

## **Synthesis of Androgens and Estrogens from cholesterol**

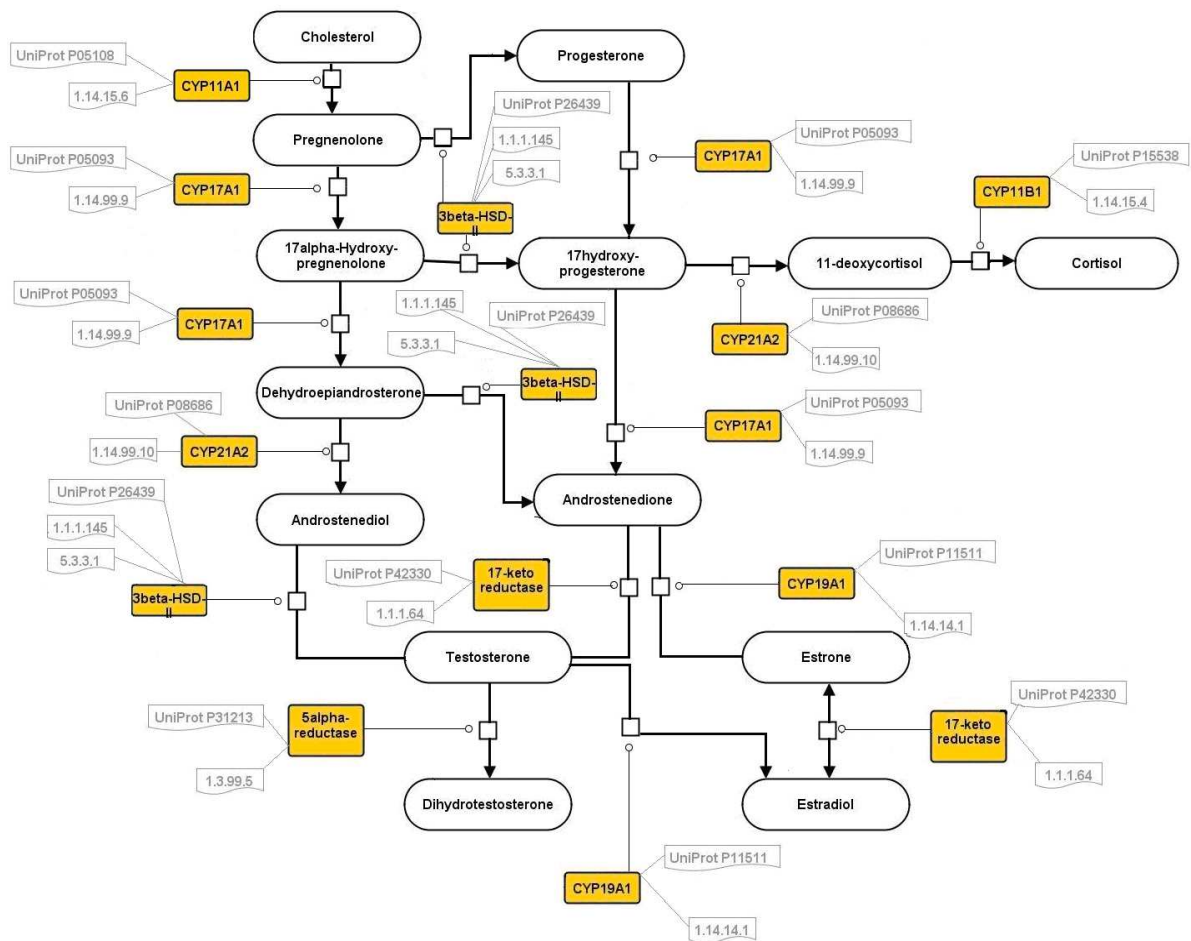
Aruna Sridhar

Division of Pathway Medicine, University of Edinburgh Medical School, Chancellor's Building, Little France Crescent, Edinburgh, EH16 4SB, Scotland, UK.

The synthesis of androgen and estrogen is a key process carried out in the human body. This is initiated from cholesterol. Pregnenolone is the key precursor here, which is synthesized from cholesterol with the help of desmolase which is present in the mitochondria. Each reaction in the pathway was important and it was found that even if one reaction did not take place, it could result in mutations. It was like a chain of events linked to each other. It also analyses diseases are associated with this pathway, which occur as a result of malfunctioning of genes or due to mutations. This paper deals with the pathway modelling of this process with the help of systems biology graphical notation (SBGN). This process enabled us to clearly identify the setbacks and provided a clearer view of the functional aspects. The pathway map was constructed using yEd which is a computational tool. This yED employs a flowchart like symbology to depict the various types of reactions. All the steps in the process have supporting data in the form of research papers or journal articles to back them up. Also excel sheets were used to record information about all the compounds and enzymes in a more organized way. Since this pathway diagram produces a clarified version of the process, it can be used for therapeutic and clinical purposes with staunch verification by research and statistics.

This work was produced toward fulfilment of an MSc in Genomics and Pathway Biology from the Division of Pathway Medicine (<http://www.ed.ac.uk/schools-departments/pathway-medicine>) at the University of Edinburgh. Note, this work has not been peer-reviewed and formed part of a student project/dissertation.

The Genomics and Pathway Biology MSc programme started in 2003 and has had a number of supervisors and contributors. Profs Peter Ghazal and Douglas Roy have supervised the programme throughout. Other supervisors include Dr Stuart Moodie (2004-5), Dr Kevin Robertson (2004-7), Prof Tom Freeman (2006-7), Dr Steven Watterson (2008-10), Dr Alexander Mazein (2009-11) and Dr Kai Kropp (2010-11).



This diagram shows the pathway map constructed using SBN. It shows the production of androgens (testosterone and dihydrotestosterone) and estrogens (estradiol and estrone) from cholesterol. The enzymes catalyzing each reaction are shown adjacent to the reactions with the UniProt ID and E.C. no. The other details regarding the substances involved in the reaction have been recorded in the form of tables in excel sheets. The PMID and KEGG identification data are not listed here as it would look very congested. They are listed in the excel sheet.

Pathway	Reaction equation	EC	Protein Name	Protein ID	Subcellular Location	Organism	Cell type	Reference1 (reaction exists)	Reference2 (enzyme catalyzes this reaction)	(enzyme subcellular)
Lipid metabolism; C21-steroid hormone metabolism	Cholesterol->Pregnenolone	1.14.15.6		P05108	Mitochondrion membrane.	Homo sapiens		PMID: 12573509	Cholesterol desmolase	
Lipid metabolism; steroid biosynthesis	Pregnenolone->17-alpha hydroxy pregnenolone	1.14.99.9		P05093	Membrane	Homo sapiens		PMID: 22138857	Steroid 17-alpha-hydroxylase/17,20 lyase	
Lipid metabolism; steroid biosynthesis	Pregnenolone->Progesterone	1.1.1.145.5.3.3.1 (constitutes 2 domains)		P26439	Endoplasmic reticulum membrane; Single-pass membrane protein. Mitochondrion membrane; Single-pass membrane protein.	Homo sapiens		PMID: 22024430	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 2	
Lipid metabolism; steroid biosynthesis	Progesterone->17-hydroxy progesterone	1.14.99.9		P05093	Membrane	Homo sapiens		PMID: 18068870	Steroid 17-alpha-hydroxylase/17,20 lyase	
Lipid metabolism; steroid biosynthesis	17-alpha hydroxy pregnenolone->17-hydroxy progesterone	1.1.1.145.5.3.3.1 (constitutes 2 domains)		P26439	Endoplasmic reticulum membrane; Single-pass membrane protein. Mitochondrion membrane; Single-pass membrane protein.	Homo sapiens		PMID: 22024430	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 2	
Steroidogenesis	17-hydroxy progesterone->11-deoxycortisol	1.14.99.10		P08686	Endoplasmic reticulum membrane; Peripheral membrane protein. Microsome membrane; Peripheral membrane protein.	Homo sapiens		PMID: 22001566	Steroid 21-hydroxylase	
Lipid metabolism; Steroid metabolism; Steroidogenesis	11-deoxycortisol->Cortisol	1.14.15.4		P15538	Mitochondrion membrane.	Homo sapiens		PMID: 15026188	Steroid 11-beta-hydroxylase	
Lipid metabolism; steroid biosynthesis	17-alpha hydroxy pregnenolone->Dehydroepiandrosterone	1.14.99.9		P05083	Membrane	Homo sapiens		PMID: 18068870	Steroid 17-alpha-hydroxylase/17,20 lyase	
Lipid metabolism; steroid biosynthesis	Dehydroepiandrosterone->Androstenediol	1.1.1.64		P42330	Cytoplasm	Homo sapiens		PMID: 20659685	Aldo-keto reductase family 1 member C3	
Lipid metabolism; steroid biosynthesis	Androstenediol->Testosterone	1.1.1.145.5.3.3.1 (constitutes 2 domains)		P26439	Endoplasmic reticulum membrane; Single-pass membrane protein. Mitochondrion membrane; Single-pass membrane protein.	Homo sapiens		PMID: 18067894	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 2	
Differentiation; Sexual differentiation	Testosterone->Dihydrotestosterone	1.3.99.5		P31213	Microsome membrane; Multi-pass membrane protein. Endoplasmic reticulum membrane; Multi-pass membrane protein	Homo sapiens		PMID: 18067894	3-oxo-5-alpha-steroid 4-dehydrogenase 2	
estrogen biosynthetic process; xenobiotic metabolic process	Testosterone->Estradiol	1.1.1.64		P42330	Cytoplasm	Homo sapiens		PMID: 10731101	Cytochrome P450 19A1	
Lipid metabolism; steroid biosynthesis	Dehydroepiandrosterone->Androstenedione	1.1.1.145.5.3.3.1 (constitutes 2 domains)		P26439	Endoplasmic reticulum membrane; Single-pass membrane protein. Mitochondrion membrane; Single-pass membrane protein.	Homo sapiens		PMID: 11339818	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 2	
Lipid metabolism; steroid biosynthesis	17-hydroxyprogesterone->Androstenedione	1.14.99.9		P05093	Membrane	Homo sapiens		PMID: 22138857	Steroid 17-alpha-hydroxylase/17,20 lyase	
prostaglandin metabolic process	Androstenedione->Testosterone	1.1.1.64		P42330	Cytoplasm	Homo sapiens		PMID: 21185375	Aldo-keto reductase family 1 member C3	
estrogen biosynthetic process; xenobiotic metabolic process	Androstenedione->Estrone	1.14.14.1		P11511	Membrane; Peripheral membrane protein.	Homo sapiens		PMID: 15784278	Cytochrome P450 19A1	
prostaglandin metabolic process	Estrone->Estradiol	1.1.1.64		P42330	Cytoplasm	Homo sapiens		PMID: 15784278	Aldo-keto reductase family 1 member C3	

complex name	Protein Name	Type	UniProt ID	Synonyms	Comment
	Cholesterol desmolase		P05108		
	Steroid 17-alpha-hydroxylase/17,20 lyase		P05093		
	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2		P26439		
	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2		P26439		
	Steroid 21-hydroxylase		P08686		
	Steroid 11-beta-hydroxylase		P15538		
	Steroid 17-alpha-hydroxylase/17,20 lyase		P05093		
	Aldo-keto reductase family 1 member C3		P42330		
	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2		P26439		
	3-oxo-5-alpha-steroid 4-dehydrogenase 2		P31213		
	Cytochrome P450 19A1		P42330		
	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2		P26439		
	Steroid 17-alpha-hydroxylase/17,20 lyase		P05093		
	Aldo-keto reductase family 1 member C3		P42330		
	Cytochrome P450 19A1		P11511		
	Aldo-keto reductase family 1 member C3		P42330		

Compound Name	KEGG CID	ChEBI	Comments
Cholesterol		17002	
Pregnenolone		16581	
Progesterone		17026	
17-alpha hydroxy pregnenolone		16581	Showed up the same results as for pregnenolone
17-hydroxy progesterone		17026	
11-deoxycortisol		28324	
Cortisol		23396	
Dehydroepiandrosterone		28689	
Androstenediol			Did not show up any results in ChEBI
Testosterone		17347	
Dihydrotestosterone		GO:0035410	
Estradiol		GO:0047882	
Androstenedione		GO:0035941	
Estrone		17263	