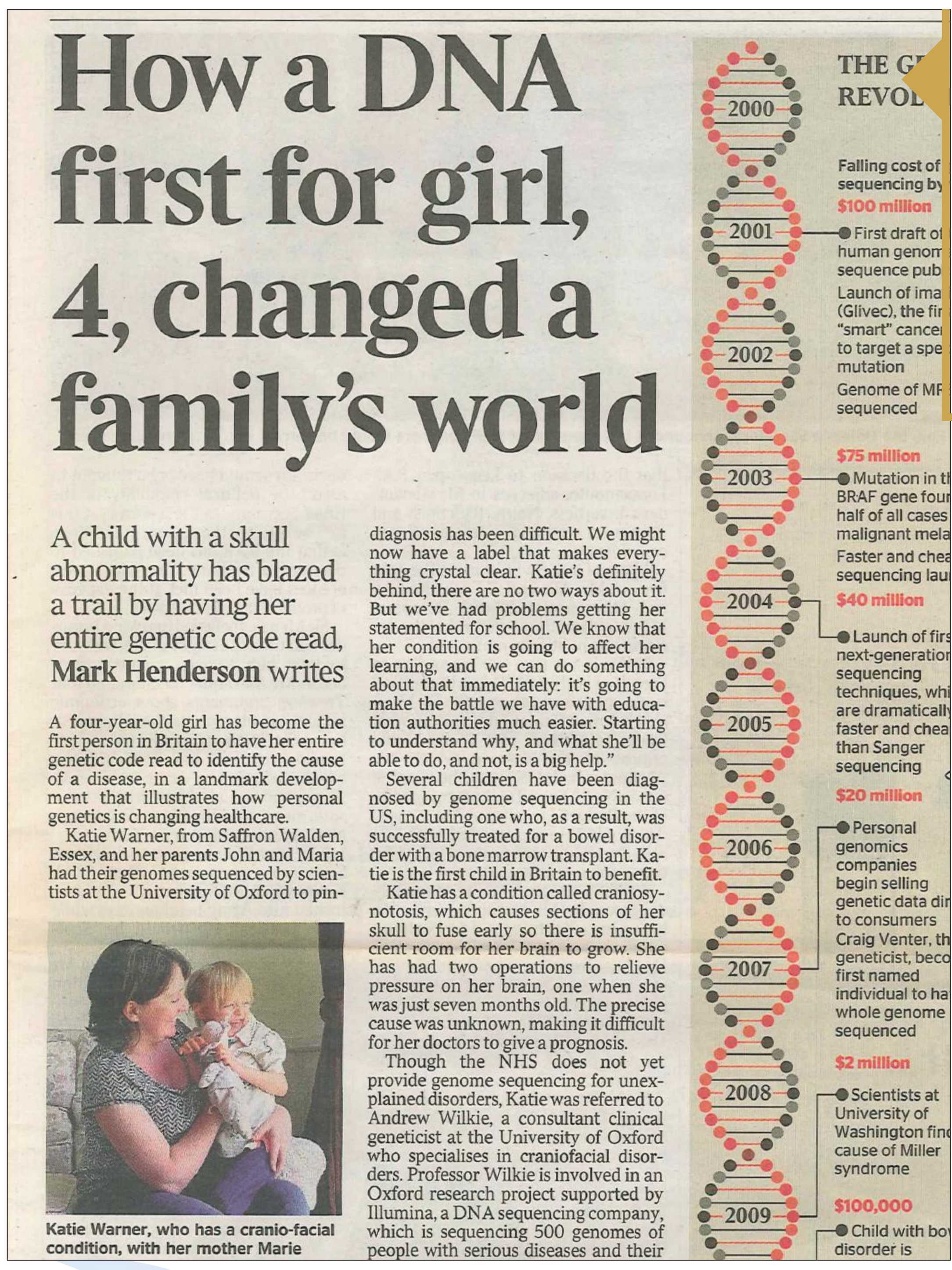
The Wellcome Trust Centre for

Human Genetics

UNIVERSITY OF OXFORD

WGS 500: Practical application of human genome sequencing in the clinic



How a DNA first for girl, 4, changed a family's world

A child with a skull abnormality has blazed a trail by having her entire genetic code read, **Mark Henderson** writes

A four-year-old girl has become the first person in Britain to have her entire genetic code read to identify the cause of a disease, in a landmark development that illustrates how personal genetics is changing healthcare.

Katie Warner, from Saffron Walden, Essex, and her parents John and Maria had their genomes sequenced by scientists at the University of Oxford to pin-

diagnosis has been difficult. We might now have a label that makes everything crystal clear. Katie's definitely behind, there are no two ways about it. But we've had problems getting her statemented for school. We know that her condition is going to affect her learning, and we can do something about that immediately: it's going to make the battle we have with education authorities much easier. Starting to understand why, and what she'll be able to do, and not, is a big help."

Several children have been diagnosed by genome sequencing in the US, including one who, as a result, was successfully treated for a bowel disorder with a bone marrow transplant. Katie is the first child in Britain to benefit.

Katie has a condition called craniosynostosis, which causes sections of her skull to fuse early so there is insufficient room for her brain to grow. She has had two operations to relieve pressure on her brain, one when she was just seven months old. The precise cause was unknown, making it difficult for her doctors to give a prognosis.

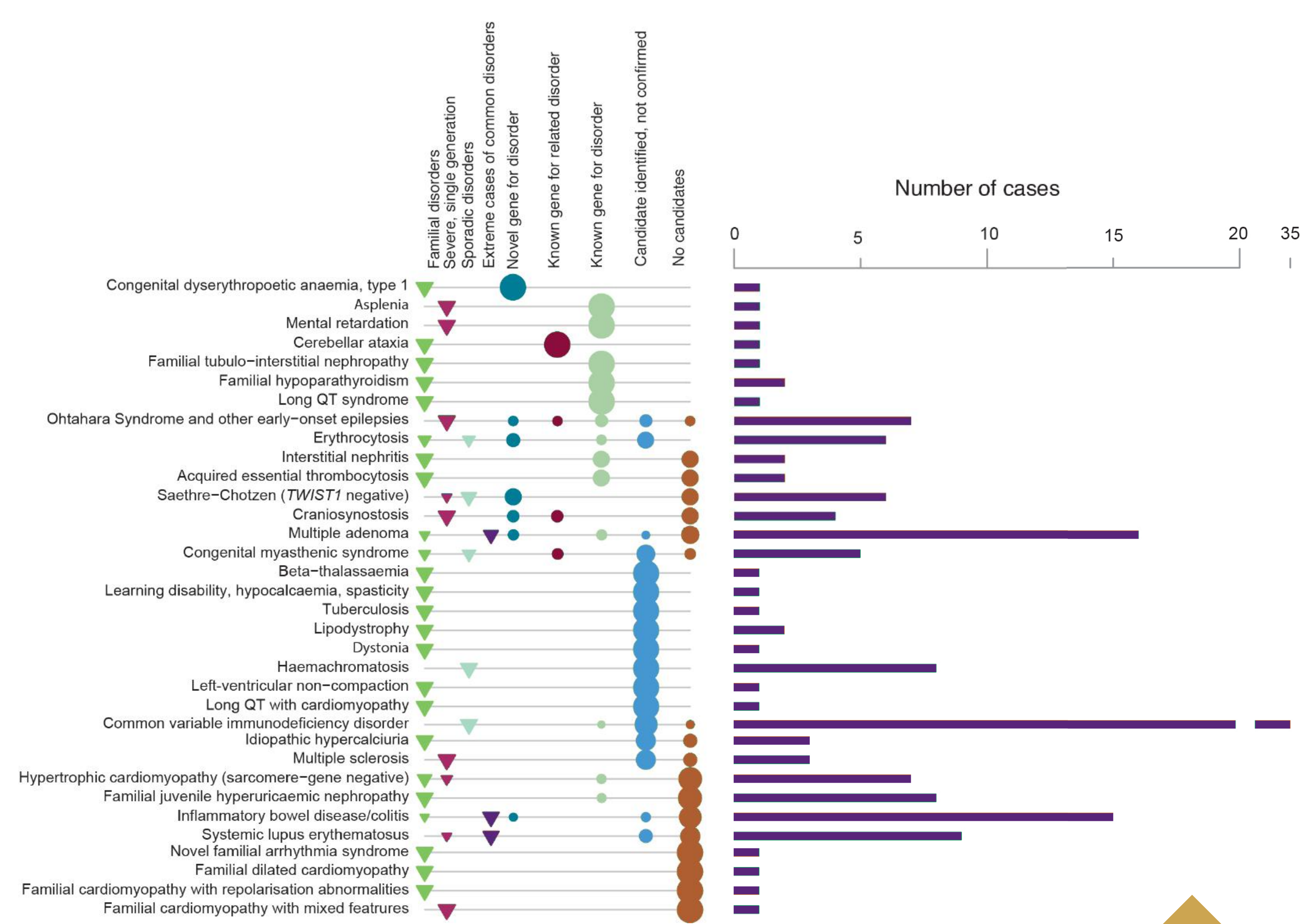
Though the NHS does not yet provide genome sequencing for unexplained disorders, Katie was referred to Andrew Wilkie, a consultant clinical geneticist at the University of Oxford who specialises in craniofacial disorders. Professor Wilkie is involved in an Oxford research project supported by Illumina, a DNA sequencing company, which is sequencing 500 genomes of people with serious diseases and their

Katie Warner, who has a cranio-facial condition, with her mother Marie

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009

$100 million
$75 million
$40 million
$20 million
$2 million
$100,000

News story reporting the discovery of a candidate gene variant in the family of a girl with craniosynostosis



Overview of projects and results

WHAT WAS KNOWN

- Many clinical disorders arise from inherited genetic variation
- Whole-genome sequencing (WGS) can characterize all types of genetic variation in all parts of the genome
- Where pathogenic variants are identified, there can be implications for diagnosis, genetic counselling and treatment
- Challenges to clinical use of WGS include cost, speed of delivery, sensitivity, specificity and heterogeneity in variant detection, ambiguities and errors in variant annotation, a substantial informatics burden and the difficulties posed by incidental findings
- The reach of WGS into the clinic has therefore been limited

WHAT WE DID

- Sequenced 500 patient genomes from diverse genetic disorders referred by a range of medical specialists to assess whether genome sequencing could be used in mainstream medicine

WHAT THIS ADDS

- Whole-genome sequencing is effective for the molecular diagnosis of severe disorders for which a strong genetic component is suspected but where screening of known associated genes has previously failed to identify candidate variants
- Candidate variants were identified in non-coding as well as coding regions
- In 21% of cases, we identified at least one variant with a high level of evidence of pathogenicity, 12 of which were in novel genes
- Calling variants jointly between children and parents substantially increased the accuracy of *de novo* mutation detection in families
- Multiple annotation approaches are needed to reliably identify candidate variants
- Many people with variants in candidate genes for congenital disorders have no symptoms of that disorder, therefore care needs to be taken on interpreting results
- A gene variant that appears to be associated with a severe and complex condition such as craniosynostosis in one individual may not predict the involvement of the same variant in others with the same condition
- Resources and expertise for genetic and functional validation studies are critical to the assignment of causality

REFERENCES

Factors influencing success of clinical genome sequencing across a broad spectrum of disorders.

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