Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy

Stuart A. Scott[1], Katrin Sangkuhl[2], Eric E. Gardner[3], C. Michael Stein[4], Jean-Sebastien Hulot[5], Julie A. Johnson[6], Dan M. Roden[7], Teri E. Klein[2], Alan R. Shuldiner[8]

[1] Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY, 10029
[2] Department of Genetics, Stanford University, Stanford, CA, 94305
[3] University of Pittsburgh School of Pharmacy, Pittsburgh, PA, 15261
[4] Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232
[5] Université Pierre et Marie Curie-Paris 6, INSERM UMR S 956, Pharmacology Department, Pitié-Salpêtrière University Hospital, Paris, France and Cardiovascular Research Center, Mount Sinai School of Medicine, New York, NY, 10029
[6] Department of Pharmacotherapy and Translational Research and Department of Medicine (Cardiology), Colleges of Pharmacy and Medicine; and Center for Pharmacogenomics; University of Florida, Gainesville, FL, 32610
[7] Departments of Medicine and Pharmacology, Office of Personalized Medicine, Vanderbilt University School of Medicine, Nashville, TN, 37232
[8] Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD 21201, and Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD, 21201

Corresponding Author: Alan R. Shuldiner, M.D.
University of Maryland School of Medicine
660 West Redwood Street, Room 494
Baltimore, MD 21201
Tel: 410-706-1623
Fax: 410-706-1622
Email: ashuldin@medicine.umaryland.edu

CPIC Updates
Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

Literature Review
The PubMed database (NCBI) was searched using the keywords (CYP2C19 OR cytochrome P450-2C19) AND (clopidogrel) from 1966 to February 2011. Key publications of clinical pharmacogenetic studies on clopidogrel response include: (1-10). For additional reviews and consensus statements, see references: (11-20). For additional information on clopidogrel pharmacogenetics, see PharmGKB: http://www.pharmgkb.org/clinical/clopidogrel.jsp

To construct a *CYP2C19* minor allele frequency table based on ethnicity, the PubMed® database (1966 to January 2011) and Ovid MEDLINE (1950 to January 2011) were searched using the following criteria: ((CYP2C19 or 2C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity)) with filter limits set to retrieve "full-text" and "English" literature. Studies were considered for inclusion if, (1) the ethnicity of the population was clearly indicated; (2) either allele frequencies or alleles for *CYP2C19* genotypes were reported; (3) the method by which *CYP2C19* was genotyped appeared reliable; (4) the sample population consisted of at least 50 individuals, and (5) the study represented publication of novel data (no reviews or meta-analyses). In instances where genotype data from large cohorts of ethnically-diverse individuals were reported, without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority.

The combined analysis grouped subpopulations based on the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21-22) and included 7,970 Africans, 7,920 Americans, 36,030 East Asians, 121,808 Europeans, 2,140 Middle Easterns, 13,742 Oceanians, and 7,248 South/Central Asians.

Gene: *CYP2C19*
Genetic Test Interpretation
The haplotype, or star (*) allele name, is determined by the combination of single nucleotide polymorphisms (SNPs) that are interrogated in the genotyping analysis. Each star (*) allele is defined by a specific functional SNP or combination of SNP genotypes. For example, the *CYP2C19*2* haplotype is defined by the c.681G>A SNP that results in aberrant gene splicing; however, sub-alleles of **2* have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2C19*2A*, **2B*, **2C*, and **2D*; see *http://www.cypalleles.ki.se/cyp2c19.htm*). Thus, only analyzing the defining SNP (**2* in this case) is usually sufficient to determine a *CYP2C19* haplotype. The major nucleotide variants that constitute the most commonly tested haplotypes or star (*) alleles for *CYP2C19*, their respective RefSNP accession ID numbers (*http://www.ncbi.nlm.nih.gov/snp/*), and their effect on the CYP2C19 protein are summarized in Supplemental Table S1. The functional consequences of these variant alleles on CYP2C19 enzymatic activity are summarized in Supplemental Table S2 and their multi-ethnic frequencies are listed in Supplemental Tables S3 and S4.

CYP2C19 genotyping results are reported as a diplotype, which includes one maternal and one

paternal star (*) allele (e.g., **1/*2*). Notably, one of the inherent limitations in a commercial genotyping test is that rare or previously undiscovered variants will not usually be included in targeted *CYP2C19* testing panels and the *CYP2C19*1* allele is, therefore, assigned in the absence of detected variant alleles. As a result, a novel or rare *CYP2C19* mutation not included in a commercial genotyping panel would be incorrectly defined as *CYP2C19*1*. Fortunately, these variant alleles will typically be rare in the general population (although the **3* loss-of-function allele is prevalent in Asians; Supplemental Tables S3 and S4). Additional predicted metabolizer phenotypes based on *CYP2C19* genotype combinations and their average frequencies are summarized in Supplemental Table S5.

Available Genetic Test Options

Commercially available genetic testing options change over time and a number of different platforms are currently available for *CYP2C19* genotyping, some of which are approved by the U.S. Food and Drug Administration (FDA). In addition, some clinical laboratories perform *CYP2C19* testing using analyte-specific reagents as in-house validated Laboratory Developed Tests (LDTs). Consequently, diagnostic laboratories may have different variant alleles included in their *CYP2C19* testing panels, which could lead to discrepant results between methodologies (see above, **Genetic Test Interpretation**).

At the time of this manuscript writing, two *CYP2C19* genotyping platforms have been approved by the U.S. FDA: the AmpliChip® CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, CA) and the Infiniti® CYP2C19 Assay (AutoGenomics, Inc., Vista, CA). The AmpliChip® CYP450 Test includes *CYP2C19*2* and **3* (in addition to cytochrome P450-2D6 (*CYP2D6*) variant alleles) and the Infiniti® CYP2C19 Assay includes *CYP2C19*2*, **3*, and **17*. AutoGenomics, Inc., also offers the expanded Infiniti® CYP450 2C19+ Assay that includes *CYP2C19*2*, **3*, **4*, **6*, **7*, **8*, **9*, **10* and **17*, which is not currently FDA-approved. Other commercial *CYP2C19* platforms not currently approved by the FDA include the xTAG™ CYP2C19 Kit from Luminex Molecular Diagnostics (Toronto, ON, Canada) that interrogates *CYP2C19*2*, **3*, **4*, **5*, **6*, **7* and **8*, and the eSensor® 2C19 Test from GenMark Diagnostics, Inc. (Carlsbad, CA) that interrogates *CYP2C19*2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **13* and **17*.

In addition to commercial assays, various other *CYP2C19* LDTs have been reported that utilize real-time PCR allelic-discrimination (TaqMan, Applied Biosystems, Foster City, CA) (5, 23-25), oligonucleotide ligation (SNPlex, Applied Biosystems, Foster City, CA) (5), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (26), the Affymetrix DMET™ Plus Panel Kit (Affymetrix, Santa Clara, CA) (2), and restriction fragment length polymorphism (RFLP) analyses (1, 27-28). Illumina® (San Diego, CA) also has a pharmacogenetic testing panel that includes *CYP2C19* (VeraCode ADME Core Panel), which has an FDA 510k exemption that allows its BeadXpress platform to be used clinically. Any clinical genetic or molecular pathology laboratories using these assays still need to implement these tests using CLIA standards.

Given the number of different molecular assays available to interrogate *CYP2C19*, no specific Current Procedural Terminology (CPT) code exists for *CYP2C19* genotyping; however, it is the responsibility of the service provider to determine proper coding based on the genotyping platform used. The costs of *CYP2C19* testing are not typically covered by insurance companies at the time of this manuscript writing. However, for some pharmacogenetic testing, a pre-

authorization letter to insurance providers by a referring physician, with or without a letter of medical necessity, may assist in obtaining reimbursement for *CYP2C19* genotyping. If this is a concern, whenever possible the insurance provider should be contacted prior to ordering *CYP2C19* genotyping.

Several academic clinical laboratories offer *CYP2C19* testing along with some reference laboratories (e.g., see http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp).

Other Considerations

The defining polymorphisms of *CYP2C19*2* and **17* are c.681G>A and c.-806C>T, respectively. There is linkage disequilibrium between c.681G and c.-806T (e.g., D'=1.0 and r^2=0.064 in CEU HapMap sample; D'=1.0 and r^2=0.065 in YRI HapMap sample; and D'=1.0 and r^2=0.074 in CHB HapMap sample). This means that the less common **17* variant (c.-806T) always tracks on the same allele with the more common c.681G. This complicates any interpretation of whether these two variants act independently of one another, and published articles argue both for (24) and against (15, 29) this point. *CYP2C19* loss-of-function alleles do not account for all of the variability in clopidogrel response. Other genetic variants with smaller effects and rare variants might also influence the response to clopidogrel. Some candidate gene and clinical studies have implicated variants in other genes (e.g., *ABCB1* (5, 8), *CYP2B6* (2), *CYP2C9* (27, 30-31), *CYP3A4* (32), *PON1* (33), and *P2RY12* (34-35)) in association with clopidogrel response; however, these studies have not been consistently replicated.

Drug: Clopidogrel

Linking Genetic Variability to Variability in Drug-Related Phenotypes

Clopidogrel response is a highly heritable trait (3) and *CYP2C19*2* has been associated with lower active metabolite exposure in clopidogrel treated subjects (2, 27, 36-38). Furthermore, *CYP2C19*2* and other loss-of-function variants have been associated with decreased platelet responsiveness to clopidogrel *ex vivo*. (1-3, 5, 7, 9, 23, 25, 39). Importantly, a genome-wide association study identified *CYP2C19*2* as the major genetic determinant for clopidogrel response, which accounted for ~12% of the association with diminished platelet response (3). Further support for the role of *CYP2C19* in clopidogrel response comes from recent large meta-analyses, which concluded that patients with acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI) who carry *CYP2C19* loss-of-function alleles are at increased risk of major adverse cardiovascular events including stent thrombosis (6-7, 9), even among heterozygotes (6-7). However, lack of effect of *CYP2C19* loss-of-function alleles on cardiovascular risk has been reported among clopidogrel-treated patients with lower clinical risks; i.e., in clinical trials with fewer patients receiving PCI with stenting, and in patients receiving clopidogrel for atrial fibrillation and stroke (40-41).

Studies linking *CYP2C19* genotype with variability in clopidogrel response (phenotype) are summarized in Supplemental Tables S6-S8, and it is this body of evidence, rather than randomized clinical trials, which provides the basis for the therapeutic recommendations in Table 2. These supplemental tables were subdivided based on those studies reporting *CYP2C19* genotype and platelet function/clinical outcomes (Table S6), meta-analyses (Table S7) and clopidogrel dose escalation (Table S8). With alternatives to standard clopidogrel treatment

available (e.g., prasugrel), these studies offer a compelling rationale for pharmacogenetic-guided antiplatelet drug selection and/or dosing (13, 16).

Levels of Evidence Linking Genotype to Phenotype

Based on previously published criteria (42), a simple scale of high, moderate, or weak to grade the levels of evidence was chosen:

- **High:** Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies and to take into consideration all available peer-reviewed published literature, which provided the framework for the strength of therapeutic recommendations.

Strength of Therapeutic Recommendations

Multiple rating schemes for strength of recommendations in a number of clinical guidelines were evaluated. Ultimately, we chose to use a slight modification of a transparent and simple system for just three categories for recommendations: strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action. CPIC's therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* clinical outcome data for clopidogrel, *in vivo* pharmacokinetic and pharmacodynamic data for clopidogrel, *in vitro* enzyme activity of expressed wild-type or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of CYP2C19 protein stability or enzyme activity.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents.

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

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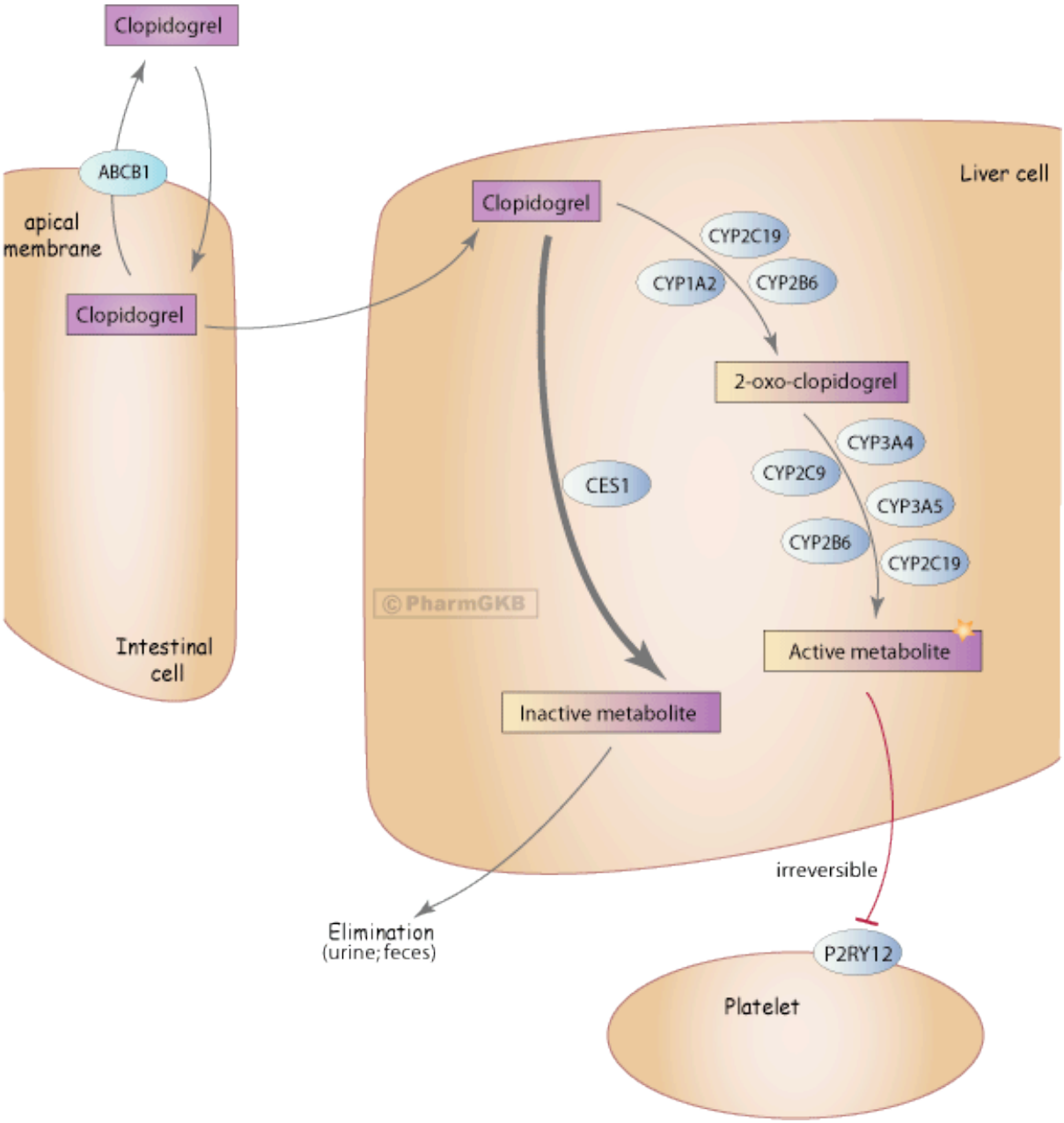
Supplemental Figure S1. Hepatic metabolism of clopidogrel (86). For a detailed and updated description, see: *http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway*. Reproduced with permission by PharmGKB and Stanford University.



Supplemental Table S1. Commonly tested *CYP2C19* variant alleles and their effect on CYP2C19 protein

Allele[1]	Major Nucleotide Variation[2]	dbSNP Number[3]	Effect on CYP2C19 Protein
1	-	-	-
2	c.681G>A	rs4244285	Splicing defect
3	c.636G>A	rs4986893	W212X
4[4]	c.1A>G	rs28399504	M1V
5	c.1297C>T	rs56337013	R433W
6	c.395G>A	rs72552267	R132Q
7	c.819+2T>A	rs72558186	Splicing defect
8	c.358T>C	rs41291556	W120R
17[5]	c.-806C>T	rs12248560	Increased expression

[1] See Human Cytochrome P450 Allele Nomenclature Committee (*http://www.cypalleles.ki.se*) for comprehensive haplotype definitions of *CYP2C19* variant alleles and updated allele information.

[2] All coordinates refer to GenBank CYP2C19 mRNA sequence M61854.1 as detailed at http://www.cypalleles.ki.se/cyp2c19.htm. All variants are annotated to the positive DNA strand.

[3] RefSNP accession ID number (*http://www.ncbi.nlm.nih.gov/snp/*).

[4] Of note, the *CYP2C19*4* loss-of-function allele has been identified in linkage disequilibrium with **17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated *CYP2C19*4B* (43).

[5] There is linkage disequilibrium between c.681G and c.-806T (e.g., D'=1.0 and r^2=0.064 in CEU HapMap sample; D'=1.0 and r^2=0.065 in YRI HapMap sample; and D'=1.0 and r^2=0.074 in CHB HapMap sample). This means that the less common **17* variant (c.-806T) always tracks on the same allele with the more common c.681G. This complicates any interpretation of whether these two variants act independently of one another, and published articles argue both for (24) and against (15, 29) this point.

Supplemental Table S2. Association between *CYP2C19* allelic variants and enzyme activity

Functional Status	Alleles	References
Functional / normal activity / wild-type[1]	**1*	(44)
Loss-of-function / no or decreased activity	**2, *3, *4, *5, *6, *7, *8*	(45-51)
Increased function / increased activity	**17*	(52-54)

[1] An important caveat for all genotyping tests is that the "wild-type" (**1*) status is reported if all other alleles that are measured are absent. Some genotype tests do not interrogate the rare loss of function alleles and therefore, if present, they may be erroneously reported as "wild type". Furthermore, in human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer altered enzyme function in an individual, and thus lead to the rare possibility of a loss-of-function allele being erroneously called as "wild-type" (**1*).

Supplemental Table S3. Frequencies[1] of *CYP2C19* alleles in major race/ethnic groups[2]

Allele	African	American	East Asian	European	Middle Eastern	Oceanian	South/Central Asian
1[3]	0.68	0.69	0.60	0.63	0.87	0.24	0.62
2	0.15	0.12	0.29	0.15	0.12	0.61	0.35
3	0.0052	0.00028	0.089	0.0042	0.011	0.15	0.024
4	0.00093	0.0024	0.00049	0.0025	ND	ND	0.00
5	ND	0.00	0.00062	0.000073	ND	ND	0.00
6	0.00	0.00	0.00	0.00017	ND	ND	0.00
7	ND	ND	ND	0.00	ND	ND	ND
8	0.00	0.0012	0.00	0.0035	ND	ND	ND
17	0.16	0.18	0.027	0.21	ND	ND	ND

ND: not determined.

[1] Average frequencies are based on actual numbers of subjects with each allele reported in multiple studies. See Supplemental Table S4 for details and references.

[2] Worldwide race/ethnic designations correspond to the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21-22) as indicated in Supplemental Table S4.

[3] Note that because *CYP2C19*1* is not genotyped directly, its inferred frequency is calculated as: 1 - (sum of variant allele frequencies).

Supplemental Table S4. *CYP2C19* minor allele frequencies

HGDP-CEPH Grouping[1]	Ethnicity	PMID[2]	CYP2C19 minor allele frequency (%)[3]								Total Individuals	Total Alleles	CYP2C19 minor alleles reported[3]							
			*2	*3	*4	*5	*6	*7	*8	*17[4]			*2	*3	*4	*5	*6	*7	*8	*17[4]
Africa	African	20173083	**19.2**	**0.2**	**0**	**-**	**0**	**-**	**0**	**-**	250	500	96	1	0	-	0	-	0	-
Africa	African American	16815315	**18.2**	**0.8**	**-**	**-**	**-**	**-**	**-**	**-**	236	472	86	4	-	-	-	-	-	-
Africa	African-American	9110363	**25**	**0**	-	-	-	-	-	-	108	216	54	0	-	-	-	-	-	-
Africa	African-American	19169185	**18.3**	**0.1**	-	-	-	-	-	-	441	882	161	1	**-**	**-**	**-**	**-**	**-**	-
Africa	African-American	8873222	19.1	-	-	-	-	-	-	-	76	152	**29**	-	-	-	-	-	-	-
Africa	African-American	8823231	16.0	-	-	-	-	-	-	-	100	200	**32**	-	-	-	-	-	-	-
Africa	Beninese	14616425	**13**	-	-	-	-	-	-	-	111	222	29	-	-	-	-	-	-	-
Africa	Black	21247447	19.9	0		-	0	-	0	-	289	578	**115**	**0**	**1**	**-**	**0**	**-**	**0**	**120**
Africa	Cape Mixed Ancestry	20712527	**17**	**7**	-	-	-	-	-	**14**	75	150	26	11	-	-	-	-	-	21
Africa	Egyptian	12047484	10.9	0.2	-	-	-	-	-	-	247	494	**54**	**1**	-	-	-	-	-	-
Africa	Ethiopian	9014201	**14**	**2**	-	-	-	-	-	-	114	228	32	5	-	-	-	-	-	-
Africa	Ethiopian	12142727	12.1	2.9	-	-	-	-	-	-	70	140	**17**	**4**	-	-	-	-	-	-
Africa	Ethiopian	16413245	-	-	-	-	-	-	-	13.2	190	380	**-**	**-**	-	-	-	-	-	**50**
Africa	Ghanaian	19954515	5.9	0	-	-	-	-	-	-	169	338	**20**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Africa	Nigerian	20831548	15.5	0	-	-	-	-	-	-	158	316	**49**	**0**	-	-	-	-	-	-
Africa	South African (Venda)	11372584	21.7	0	-	-	-	-	-	-	76	152	**33**	**0**	-	-	-	-	-	-
Africa	Tanzanian	10510152	**10**	**0**	-	-	-	-	-	-	195	390	39	0	-	-	-	-	-	-
Africa	Tanzanian	9797796	**17.9**	**0.6**	-	-	-	-	-	-	251	502	90	3	-	-	-	-	-	-
Africa	Tanzanian	11372584	18.0	0.3	-	-	-	-	-	-	192	384	**69**	**1**	-	-	-	-	-	-
Africa	Tunisian	18423013	10.5	-	-	-	-	-	-	-	544	1088	**114**	**-**	-	-	-	-	-	**-**
Africa	Ugandan	19002442	12.6	1.0	-	-	-	-	-	17.2	99	198	**25**	**2**	**-**	**-**	**-**	**-**	**-**	**34**
Africa	Xhosa	20712527	**21**	**0**	-	-	-	-	-	**10**	100	200	42	0	-	-	-	-	-	20
Africa	Zimbabwean Shona	7781265	4.2	-	-	-	-	-	-	-	84	168	**7**	-	-	-	-	-	-	-
Americas	Bolivian	15776277	7.8	0.1	-	-	-	-	-	-	778	1556	**121**	**1**	-	-	-	-	-	-
Americas	Brazilian (mixed)	21247447	16.1	0	**0.3**	0	-	-	-	19.2	1212	2424	**390**	**0**	7	**0**	-	-	-	**466**
Americas	Brazilian (mixed)	21173785	13.2	-	-	-	-	-	-	-	1034	2068	**273**	**1**	**-**	**-**	**-**	**-**	**-**	**358**
Americas	Columbian Mestizo	17623107	8.7	0	0	0	0	-	0	-	189	378	**33**	**0**	**0**	**0**	**0**	**-**	**0**	**-**
Americas	Mexican Americans	16815315	**9.7**	**0.1**	**-**	**-**	**-**	**-**	**-**	**-**	346	692	67		**-**	**-**	**-**	**-**	**-**	**-**
Americas	Native Canadian Indian	9797794	8.8	0	-	-	-	-	-	-	159	318	**28**	**0**	-	-	-	-	-	-
Americas	White Hispanic	21247447	12.6	0	0.2	-	0	-	0.2	14.0	242	484	**61**	**0**	**1**	**-**	**0**	**-**	**1**	**68**
East Asia	Bai Chinese	9103550	**25.7**	**5.2**	-	**0.3**	-	-	-	-	202	404	104	21	-	1	-	-	-	-
East Asia	Burmese	16946555	**30**	**4**	-	-	-	-	-	-	127	254	76	10	**-**	**-**	**-**	**-**	**-**	**-**

East Asia	Chinese	15327595	23.1	4.6	-	-	-	-	-	-	54	108	**25**	**5**	-	-	-	-	-	-
East Asia	Chinese	18231117	**29.7**	**3.5**	**0**	**0**	**-**	**-**	**-**	**0.5**	101	202	60	7	0	0	-	-	-	1
East Asia	Chinese	19636337	**25.5**	**2**	**0.5**	**-**	**-**	**-**	**-**	**3**	100	200	51	4	4	-	-	-	-	6
East Asia	Chinese	20173083	**30.7**	**4.5**	**0**	**-**	**0**	**-**	**0**	**-**	398	796	244	36	0	-	0	-	0	-
East Asia	Chinese	16855453	30.2	6.6	-	-	-	-	-	-	53	106	**32**	**7**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	17450472	29.7	5.9	-	-	-	-	-	-	59	118	**35**	**7**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	11686476	44.2	4.5	-	-	-	-	-	-	121	242	**107**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	19745563	24.8	7.0	-	-	-	-	-	-	107	214	**53**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	20831535	30.6	3.7	-	-	-	-	-	-	204	408	**125**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	19756559	30.7	7.1	-	-	-	-	-	-	287	574	**176**	**41**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	21163112	23.1	-	-	-	-	-	-	-	722	1444	**334**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Chinese	15301728	**35**	**7**	-	-	-	-	-	-	70	140	49	10	-	-	-	-	-	-
East Asia	Dai Chinese	11956668	**30.3**	**3.4**	-	-	-	-	-	-	386	772	234	26	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	East Asian	20173083	**32.4**	**8**	**0**	**-**	**0**	**-**	**0**	**-**	246	492	159	39	0	-	0	-	0	-
East Asia	East Asian	16815315	**28.9**	**9.6**	-	-	-	-	-	-	161	322	93	31	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	18518848	**24.7**	**3.3**	**-**	**-**	**-**	**-**	**-**	**1.6**	400	800	198	26	-	-	-	-	-	13
East Asia	Han Chinese	19444287	29.1	7.3	-	-	-	-	-	-	103	206	**60**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	15612662	34.1	8.2	-	-	-	-	-	-	104	208	**71**	**17**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Han Chinese	9103550	**36.6**	**7.4**	-	-	-	-	-	-	101	202	74	15	-	-	-	-	-	-
East Asia	Han Chinese	10585366	**30.7**	**3.8**	**0.4**	**0**	-	-	-	-	119	238	73	9	9	0	-	-	-	-
East Asia	Japanese	19881258	14.5	8.2	-	-	-	-	-	-	55	110	**16**	**9**	-	-	-	-	-	-
East Asia	Japanese	20173083	**30.3**	**13.1**	**0**	**-**	**0.1**	**-**	**0**	**-**	500	1000	303	131	0	-		-	0	-
East Asia	Japanese	16141610	26.7	12.8	-	-	-	-	-	-	253	506	**135**	**65**	**-**	**-**	**-**	**-**	**-**	**4**
East Asia	Japanese	9867757	28.2	6.5	-	-	-	-	-	-	62	124	**35**	**8**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16595916	28.7	8.3	-	-	-	-	-	-	54	108	**31**	**9**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	20528170	32.4	10.8	-	-	-	-	-	-	51	102	**33**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16338280	34.1	11.1	-	-	-	-	-	-	63	126	**43**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	10579481	25.5	6.5	-	-	-	-	-	-	108	216	**55**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	12386647	30.0	11.5	-	-	-	-	-	-	65	130	**39**	**15**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11477314	29.4	11.3	-	-	-	-	-	-	80	160	**47**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	19259653	24.6	9.3	-	-	-	-	-	-	124	248	**61**	**23**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17377957	20.5	17.1	-	-	-	-	-	-	73	146	**30**	**25**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11434512	28.2	12.9	-	-	-	-	-	-	101	202	**57**	**26**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11686476	26.0	14.6	-	-	-	-	-	-	96	192	**50**	**28**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9860067	24.6	10.4	-	-	-	-	-	-	134	268	**66**	**28**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	15952098	31.6	11.3	-	-	-	-	-	-	141	282	**89**	**32**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	15710002	24.0	11.0	-	-	-	-	-	-	173	346	**83**	**38**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9511186	23.4	11.1	-	-	-	-	-	-	175	350	**82**	**39**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	21168310	30.8	10.0	-	-	-	-	-	-	201	402	**124**	**40**	**-**	**-**	**-**	**-**	**-**	**-**

East Asia	Japanese	8988068	28.8	12.4	-	-	-	-	-	-	186	372	**107**	**46**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	14568772	27.3	12.0	-	-	-	-	-	-	196	392	**107**	**47**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	19156902	31.7	13.5	-	-	-	-	-	-	178	356	**113**	**48**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16307177	29.6	12.8	-	-	-	-	-	-	203	406	**120**	**52**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	11240980	31.0	10.9	-	-	-	-	-	-	261	522	**162**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17215846	27.8	12.3	-	-	-	-	-	-	300	600	**167**	**74**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	15017629	28.7	11.6	-	-	-	-	-	-	350	700	**201**	**81**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17357148	27.7	14.3	-	-	-	-	-	-	352	704	**195**	**101**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16268979	27.6	13.1	-	-	-	-	-	-	426	852	**235**	**112**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	17052843	31.1	14.6	-	-	-	-	-	-	487	974	**303**	**142**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	16338278	15.4	-	-	-	-	-	-	-	205	410	**63**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	21102498	**28.4**	-	-	-	-	-	-	-	58	116	33	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Japanese	9110363	**23**	**10.4**	-	-	-	-	-	-	53	106	24	11	-	-	-	-	-	-
East Asia	Japanese	8807668	**27.4**	**10.8**	-	-	-	-	-	-	217	434	119	47	-	-	-	-	-	-
East Asia	Japanese	9631918	**35**	**11**	-	-	-	-	-	-	140	280	98	31	-	-	-	-	-	-
East Asia	Japanese	8890945	**21.9**	**11.7**	-	-	-	-	-	-	233	466	102	55	-	-	-	-	-	-
East Asia	Japanese	17502835	**31.1**	**12.6**	-	-	-	-	-	-	103	206	64	26	-	-	-	-	-	-
East Asia	Japanese	11763000	**27.5**	**12.8**	-	-	-	-	-	-	51	102	28	13	-	-	-	-	-	-
East Asia	Japanese	19696793	**26**	**13**	-	-	-	-	-	-	219	438	114	57	-	-	-	-	-	-
East Asia	Japanese	15691505	**32.7**	**13.7**	-	-	-	-	-	-	139	278	91	38	-	-	-	-	-	-
East Asia	Japanese	19696793	**31**	**18**	-	-	-	-	-	-	184	368	114	66	-	-	-	-	-	-
East Asia	Japanese	18241287	-	-	-	-	-	-	-	1.3	265	530	-	-	-	-	-	-	-	**7**
East Asia	Japanese (1st generation)	18231117	**26.2**	**10**	**0**	**0**	**-**	**-**	**-**	**1**	105	210	55	21	0	0	-	-	-	2
East Asia	Japanese (3rd generation)	18231117	**33.1**	**13.3**	**0**	**0**	**-**	**-**	**-**	**1.2**	84	168	56	22	0	0	-	-	-	2
East Asia	Japanese (native)	18231117	**34.5**	**9**	**0**	**0**	**-**	**-**	**-**	**0.5**	100	200	69	18	0	0	-	-	-	1
East Asia	Japanese (mixed descendents)	19882083	25.9	11.9	-	-	-	-	-	-	139	278	**72**	**33**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Karen	16946555	**28**	**1**	-	-	-	-	-	-	131	262	73	-	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Kazakh Chinese	19444287	15.4	7.9	-	-	-	-	-	-	107	214	**33**	**17**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	18231117	**25**	**8**	**0**	**0**	**-**	**-**	**-**	**1.5**	100	200	50	16	0	0	-	-	-	3
East Asia	Korean	20499227	**16**	**-**	**-**	**-**	**-**	**-**	**-**	**20**	150	300	48	**-**	-	-	-	-	-	60
East Asia	Korean	20173083	**28.6**	**7.4**	**0**	**-**	**0**	**-**	**0**	**-**	200	400	114	30	0	-	0	-	0	-
East Asia	Korean	17424941	31.1	7.6	-	-	-	-	-	-	66	132	**41**	**10**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	19220726	34.9	6.6	-	-	-	-	-	-	136	272	**95**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	17562299	21.1	9.8	-	-	-	-	-	-	97	194	**41**	**19**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20650435	31.0	8.7	-	-	-	-	-	-	126	252	**78**	**22**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20724801	31.3	6.5	-	-	-	-	-	-	176	352	**110**	**23**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	9014204	20.9	11.7	-	-	-	-	-	-	103	206	**43**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	14695703	26.7	10.3	-	-	-	-	-	-	116	232	**62**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20823393	34.0	9.7	-	-	-	-	-	-	134	268	**91**	**26**	**-**	**-**	**-**	**-**	**-**	**-**

East Asia	Korean	21075428	30.3	6.8	-	-	-	-	-	-	190	380	**115**	**26**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	19891553	-	8.8	-	-	-	-	-	-	226	452	**-**	**40**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	18637061	26.0	8.7	-	-	-	-	-	-	327	654	**170**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	17667801	28.2	7.6	-	-	-	-	-	-	377	754	**213**	**57**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	19576320	27.3	9.3	-	-	-	-	-	-	387	774	**211**	**72**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	20559522	29.9	9.5	-	-	-	-	-	-	463	926	**277**	**88**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Korean	21054462	28.4	10.1	-	-	-	-	-	1.5	271	542	**154**	**55**	**-**	**-**	**-**	**-**	**-**	**8**
East Asia	Li Chinese	17439410	35.8	3.0	-	-	-	-	-	-	165	330	**118**	**10**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Malay	15327595	30.9	10.3	-	-	-	-	-	-	68	136	**42**	**14**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Mongolian Chinese	20857895	24.3	4.3	-	-	-	-	-	-	280	560	**136**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Northeastern Thai	11927837	26.6	2.3	-	-	-	-	-	-	107	214	**57**	**5**	-	-	-	-	-	-
East Asia	Southeast Asian	16815315	**31.2**	**5.7**	-	-	-	-	-	-	80	160	50	9	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	20350136	**32**	**2.5**	-	-	-	-	-	**0.5**	100	200	64	5	-	-	-	-	-	1
East Asia	Taiwanese	16924387	32.2	5.0	-	-	-	-	-	-	180	360	**116**	**18**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	20457439	57.9	20.0	-	-	-	-	-	-	95	190	**110**	**38**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Taiwanese	15385837	**34**	**5.3**	-	-	-	-	-	-	169	338	115	18	-	-	-	-	-	-
East Asia	Taiwanese	9110363	**32**	**5.5**	-	-	-	-	-	-	118	236	76	13	-	-	-	-	-	-
East Asia	Thai	11686476	34.7	4.5	-	-	-	-	-	-	121	242	**84**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Thai	20358205	24.6	**-**	-	-	-	-	-	-	71	142	**35**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Thai	16946555	**29**	**3**	-	-	-	-	-	-	774	1548	449	46	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	18979093	30.6	6.3	-	-	-	-	-	-	72	144	**44**	**9**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	17667801	26.4	4.8	-	-	-	-	-	-	165	330	**87**	**16**	**-**	**-**	**-**	**-**	**-**	**-**
East Asia	Vietnamese	11686476	26.7	13.3	-	-	-	-	-	-	90	180	**48**	**24**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Ashkenazi Jewish	18240905	15.2	**-**	1.8	**-**	**-**	**-**	**-**	**-**	250	500	**76**	**-**	**9**	**-**	**-**	**-**	**-**	**-**
Europe	Belgian	14616425	**9.1**	-	-	-	-	-	-	-	121	242	22	-	-	-	-	-	-	-
Europe	Bosnian	21108610	16.9	-	-	-	-	-	-	-	77	154	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Bulgarian	18021343	13.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	96	192	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	18231117	**13.6**	**0**	**0.3**	**0**	**-**	**-**	**-**	**20.1**	143	286	39	0	1	0	**-**	**-**	**-**	57
Europe	Caucasian	19463375	13.3	-	2.5	-	-	-	-	20.8	60	120	**16**	**-**	**3**	**-**	**-**	**-**	**-**	**25**
Europe	Caucasian	18521743	**-**	**-**	**-**	**-**	**-**	**-**	**-**	23.1	1989	3978	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**919**
Europe	Caucasian	20173083	**15**	**0.1**	**0.1**	**-**	**0.1**	**-**	**0.1**	**-**	454	908	136	1	1	-		-	0	-
Europe	Caucasian	12823155	14.2	0	0	-	-	-	-	-	60	120	**17**	**0**	**0**	-	-	-	-	-
Europe	Caucasian	15590749	16.9	0	0	-	-	-	-	-	59	118	**20**	**0**	**0**	-	-	-	-	-
Europe	Caucasian	20857895	14.0	0	-	-	-	-	-	-	203	406	**57**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	21047200	17.9	0	-	-	-	-	-	-	215	430	**77**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	21108329	15.4	0.1	-	-	-	-	-	-	344	688	**106**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	20064729	15.7	0.5	-	-	-	-	-	-	289	578	**91**	**3**	-	-	-	-	-	-
Europe	Caucasian	19337788	14.5	6.5	-	-	-	-	-	-	186	372	**54**	**24**	-	-	-	-	-	-

Europe	Caucasian	18496131	16.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	124	248	**41**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	20179710	15.2	-	-	-	-	-	-	-	230	460	**70**	-	-	-	-	-	-	-
Europe	Caucasian	18482659	16.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	797	1594	**262**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	11037802	14.0	-	-	-	-	-	-	-	952	1904	**267**	-	-	-	-	-	-	-
Europe	Caucasian	18521743	14.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	1960	3920	**570**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Caucasian	16815315	**12.7**	**0.9**	**-**	**-**	**-**	**-**	**-**	**-**	273	546	69	5	-	-	-	-	-	**-**
Europe	Caucasian	19169185	**14.2**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	3774	7548	1072	0	-	-	-	-	-	-
Europe	Central European	19581389	8.5	-	-	-	-	-	-	33.8	71	142	**12**	**-**	**-**	**-**	**-**	**-**	**-**	**48**
Europe	Croatian	12950145	15.0	-	-	-	-	-	-	-	200	400	**60**	-	-	-	-	-	-	-
Europe	Danish	20665013	15.0	-	-	-	-	-	-	20.1	276	552	**83**	**-**	**-**	**-**	**-**	**-**	**-**	**111**
Europe	Danish	16044105	13.8	0	**-**	**-**	**-**	**-**	**-**	**-**	69	138	**19**	**0**	-	-	-	-	-	-
Europe	Danish	19192051	13.0	0	-	-	-	-	-	-	300	600	**78**	**0**	-	-	-	-	-	-
Europe	Danish	9754988	16.5	0.0	-	-	-	-	-	-	303	606	**100**	**0**	-	-	-	-	-	-
Europe	Danish	20684753	**10.9**	-	-	-	-	-	-	-	339	678	74	-	-	-	-	-	-	-
Europe	Dutch	20531370	13.3	-	-	-	-	-	-	22.1	678	1356	**181**	**-**	**-**	**-**	**-**	**-**	**-**	**299**
Europe	Dutch	19884907	15.4	-	-	-	-	-	-	24.4	178	356	**55**	**-**	**-**	**-**	**-**	**-**	**-**	**87**
Europe	Dutch	19934793	16.8	0.2	-	-	-	-	-	-	428	856	**144**	**2**	-	-	-	-	-	-
Europe	Dutch	11829201	12.9	0.2	-	-	-	-	-	-	765	1530	**198**	**3**	-	-	-	-	-	-
Europe	Dutch	18854779	17.7	-	-	-	-	-	-	-	113	226	**40**	-	-	-	-	-	-	-
Europe	Dutch	17667959	**15**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	181	362	54	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	English	12419832	13.4	-	-	-	-	-	-	-	1082	2164	**291**	-	-	-	-	-	-	-
Europe	European	9435198	**13**	**0.3**	**0.6**	-	-	-	-	-	173	346	45	1	2	-	-	-	-	-
Europe	European-American	9110363	**13**	**0**	-	-	-	-	-	-	105	210	27	0	-	-	-	-	-	-
Europe	Faroese	20665013	18.6	-	-	-	-	-	-	15.4	311	622	**116**	**-**	**-**	**-**	**-**	**-**	**-**	**96**
Europe	Faroese	16025294	**18.8**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	312	624	117	0	-	-	-	-	-	-
Europe	Finnish	16024198	**16.4**	**0**	**-**	**-**	**-**	**-**	**-**	**-**	177	354	58	0	-	-	-	-	-	-
Europe	Finnish	17635176	17.6	**-**	**-**	**-**	**-**	**-**	**-**	**-**	449	898	**158**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	French	19496924	-	-	0.7	0	0.1	-	-	20.0	598	1196	**-**	**-**	**8**	**0**	**1**	**-**	**-**	**239**
Europe	French	18205890	18.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	359	718	**132**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	French	20708365	17.6	-	-	-	-	-	-	-	411	822	**145**	-	-	-	-	-	-	-
Europe	French	18394438	15.7	-	-	-	-	-	-	-	603	1206	**189**	-	-	-	-	-	-	-
Europe	German	20492469	13.5	-	-	-	-	-	-	21.3	986	1972	**267**	**-**	**-**	**-**	**-**	**-**	**-**	**421**
Europe	German	20083681	-	-	-	-	-	-	-	22.9	1524	3048	-	-	-	-	-	-	-	**698**
Europe	German	18781853	15.1	0.0	-	-	-	**-**	**-**	25.7	423	846	**128**	**0**	**-**	**-**	**-**	**-**	**-**	**217**
Europe	German	20826260	14.4	-	-	-	-	-	-	-	928	1856	**268**	**-**	**-**	**-**	**-**	**-**	**-**	**417**
Europe	German	16116487	15.8	0	**-**	**-**	**-**	**-**	**-**	**-**	60	120	**19**	**0**	-	-	-	-	-	-
Europe	German	7663532	12.1	0	-	-	-	-	-	-	174	348	**42**	**0**	-	-	-	-	-	-
Europe	German	17680025	11.9	3.8	**-**	**-**	**-**	**-**	**-**	**-**	572	1144	**136**	**44**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	German	14586385	15.6	-	-	-	-	-	-	-	96	192	**30**	-	-	-	-	-	-	-

Europe	German	15371981	18.3	-	-	-	-	-	-	-	131	262	**48**	-	-	-	-	-	-	-
Europe	German	19415824	15.0	-	-	-	-	-	-	-	533	1066	**160**	-	-	-	-	-	-	-
Europe	German	12713578	15.0	-	-	-	-	-	-	-	562	1124	**169**	-	-	-	-	-	-	-
Europe	German	20510210	16.3	-	-	-	-	-	-	-	760	1520	**248**	-	-	-	-	-	-	-
Europe	German	19193675	14.6	-	-	-	-	-	-	-	2485	4970	**727**	-	-	-	-	-	-	-
Europe	German	19424794	14.6	-	-	-	-	-	-	-	8609	17218	**2510**	-	-	-	-	-	-	-
Europe	German	16413243	**12.7**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	51	102	13	-	1	-	-	-	-	-
Europe	Greek	19102714	13.1	0	-	-	-	-	-	19.6	283	566	**74**	**0**	**-**	**-**	**-**	**-**	**-**	**111**
Europe	Italian	20309015	14.3	-	-	-	-	-	-	17.6	182	364	**52**	-	-	-	-	-	-	**64**
Europe	Italian	15177309	**11.1**	**0**	-	-	-	-	-	-	360	720	80	0	-	-	-	-	-	-
Europe	Italian	12496751	12.4	-	-	-	-	-	-	-	93	186	**23**	-	-	-	-	-	-	-
Europe	Italian	19268736	17.7	-	-	-	-	-	-	-	772	1544	**273**	-	-	-	-	-	-	-
Europe	Italian	18004210	17.1	-	-	-	-	-	-	-	1419	2838	**485**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Norwegian	20565970	17.8	-	-	-	-	-	-	21.7	90	180	**32**	**-**	**-**	**-**	**-**	**-**	**-**	**39**
Europe	Norwegian	20665013	15.2	-	-	-	-	-	-	22.0	309	618	**94**	**-**	**-**	**-**	**-**	**-**	**-**	**136**
Europe	Norwegian	18677622	**-**	**-**	**-**	**-**	**-**	**-**	**-**	23.6	121	242	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**57**
Europe	Norwegian	17625515	18.1	0.6	**-**	**-**	**-**	**-**	**-**	**-**	166	332	**60**	**2**	**-**	**-**	**-**	**-**	**-**	**73**
Europe	Norwegian	12835613	15.2	0	0	-	-	-	-	-	128	256	**39**	**0**	**0**	-	-	-	-	-
Europe	Norwegian	16418702	19.9	-	-	-	-	-	-	-	83	166	**33**	-	-	-	-	-	-	**-**
Europe	Polish	16912869	11.6	-	-	-	-	-	-	27.2	125	250	**29**	**-**	**-**	**-**	**-**	**-**	**-**	**68**
Europe	Polish	20376628	12.6	-	-	-	-	-	-	28.1	139	278	**35**	**-**	**-**	**-**	**-**	**-**	**-**	**78**
Europe	Polish	15976989	10.0	-	-	-	-	-	-	-	70	140	**14**	-	-	-	-	-	-	-
Europe	Polish	18577829	10.5	**-**	**-**	**-**	**-**	**-**	**-**	**-**	105	210	**22**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Polish	20924183	11.9	-	-	-	-	-	-	-	261	522	**62**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Portuguese	9295062	13.1	0	-	-	-	-	-	-	153	306	**40**	**0**	-	-	-	-	-	-
Europe	Portuguese	18240903	**14**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	126	252	35	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Russian	12879168	11.4	0.3	-	-	-	-	-	-	290	580	**66**	**2**	-	-	-	-	-	-
Europe	Russian	18061941	9.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	159	318	**30**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Russian	20373852	13.1	-	-	-	-	-	-	-	352	704	**92**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Siberian	18597650	**-**	3.5	**-**	**-**	**-**	**-**	**-**	**-**	437	874	**-**	**31**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Siberian	18597650	17.3	**-**	**-**	**-**	**-**	**-**	**-**	**-**	433	866	**150**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Slovenian	18496682	10.5	**-**	**-**	**-**	**-**	**-**	**-**	32.9	105	210	**22**	**-**	**-**	**-**	**-**	**-**	**-**	**69**
Europe	Spanish	15728438	13.7	-	-	-	-	-	-	-	300	600	**82**	-	-	-	-	-	-	-
Europe	Spanish	16006997	13.9	-	-	-	-	-	-	-	672	1344	**187**	-	-	-	-	-	-	-
Europe	Swedish	20499227	**28**	**11**	**-**	**-**	**-**	**-**	**-**	**0.3**	185	370	104	41	-	-	-	-	-	1
Europe	Swedish	16413245	-	-	-	-	-	-	-	6.4	314	628	**-**	-	-	-	-	-	-	**40**
Europe	Swedish	19907421	14.5	-	0.1	-	-	-	-	17.7	713	1426	**207**	**-**	**1**	**-**	**-**	**-**	**-**	**252**
Europe	Swedish	20468063	15.1	-	-	-	-	-	-	19.0	1416	2832	**427**	**-**	**-**	**-**	**-**	**-**	**-**	**537**
Europe	Swedish	8747407	11.7	0.3	-	-	-	-	-	-	175	350	**41**	**1**	-	-	-	-	-	-

Europe	Swedish	9776439	14.5	0.4	-	-	-	-	-	-	245	490	**71**	**2**	-	-	-	-	-	-
Europe	Swedish	9772024	15.5	0	-	-	-	-	-	-	110	220	**34**	**4**	-	-	-	-	-	-
Europe	Swedish	9829356	12.6	1.4	-	-	-	-	-	-	143	286	**36**	**4**	-	-	-	-	-	-
Europe	Swiss	16338275	16.3	0.2	**-**	**-**	**-**	**-**	**-**	**-**	208	416	**68**	**1**	-	-	-	-	-	-
Europe	Swiss	17697139	13.8	**-**	**-**	**-**	**-**	**-**	**-**	**-**	94	188	**26**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Swiss	17681590	17.9	**-**	**-**	**-**	**-**	**-**	**-**	**-**	81	162	**29**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Swiss	11809184	13.4	-	-	-	-	-	-	-	123	246	**33**	-	-	-	-	-	-	-
Europe	Swiss	17178267	**16.7**	**0.1**	**-**	**-**	**-**	**-**	**-**	**-**	245	490	82	0	-	-	-	-	-	-
Europe	Turkish	10460072	**12**	**0.4**	**0**	**0**	-	-	-	-	404	808	97	3	0	0	-	-	-	-
Europe	Turkish	19499406	12.0	0	-	-	-	-	-	-	100	200	**24**	**0**	-	-	-	-	-	-
Europe	Turkish	17269966	11.5	0	**-**	**-**	**-**	**-**	**-**	**-**	169	338	**39**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	17290075	21.7	0	**-**	**-**	**-**	**-**	**-**	**-**	182	364	**79**	**0**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	20533108	11.4	5.2	-	-	-	-	-	-	105	210	**24**	**11**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	17868191	12.1	4.0	**-**	**-**	**-**	**-**	**-**	**-**	199	398	**48**	**16**	**-**	**-**	**-**	**-**	**-**	**-**
Europe	Turkish	11908757	9.4	8.9	-	-	-	-	-	-	96	192	**18**	**17**	-	-	-	-	-	-
Europe	Turkish	19821196	**13**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	100	200	26	2	-	-	-	-	-	-
Europe	White	19106084	-	-	-	-	-	-	-	19.5	2164	4328	-	-	-	-	-	-	-	**844**
Europe	White	20801498	14.1	0.1	0.1	0.0	0.0	0	0.4	22.3	10285	20570	**2899**	**16**	**26**	**1**	**2**	**0**	**74**	**4590**
Europe	White	19106083	-	-	-	0.0	-	-	-	-	2176	4352	-	-	-	**1**	-	-	-	-
Europe	White	19106083	-	-	0.5	-	-	-	-	-	2189	4378	-	-	**21**	-	-	-	-	-
Europe	White	19106083	-	0.0	-	-	-	-	-	-	2187	4374	**-**	**1**	-	-	-	-	-	-
Europe	White	19106083	15.4	**-**	**-**	**-**	**-**	**-**	**-**	**-**	2178	4356	**670**	-	-	-	-	-	-	-
Europe	White/Non-Hispanic	21192344	13.3	0	0.4	-	0.0	-	0.4	22.5	1253	2506	**333**	**0**	**10**	**-**	**1**	**-**	**10**	**564**
Middle East	Bedouin	15651900	**12.0**	**1.0**	-	-	-	-	-	-	50	100	12	1	-	-	-	-	-	-
Middle East	Iranian	17201743	14.0	0.0	-	-	-	-	-	-	200	400	**56**	**0**	-	-	-	-	-	-
Middle East	Iranian	20804307	13.4	1.8	-	-	-	-	-	-	82	164	**22**	**3**	-	-	-	-	-	-
Middle East	Iranian	20637959	11.1	1.0	-	-	-	-	-	-	99	198	**22**	**2**	-	-	-	-	-	-
Middle East	Iranian	20885015	12.3	0.7	-	-	-	-	-	-	150	300	**37**	**2**	-	-	-	-	-	-
Middle East	Jewish Israeli	10096259	15.4	0.7	-	-	-	-	-	-	140	280	**43**	**2**	-	-	-	-	-	-
Middle East	Palestinian	19193970	7.1	2.6	-	-	-	-	-	-	252	504	**36**	**13**	-	-	-	-	-	-
Middle East	Saudi Arabians	9110363	**15.0**	**0.0**	-	-	-	-	-	-	97	194	29	0	-	-	-	-	-	-
Oceania	Filipinos	9110363	**39**	**7.7**	-	-	-	-	-	-	52	104	41	8	-	-	-	-	-	-
Oceania	Maori	18425152	**24**	**1.7**	**-**	**-**	**-**	**-**	**-**	**-**	60	120	29	2	**-**	**-**	**-**	**-**	**-**	**-**
Oceania	Sepik (pooled study)	14583683	**45**	**16**	-	-	-	-	-	-	401	802	361	127	-	-	-	-	-	-
Oceania	Vanuatuan (pooled study)	10591538	**63**	**15**	-	-	-	-	-	-	5638	11276	7132	1660	-	-	-	-	-	-
Oceania	Vanuatuan (pooled study)	9093256	70.8	13.3	-	-	-	-	-	-	493	986	**698**	**131**	-	-	-	-	-	-
Oceania	Western Australian Aboriginese	11207032	**35.5**	**14.3**	-	-	-	-	-	-	227	454	161	65	-	-	-	-	-	-

South/Central Asia	Maharashtrian (India)	17978853	46.0	1.1	-	-	-	-	-	-	139	278	**128**	**3**	-	-	-	-	-	-
South/Central Asia	North Indian	11014415	29.8	0	-	-	-	-	-	-	121	242	**72**	**0**	-	-	-	-	-	-
South/Central Asia	North Indian	20602612	36.3	0.4	-	-	-	-	-	-	457	914	**332**	**4**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	North Indian	18644391	34.1	5.8	-	-	-	-	-	-	600	1200	**409**	**70**	-	-	-	-	-	-
South/Central Asia	North Indian	19954746	34.9	-	-	-	-	-	-	-	750	1500	**523**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	North Indian	19942749	29.1	-	-	-	-	-	-	-	91	182	**53**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
South/Central Asia	Pakistani	20102361	27.2	**-**	-	-	-	-	-	-	68	136	**37**	-	-	-	-	-	-	-
South/Central Asia	South Indian	15662508	36.7	0.5	0	0	0	-	-	-	300	600	**220**	**3**	**0**	**0**	**0**	-	-	-
South/Central Asia	South Indian	15660966	34.2	0.6	-	-	-	-	-	-	341	682	**233**	**4**	-	-	-	-	-	-
South/Central Asia	South Indian	20045989	**38**	**2**	**-**	**-**	**-**	**-**	**-**	**-**	50	100	38	2	-	-	-	-	-	-
South/Central Asia	South Indian	19430176	**37.1**	**2.5**	-	-	-	-	-	-	58	116	43	3	-	-	-	-	-	-
South/Central Asia	Tamilian	20390258	42.0	0.7	-	-	-	-	-	-	292	584	**245**	**4**	-	-	-	-	-	-
South/Central Asia	Tamilian	12919183	**37.9**	**2.2**	-	-	-	-	-	-	112	224	85	5	-	-	-	-	-	-
South/Central Asia	Uighur Chinese	20460345	-	2.4	-	-	-	-	-	-	706	1412	**-**	**34**	-	-	-	-	-	-
South/Central Asia	Uigur Chinese	15612662	49.0	1.6	-	-	-	-	-	-	96	192	**94**	**3**	-	-	-	-	-	-
South/Central Asia	Uygur Chinese	19444287	16.1	9.4	-	-	-	-	-	-	149	298	**48**	**28**	**-**	**-**	**-**	**-**	**-**	**-**

[1] Worldwide subpopulations and ethnicities were grouped based on the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) (21-22).

[2] PMID is a unique PubMed Identifier number assigned to each PubMed citation of life sciences and biomedical scientific journal articles: *http://www.ncbi.nlm.nih.gov/pubmed/*

[3] Data in bold were manually retrieved from each study; non-bold data were calculated and derived from the applicable reported (bold) data. Alleles not interrogated in a given study are noted by a dashed line ('-').

[4] Because the *CYP2C19*17* allele was identified in 2006 (52), *CYP2C19* studies prior to this date did not include this allele.

Supplemental Table S5. Predicted metabolizer phenotypes based on *CYP2C19* genotype and predicted average frequencies

	Predicted Metabolizer Phenotype (Average Multi-Ethnic Frequency[1])								
Allele	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***17***
1	EM (35-50%)	IM (17-35%)	IM (1-11%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	UM (3-27%)
2		PM (2-8%)	PM (0-5%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (1-6%)
3			PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
4				PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
5					PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
6						PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
7							PM (<1%)	PM (<1%)	IM[2] (<1%)
8								PM (<1%)	IM[2] (<1%)
17									UM (1-5%)

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer.

[1] Frequencies of predicted metabolizer phenotypes were determined using the allele frequencies from Supplemental Tables S3 and S4 and the Hardy-Weinberg equation.

[2] The predicted metabolizer phenotype of this genotype is based on reference (55), where the **17* gain-of-function allele was unable to completely compensate for the **2* loss-of-function allele; however, this data has not been independently replicated and is therefore a provisional classification.

Supplemental Table S6. Evidence linking *CYP2C19* genotype with clopidogrel response.

Type of Experimental Model	Major Findings	References	Level of Evidence*
In vitro	*CYP2C19*2* (c.681G>A; rs4244285) is a common polymorphism that results in a splicing defect and non-functional CYP2C19 protein.	de Morais, *et al*. 1994 (45)	High
In vitro	The *CYP2C19*3* - **8* variant alleles result in loss-of-function.	de Morais, *et al*. 1994 (46), Xiao, *et al*. 1997 (47), Ferguson, *et al*. 1998 (48), Ibeanu, *et al*. 1998 (49), Ibeanu, *et al*. 1998 (50), Ibeanu, *et al*. 1999 (51)	High
In vitro/In vivo	*CYP2C19*17* (c.-806C>T; rs12248560) is a common polymorphism that results in increased activity as a consequence of enhanced transcription.	Sim, *et al*. 2006 (52), Rudberg, *et al*. 2008 (53), Li-Wan-Po, *et al*. 2010 (54)	High
In vitro	CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 are involved in the hepatic metabolism of clopidogrel.	Savi*, et al*. 1992 (56), Savi*, et al*. 2000 (57), Clarke, *et al.* 2003 (58), Farid, *et al*. 2007 (59), Kazui, *et al*. 2010 (60)	High
In vitro	CYP2C19 contributes substantially to both oxidative steps of clopidogrel metabolism during the formation of its active metabolite.	Kazui, *et al*. 2010 (60)	High
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Brandt, *et al.* 2007 (27), Kim, *et al*. 2008 (36), Umemura, *et al*. 2008 (37), Mega, *et al.* 2009 (2)	High
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in ACS/PCI patients treated with clopidogrel.	Varenhorst, *et al*. 2009 (38)	High

Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Hulot, *et al.* 2006 (1), Brandt, *et al.* 2007 (27), Fontana, *et al*. 2007 (61), Chen, *et al*. 2008 (62), Kim, *et al*. 2008 (36), Umemura, *et al*. 2008 (37), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3)	High
Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Giusti, *et al.* 2007 (39), Frere, *et al.* 2008 (28), Geisler, *et al.* 2008 (26), Trenk, *et al.* 2008 (25), Jinnai, *et al*. 2009 (63), Shuldiner, *et al.* 2009 (3), Varenhorst, *et al*. 2009 (38), Harmsze, *et al*. 2010 (31), Hochholzer, *et al*. 2010 (64), Jeong, *et al*. 2010 (65), Kang, *et al*. 2010 (66), Sibbing, *et al*. 2010 (55), Yamamoto, *et al*. 2010 (67), Hwang, *et al*. 2011 (68), Maeda, *et al*. 2011 (69)	High
Clinical	*CYP2C19*2* is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Trenk, *et al.* 2008 (25), Collet, *et al.* 2009 (23), Giusti, *et al*. 2009 (70), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3), Sibbing, *et al.* 2009 (4), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (71), Malik, *et al*. 2010 (72), Yamamoto, *et al*. 2010 (67)	High

Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with lower formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Kim, *et al*. 2008 (36), Umemura, *et al*. 2008 (37), Mega, *et al.* 2009 (2)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Chen, *et al*. 2008 (62), Kim, *et al*. 2008 (36), Umemura, *et al*. 2008 (37), Mega, *et al.* 2009 (2)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Jinnai, *et al*. 2009 (63), Lee, *et al*. 2009 (73), Jeong, *et al*. 2010 (65), Kang, *et al*. 2010 (66), Yamamoto, *et al*. 2010 (67), Hwang, *et al*. 2011 (68), Maeda, *et al*. 2011 (69)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Collet, *et al.* 2009 (23), Mega, *et al.* 2009 (2), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (71), Yamamoto, *et al*. 2010 (67)	Moderate/ High
Clinical	*CYP2C19*17* is associated with lower on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Frere, *et al*. 2009 (74), Sibbing, *et al*. 2010 (24), Sibbing, *et al*. 2010 (55)	Moderate
Clinical	*CYP2C19*17* is associated with enhanced clopidogrel response and an increased bleeding risk in ACS/PCI patients treated with clopidogrel.	Sibbing, *et al*. 2010 (24), Tiroch, *et al*. 2010 (75)	Moderate
Clinical	*CYP2C19* loss-of-function alleles are not associated with adverse cardiovascular outcomes in coronary patients with low frequencies of PCI and with other indications (e.g., atrial fibrillation) treated with clopidogrel.	Pare, *et al*. 2010 (41), Wallentin, *et al*. 2010 (10)	High
Clinical	ACS/PCI patients with *CYP2C19* reduced metabolizer genotypes have reduced risks of primary outcome with prasugrel compared to clopidogrel. However, for *CYP2C19*	Sorich, *et al*. 2010 (76)	High

	EMs, the risks with prasugrel and clopidogrel are not significantly different.		

ACS: acute coronary syndrome; EM: extensive metabolizer; PCI: percutaneous coronary intervention
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'.

Supplemental Table S7. Evidence linking *CYP2C19* genotype with clopidogrel response (META-ANALYSES)

Study	Major Findings	***CYP2C19* Alleles Tested** ***CYP2C19* Diplotypes Detected**	References	Level of Evidence*
Meta-analysis of *CYP2C19*2* and PPI (October 2009)	11,959 patients, 23 studies: *CYP2C19*2* significantly associated with an increased risk of MACE, mortality, and ST; apparent in both heterozygotes and homozygotes.	**2* **1/*1*, **1/*2*, **2/*2*	Hulot, *et al*. 2010 (6)	High
Meta-analysis of *CYP2C19*2* (December 2009)	8,280 patients, 8 studies: *CYP2C19*2* significantly associated with an increased risk of adverse cardiovascular events.	**2* **1/*1*, **1/*2*, **2/*2*	Jin, *et al*. 2010 (77)	High
Meta-analysis of *CYP2C19* reduced-function alleles (August 2010)	9,685 patients, 9 studies: *CYP2C19* reduced-function allele heterozygotes and homozygotes had significantly associated increased risk of cardiovascular death, MI, or stroke. Also significantly increased risk of ST compared with noncarriers.	**2, *3, *4, *5, *8 (Depended on the study.)* *Depended on the study.*	Mega, *et al*. 2010 (7)	High
Meta-analysis of *CYP2C19*2* (January 2010)	8,043 patients, 7 studies: *CYP2C19*2* significantly associated with an increased risk of major adverse cardiovascular event. 4,975 patients, four cohorts: *CYP2C19*2* significantly associated with an increased risk of ST.	**2* **1/*1*, **1/*2*, **2/*2*	Sofi, *et al*. 2010 (9)	High

MACE: major adverse cardiovascular events; MI: myocardial infarction; PPI: proton pump inhibitor; ST: stent thrombosis.
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'

Supplemental Table S8. Evidence linking *CYP2C19* genotype with phenotype (CLOPIDOGREL DOSE ESCALATION)

Study Endpoints	Major Findings	References	Level of Evidence*
ex vivo platelet aggregation following increased clopidogrel dose	Higher-dose clopidogrel regimens can increase the degree of platelet inhibition in patients with genotypes predictive of poor response.	Gladding, *et al*. 2008 (78), Gladding, *et al*. 2009 (30), Bonello, *et al*. 2010 (79)	Moderate
ex vivo platelet aggregation	Pilot study; 150mg/day clopidogrel significantly reduce platelet reactivity in patients with high on-treatment reactivity. No difference according to *CYP2C19* status.	Barker, *et al*. 2010 (80)	Moderate
composite end point of cardiovascular death, MI and ST	Examined increased clopidogrel dose (150mg/day) on the basis of platelet function testing after PCI; no benefit of doubling dose in non-responders at 6 months.	Price, *et al*. 2009 (81), Price, *et al*. 2010 (82), Gensch, *et al*. 2011 (83) Price, *et al.* 2011 (84)	Moderate
definite ST, MACE	Among clopidogrel-resistant patients, a 150 mg/day dosage of clopidogrel was associated with a reduced risk of definite ST and MACE compared with 75 mg/day	Tavassoli, *et al*. 2010 (85)	Moderate

MACE: major adverse cardiovascular events; ST: stent thrombosis.
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'.