Supplemental Appendix for:

Boland MR, Tatonetti NP.

Investigation of 7-DeHydroCholesterol Reductase Pathway to Elucidate Off-Target Prenatal Effects of Pharmaceuticals: A Systematic Review

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Three Toxins Decrease DHCR7 Expression: Details

Three toxins resulted in decreased DHCR7 expression including one naturally occurring toxin, Ochratoxin A [1]; one industrial toxin (a byproduct of water treatment) [2]; and one metabolite of inorganic arsenic, Monomethylarsonous acid [3]. Arsenic is a common water contaminant in certain areas [4], and the arsenite metabolite, Monomethylarsonous acid, has been found to be more toxic than arsenite among certain populations [5]. Arsenic poisoning can result in trans-placental carcinogenic effects particularly of the reproductive system [6]. Interestingly Ochratoxin A is a commonly occurring toxin produced by fungi of the families' *aspergillus* and *penicillium.* The toxin has been found in both human and cow milk with higher levels reported in human milk [7]. Small amounts are not toxic, but cancer can result if large quantities are ingested.

Methods for PubMed Retrieval of Articles Pertaining to Prenatal Drug Exposure and Fetal Outcomes

To retrieve all relevant observational studies on each drug's teratogenicity, we queried PubMed using automated queries. The general form of the query we used was: [drug_name] AND "pregnancy outcome" NOT "rat" NOT "mouse" NOT "cell" NOT "tissue" where drug_name was equal to each of the investigated drugs namely, clozapine, chlorpromazine, haloperidol, simvastatin, tamoxifen, doxorubicin, isotretinoin. The initial query for levothyroxine returned 132 publications, many related to thyroxine and not levothyroxine specifically. Therefore, we added quotes around levothyroxine to only retrieve publications pertaining to levothyroxine. Progesterone initially returned 752 publications and many of these were off-topic relating to progesterone's role as an essential hormone in pregnancy. Therefore we refined the query for progesterone only to: Progesterone AND "teratogen". This returned a manageable number of publications (i.e., 10). PubMed was queried on April 27th, 28th, 29th in 2015.We manually added additional relevant publications retrieved from other locations, such as Google scholar, to increase the breadth of our search.

Seven exclusion criteria were applied to remove retrieved articles that were not relevant for our purposes upon manual review. These included: 1) all studies not in humans; 2) all non-main research articles that simply comment on teratogenicity or policy decisions; 3) all studies not in English; 4) all human tissue studies and cell cultures (i.e., not whole organism studies); 5) interview articles that contain patient perceptions on teratogenicity; 6) articles where the abstract did not contain full details of the study and full-text was not freely accessible; and 7) studies on teratogenicity of drug when used in combination with assisted-reproductive technologies (use of assisted-reproductive technologies adds an additional bias when studying pregnancy outcomes). The total number of publications considered for each drug, along with its FDA pregnancy safety category are given in **Figure S2.**

Table S1. Allele Frequencies For DHCR7 Mutations in 523 (9 true heterozygotes with only 1 allele) SLOS Patients from 30 Studies

Allele's Effect on Coding Sequence	Intron/ Exon[1]	Allele Frequency from 514 patients (1037 alleles)	Overall Incidence (%)	Reference(s)
M1 (I)	Exon 3	2	0.193	8
M1V	Exon 3	2	0.193	9, 10
G30A§	Exon 3	-	-	11
W33-S65 del	Exon 3	2	0.193	8, 12
IVS3-1-95 Frameshift	Exon 4	1	0.096	13
W37X	Exon 4	1	0.096	8
E37X	Exon 4	1	0.096	14
A50N	Exon 4	1	0.096	9
P51S	Exon 4	12	1.157	8, 14-18
P51H	Exon 4	1	0.096	19
M59R	Exon 4	1	0.096	8
D62V	Exon 4	1	0.096	8
L68P	Exon 4	3	0.289	9, 20
T93M	Exon 4	103	9.932	8-10, 12, 14-19, 21-27
Q98X	Exon 4	4	0.386	9, 22, 28
L99P	Exon 4	9	0.868	8, 14, 16, 17, 19, 21
Q107H	Exon 4	3	0.289	8, 12 17, 21
Q107H + 12 amino acids	Exon 4	1	0.096	24
L109P	Exon 5	10	0.964	8, 17, 23-25, 29
S113C	Exon 5	1	0.096	20
H119L	Exon 5	5	0.482	8, 18, 21, 23, 30
H119fsX8	Exon 5	1	0.096	9
384-IVS5+4del Frameshift	Exon 5	2	0.193	8, 27
Del 385-412 (null mutation)	Exon 5	1	0.096	21
385-IVS5+5del Frameshift	Exon 5	1	0.096	8, 17
G138V	Exon 5	2	0.193	20
(I)145L	Exon 5	3	0.289	20, 29
N146K	Exon 5	1	0.096	29
G147D	Exon 6	7	0.675	8, 17, 18, 21, 24
L148R	Exon 6	2	0.193	8, 14
Q149X	Exon 6	1	0.096	8
W151X	Exon 6	87	8.390	8, 9, 16, 17, 21, 24-29
T154M	Exon 6	9	0.868	8, 12, 17, 23, 24, 29
T154R	Exon 6	2	0.193	10, 21
L157P	Exon 6	7	0.675	8, 16, 17, 21, 25, 29
W158C§§	Exon 6	-	-	31

[1] Intron/Exon Boundaries Obtained from: http://www.rcsb.org/pdb/gene/DHCR7

F168I	Exon 6	2	0.193	8, 14
S169L	Exon 6	9	0.868	8, 12, 14, 17, 18
F174S	Exon 6	1	0.096	22
D175H	Exon 6	2	0.193	8, 14
W177R	Exon 6	2	0.193	12, 24
I178F	Exon 6	2	0.193	9
I178N	Exon 6	1	0.096	21
P179L	Exon 6	2	0.193	8, 14
W182L	Exon 6	4	0.386	8, 9, 22, 23
W182C	Exon 6	2	0.193	8, 17, 18
C183Y	Exon 6	3	0.289	8, 23
S192F	Exon 6	2	0.193	9, 32
K198E	Exon 6	2	0.193	8, 23
Y217X	Exon 7	1	0.096	8
Y219D	Exon 7	1	0.096	29
E224K	Exon 7	1	0.096	9
P227S	Exon 7	1	0.096	33
682Cins Frameshift	Exon 7	3	0.289	8, 12, 13
R228W	Exon 7	1	0.096	9
D234Y	Exon 7	1	0.096	34
F235S	Exon 7	1	0.096	20
720-735del Frameshift	Exon 7	2	0.193	8, 16, 17
R242C	Exon 7	12	1.157	8, 12, 17, 20, 21, 24, 25
R242H	Exon 7	9	0.868	8, 18, 21, 23, 24, 32
P243R	Exon 7	5	0.482	8, 14, 18
G244R	Exon 7	6	0.579	8, 18, 23, 26, 30
A247V	Exon 7	6	0.579	8, 12, 16, 17, 21, 24
W248C	Exon 7	4	0.386	8, 23, 29, 30
W248R	Exon 7	1	0.096	25
I251M	Exon 7	1	0.096	8
I251N	Exon 7	1	0.096	35
N252S	Exon 7	2	0.193	8
S254A	Exon 7	1	0.096	18
762Tins Frameshift	Exon 7	2	0.193	8, 13
F255L	Exon 7	2	0.193	8, 23
M270V	Exon 7	2	0.193	8, 21
V273G	Exon 7	1	0.096	9
N274K	Exon 7	4	0.386	10, 18, 22
Y280C	Exon 8	2	0.193	25, 36
V281A	Exon 8	-	-	17
V281M	Exon 8	2	0.193	8, 17, 34
F284L	Exon 8	4	0.386	8, 14, 21
N287K	Exon 8	8	0.771	8, 14, 37
E288K	Exon 8	1	0.096	15, 35
T289I	Exon 8	6	0.579	8, 17, 21, 24, 25
I297T	Exon 8	1	0.096	20
H301R	Exon 8	2	0.193	22
H301Q	Exon 8	2	0.193	18

F302L	Exon 8	12	1.157	8, 12, 14, 18, 21, 34
G303R	Exon 8	6	0.579	32, 33
G307D	Exon 8	-	-	15
G309S	Exon 8	1	0.096	15, 21
C311G	Exon 8	-	-	17
C311Y	Exon 8	-	-	17
L317R	Exon 8	1	0.096	10
Y318N	Exon 8	2	0.193	24, 25
T319M	Exon 8	1	0.096	8
T319A	Exon 8	-	-	15
G963 insertion of 134bp Frameshift (could be either >T or >C)	Intron 8	3	0.289	30
IVS8-1G>T	Intron 8	4	0.386	8, 23, 28
IVS8-1G>C*	Intron 8	291	28.062	8, 9 12-14, 16-26, 28, 34, 36, 38, 39
G322 frameshift	Exon 9	3	0.289	29
Y324H	Exon 9	6	0.579	8, 14, 17, 21
V326R	Exon 9	3	0.289	9
V326L†	Exon 9	52	5.014	8, 14, 16-18, 21, 25, 29, 38
P329L	Exon 9	2	0.193	8, 26
V330M	Exon 9	1	0.096	26
L341P	Exon 9	1	0.096	24
G344D§§§	Exon 9	-	-	40
G344R	Exon 9	1	0.096	20
G347S	Exon 9	1	0.096	9
R352W†	Exon 9	36	3.472	8, 10, 14, 16-18, 21, 25, 27, 29, 33
R352Q	Exon 9	22	2.122	8, 17, 29, 32, 33, 37
R352L	Exon 9	2	0.193	37
1057Gdel Frameshift	Exon 9	1	0.096	8
V353A	Exon 9	1	0.096	8, 17
N355D	Exon 9	1	0.096	8
356delH	Exon 9	1	0.096	38
L360P	Exon 9	2	0.193	9
R362C	Exon 9	1	0.096	8, 17
R363C	Exon 9	1	0.096	26
K376R frameshift-37	Exon 9	1	0.096	33
G366V	Exon 9	1	0.096	39
C380S	Exon 9	4	0.386	8, 16, 17, 21
C380R	Exon 9	1	0.096	8, 17
C380Y	Exon 9	5	0.482	8, 12, 17, 25
S397L	Exon 9	1	0.096	8, 17
R404C§§§	Exon 9	36	3.472	8, 16-18, 20, 21, 25
R404S	Exon 9	4	0.386	8, 14, 17
H405Y	Exon 9	2	0.193	20
N407Y	Exon 9	3	0.289	8, 18, 27

Y408H	Exon 9	6	0.579	8, 17, 18, 20, 21, 24, 25
G410S§§§	Exon 9	15	1.446	8, 10, 14, 16-18, 21
G410R	Exon 9	2	0.193	8, 17, 21
H426P	Exon 9	1	0.096	20
Y432C	Exon 9	2	0.193	9
R443C	Exon 9	3	0.289	8, 17, 21
R443H	Exon 9	1	0.096	21
C444Y	Exon 9	2	0.193	12, 24
R446Q	Exon 9	7	0.675	8, 17, 18, 21, 26, 29
E448Q	Exon 9	2	0.193	8, 17, 21
E448K	Exon 9	25	2.411	8, 14, 17, 19, 21, 24-27, 29, 38
R450L	Exon 9	3	0.289	8, 17, 19, 21
Y462H	Exon 9	2	0.193	8, 14
V466A	Exon 9	1	0.096	10
P467L	Exon 9	4	0.386	15, 41
R469P	Exon 9	4	0.386	8, 14
L470Q	Exon 9	2	0.193	12
F475S	Exon 9	1	0.096	9
X476Q	Exon 9 stop codon	1	0.096	32
Unidentified Suspected Variant	-	13	1.254	9, 13, 14, 21, 22, 25, 29
Total		1037		

*Annotated as: c.964-1G>C in some literature articles

† SLOS patients with single mutations (true heterozygotes) were found (N=3), 2 had mutations in V326L and 1 had a mutation in R352W [16]. Both mutations were shown to reduce expression of DHCR7 upon heterologous expression by >90% [16].

+ Frequencies from [17] not included in analysis because only counts from frequent mutations were reported

§ Allele frequencies were not provided in the paper [11], but presence of this allele is believed to be implicated in SLOS

§§ Unaffected sibling [31]

§§§ DHCR7 mutation resulted in non-SLOS holoprosencephaly [40], only SLOS patients are included in the allele frequency counts

Table S2. Allele Frequencies For DHCR7 Mutations in 523 (9 true heterozygotes with only 1 allele) SLOS Patients from 30 Studies and their ExAC [42] Allele Frequencies

Please see Excel sheet attached separately.

Table S3. Chemicals Predicted to Modulate DHCR7 Expression from the Comparative Toxicogenomics Database

Chemical/Drug	PubMedID	Reference (s)
Predicted to Increase Expression (up-regulate)		
Estradiol	19167446	[43]
8-Bromo Cyclic Adenosine Monophosphate	22079614	[44]
Catechin	24763279	[45]
Grape Seed Proanthocyanidins	24763279	[45]
Coumestrol	19167446	[43]
resveratrol	19167446	[43]
Hydrogen Peroxide	18032389	[46]
isoquercitrin	18032389	[46]
pirinixic acid	19710929	[47]
Selenium	19244175	[48]
Predicted to Decrease Expression (down-regulate)		
sulindac sulfide	16184548	[49]
motexafin gadolinium	16357179	[50]
Zinc Acetate	16357179	[50]
Arachidonic Acid	16704987	[51]
triacsin C	16704987	[51]
Dronabinol	18454173	[52]
cobaltous chloride	19320972	[53]
22-hydroxycholesterol	19426978	[54]
Copper Sulfate	19549813	[55]
Benzo(a)pyrene	20106945	[56]
Isotretinoin	20436886	[57]
Copper	20971185	[58]
NSC 689534	20971185	[58]
Quercetin	21632981	[59]
Acetaminophen	22230336	[60]
Thapsigargin	22378314	[61]
Tunicamycin	22378314	[61]
Valproic Acid	23179753	[62]
Ethyl Methanesulfonate	23649840	[63]
Formaldehyde	23649840	[63]
Methyl Methanesulfonate	23649840	[63]
Tretinoin	23724009	[64]
Cyclosporine	20106945	[56]

Table S4. Aggregation of Chemicals that Modulate DHCR7 By Compound Type

Affect on DHCR7	Pharmaceutical Drug/Vitamin	Investigational Pharmaceuticals		Inorganic Compounds	Toxins
		Clinical Trials	Preclinical		
Increase Expression	**5**			2	
Decrease Expression					3
Decrease Protein Activity					1
Direct Inhibitors	**2**	3	7		

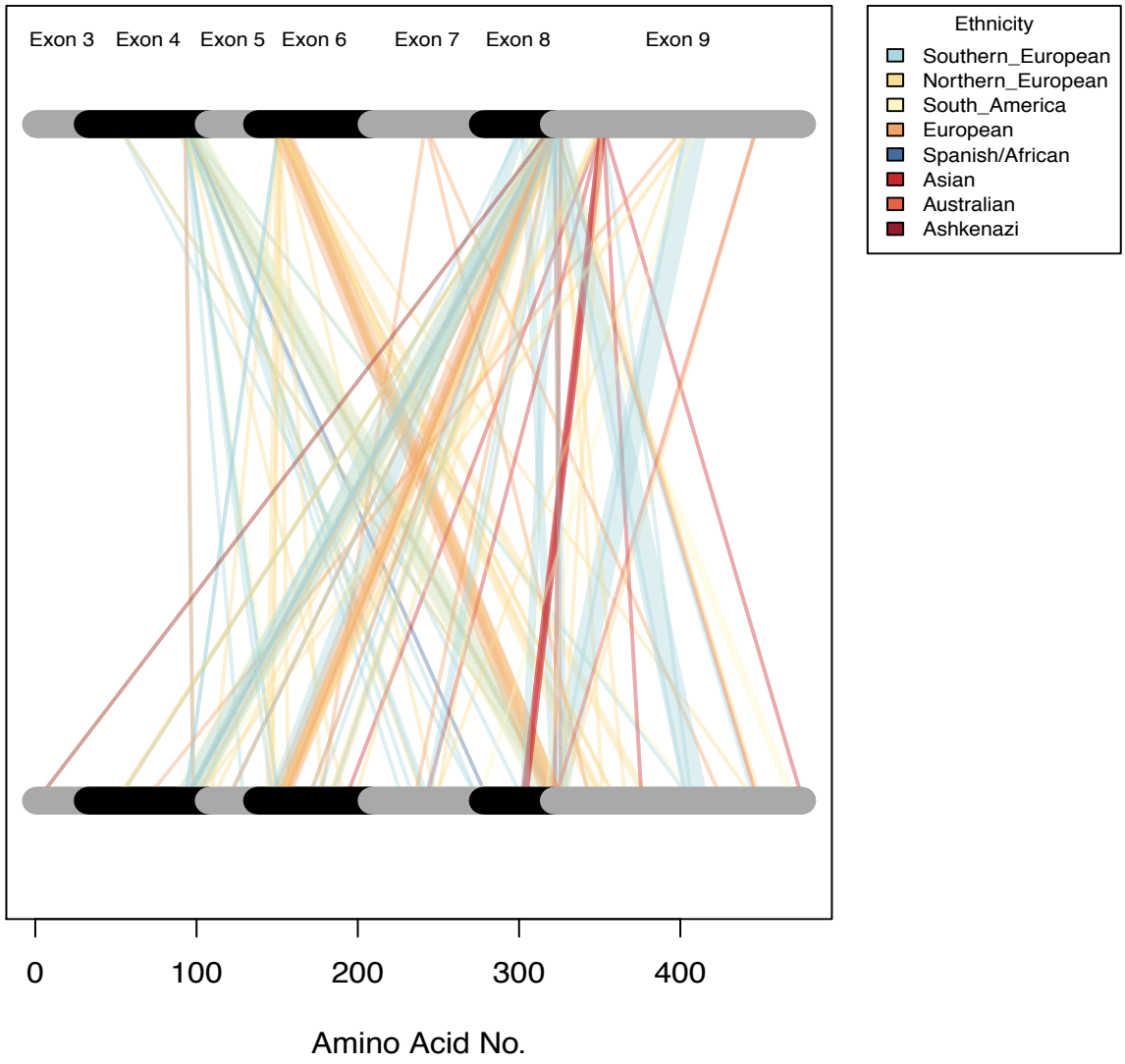

Figure S1. Graphical Relationship Between Compound Heterozgous Pairs and Ethnicity. Common DHCR7 mutations (>=1% frequency) are included on the top bar and all other DHCR7 mutations are on the bottom bar. Because patients contain 2 DHCR7 mutations they typically contain 1 common mutation and one less common mutation (bottom graphic). This graphic shows how certain ethnicities contain certain pairs more frequently than others. Edge thickness indicates the number of patients with that particular combination.

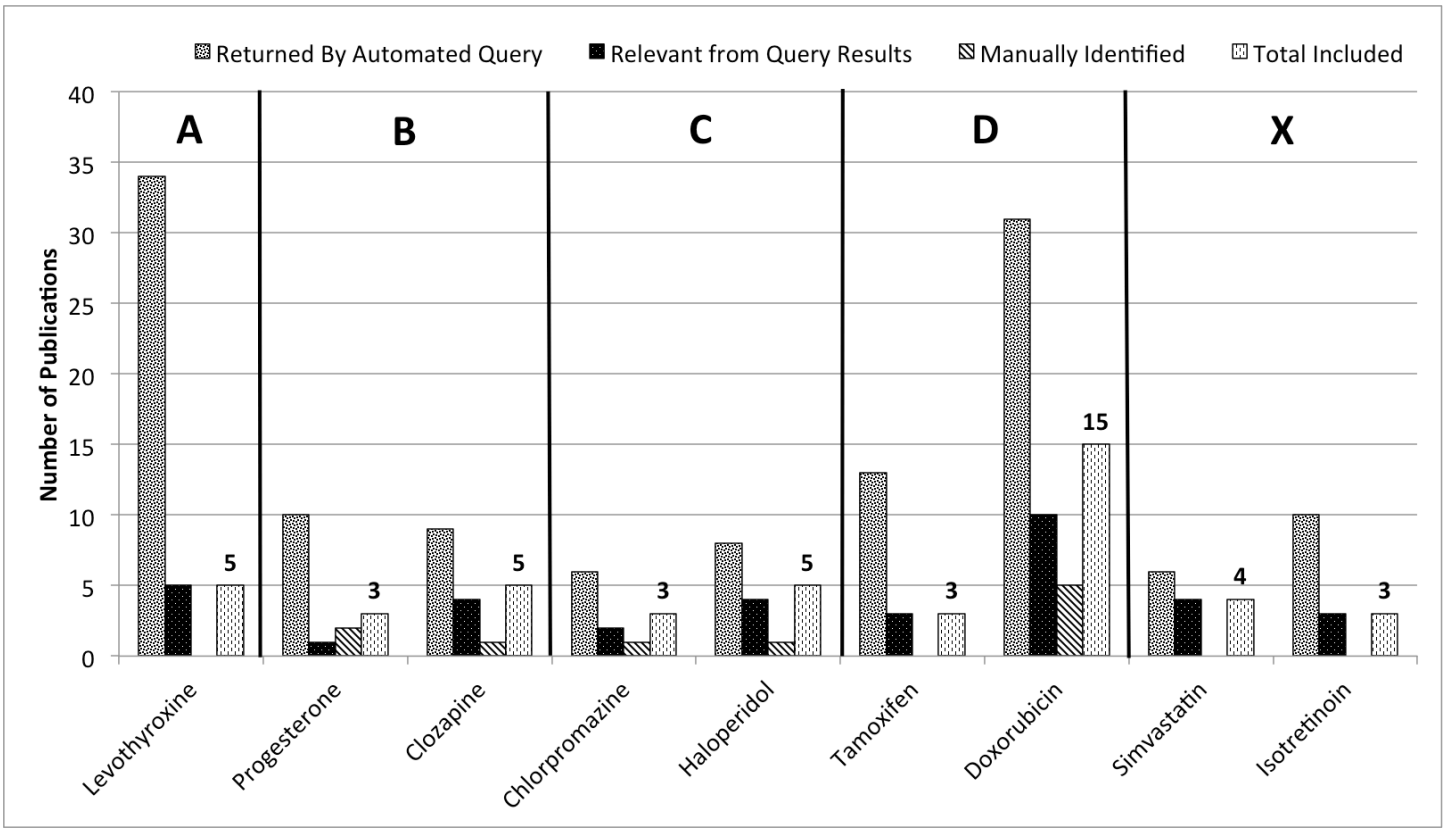

Figure S2. Publications Pertaining to Teratogenicity and Pregnancy Outcomes of DHCR7 Modulators and One Known Teratogen (i.e., Isotretinoin) and One Known Pregnancy-Safe Drug (i.e., Levothyroxine).

We queried PubMed using automated queries. The general form of the query we used was: [drug_name] AND "pregnancy outcome" NOT "rat" NOT "mouse" NOT "cell" NOT "tissue" where drug_name was equal to each of the investigated drugs namely, clozapine, chlorpromazine, haloperidol, simvastatin, tamoxifen, doxorubicin, Isotretinoin. The initial query for levothyroxine returned 132 publications, many related to thyroxine and not levothyroxine specifically. Therefore, we added quotes around levothyroxine to only retrieve publications pertaining to levothyroxine. Progesterone initially returned 752 publications and many of these were off-topic relating to progesterone's role as an essential hormone in pregnancy. Therefore we refined the query for progesterone only to: Progesterone AND "teratogen". This returned 10 publications, with 1 being relevant after manual review. Two additional relevant progesterone publications were identified manually and included in our analyses. We manually added additional relevant publications retrieved from other locations, such as Google scholar, to increase the breadth of our search.

Seven exclusion criteria were applied to remove articles retrieved automatically that were not relevant. These included: 1) all studies not in humans (e.g., baboon), 2) all non-main research articles that simply comment on teratogenicity or policy decisions, 3) all studies not in English, 4) all human tissue studies and cell cultures (i.e., not whole organism studies), 5) interview articles that contain patient perceptions on teratogenicity, 6) articles where the abstract did not contain full details of the study and full-text was not freely accessible, and 7) studies on teratogenicity of drug when used in combination with assisted-reproductive technologies (these were removed to control for biases that use of these technologies can have on pregnancy outcomes.

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