Published in final edited form as:

Pharmacogenet Genomics. 2013 November ; 23(11): 643–647. doi:10.1097/FPC.0b013e3283656bc1.

PharmGKB summary: tamoxifen pathway, pharmacokinetics

Daniel J. Klein^a, Caroline F. Thorn^a, Zeruesenay Desta^c, David A. Flockhart^c, Russ B. Altman^{a,b}, and Teri E. Klein^a

^aDepartment of Genetics, Stanford University Medical Center, Stanford, California

^bDepartment of Bioengineering, Stanford University Medical Center, Stanford, California

^cDepartment of Medicine, Indiana University Simon Cancer Center, Indianapolis, Indiana, USA

Keywords

breast cancer; pathway; pharmacogenomics; tamoxifen

Introduction

Tamoxifen, a selective estrogen receptor modulator, is important for the treatment and prevention of estrogen receptor (ER)-positive breast cancer. It has been shown to decrease disease recurrence and mortality rates by as much as 50 and 30%, respectively, and has also been used as a prophylactic treatment for those at high risk of developing breast cancer [1–6]. The response to tamoxifen has a high degree of interindividual variability, the cause of which may partly be due to differences in its metabolism *in vivo* [2] (Fig. 1). Hot flashes, the most common side effect of tamoxifen, affect up to 80% of women [7–9]. Patients receiving tamoxifen also seem to have a ~2.5 times higher risk of developing endometrial cancer [3,10,11]. In addition, tamoxifen may contribute to an increased risk for thromboembolic events and clinical depression [3,8]. Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat both hot flashes and depression; however, clinicians need to choose carefully when deciding which SSRI to prescribe, as many may have the capacity to decrease the efficacy of tamoxifen treatment [8,9,12–14].

Tamoxifen is used as an ER antagonist, which competitively inhibits cancerous ER-positive cells from obtaining the estrogen required for growth [10,15,16]. However, it has long been thought that tamoxifen is actually a prodrug and that its metabolites are likely to be the causative factors for the success seen in tamoxifen therapy [17,18]. For more information on the seminal works on tamoxifen, please see this excellent review by Jordan [19]. Apart from acting as selective estrogen receptor modulators, it has recently been found that some of tamoxifen's metabolites also act as aromatase inhibitors *in vitro* [20,21]. Aromatase converts steroids, for example, testosterone to estradiol, the inhibition of which severely decreases the

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Correspondence to Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, 1501 S. California Ave, Palo Alto, CA 94304, USA Tel: + 1 650 723 2956; fax: + 1 650 725 3863; feedback@pharmgkb.org.

Conflicts of interest

There are no conflicts of interest.

amount of available estrogen in the body. A previously unrecognized metabolite of tamoxifen, norendoxifen, is the most potent aromatase inhibitor of the tamoxifen metabolites. It causes the same decrease *in vitro* in aromatase activity as does letrozole, a drug that is exclusively marketed as an aromatase inhibitor [21].

This pathway summary illustrates many of the genes involved in the complex network of tamoxifen metabolism and provides a brief overview of why a variation in these genes may perturb the balance of the different tamoxifen metabolites and result in different drug response outcomes.

Pharmacokinetics

Tamoxifen is extensively metabolized predominantly by the cytochrome P450 (CYP) system into several primary and secondary metabolites, some of which exhibit more antiestrogenic effects in breast cancer cells than tamoxifen itself [2,22,23]. Tamoxifen metabolism mostly occurs through two pathways, 4-hydroxylation and N-demethylation, both of which result in the very potent secondary metabolite, endoxifen. Originally, the 4-hydroxylation path, which is catalyzed by multiple CYPs including CYP2D6, was given much attention because the immediately resulting metabolite, 4-hydroxytamoxifen, was shown to be ~30–100-fold more potent as an antiestrogen than tamoxifen [2,18]. However, this pathway only contributes to ~7% of tamoxifen metabolism. The conversion of tamoxifen by N-demethylation to N-desmethyltamoxifen, catalyzed primarily by CYP3A4 and CYP3A5, contributes to ~92% of tamoxifen metabolism [2,9,22]. N-desmethyltamoxifen is further oxidized to a number of metabolites that appear important to tamoxifen activity, the most important being endoxifen. Endoxifen, first identified in human bile [24], is formed from N-desmethyltamoxifen through hydroxylation by CYP2D6 and from 4-hydroxytamoxifen through demethylation by CYP3A4 [9,22]. Although 4-hydroxytamoxifen and endoxifen have similar potencies in terms of antiestrogenic activity, endoxifen plasma concentrations in those receiving tamoxifen therapy are, on average, over 10-fold higher than those observed with 4-hydroxytamoxifen with large inter-patient variability [5,9,23,25]. In addition to the ER inhibition exhibited by endoxifen, it also uniquely targets ER α (coded for by the *ESR1* gene) for proteasomal degradation. Endoxifen alone causes a decrease in ER α protein levels, whereas the other metabolites of tamoxifen merely stabilize them. Because of this added effect, endoxifen is likely to be the primary metabolite responsible for the success seen in tamoxifen treatment [26].

Tamoxifen is also metabolized by the flavin monooxygenases FMO1 and FMO3 to form tamoxifen-N-oxide (TNO). This can then be reduced back to tamoxifen *in vitro* by multiple CYP450s, the most prominent in terms of velocity of reduction being CYP1A1, CYP2A6, and CYP3A4. Further, it should be noted that only reduction of TNO by CYP3A4 produced tamoxifen that was further metabolized. However, it has been shown that TNO can be reduced to tamoxifen by hemoglobin and NADPH-P450 oxidoreductase. This yields the possibility that the reduction of TNO is not enzymatically dependent but may be accomplished by the heme-iron complex that hemoglobin and the cytochromes have in common. This suggests that an in-vivo cycle may exist that uses TNO as a storage unit for tamoxifen [27]. In accordance with this possibility, it has been shown that the ratio of tissue

to serum concentration of TNO decreases with increasing doses of tamoxifen, whereas the tissue to serum concentration ratios of tamoxifen and its other metabolites remain constant. This is likely owing to a quick reduction of TNO to tamoxifen in tumor cells, wherein the anticancer activity of tamoxifen is most needed [28]. Although these observations are interesting, the likelihood that TNO may be chemically reduced during sample preparation cannot be excluded, which makes it currently difficult to determine the precise role of TNO in the overall metabolism and effect of tamoxifen.

Although breast tissue does not usually express the multidrug resistance gene 1/ATP-binding cassette B1 (*MDR1/ABCB1*), some tumors do express this gene. Breast cancer can metastasize to the brain, behind the blood–brain barrier, where *ABCB1* is also expressed. As tamoxifen and its metabolites, particularly endoxifen, are substrates of P-glycoprotein, *ABCB1* may keep cellular concentrations of tamoxifen and its metabolites low, at subtherapeutic levels. At high doses, tamoxifen is used to treat tumors that have metastasized to the brain. It is likely that at the doses used in these settings, drug transporters in the blood–brain barrier may be already saturated and may not prevent tamoxifen and metabolites to access the brain [29,30].

Tamoxifen and its metabolites are inactivated through glucuronidation and sulfation through various UGTs and SULTs, respectively [31,32]. Glucuronidation is the more prominent pathway; ~75% of the tamoxifen dose is excreted into the biliary tract as glucuronides [33]. Most of the human UGTs exhibit some activity with tamoxifen or its metabolites, whereas sulfation is mainly accomplished by *SULT1A1* [22,31,34,35].

Pharmacogenomics

Given the preponderance of enzymes that participate in tamoxifen metabolism, there are many gene variants that may affect the relative amounts of the different tamoxifen metabolites. The CYP450 enzymes are highly polymorphic with many well-characterized variants, as are the UGT and SULT genes.

CYP2D6

Observational studies examining the treatment of tamoxifen side effects with SSRIs first pointed toward the role of *CYP2D6* as a modulator of efficacy [9]. During the past 10 years, more than 20 published studies have examined the role of the *CYP2D6* genotype in tamoxifen treatment outcome [36]. There is still much debate about its clinical relevance [37].

The majority of studies of tamoxifen pharmacogenomics have been candidate gene based and have examined the role of the *CYP2D6* gene (<http://pharmgkb.org/gene/PA128?tabType=tabVip>). *CYP2D6* has variants that can result in enzymes that correlate to a wide range of metabolic activity. There are four phenotypic categories to which patients can be assigned on the basis of their *CYP2D6* enzymatic function: poor metabolizers have enzymes with no activity, intermediate metabolizers have reduced functional enzymes, extensive metabolizers have enzymes with normal function, and ultrarapid metabolizers have enzymes with above-average enzyme function [38].

Because CYP2D6 is responsible for the hydroxylation of *N*-desmethyldoxifen to endoxifen, genetic variations that cause differences in the CYP2D6 metabolizer status may play a role in individual therapeutic benefit. This has led to research into the possible association between *CYP2D6* genotype and maximum benefit from tamoxifen therapy. Some studies suggest that CYP2D6 poor metabolizers have worse prognoses than those with typical enzyme activity [4,6,7,12,14,25,26,29,33,39–41], although contradictory evidence does exist [42–44]. In particular, two large studies have recently been published providing evidence against this association and asserting that *CYP2D6* genotyping before treatment serves no clinical benefit [45,46]. These two studies have been the subject of intense discussion among scientists in this field [37,47–49]. There are a number of reasons for why these differences in outcomes are seen. The International Tamoxifen Pharmacogenomics Consortium (ITPC) is in the process of publishing a manuscript detailing the difficulties of reaching consensus with regard to the *CYP2D6* genotype as a predictor for tamoxifen response [50]. Principle among these difficulties may be accurately genotyping and phenotyping CYP2D6. The copy number is not always assessed, which may cause a misclassification of the metabolizer status. *CYP2D6* also has pseudogenes that alter enzymatic activity and are hard to detect. For example, upon further inspection of *CYP2D6**4, one of the more common nonfunctional alleles, one study found that 18.7% of the *CYP2D6**4 alleles were actually *CYP2D6*–*2D7* hybrid alleles [51]. Environmental factors, such as the menopausal status or potential drug interactions with CYP2D6 inhibitors such as SSRIs, are also not always considered but can cause a big change in phenotype [37].

Other candidate pharmacogenes

The *CYP2C19**17 higher functioning variant has been associated with better responses to treatment, lower adverse reactions, and increased disease-free survival [6,32]. Because of the increased metabolism exhibited by the *17 allele, tamoxifen may be converted more efficiently into its more active metabolites. Patients with the *17 allele also seem to be at a decreased risk for developing breast cancer in general [32,52]. This may be because of the increased metabolism of, and thus decreased levels of, endogenous estrogens [32,52]. The lower levels of endogenous estrogens may also explain why patients with the *17 allele seem to respond better to treatment with tamoxifen. If the body decreases the amount of available estrogen before treatment, the continued decrease in exposure to estrogen resulting from the treatment should result in better patient outcome. However, the association with the *17 allele and increased disease-free survival has not been shown in all studies [5].

SULT1A1 is the most prominent gene involved in sulfation and has two major alleles: *SULT1A1**1 and *SULT1A1**2. *SULT1A1**1, the higher functioning allele, is associated with better patient survival as compared with *SULT1A1**2 [34,42,43]. The *SULT1A1* copy number, which has also been shown to affect enzyme activity, seems to have no effect on survival [5]. Variants in *UGT2B15*, known for metabolizing steroids and xenobiotics, have also been shown to affect survival and disease recurrence. *UGT2B15**2, the higher functioning variant, has been associated with decreased overall survival and increased disease recurrence. This association is much stronger when both *SULT1A1* and *UGT2B15* genotypes are evaluated together [42].

Two single-nucleotide polymorphisms (SNPs) outside the CYP450s have been associated with the clinical outcomes of tamoxifen therapy. A genome-wide association study on a Japanese population revealed that rs10509373 on chromosome 10, open reading frame 11 (*C10orf11*), at the 10q22 locus is associated with an increased recurrence-free survival, although this SNP is in an intronic region and may not be directly responsible for this association. This SNP is located within a 172-kb linkage disequilibrium block including the *C10orf11* gene, and thus the causative SNP may be contained within this region [53]. rs3740065, located in *ABCC2* gene, is associated with an increased expression of *ABCC2*, which may lead to lower exposure of breast tissue to the active metabolites and is associated with a decreased disease survival time [33].

Conclusion

The clinical importance of the *CYP2D6* genotype in treatment outcome has yet to be fully determined. Nonetheless, tamoxifen continues to be widely and relatively successfully used to treat ER-positive breast cancer. Although the cumulative research has been unable to completely explain the high degree of interindividual variability, reasons for the contradictory evidence are currently emerging and should be implemented in the study design of future research. In particular, as evidenced by the lack of a known therapeutic concentration, studies relating in-vivo concentrations of tamoxifen metabolites to clinical outcomes are scant. Thus, it will be necessary to examine network effects across variants in all pathway genes. Study cohorts with clearly defined and tightly controlled phenotypes (menopausal status, indication, dose and duration, cotreatments, outcomes, and follow-up) and strict genotypes/metabolizer status groupings may cut down the confounding issues.

Acknowledgments

PharmGKB is supported by the National Institutes of Health/National Institute of General Medical Sciences (R24 GM61374).

References

1. Boocock DJ, Maggs JL, Brown K, White IN, Park BK. Major inter-species differences in the rates of O-sulphonation and O-glucuronylation of alpha-hydroxytamoxifen in vitro: a metabolic disparity protecting human liver from the formation of tamoxifen-DNA adducts. *Carcinogenesis*. 2000; 21:1851–1858. [PubMed: 11023543]
2. Desta Z, Ward BA, Soukhova NV, Flockhart DA. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther*. 2004; 310:1062–1075. [PubMed: 15159443]
3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998; 90:1371–1388. [PubMed: 9747868]
4. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol*. 2005; 23:9312–9318. [PubMed: 16361630]
5. Moyer AM, Suman VJ, Weinshilboum RM, Avula R, Black JL, Safgren SL, et al. SULT1A1, CYP2C19 and disease-free survival in early breast cancer patients receiving tamoxifen. *Pharmacogenomics*. 2011; 12:1535–1543. [PubMed: 21961651]

6. Schroth W, Antoniadou L, Fritz P, Schwab M, Muerdter T, Zanger UM, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol*. 2007; 25:5187–5193. [PubMed: 18024866]
7. Goetz MP, Loprinzi CL. A hot flash on tamoxifen metabolism. *J Natl Cancer Inst*. 2003; 95:1734–1735. [PubMed: 14652227]
8. Henry NL, Stearns V, Flockhart DA, Hayes DF, Riba M. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. *Am J Psychiatry*. 2008; 165:1251–1255. [PubMed: 18829880]
9. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003; 95:1758–1764. [PubMed: 14652237]
10. Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med*. 1998; 339:1609–1618. [PubMed: 9828250]
11. Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfversward C, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet*. 1989; 1:117–120. [PubMed: 2563046]
12. Goetz MP, Knox SK, Suman VJ, Rae JM, Safgren SL, Ames MM, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*. 2007; 101:113–121. [PubMed: 17115111]
13. Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*. 2005; 97:30–39. [PubMed: 15632378]
14. Takimoto CH. Can tamoxifen therapy be optimized for patients with breast cancer on the basis of CYP2D6 activity assessments? *Nat Clin Pract Oncol*. 2007; 4:152–153. [PubMed: 17245346]
15. Jordan VC, Koerner S. Tamoxifen (ICI 46,474) and the human carcinoma 8S oestrogen receptor. *Eur J Cancer*. 1975; 11:205–206. [PubMed: 165942]
16. Lippman ME, Bolan G. Oestrogen-responsive human breast cancer in long term tissue culture. *Nature*. 1975; 256:592–593. [PubMed: 170527]
17. Allen KE, Clark ER, Jordan VC. Evidence for the metabolic activation of nonsteroidal antioestrogens: a study of structure–activity relationships. *Br J Pharmacol*. 1980; 71:83–91. [PubMed: 7470748]
18. Jordan VC, Collins MM, Rowsby L, Prestwich G. A monohydroxylated metabolite of tamoxifen with potent antioestrogenic activity. *J Endocrinol*. 1977; 75:305–316. [PubMed: 591813]
19. Jordan VC. Tamoxifen: a most unlikely pioneering medicine. *Nat Rev Drug Discov*. 2003; 2:205–213. [PubMed: 12612646]
20. Lu WJ, Desta Z, Flockhart DA. Tamoxifen metabolites as active inhibitors of aromatase in the treatment of breast cancer. *Breast Cancer Res Treat*. 2012; 131:473–481. [PubMed: 21390495]
21. Lu WJ, Xu C, Pei Z, Mayhoub AS, Cushman M, Flockhart DA. The tamoxifen metabolite norendoxifen is a potent and selective inhibitor of aromatase (CYP19) and a potential lead compound for novel therapeutic agents. *Breast Cancer Res Treat*. 2012; 133:99–109. [PubMed: 21814747]
22. Kiyotani K, Mushiroda T, Nakamura Y, Zembutsu H. Pharmacogenomics of tamoxifen: roles of drug metabolizing enzymes and transporters. *Drug Metab Pharmacokinet*. 2012; 27:122–131. [PubMed: 22041137]
23. Muerdter TE, Schroth W, Bacchus-Gerybadze L, Winter S, Heinkel G, Simon W, et al. Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in plasma. *Clin Pharmacol Ther*. 2011; 89:708–717. [PubMed: 21451508]
24. Lien EA, Solheim E, Kvinnsland S, Ueland PM. Identification of 4-hydroxy-N-desmethyldtamoxifen as a metabolite of tamoxifen in human bile. *Cancer Res*. 1988; 48:2304–2308. [PubMed: 3349495]
25. Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther*. 2006; 80:61–74. [PubMed: 16815318]

26. Wu X, Hawse JR, Subramaniam M, Goetz MP, Ingle JN, Spelsberg TC. The tamoxifen metabolite, endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. *Cancer Res.* 2009; 69:1722–1727. [PubMed: 19244106]
27. Parte P, Kupfer D. Oxidation of tamoxifen by human flavin-containing monooxygenase (FMO) 1 and FMO3 to tamoxifen-N-oxide and its novel reduction back to tamoxifen by human cytochromes P450 and hemoglobin. *Drug Metab Dispos.* 2005; 33:1446–1452. [PubMed: 15987777]
28. Gjerde J, Gandini S, Guerrieri-Gonzaga A, Haugan Moi LL, Aristarco V, Mellgren G, et al. Tissue distribution of 4-hydroxy-N-desmethyltamoxifen and tamoxifen-N-oxide. *Breast Cancer Res Treat.* 2012; 134:693–700. [PubMed: 22562123]
29. Iusuf D, Teunissen SF, Wagenaar E, Rosing H, Beijnen JH, Schinkel AH. P-glycoprotein (ABCB1) transports the primary active tamoxifen metabolites endoxifen and 4-hydroxytamoxifen and restricts their brain penetration. *J Pharmacol Exp Ther.* 2011; 337:710–717. [PubMed: 21378205]
30. Teft WA, Mansell SE, Kim RB. Endoxifen, the active metabolite of tamoxifen, is a substrate of the efflux transporter P-glycoprotein (multidrug resistance 1). *Drug Metab Dispos.* 2011; 39:558–562. [PubMed: 21148080]
31. Falany JL, Pilloff DE, Leyh TS, Falany CN. Sulfation of raloxifene and 4-hydroxytamoxifen by human cytosolic sulfotransferases. *Drug Metab Dispos.* 2006; 34:361–368. [PubMed: 16381672]
32. Gjerde J, Geisler J, Lundgren S, Ekse D, Varhaug JE, Mellgren G, et al. Associations between tamoxifen, estrogens, and FSH serum levels during steady state tamoxifen treatment of postmenopausal women with breast cancer. *BMC Cancer.* 2010; 10:313. [PubMed: 20565970]
33. Kiyotani K, Mushiroda T, Imamura CK, Hosono N, Tsunoda T, Kubo M, et al. Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. *J Clin Oncol.* 2010; 28:1287–1293. [PubMed: 20124171]
34. Nowell S, Sweeney C, Winters M, Stone A, Lang NP, Hutchins LF, et al. Association between sulfotransferase 1A1 genotype and survival of breast cancer patients receiving tamoxifen therapy. *J Natl Cancer Inst.* 2002; 94:1635–1640. [PubMed: 12419790]
35. Sun D, Sharma AK, Dellinger RW, Blevins-Primeau AS, Balliet RM, Chen G, et al. Glucuronidation of active tamoxifen metabolites by the human UDP glucuronosyltransferases. *Drug Metab Dispos.* 2007; 35:2006–2014. [PubMed: 17664247]
36. Hertz DL, McLeod HL, Irvin WJ Jr. Tamoxifen and CYP2D6: a contradiction of data. *Oncologist.* 2012; 17:620–630. [PubMed: 22531359]
37. Brauch H, Schroth W, Goetz MP, Murdter TE, Winter S, Ingle JN, et al. Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. *J Clin Oncol.* 2013; 31:176–180. [PubMed: 23091108]
38. Owen RP, Sangkuhl K, Klein TE, Altman RB. Cytochrome P450 2D6. *Pharmacogenet Genomics.* 2009; 19:559–562. [PubMed: 19512959]
39. Bonanni B, Macis D, Maisonneuve P, Johansson HA, Gucciardo G, Oliviero P, et al. Polymorphism in the CYP2D6 tamoxifen-metabolizing gene influences clinical effect but not hot flashes: data from the Italian Tamoxifen Trial. *J Clin Oncol.* 2006; 24:3708–3709. author reply 3709. [PubMed: 16877740]
40. Lim HS, Ju Lee H, Seok Lee K, Sook Lee E, Jang IJ, Ro J. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. *J Clin Oncol.* 2007; 25:3837–3845. [PubMed: 17761971]
41. Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA.* 2009; 302:1429–1436. [PubMed: 19809024]
42. Nowell SA, Ahn J, Rae JM, Scheys JO, Trovato A, Sweeney C, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. *Breast Cancer Res Treat.* 2005; 91:249–258. [PubMed: 15952058]
43. Wegman P, Elingarami S, Carstensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. *Breast Cancer Res.* 2007; 9:R7. [PubMed: 17244352]

44. Wegman P, Vainikka L, Stal O, Nordenskjold B, Skoog L, Rutqvist LE, et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res.* 2005; 7:R284–R290. [PubMed: 15987423]
45. Rae JM, Drury S, Hayes DF, Stearns V, Thibert JN, Haynes BP, et al. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. *J Natl Cancer Inst.* 2012; 104:452–460. [PubMed: 22395643]
46. Regan MM, Leyland-Jones B, Bouzyk M, Pagani O, Tang W, Kammler R, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1–98 trial. *J Natl Cancer Inst.* 2012; 104:441–451. [PubMed: 22395644]
47. Goldberg P. Experts claim errors in breast cancer study, demand retraction of practice-changing paper. *Cancer Lett.* 2012; 38:1–11.
48. Nakamura Y, Ratain MJ, Cox NJ, McLeod HL, Kroetz DL, Flockhart DA. Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1–98 trial. *J Natl Cancer Inst.* 2012; 104:1266–1268. 1264. author reply.
49. Stanton V Jr. Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1–98 trial. *J Natl Cancer Inst.* 2012; 104:1265–1266. author reply 1266–1268. [PubMed: 22851267]
50. Province MA, Goetz MP, Brauch H, Flockhart DA, Hebert JM, Whaley R, et al. Heterogeneity of study populations impacts the effect of CYP2D6 genotype in the adjuvant tamoxifen treatment of breast cancer. *Clin Pharmacol Ther.* 2013 in press.
51. Skierka JM, Walker DL, Peterson SE, O’Kane DJ, Black JL III. CYP2D6*11 and challenges in clinical genotyping of the highly polymorphic CYP2D6 gene. *Pharmacogenomics.* 2012; 13:951–954. [PubMed: 22676198]
52. Justenhoven C, Hamann U, Pierl CB, Baisch C, Harth V, Rabstein S, et al. CYP2C19*17 is associated with decreased breast cancer risk. *Breast Cancer Res Treat.* 2009; 115:391–396. [PubMed: 18521743]
53. Kiyotani K, Mushiroda T, Tsunoda T, Morizono T, Hosono N, Kubo M, et al. A genome-wide association study identifies locus at 10q22 associated with clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients in Japanese. *Hum Mol Genet.* 2012; 21:1665–1672. [PubMed: 22180457]

Fig. 1.

Graphic representation of the candidate genes involved in the pharmacokinetics of tamoxifen. A fully interactive version of this pathway is available online at PharmGKB at <http://www.pharmgkb.org/pathway/PA145011119>.