Joris Veltman, PhD
Director of the Institute of Genetic Medicine & Jacobson chair of Personalized Medicine, Newcastle University, Newcastle, United Kingdom
Professor of Translational Genomics, Department of Human Genetics, Radboud University, Nijmegen, The Netherlands

My research has contributed significantly to unravelling the genetic causes of rare disease, to our understanding of mutational mechanisms underlying genetic disorders and to the implementation of genomics approaches in medicine. Early on in my career, my research using genomic microarrays enhanced our understanding of structural genomic variation and its role in intellectual disability and rare syndromes. Following this success we were the first in the world to implement genomic microarrays in diagnostics in Nijmegen, The Netherlands. More recently, our research using both exome and genome sequencing revealed the genetic cause for more than 50 clinical syndromes and provided strong experimental evidence for a *de novo* paradigm in severe early-onset disorders. We could show that *de novo* germline mutations, detected by comparing exomes or genomes of patients to that of their unaffected parents, are the major cause of severe intellectual disability. Following this success we implemented exome sequencing in diagnostics in 2011. Last year, diagnostic exome sequencing was performed in more than 5000 patients in Nijmegen. In addition, we have pioneered the use of genome sequencing in medical genetics. Application of this ultimate genetic test in our research allowed us to diagnose the majority of patients with severe intellectual disability, data used by Sir John Bell in 2013 to promote the establishment of Genomics England and start the 100,000 genomes.
Since our first publication on the detection of *de novo* mutations in intellectual disability in 2010, I have focused my research on further understanding the frequency, generation, risk factors and role of these *de novo* mutations in genetic disease. This has provided insight into the presence and role of the different types of *de novo* mutations in the genome of patients with intellectual disability, from single point mutations to structural rearrangements. Also, we obtained insight into the paternal origin of *de novo* germline mutations and identified parent-of-origin-specific mutation signatures becoming more pronounced with increased parental age, pointing to different mutational mechanisms in spermatogenesis and oogenesis. Most notably, work by others and us has clearly demonstrated that advanced paternal age increased the number of *de novo* mutations in the offspring and thereby is a risk factor for severe genetic disorders in the offspring. Furthermore, we optimized and applied highly sensitive single molecule Molecular Inversion Probe (smMIP) technology to distinguish germline from somatic *de novo* mutations. This allowed us to demonstrate that an important fraction of *de novo* mutations presumed to be germline in fact occurred either post-zygotically in the offspring or were inherited from a low-level mosaicism in one of the parents. At this moment I am actively studying the role of de novo mutations in severe male infertility for which I was recently awarded a Wellcome Trust investigator award. In 2016, Han Brunner and I were awarded the King Faisal International Prize for Medicine for our work on the introduction of Next Generation Sequencing in clinical medicine, specifically for the diagnosis of rare diseases.

Key publications:
1. Goldmann et al. Germline de novo mutation clusters arise during oocyte aging in genomic regions with high double-strand-break incidence. Nature Genetics 50: 487-492 (2018).
2. Lelieveld et al. Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. Nature Neuroscience 19: 1194-6 (2016).
3. Gilissen et al. Genome sequencing identifies major causes of severe intellectual disability. Nature 511: 344-7 (2014).
4. de Ligt et al. Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability. New England Journal of Medicine 367: 1921-1929 (2012).
5. Vissers et al. A de novo paradigm for mental retardation. Nature Genetics 42: 1109-12 (2010).