Pharmacogenetic analysis of human steroid 5α-reductase type II: comparison of finasteride and dutasteride

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Abstract

Human steroid 5α-reductase type II is a prostate-specific, membrane-associated enzyme that catalyzes the conversion of testosterone to dihydrotestosterone, the most potent androgen in the prostate gland. Genetic variants of this enzyme have been associated with both the development and the progression of prostate cancer. Both finasteride and dutasteride are competitive inhibitors of the type II steroid 5α-reductase that have been effectively used for the treatment of benign prostatic hyperplasia. Finasteride has also been successfully utilized for prostate cancer chemoprevention. We here investigate 5α-reductase inhibition assays in vitro to measure the effect of incubation time on the apparent inhibition constant (K<sub>i</sub>) for both constitutional and somatic (prostate cancer) enzyme variants. Our systematic pharmacogenetic analysis shows that both finasteride and dutasteride are slow, time-dependent inhibitors of steroid 5α-reductase type II, and that the inhibition kinetics depend on the 5α-reductase genotype. We also show that, overall, dutasteride is a more efficient steroid 5α-reductase inhibitor than finasteride. Based on our data, we are able to map areas of the enzyme that are responsible for this time-dependent inhibition for either (or both) enzyme inhibitor(s). This comprehensive pharmacogenetic analysis of steroid 5α-reductase variants unveiled significant pharmacogenetic variation for both finasteride and dutasteride and thus should be taken into account when designing protocols for treatment and/or chemoprevention of prostatic diseases with either one of these 5α-reductase inhibitors since there is considerable pharmacogenetic variation for both drugs.

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Introduction

The prostate gland depends on androgens for both its growth and development (Cheng et al. 1993). We have reported evidence that increased intraprostatic androgen metabolism, particularly through genetic variants of the enzyme steroid 5α-reductase, may play an important role in both predisposition to prostate cancer (Makridakis et al. 1999) as well as prostate cancer progression (Makridakis et al. 2004). Human prostatic (type II) steroid 5α-reductase is encoded by the SRD5A2 gene located in chromosome band 2p23 (Russell & Wilson 1994). Steroid 5α-reductase is a membrane-associated enzyme that catalyzes the conversion of testosterone to dihydrotestosterone (DHT), the most potent androgen in the prostate (e.g. Cheng et al. 1993). Thus, genetic variants encoded by the SRD5A2 gene may play an important role in both the development and the progression of prostate cancer (Ross et al. 1998).

Finasteride is a specific competitive inhibitor of the prostatic (type II) steroid 5α-reductase, both in vivo and in vitro (Stoner 1996, Span et al. 1999). These properties have made finasteride an attractive drug for the treatment of benign prostatic hyperplasia (BPH) (McConnell et al. 1998, Lowe et al. 2003) and prostate cancer chemoprevention (Thompson et al. 2003), with successful results. Specifically, the prostate cancer prevention trial (PCPT) showed that treatment of men 55 years of age or older with finasteride resulted in a significant decrease in prostate cancer incidence measured over a seven-year period (Thompson et al. 2003), suggesting that finasteride prevents or delays the appearance of prostate cancer. However, finasteride treatment also resulted in a significant increase in the incidence of prostate tumors of high grade (7 or higher) Gleason score (Thompson et al. 2003). Dutasteride (or GG745), a competitive inhibitor of both steroid 5α-reductase isoforms (type I and type II; Bramson et al. 1997), has also been shown to improve the symptoms associated with BPH without any significant increase in adverse side effects (Brown & Nuttall 2003, Clark et al. 2004).

We have reported significant genetic and pharmacogenetic variation for both finasteride and dutasteride at
the SRD5A2 locus in both somatic prostate cancer tissue and constitutional DNA of prostate cancer patients (Makridakis et al. 2000, 2004). Some of these SRD5A2 mutations resulted in increased enzyme activity and lowered inhibition by finasteride (Makridakis et al. 2000, 2004). These findings suggest that the presence of specific SRD5A2 mutants that are not efficiently inhibited by finasteride may, at least partially, explain the unexpected finding of an increase in high grade prostate cancer rate in the PCPT (reported by Thompson et al. 2003) since these mutants might result in more aggressive growth of tumors.

The kinetics of steroid 5α-reductase inhibition that we reported previously (Makridakis et al. 2000, 2004) were based on 10-min incubations for all enzyme variants. Finasteride, however, dissociates from the enzyme very slowly, and therefore is a time-dependent inhibitor of steroid 5α-reductase (Faller et al. 1993, Tian et al. 1994, 1995). In addition, dutasteride (Frye et al. 1998), like finasteride, retains the Δ1,2 bond that is critical for time-dependent inhibition in 4-azasteroids (Russell & Wilson 1994). Thus we decided to compare the kinetics of steroid 5α-reductase inhibition using 10- and 30-min incubation of the enzyme with either finasteride or dutasteride.

We report here that, like finasteride, dutasteride is a time-dependent inhibitor of steroid 5α-reductase type II. We also show that dutasteride is a more efficient steroid 5α-reductase inhibitor than finasteride for most of the enzyme variants that we studied. Based on our data, we are able to map areas of the enzyme that when mutated result in time-independent inhibition for either (or both) enzyme inhibitor(s). This comprehensive pharmacogenetic analysis of steroid 5α-reductase variants unveiled significant pharmacogenetic variation for both finasteride and dutasteride and this should be taken into account when designing protocols for treatment and/or chemoprevention of prostatic diseases with either one of these drugs.

Materials and methods
Steroid inhibitors
Finasteride was obtained from Merck (Rahway, NJ, USA) and dutasteride was synthesized by Pharmacia & Upjohn (Nerviano, Italy) (Makridakis et al. 2000).

Pharmacogenetic analysis
Individual missense substitutions were reconstructed in the SRD5A2 cDNA mammalian expression vector pS303–5αR2 (originally obtained from Dr D Russell, UT Southwestern Medical College, Dallas, TX, USA), by site-directed mutagenesis using the QuickChange kit (Stratagene, San Diego, CA, USA) with custom primers (Invitrogen, Carlsbad, CA, USA) (Makridakis et al. 2000). The various SRD5A2 cDNAs were electroporated into COS 7 cells together with a β-galactosidase control plasmid (pCMVβ, obtained originally from Dr Larry Kedes, University of Southern California, Los Angeles, CA, USA), and the respective protein extracts were collected 48 h later, by sonication. Total protein was quantified with a BioRad protein assay (Hercules, St Louis, MO, USA) and normalized protein extracts was added to specific amounts of each inhibitor at room temperature. Then, 0·8 or 1·6 µM [14C]testosterone (NEN, Boston, MA, USA) and 0·1 M Tris–citrate buffer of optimum pH for each variant (Makridakis et al. 2000, 2004) were added to the mix, and the reactions were placed at 37 °C for either 10 or 30 min. Initially, the concentration of the inhibitor was varied in 10-fold increments between 10−10 and 10−5 M, to approximate the apparent inhibition constant (Ki). After the initial approximation, the concentration was varied in five increments around the approximate Ki in triplicate experiments. Following incubation at 37 °C, the reactions were stopped with methylene chloride, and after extraction of the organic phase, steroids were dried, redissolved in ethanol and separated by thin-layer chromatography (TLC) using K6 silica TLC plates (Whatman, Clifton, NJ, USA) (Makridakis et al. 1999, 2000). Dried TLC plates were then exposed on phosphorimager screens (Molecular Dynamics, Mountain View, CA, USA) and quantified on a Storm phosphorimager (Molecular Dynamics). Then, substrate-to-product conversion values were translated into velocity values and plotted using Cricket Graph 1·3 (Cricket Software, Malvern, PA, USA). Linear regression analysis of the respective Lineweaver–Burk plots was used to calculate Ki values. The apparent Ki for each variant was determined by averaging the Ki values from three independent experiments. Further experimental details can be found in Makridakis et al. (2000).

Results
We previously reported significant genetic and pharmacogenetic variation at the SRD5A2 locus for both finasteride and dutasteride in both somatic prostate cancer tissue and constitutional DNA of prostate cancer patients (Makridakis et al. 2000, 2004). Some of the SRD5A2 mutations we characterized are common and/or recurrent, including the A49T (alanine-49 to threonine) mutation, which has been found to be
involved in prostate cancer predisposition and progression (Makridakis et al. 1999, 2004). The apparent $K_i$ for both finasteride and dutasteride in those experiments was calculated after transient expression of the reconstructed variant clones in mammalian cells followed by 10-min in vitro enzyme assays (Makridakis et al. 2000, 2004). However, finasteride is a slow, time-dependent inhibitor of steroid 5α-reductase (Faller et al. 1993, Tian et al. 1994, 1995). Therefore, longer finasteride incubations with the wild-type enzyme are expected to result in better inhibition, or lower apparent $K_i$ (see e.g. Moss et al. 1996). We decided to test this hypothesis for both finasteride and dutasteride and all the steroid 5α-reductase type II variants, using 30-min incubations.

As expected, the apparent $K_i$ for finasteride dropped significantly, from 60 nM for the 10-min enzyme assays to 23 nM for the 30-min enzyme assays for the normal (aka wild-type) protein (Table 1). The apparent $K_i$ for dutasteride also dropped significantly, from 17 nM to 4·3 nM (Table 2), suggesting that, like finasteride, the 4-azasteroid dutasteride is also a slow, time-dependent inhibitor of steroid 5α-reductase type II. The majority of the steroid 5α-reductase enzyme variants resulted in a reduction of the apparent $K_i$ for both inhibitors from the 10-min to the 30-min reaction, and thus behave like the wild-type enzyme (Tables 1 and 2). The significance of these findings is emphasized by the small variability observed in the values measured from three independent experiments (Tables 1 and 2 and data not shown). However, several variants resulted in an increase of the apparent $K_i$ for each inhibitor or no significant change between the 10- and 30-min reactions (Fig. 1 and Tables 1 and 2), and thus they exhibit time-independent inhibition.

### Table 1 Apparent inhibition constant ($K_i$) values for finasteride (the wild-type protein and enzyme variants) at the standard reaction time of 10 mins and at the extended reaction time of 30 mins

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>Wild type (normal variation)</th>
<th>Constitutional variants</th>
<th>Somatic variants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 min</td>
<td>30 min</td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>60 (52–72)</td>
<td>23 (17–29)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>2·6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5R</td>
<td>63</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>P30L</td>
<td>420</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>P48R</td>
<td>22</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>A49T</td>
<td>180</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>A51T</td>
<td>49</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>V89L</td>
<td>113</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>T187M</td>
<td>70</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>F194L</td>
<td>7</td>
<td>1·9</td>
<td></td>
</tr>
<tr>
<td>R227Q</td>
<td>260</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>F234L</td>
<td>200</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>60</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Somatic variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V3I</td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>A49T</td>
<td>180</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>V63M</td>
<td>38</td>
<td>6</td>
<td>89·7</td>
</tr>
<tr>
<td>F118L</td>
<td>5</td>
<td>3·2</td>
<td>1·6</td>
</tr>
<tr>
<td>G183D</td>
<td>45</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>V189A</td>
<td>90</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>G191E</td>
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<td>13</td>
<td></td>
</tr>
<tr>
<td>L221P</td>
<td>57</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>L226P</td>
<td>105</td>
<td>5·3</td>
<td></td>
</tr>
<tr>
<td>A248V</td>
<td>85</td>
<td>2·6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>36</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

*Range=fold variation between the lowest and highest values.*
apparent \( K_i \) than finasteride for most of the enzyme variants, including the wild-type enzyme and the A49T mutant (Tables 1 and 2). The P30L and A49T mutants, in particular, display a more than 100-fold lower apparent \( K_i \) for dutasteride than for finasteride, independently of reaction time (Tables 1 and 2).

However, two of the enzyme variants do not follow this trend: the F194L variant (independently of reaction time) and the P48R variant (but only in the 10-min reaction) display lower apparent \( K_i \) (higher affinity) for finasteride than dutasteride (Tables 1 and 2).

Overall, we report a significant pharmacogenetic variation for both somatic and constitutional SRD5A2 variants and for both finasteride and dutasteride (Tables 1 and 2). The distribution of the apparent \( K_i \) for finasteride for the distinct SRD5A2 missense substitutions

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>10 min</th>
<th>30 min</th>
<th>Change (10 min vs 30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type (normal variation)</td>
<td>17 (15–20)</td>
<td>4·3 (3·9–4·9)</td>
<td>4·0</td>
</tr>
<tr>
<td>Constitutional variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5R</td>
<td>18</td>
<td>4·5</td>
<td>4·0</td>
</tr>
<tr>
<td>P30L</td>
<td>12</td>
<td>6</td>
<td>2·0</td>
</tr>
<tr>
<td>P48R</td>
<td>27</td>
<td>3·8</td>
<td>7·1</td>
</tr>
<tr>
<td>A49T</td>
<td>1·1</td>
<td>2·3</td>
<td>0·5</td>
</tr>
<tr>
<td>A51T</td>
<td>29</td>
<td>2·2</td>
<td>13·2</td>
</tr>
<tr>
<td>V89L</td>
<td>9</td>
<td>2·1</td>
<td>4·3</td>
</tr>
<tr>
<td>T187M</td>
<td>21</td>
<td>5</td>
<td>4·2</td>
</tr>
<tr>
<td>F194L</td>
<td>21</td>
<td>12</td>
<td>1·8</td>
</tr>
<tr>
<td>R227Q</td>
<td>3·2</td>
<td>7</td>
<td>0·5</td>
</tr>
<tr>
<td>F234L</td>
<td>6</td>
<td>11</td>
<td>0·5</td>
</tr>
<tr>
<td>Range</td>
<td>25</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Somatic variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V3I</td>
<td>93</td>
<td>15</td>
<td>6·2</td>
</tr>
<tr>
<td>A49T</td>
<td>1·1</td>
<td>2·3</td>
<td>0·5</td>
</tr>
<tr>
<td>V63M</td>
<td>36</td>
<td>5</td>
<td>7·2</td>
</tr>
<tr>
<td>F118L</td>
<td>4</td>
<td>0·5</td>
<td>8</td>
</tr>
<tr>
<td>G183D</td>
<td>13</td>
<td>3·1</td>
<td>4·2</td>
</tr>
<tr>
<td>V189A</td>
<td>23</td>
<td>5</td>
<td>4·6</td>
</tr>
<tr>
<td>G191E</td>
<td>25</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>L221P</td>
<td>14</td>
<td>4·2</td>
<td>3·3</td>
</tr>
<tr>
<td>L226P</td>
<td>9</td>
<td>7</td>
<td>1·3</td>
</tr>
<tr>
<td>A248V</td>
<td>13</td>
<td>2·9</td>
<td>4·5</td>
</tr>
<tr>
<td>Range</td>
<td>85</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Range = fold variation between the lowest and highest values.

Figure 1 Mapping of enzyme residues that do not show time-dependent inhibition for finasteride (regular font) and dutasteride (italics). Black blocks under the sequence indicate 5α-reductase enzyme binding regions for both finasteride and dutasteride (deduced from the effect of specific enzyme variants on the apparent \( K_i \)).
varied 84-fold (5–420 nM) in the 10-min reactions and
142-fold (1.9–270 nM) in the 30-min reactions (Table 1).
The distribution of the apparent $K_i$ for dutasteride varied
85-fold (1-93 nM) in the 10-min reactions and 30-fold
(0.5–15 nM) in the 30-min reactions (Table 2). Thus,
30-min incubations with dutasteride resulted in the
lowest apparent $K_i$ values overall and the lowest
variation (Tables 1 and 2).

Discussion

Both finasteride and dutasteride are important
4-azasteroid inhibitors of steroid 5α-reductase that have
been successfully utilized in vivo for the treatment and
prevention of prostatic diseases. We previously reported
significant pharmacogenetic variation of steroid 5α-
reductase for both finasteride and dutasteride in both
somatic prostate cancer tissue and constitutional DNA
(Makridakis et al. 2000, 2004). Those results, however,
were based on 10-min reactions, while finasteride is a
slow, time-dependent inhibitor of steroid 5α-reductase
(e.g. Faller et al. 1993, Tian et al. 1994). Thus, we
reasoned that longer incubations with either inhibitor
would be better approximations of the true inhibition
in vivo. Due to the lability of the enzyme in vitro and
the loss of linearity in the DHT production versus
time curve after 40 min for the overactive A49T
mutant (data not shown), we decided to use 30-min
incubations for all the enzyme variants as the longer
reaction time.

Comparison of the apparent $K_i$ values between our
standard (10 min) reactions and the extended (30 min)
reactions for finasteride (Table 1) indicates that, as
reported previously, finasteride is a time-dependent
inhibitor of steroid 5α-reductase. This fact is not only
ture for the wild-type protein, but also for most of the
enzyme variants, whether constitutional or somatic
(Table 1). Dutasteride is a dual (i.e. type I and type II)
5α-reductase inhibitor (Bramson et al. 1997) and thus
may be more efficacious in reducing DHT levels in
the blood, in vivo. In addition, most of the 5α-reductase
enzyme variants resulted in significantly lower apparent
$K_i$ values for dutasteride in the 30-min reactions
compared with the 10-min reactions (Table 2). Therefore,
dutasteride is, like finasteride, a slow, time-dependent inhibitor of steroid 5α-reductase. This
finding is not surprising since both dutasteride and
finasteride retain the $\Delta_1^{1,2}$ bond that is critical for
time-dependent inhibition in 4-azasteroids (Russell &
Wilson 1994). These results also suggest a similar
mechanism of time-dependent steroid 5α-reductase
inhibition for both finasteride and dutasteride.

Comparison of the apparent $K_i$ values for each
inhibitor suggests that dutasteride was the steroid
5α-reductase inhibitor that exhibited the lowest appar-
ent $K_i$ for most steroid 5α-reductase variants, including the wild-type, in both the 10-min and the 30-min
reactions (Tables 1 and 2). The only exceptions to this
observation were the F194 L variant (independently of
reaction time) and the P48R variant (but only in the
10-min reaction). The disease-relevant A49T variant is
of particular interest, since it is inhibited much more
efficiently by dutasteride than finasteride, irrespective
of the reaction time (Tables 1 and 2). Overall, the dual
5α-reductase inhibitor, dutasteride, has higher affinity for
steroid 5α-reductase type II than finasteride, irrespective
of genotype. Dutasteride is also expected to result in
lower pharmacogenetic variation than finasteride in vivo,
since it displays significantly lower pharmacogenetic
variation of the apparent $K_i$ than finasteride in the
30-min assays (see below; Tables 1 and 2). Thus, this
compound may also be a better choice in vivo.

Thirty-minute 5α-reductase inhibition reactions are
expected to be more representative of the in vivo
5α-reductase inhibition than the 10-min reactions we
previously reported (Makridakis et al. 2000, 2004). The
distribution of the apparent $K_i$ for the distinct SRD5A2
variants in the 30-min reactions varied 142-fold
(1.9–270 nM) for finasteride (Table 1) and 30-fold
(0.5–15 nM) for dutasteride (Table 2). Thus the
apparent $K_i$ values for the distinct SRD5A2 variants vary
widely, irrespective of reaction time. This significant
SRD5A2 pharmacogenetic variation may be important
in vivo and should be taken into account when using
finasteride or dutasteride for the treatment or prevention
of prostate cancer. The PCPT trial reported that
finasteride treatment in men followed over seven years
resulted in a significant decrease in the overall rates of
prostate cancer, but also in a significant increase in the
rates of high-grade prostate tumors (Thompson et al.
2003). This unexpected finding of an increase in high
grade prostate cancer rate in the PCPT may, at least
partially, be explained by the presence of specific
SRD5A2 variants (like A49T) in a subset of the study
population that are not efficiently inhibited by
finasteride. For individuals carrying the A49T allele,
dutasteride might have been a better choice (Table 2
versus Table 1). Thus, future trials such as the PCPT
and treatment protocols using 5α-reductase inhibitors
should consider genotyping men for SRD5A2 variants.
In fact, we note that the pharmacogenetic inhibition
increases for finasteride with time (Table 1) while it
decreases for dutasteride (Table 2). This may suggest
that dutasteride has a ‘tighter’ range for allelic and somatic
variants, which may lessen the still considerable impact
of pharmacogenetic variation in vivo. Thus, this compound
can be generally better tolerated in vivo as well.

The inclusion of a high number of naturally occurring
constitutional or somatic (prostate cancer) SRD5A2
variants in our pharmacogenetic analysis allowed us to
identify areas of the protein that are important for the

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slow, time-dependent inhibition, for both 4-azasteroid inhibitors (Fig. 1). The wild-type as well as most of the steroid 5α-reductase variants resulted in a reduction of the apparent $K_i$ for both inhibitors from the 10-min to the 30-min reaction, and thus display time-dependent inhibition (Tables 1 and 2). However, several 5α-reductase variants resulted in time-independent inhibition: (a) the A49T and F118L variants for finasteride, and (b) the A49T, L226P, R227Q and F234L variants for dutasteride (Fig. 1, Tables 1 and 2). These enzyme variants affect residues in both the amino-terminus and the carboxy-terminus of the protein (Fig. 1). Comparison of the wild-type versus mutant residue at positions 49, 118, 226, 227 and 234 indicates that the mutant residues are less hydrophobic. Indeed, the average hydropathy index (Kyte & Doolittle 1982) for residues 49 and 118 (for finasteride) is +2·3 for the wild-type residues and +1·5 for the mutant residues. Similarly, for dutasteride, the average hydropathy index (Kyte & Doolittle 1982) for residues 49, 226, 227 and 234 is +1·0 for the wild-type residues and +0·3 for the mutant residues. Thus, hydrophobic interactions between the 4-azasteroid (finasteride/dutasteride) and specific wild-type 5α-reductase residues may be important for the slow, time-dependent inhibition displayed by these inhibitors. Pharmacogenetic analysis of these 5α-reductase variants with another 4-azasteroid, such as PNU157706 (di Salle et al. 1998) may be instrumental in confirming this observation.

In summary, our systematic analysis of both constitutional and somatic (prostate cancer) variants of steroid 5α-reductase type II indicates that dutasteride is a more efficient steroid 5α-reductase type II inhibitor than finasteride in vitro for most of the enzyme variants, and that dutasteride treatment is also expected to result in lower pharmacogenetic variation in vivo than finasteride treatment. However, the pharmacogenetic variation we uncovered for both finasteride and dutasteride is still very significant and this should be taken into account when designing protocols for treatment and/or chemoprevention of prostate diseases with either one of these drugs. Our data also suggest that both finasteride and dutasteride are slow, time-dependent inhibitors of steroid 5α-reductase type II and allow us to map areas of the wild-type enzyme that are (at least partially) responsible for this time-dependent inhibition for either (or both) enzyme inhibitor(s). Pharmacogenetic analyses such as the one presented here may one day help in achieving individualized prostate cancer treatment (and perhaps even prevention).

Acknowledgements

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