1998073-VRV0270 |                                                                         | male acd-Blood | H     |
|                          |                  | SRX658822 | VCAC-2005088-VRV1273 |                                                                         | female whole blood | H |
|                          | PRJNA168527      | SRX3266835| CASA-091214_gDN_A_85616_Tube1 |                                                                         | blood | H     |

Continues next page
| Species                      | Project          | SRX | Sample          | origin                                                   | observations | H558R |
|------------------------------|------------------|-----|-----------------|----------------------------------------------------------|--------------|-------|
| *Pithecia pithecia*          | PRJNA399413      | SRX8010141 | PitPit_1_DIS litter COVAR | San Diego Zoo Institute for Conservation Research |              |       |
| *Callithrix jacchus*         | PRJNA566173      | SRX7047414  | SAMN12783 337 | Wisconsin Primate Research Center | female skin cell line cj17000 |       |
|                              | PRJNA401030      | SRX7001670  |                |                                                          |              | H     |
| *Cebus capucinus imitator*   | PRJNA298580      | SRX1560048  | CJ-08-46       |                                                          |              |       |
|                              | PRJNA298580      | SRX1560050  | 569822         |                                                          |              | H     |
|                              | PRJNA298580      | SRX1435930  | 569789         |                                                          |              | H     |
Table S4. rs1805124 minor allele frequency distribution in all populations analysed collected from the 1KGP Phase 3. ACB- African Caribbeans in Barbados; ASW- Americans of African Ancestry in SW USA; ESN- Esan in Nigeria; GWD- Gambian in Western Divisions in the Gambia; LWK- Luhya in Webuye, Kenya; MSL- Mende in Sierra Leone; YRI- Yoruba in Ibadan, Nigeria; CLM- Colombians from Medellin, Colombia; MXL- Mexican Ancestry from Los Angeles USA; PEL- Peruvians from Lima, Peru; PUR- Puerto Ricans from Puerto Rico; CDX- Chinese Dai in Xishuangbanna, China; CHB- Han Chinese in Beijing, China; CHS- Southern Han Chinese; JPT- Japanese in Tokyo, Japan; KHV- Kinh in Ho Chi Minh City, Vietnam; CEU- Utah Residents (CEPH) with Northern and Western European Ancestry; FIN- Finnish in Finland; GBR- British in England and Scotland; IBS- Iberian Population in Spain; TSI- Tuscany in Italia; BEB- Bengali from Bangladesh; GIH- Gujarati Indian from Houston, Texas; ITU- Indian Telugu from the UK; PJL- Punjabi from Lahore, Pakistan; STU- Sri Lankan Tamil from the UK.

| POPULATION | RS1805124 | T (His) | C (Arg) | TT | CC | CT |
|------------|-----------|---------|---------|----|----|----|
| AFRICAN    |           |         |         |    |    |    |
| ACB        | 0.691     | 0.309   | 0.487   | 0.106 | 0.407 |
| ASW        | 0.719     | 0.281   | 0.542   | 0.104 | 0.354 |
| ESN        | 0.783     | 0.217   | 0.596   | 0.030 | 0.374 |
| GWD        | 0.628     | 0.372   | 0.442   | 0.186 | 0.372 |
| LWK        | 0.697     | 0.303   | 0.485   | 0.091 | 0.424 |
| MSL        | 0.618     | 0.382   | 0.388   | 0.153 | 0.459 |
| YRI        | 0.671     | 0.329   | 0.426   | 0.083 | 0.491 |
| AMERICAN   |           |         |         |    |    |    |
| CLM        | 0.761     | 0.239   | 0.543   | 0.021 | 0.436 |
| MXL        | 0.836     | 0.164   | 0.703   | 0.031 | 0.266 |
| PEL        | 0.776     | 0.224   | 0.624   | 0.071 | 0.306 |
| PUR        | 0.740     | 0.260   | 0.558   | 0.077 | 0.365 |
| EAST ASIAN |           |         |         |    |    |    |
| CDX        | 0.930     | 0.070   | 0.871   | 0.011 | 0.118 |
| CHB        | 0.874     | 0.126   | 0.748   | -    | 0.252 |
| CHS        | 0.905     | 0.095   | 0.819   | 0.010 | 0.171 |
| JPT        | 0.865     | 0.135   | 0.740   | 0.010 | 0.250 |
| KHV        | 0.924     | 0.076   | 0.848   | -    | 0.152 |
| EUROPEAN   |           |         |         |    |    |    |
| CEU        | 0.818     | 0.182   | 0.657   | 0.020 | 0.323 |
| FIN        | 0.823     | 0.177   | 0.667   | 0.020 | 0.313 |
| GBR        | 0.775     | 0.225   | 0.593   | 0.044 | 0.363 |
| IBS        | 0.738     | 0.262   | 0.561   | 0.084 | 0.355 |
| TSI        | 0.766     | 0.234   | 0.579   | 0.047 | 0.374 |
| SOUTH ASIAN|           |         |         |    |    |    |
| BEB        | 0.721     | 0.279   | 0.500   | 0.058 | 0.442 |
| GIH        | 0.796     | 0.204   | 0.612   | 0.019 | 0.369 |
| ITU        | 0.706     | 0.294   | 0.529   | 0.118 | 0.353 |
| PJL        | 0.740     | 0.260   | 0.531   | 0.052 | 0.417 |
| STU        | 0.672     | 0.328   | 0.480   | 0.137 | 0.382 |
Table S5. Bayesian One Sample T-Test, using the Two-sided alternative hypothesis that the superpopulation mean is not equal to the test value (H0). a- Average frequency of all populations from 1KGP, b-Average frequency of all populations within the 95% confidence interval, N- Number of populations included in the test, SD standard deviation, SE standard error of the mean, BF01 and BF10 Bayes factors of likelihood of H0 and H1, respectively. ESN-Esan in Nigeria, GWD- Gambian in Western Divisions in the Gambia, MSL-Mende in Sierra Leone, CDX-Chinese Dai in Xishuangbanna and IBS in Spain.

| Population     | N  | Mean (H0) | SD  | SE  | BF01 | BF10 | Error % | Lower   | Upper   | Outlier sub populations |
|----------------|----|-----------|-----|-----|------|------|---------|---------|---------|-------------------------|
| African        | 7  | 0.307     | 0.059| 0.022| 2.831| 0.353| 6.191e-6| 0.252   | 0.361   | ESN, GWD, MSL            |
| American       | 4  | 0.222     | 0.041| 0.021| 2.338| 0.428| 2.607e-7| 0.156   | 0.287   |                         |
| East Asian     | 5  | 0.100     | 0.029| 0.013| 2.515| 0.398| 6.831e-6| 0.064   | 0.137   |                         |
| European       | 5  | 0.216     | 0.036| 0.016| 2.516| 0.397| 7.009e-6| 0.171   | 0.261   | IBS                     |
| South Asian    | 5  | 0.273     | 0.046| 0.021| 2.516| 0.397| 7.009e-6| 0.216   | 0.330   |                         |
Table S6. Haplotype analysis of the 1KGP data. Haplotypes were obtained through combination of variants (rs2051211, rs3922844, rs7374004, rs7374540, rs6599222, rs11710077) found to be in LD with rs1805124. Frequency and count values refer to the sum off all populations, individual population counts are shown in the respective population columns. Bold haplotypes carry the rs1805124-C allele (Arg558).

| Haplotype | Count | Frequency | African | American | South Asian | European | East Asian |
|-----------|-------|-----------|---------|----------|-------------|----------|-----------|
| rs2051211 |       |           |         |          |             |          |           |
| rs3922844 |       |           |         |          |             |          |           |
| rs7374004 |       |           |         |          |             |          |           |
| rs7374540 |       |           |         |          |             |          |           |
| rs6599222 |       |           |         |          |             |          |           |
| rs11710077|       |           |         |          |             |          |           |

| Haplotype | Count | Frequency | African | American | South Asian | European | East Asian |
|-----------|-------|-----------|---------|----------|-------------|----------|-----------|
| H1        | 1     | 0.226     | 45      | 187      | 281         | 304      | 315       |
| H2        | 1     | 0.1342    | 117     | 87       | 88          | 82       | 298       |
| H3        | 1     | 0.0931    | 383     | 42       | 28          | 6        | 7         |
| H4        | 2     | 0.0921    | 161     | 87       | 89          | 112      | 12        |
| H5        | 2     | 0.0565    | 7       | 17       | 38          | 49       | 172       |
| H6        | 4     | 0.0501    | 39      | 56       | 64          | 81       | 11        |
| H7        | 3     | 0.0491    | 58      | 30       | 80          | 38       | 40        |
| H8        | 2     | 0.0343    | 83      | 28       | 11          | 49       | 1         |
| H9        | 2     | 0.0335    | 75      | 17       | 16          | 43       | 17        |
| H10       | 1     | 0.0325    | 132     | 13       | 12          | 6        |           |
| H11       | 2     | 0.0274    | 1       | 20       | 29          | 32       | 55        |
| H12       | 2     | 0.024     | 3       | 24       | 31          | 61       | 1         |
| H13       | 2     | 0.0208    | 63      | 10       | 10          | 4        | 17        |
| H14       | 3     | 0.0202    | 12      | 22       | 23          | 17       | 27        |
| H15       | 1     | 0.019     | 39      | 9        | 40          | 3        | 4         |
| H16       | 3     | 0.0162    | 41      | 6        | 17          | 15       | 2         |
| H17       | 0     | 0.0136    | 2       | 3        | 41          | 20       | 2         |
| H18       | 2     | 0.0114    | 11      | 7        | 20          | 19       |           |
| H19       | 3     | 0.0052    | 3       | 7        | 8           | 8        |           |
| H20       | 0     | 0.004     | 16      | 2        | 1           | 1        |           |
| H21       | 3     | 0.0038    | 3       | 6        | 9           | 1        |           |
| H22       | 1     | 0.003     | 2       | 4        | 9           |          |           |
| H23       | 2     | 0.0028    | 1       | 1        | 11          | 1        |           |
| H24       | 1     | 0.0024    | 6       | 2        | 1           | 3        |           |
| H25       | 2     | 0.0022    | 11      |          |             |          |           |
| H26       | 2     | 0.0022    | 1       | 1        | 3           | 6        |           |
| H27       | 4     | 0.0022    | 4       | 2        | 2           | 5        |           |
| H28       | 3     | 0.002     | 6       | 4        |             |          |           |
| H29       | 2     | 0.0018    | 1       | 3        | 5           |          |           |
| H30       | 2     | 0.0014    | 5       | 2        |             |          |           |
| H31       | 3     | 0.0014    | 1       | 2        | 4           |          |           |
| H32       | 2     | 0.0012    | 1       | 1        | 2           | 2        |           |
| H33       | 3     | 0.0012    | 1       | 1        | 3           | 1        |           |
| H34       | 3     | 0.0012    | 2       | 1        | 3           |          |           |
| H35       | 3     | 0.0012    | 1       | 5        |             |          |           |
| H36       | 2     | 0.0008    | 1       | 1        | 2           |          |           |
| H37       | 3     | 0.0008    | 1       | 3        |             |          |           |
| H38       | 2     | 0.0008    | 1       | 1        | 2           |          |           |
| H39       | 3     | 0.0006    | 2       | 1        |             |          |           |
| H40       | 2     | 0.0006    | 1       | 2        |             |          |           |
| H41       | 1     | 0.0006    | 1       | 2        |             |          |           |
| H42       | 1     | 0.0006    | 3       |          |             |          |           |
| H43  | A_T_A_C_C_C_A | 2   | 2   | 0.0004 | 2    |
| H44  | G_C_A_C_T_C_T | 4   | 2   | 0.0004 | 1    |
| H45  | G_T_A_C_C_C_A | 3   | 2   | 0.0004 | 2    |
| H46  | A_C_A_A_C_T_A | 2   | 1   | 0.0002 | 1    |
| H47  | A_C_T_C_T_C_A | 1   | 1   | 0.0002 | 1    |
| H48  | A_T_T_A_T_T_T | 2   | 1   | 0.0002 | 1    |
| H49  | G_C_A_A_C_T_T | 4   | 1   | 0.0002 | 1    |
| H50  | G_C_A_A_T_T_A | 3   | 1   | 0.0002 | 1    |

| Nº of haplotypes per population | 31 | 34 | 37 | 39 | 25 |