PROFESSOR LOUISE WARNICH

Biography

Louise Warnich joined the Department of Genetics as a junior lecturer in 1992, and has been appointed as a professor since 2003. Before joining the Department of Genetics, she was employed as a medical scientist in the Division of Human Genetics in the Faculty of Health Sciences, Tygerberg campus. She obtained a PhD in Human Genetics from Stellenbosch University in 1993 and also holds BSc, BSc Hons and MSc degrees (all *cum laude*) from this university. She has been the Chair of the Department of Genetics from 2004 - 2008, and the Chair of the Southern African Human Genetics Society from 2007 – 2009. Since September 2011 she has also been appointed in a 50% part time position as Vice Dean of the Faculty of AgriSciences. She is an associate editor for *Current Pharmacogenomics and Personalized Medicine* and a review editor for *Frontiers in Pharmacogenetics.*

Research areas

Pharmacogenetic applications in South African populations

Both environmental and genetic factors can influence an individual's response to medication. Much of the variation in drug response between individuals can, however, be ascribed to the patient's genetic variation in genes encoding drug receptors, metabolising enzymes and transporters. Pharmacogenetics, the study of variability in drug response due to heredity, can thus revolutionise drug therapy by facilitating both choice and dosage of drug. Genetic variation and functional defects in relevant genes can, however, differ considerably between different population groups. It is thus imperative that genetic variations in pharmacogenetically important genes are determined for different population groups and that the influence of these variations on clinical drug response be documented. Currently very little information is available for populations from Africa, especially Southern Africa. For future application of pharmacogenetics in health care in South Africa, we are now performing population based studies to determine the prevalence and frequency of genetic variants in important genes in the unique South African populations. We are also already evaluating the influence of some of the variants in patient groups with the same empirical diagnosis, but who differ in their metabolism of and sensitivity to drugs.

Currently we are focusing on two fields of application:

(i) Schizophrenia

Schizophrenia is a chronic mental illness that requires the use of medication to control the symptoms. Poor treatment response and side-effects to treatment of schizophrenia pose a major challenge. To aid in the understanding of the complex mechanisms of drug response, we aim to determine the underlying genetic variation that influences the treatment of schizophrenia. To this end the genetic profiles of poor and good treatment responders from schizophrenia patients from the Xhosa and Mixed Ancestry (Coloured) populations are analysed. By obtaining a better understanding of the mechanisms involved in the treatment of schizophrenia,

it is hoped that we may also gain insight into the genetic factors that contribute to schizophrenia susceptibility.

(ii) HIV/AIDS

The use of a potent antiretroviral drug regimen (cART) in the treatment of HIV infection has resulted in significant reductions in mortality and morbidity. However, there is considerable inter-individual variability in patient outcomes in terms of drug disposition, drug efficacy and adverse events. The basis of these differences in medication response is multifactorial, but host genetics is believed to play a significant part. In this study levels of Efavirenz are measured in HIV-positive patients who are treated with this antiretroviral drug. Drug levels are correlated with treatment outcome and adverse drug effects, and the presence of specific pharmacogenetically important novel and known gene variants in patients. The results may provide a better assessment of how well the patients are responding to drug therapy, their level of adherence, and the impact of any host genetic factors on their viral load. These results will be interpreted cautiously, but may impact upon future treatment decisions.

In silico and functional analyses of promoter regulatory targets in the heme biosynthetic pathway

Elucidation of gene regulatory complexity holds much promise towards aiding therapeutic interventions in medical research. Accurate dissection of promoter architecture using predictive bioinformatic tools, integrated with functional promoter analyses, might serve as a powerful method to gain a holistic view of combinatorial interactions, necessary to advance our understanding of gene regulation. To demonstrate proof-of-concept, we combine comprehensive *in silico* and functional promoter analysis to characterize specific clusters of *cis*-motifs (regulatory modules) that reside within the promoters of the heme biosynthetic pathway genes. *In silico* promoter models are designed and used to allow for prediction of transcription factors and "master"-regulators governing transcriptional control in response to simulated diseased states and therapeutic compounds. Functional retention of highly conserved promoter elements are evaluated in mammalian cell assays, in native (wild-type) and modified (synthetic reconstruction) promoter context. We suggest that this integrative strategy could serve as a more refined approach (experimental design) for prediction, study and understanding of transcriptional regulation associated with a specific biological process with many potential applications in medical research.

Current students

Marika Bosman (PhD)

In silico and functional analyses of regulatory elements involved in heme biosynthesis

Co-supervisor: Dr M Venter

UNIVERSITEIT STELLENBOSCH UNIVERSITY

DEPARTMENT OF GENETICS

HUMAN GENETICS

Britt Drögemöller (PhD)

Investigation of genetic variation contributing to antipsychotic treatment response in a South African first episode schizophrenia cohort

Co-supervisors: Profs R Emsley and D Niehaus

Faatiemah Higgins (MSc)

Molecular Genetic Analyses of Candidate Pharmacogenes Related to Antipsychotic Treatment Outcome in a First Episode Schizophrenia Cohort

Co-supervisor: Prof D Niehaus

Enid Nieuwoudt (MSc)

Effect of genetic variants in *NR112* and *NR113*, encoding nuclear receptors PXR and CAR, on efavirenz levels and treatment outcome in South African HIV-infected females

Co-supervisor: Dr O Ikediobi

Gustav Victor (MSc)

Pharmacogenetic analysis of HIV positive South African women undergoing efavirenz treatment

Co-supervisor for

Sunita Potgieter (PhD)

Rene Veikondis (MSc)

Selected publications

- Ozdemir V, Fisher E, Dove ES, Burton H, Wright GE, Masellis M, Warnich L (2012) End of the Beginning and Public Health Pharmacogenomics: Knowledge in 'Mode 2' and P5 Medicine. *Curr Pharmacogenomics Person Med* **10**(1):1-6. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329442/pdf/nihms2043.pdf
- van Tuyll van Serooskerken AM, Drögemöller BI, te Velde K, Bladergroen RS, Steijlen PM, Poblete-P, van Geel M, van Heerden CJ, Warnich L, Frank J (2012) Extended haplotype studies in South African and Dutch variegate porphyria families carrying the recurrent p.R59W mutation confirm a common ancestry. *Br J Dermatol* **166**:261-265. doi: 10.1111/j.1365-2133.2011.10606.x
- Drögemöller BI, Wright GEB, Niehaus DJH, Emsley RA, Warnich L (2011) Whole genome resequencing in pharmacogenomics: moving away from past disparities to globally representative applications. *Pharmacogenomics* **12**(12): 1717-1728.

- Wright GEB, Niehaus DJH, Koen L, Drögemöller BI, Warnich L (2011) Psychiatric genetics in South Africa: cutting a rough diamond. *Afr J Psychiatry* **14**:355-366. http://www.ajop.co.za/Journals/November2011/Psychiatricgenetics.pdf
- Warnich L, Drögemöller BI, Pepper MS, Dandara C, Wright GEB (2011) Pharmacogenomic research in South Africa: Lessons learned and future opportunities in the rainbow nation. (Expert review article). *Curr Pharmacogenomics Person Med* **9**(3):191-207. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228231/pdf/CPPM-9-191.pdf
- Kamal SM, Warnich L, Ferguson, LR, Srivastava S, Ray S, Avard S, Joly Y, Le Huynh M, Page M, Huzair F, Dove E, Gurwitz D, Ozdemir V (2011). Tenth Anniversary of the Human Genome Sequence and 21st Century Postgenomics Global Health -- A Close Up on Africa and Women's Health. (Foresight Report, Editorial). *Curr Pharmacogenomics Person Med* **9**(3):148-155. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3264658/pdf/nihms1945.pdf
- Ikediobi O, Aouizerat B, Xiao Y, Gandhi M, Gebhardt S, Warnich L (2011) Analysis of pharmacogenetic traits in two distinct South African populations. *Human Genomics* **5**(4):265-282. http://henrystewart.metapress.com/media/e39xlqttrl5qwku6ekdw/contributions/g/l/6/w/gl6w180j17621g17.pdf
- Drögemöller BI, Wright GEB, Niehaus DJH, Koen L, Malan S, Da Silva DM, Hillermann–Rebello R, La Grange AM, Venter M, Warnich L (2010) Characterization of the genetic profile of *CYP2C19* in two South African populations. *Pharmacogenomics* **11**(8):1095-1103.
- Wright GE, Niehaus DJ, Drögemöller BI, Koen L, Gaedigk A, Warnich L (2010) Elucidation of *CYP2D6* genetic diversity in a unique African population: implications for the future application of pharmacogenetics in the Xhosa population. *Ann Hum Genet* **74**(4):340-50.
- Venter M, Warnich L (2009) In silico promoters: modelling of cis-regulatory context facilitates target prediction. *J Cell Mol Med* 13: 270-278.
- Parathyras J, Gebhardt S, Hillermann-Rebello R, Grobbelaar N, Venter M, Warnich L (2009) A pharmacogenetic study of CD4 recovery in response to HIV antiretroviral therapy in two South African population groups. *J Human Genetics* 54: 261-265.
- Du Plessis N, Kimberg M, Zaahl MG, Sadie A, Venter M, van der Merwe L, Louw A, Warnich L (2009) Functional analysis of the 5' regulatory region of the 5-aminolevulinate synthase (*ALAS1*) gene in response to estrogen. *Mol Cell Biol* 55 (2): 20-30.
- Niehaus DJH, du Plessis SA, Koen L, Lategan BH, Steyn J, Oosthuizen PP, Warnich L, Emsley RA. (2008) Predictors of abnormal involuntary movement in an African schizophrenia population. *J Neuropsychiatry Clin Neurosci* 20(3):317-326.
- Tomlinson M, Swartz L, Warnich L (2008) Genetic research, behavioural science, and child and adolescent mental health in South Africa: an important new agenda. *Journal of Child and Adolescent Mental Health* 2 (2): 73 – 81.
- Hitzeroth A, Niehaus DJ, Koen L, Botes WC, Deleuze JF, Warnich L (2007) Association between the *MnSOD* Ala-9Val polymorphism and development of schizophrenia and abnormal involuntary movements in the Xhosa population. *Prog Neuropsychopharmacol Biol Psychiatry* 31(3):664-672.