

# European-South Africa collaboration on the genetic basis of gonadotropin-releasing hormone deficiency in failure to progress through puberty and infertility

Bob Millar, Mammal Research Institute, University of Pretoria, South Africa  
Arieh Katz, University of Cape Town, South Africa  
Nelly Pitteloud, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland  
Andrew Dwyer,

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Reproductive capacity, the key element for species survival, depends on a complex organ network involving the hypothalamus, pituitary, gonads, and internal and external genitalia. This system is centrally controlled by incompletely understood neuroendocrine mechanisms integrated at the hypothalamic level, whose elucidation is the research focus. Vertebrate reproduction depends entirely upon the neurosecretion of the decapeptide gonadotropin-releasing hormone (GnRH) from less than 4 000 GnRH neurons in the preoptic area of the hypothalamus. The coordinated pulsatile release of GnRH from this neural network directs the synthesis and secretion of the gonadotropins, luteinizing hormone and follicle-stimulating hormone, which, in turn, stimulate steroidogenesis and gametogenesis in the gonads. Although all mammalian species depend upon this common pathway to initiate reproduction, little is known about the molecular mechanisms underlying the ontogeny and regulation of GnRH neurons. The human disease model of congenital isolated GnRH deficiency, characterised by the abnormal development and/or function of GnRH neurons, and resulting in the failure of sexual maturation and infertility, has been a powerful source of novel information. This syndrome has a rich genetic and phenotypic heterogeneity, and represents a unique investigative opportunity with which to understand the biology of genes controlling human reproduction, and for the purposes of developing novel diagnostic tools and targeted therapies for infertility and reproductive medicine.

In 2012, a network of clinicians, geneticists, bioinformaticians and basic scientists formed a consortium to address pressing questions in the field, at the European Cooperation in Science and Technology (COST) Action BM1105 meeting, with a focus on "GnRH deficiency: elucidation of the neuroendocrine control of human reproduction" ([www.gnrhnetwork.eu](http://www.gnrhnetwork.eu)).

This consortium includes >150 participants spanning 28 countries, and comprises five working groups (WG):

- WG1 (Clinical) will create an international patient registry for congenital hypogonadotropic hypogonadism (CHH) and publish consensus guidelines on the diagnosis and treatment of CHH.
- WG2 (Genetics and bioinformatics) will provide support for using next-generation sequencing technologies and bioinformatic tools to elucidate the genetic basis of CHH.
- WG3 (Basic science) will identify plausible candidate genes and test them in relevant model systems.
- WG4 (Training and education) will recruit and train the next generation of investigators.
- WG5 (Patient advocacy) will engage patient groups and ensure that patient perspectives are included.

This network has spawned novel collaborations, resulting in 15 publications, 18 short-term scientific exchanges between laboratories, two highly successful training schools and has funded a grant involving South Africa and Switzerland. More specifically, Bob Millar from the University of Pretoria and University of Cape Town is a member of the steering committee, and is active in the WG3 (Basic science), as well as being an instructor for the training school.

The joint Swiss-South Africa grant, which includes Arieh Katz as an applicant, is examining the molecular basis of reproductive disorders in South African patients. Within the context of this international network, this project aims to include South African patients in the registry, and identify new genes that underlie GnRH deficiency and the control of puberty. Moreover, it aims to chart the full reproductive and non-reproductive phenotypes of these patients, and to explore the biological role of novel genes.

This project is ongoing and welcomes the collaboration and participation of South African clinicians who see and care for these patients. At present, Tanja Kemp, University of Pretoria, and Ian Ross, University of Cape Town, are the clinicians involved, while Ross Anderson and Claire Newton at the University of Pretoria, are undertaking the characterisation of the identified mutations. However, it is desirable that all centres should participate in this exciting endeavour. This effort brings together leaders

in the field of reproduction across disciplines, and is a unique opportunity to partner with practising clinicians to advance our understanding of puberty and reproduction in humans. It is hoped that novel genes and causes of GnRH deficiency will be identified, and the mechanisms in the laboratory established, leading to the publication of cutting-edge articles by participants who have made a contribution as authors.