ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Molecular Medicine Postgraduate School Departments of Bioinformatics and Urology, Erasmus MC
Project Title:	The effect of Reference Genome on cancer driver mutations and pathogenic variant detection in genetic syndromes (monogenic disorders)
Abstract:	Our reseach has focused on the developing applications to improve the detection of driver mutations in cancer (iFUSE; www.ifeuse.erasmusmc.nl) and monogenic disorders using a common set of reference genomes (Huvariome; www.huvariome.erasmusmc.nl). We have developed CGtag (http://galaxy.ctmm-trait.nl/u/saskia-hiltemann/p/cgtag) a scalable Galaxy CLOUD toolkit for whole genome sequence (WGS) analysis. The potential pathogenicity of genetic variants identified in disease based resequencing studies is often overlooked where variants have previously been reported in dbSNP, the 1000 genomes project or the NHLBI exome sequencing project (ESP). It is estimate that collectively, these databases capture ~52% of mutations (dbSNP 50.4%; 1000 genomes 4.8%; ESP 10.2%) reported as disease-causing within phenotype based locus specific databases (LSDBs). Key challenges for diagnostic NGS are missing heritability and the accurate detection of loss of function variants. To investigate these challenges we aim to introduce methods that combine patients' disease symptoms and sequencing data with prior domain knowledge to identify the causative genes for both monogenic disorders and for driver mutations in cancer. Additionally we will address the impact of the reference genome using our database of > 1000 whole genome sequences which have variant regions determined by de novo assembly methods. The outcome of these studies will be used to benchmark and implement improvements to Huvariome and pathogenic variant selection in both genetic and cancer studies.
Requirements of candidate:	Master degree: Yes Background: We are looking for a proactive, enthusiastic fellow with a background in bioinformatics (Sequence Analysis) and programming skills (preferably python and one other language), being fluent in speaking and writing English. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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	Murray DJ, Phipps JM, Sweeney E, Tomkins SE, Wilson LC, Bennett S, Cornall RJ, Broxholme J, Kanapin A; 500 Whole-Genome Sequences (WGS500) Consortium, Johnson D, Wall SA, van der Spek PJ, Mathijssen IM, Maxson RE, Twigg SR, Wilkie AO.. Nat Genet. 2013 Mar;45(3):304-7. ***NetWeAvers: an R package for integrative biological network analysis with mass spectrometry data.*** McClellan E, Moerland P van der Spek P and **Stubbs A**. Bioinformatics, 2013. ***iFUSE: integrated FUSion gene Explorer.*** Hiltemann S, McClellan E, van Nijnatten J, Horsman S, Palli I, Alves IT, Hartjes T, Trapman J, van der Spek P, Jenster G and **Stubbs A**. Bioinformatics. 2013; 29(13): 1700-1. ***Gene fusions by chromothripsis of chromosome 5q in the VCaP prostate.*** Alves IT, Hiltemann S, Hartjes T, van der Spek P, **Stubbs A**, Trapman J and Jenster G. Hum.Genet. 2013; 132(6):709-13 ***Novel RNAs derived from small non-coding RNA and their implication in cancer*** Martens-Uzunova ES, Olvedy M, Jenster G. Beyond microRNA -. Cancer Lett. 2013 Jan 29 ***miQ - a novel microRNA based diagnostic and prognostic tool for prostate cancer.*** Larne O, Martens-Uzunova E, Hagman Z, Edsjö A, Lippolis G, Vredenbregt-van den Berg MS, Bjartell A, Jenster G, Ceder Y. Int J Cancer. 2013 Jun 15;132(12):2867-75 ***Huvariome: A web server resource of whole genome next-generation sequencing allelic frequencies to aid in pathological candidate gene selection.*** **Stubbs A**, McClellan E, Horsman S, Palli I, Nouwens S, Koning AHJ, Hoogland F, Reumers J, Heijsman D, Swagemakers S, Kremer A, Meijerink J, Lambrechts D and van der Spek PJ. J Clin Bioinformatics. 2012; 2(1):19. ***Diagnostic and prognostic signatures from the small non-coding RNA transcriptome in prostate cancer.*** Martens-Uzunova ES, Jalava SE, Dits NF, van Leenders GJ, Møller S, Trapman J, Bangma CH, Litman T, Visakorpi T, Jenster G. Oncogene. 2012 Feb 23;31(8):978-91. ***Absence of common somatic alterations in genes on 1p and 19q***

***in oligodendrogliomas*.** Bralten LB, Nouwens S, Kockx C, Erdem L, Hoogenraad CC, Kros JM, Moorhouse MJ, Sillevis Smitt PA, van der Spek P, van Ijcken W, **Stubbs A**, French PJ. PLoS One. 2011;6(7):e22000

Integrated transcript and genome analyses reveal NKX2-1 and MEF2C as potential oncogenes in T cell acute lymphoblastic leukemia. Homminga I, Pieters R, Langerak AW, de Rooi JJ, **Stubbs A**, Verstegen M, Vuerhard M, Buijs-Gladdines J, Kooi C, Klous P, van Vlierberghe P, Ferrando AA, Cayuela JM, Verhaaf B, Beverloo HB, Horstmann M, de Haas V, Wiekmeijer AS, Pike-Overzet K, Staal FJ, de Laat W, Soulier J, Sigaux F, Meijerink JP. Cancer Cell. 2011 Apr 12;19(4):484-97.

Bypass mechanisms of the androgen receptor pathway in therapy-resistant prostate cancer cell models. Marques RB, Dits NF, Erkens-Schulze S, van Weerden WM, Jenster G. PLoS One. 2010 Oct 19;5(10):e13500.

Systematic structure-function analysis of androgen receptor Leu701 mutants explains the properties of the prostate cancer mutant L701H. van de Wijngaart DJ, Molier M, Lusher SJ, Hersmus R, Jenster G, Trapman J, Dubbink HJ. J Biol Chem. 2010 Feb 12;285(7):5097-105.

***Intrinsic gene expression profiles of gliomas are a better predictor of survival than histology*.** Gravendeel LA, Kouwenhoven MC, Gevaert O, de Rooi JJ, **Stubbs AP**, Duijm JE, Daemen A, Bleeker FE, Bralten LB, Kloosterhof NK, De Moor B, Eilers PH, van der Spek PJ, Kros JM, Sillevis Smitt PA, van den Bent MJ, French PJ. Cancer Res. 2009 Dec 1;69(23):9065-72.

The recurrent SET-NUP214 fusion as a new HOXA activation mechanism in pediatric T-cell acute lymphoblastic leukemia. Van Vlierberghe P, van Grotel M, Tchinda J, Lee C, Beverloo HB, van der Spek PJ, **Stubbs A**, Cools J, Nagata K, Fornerod M, Buijs-Gladdines J, Horstmann M, van Wering ER, Soulier J, Pieters R, Meijerink JP. Blood. (2008) 1;111(9):4668-80.

Anni 2.0: a multipurpose text-mining tool for the life sciences. Jelier R, Schuemie MJ, Veldhoven A, Dorssers LC, Jenster G, Kors JA Genome Biol. 2008;9(6):R96.

	Evolution of the androgen receptor pathway during progression of prostate cancer. Hendriksen PJ, Dits NF, Kokame K, Veldhoven A, van Weerden WM, Bangma CH, Trapman J, Jenster G. Cancer Res. 66(10):5012-5020 (2006) ***Mining the human genome using virtual reality.*** Stolk B, Abdolerahman F, Koning A, Wielinga P, Neefs J-M, **Stubbs AP**, de Bondt A, Leemans P and van der Spek P. Fourth Eurographics workshop on parallel graphics and visualization (2002). ***Steroid receptor induction of gene transcription: a two-step model.*** G. Jenster, T.E. Spencer, M.M. Burcin, S.Y. Tsai, M-J. Tsai and B.W. O'Malley.. Proc. Natl. Acad. Sci. USA 94: 7879-7884 (1997). ***Steroid receptor coactivator one is a histone acetyltransferase.*** T.E. Spencer, G. Jenster, M.M. Burcin, C.D. Allis, J. Zhou, S.Y., C.A. Mizzen, N.J. McKenna, S.A. Onate, S.Y. Tsai, M-J. Tsai and B.W. O'Malley. Nature 389: 194-198 (1997). First two authors made equal contributions