Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

THE PATERNAL AGE EFFECT: HIS CLOCK IS TICKING

Summary of the impact:

Research from the University of Oxford's Clinical Genetics Laboratory initiated the introduction of an upper age limit of 40 years for sperm donors in the UK and internationally and led to increased public awareness of the effect of paternal age in the transmission of inherited disease. Oxford researchers, led by Professor Andrew Wilkie, were the first to describe the exclusively paternal transmission of *de novo* mutations, in a rare craniofacial disorder called Apert Syndrome; they also showed that the accumulation of such mutations leads to a disproportionate risk of disease transmission with age. By showing that the frequency of mutations increases with paternal age, this research contributed to important changes in clinical practice relating to sperm donation. This has also had a significant cultural impact, as the research and its clinical outcomes have challenged public perceptions of paternal age.

Underpinning research:

Since 1993, the University of Oxford's Clinical Genetics Laboratory, directed by Professor Andrew Wilkie, has been collaborating closely with plastic surgeons at the Oxford Craniofacial Unit to research the genetic basis of rare craniofacial disorders. In 1995 this group discovered that mutations in the *FGFR2* gene were responsible for Apert syndrome: a rare craniofacial disorder[1]. Since previous studies had revealed a positive correlation between parental age and Apert syndrome[2], the group set out to investigate the origin of *FGFR2* mutations.

In a pivotal study of 57 Apert syndrome families published in 1996[3], the researchers revealed that without exception the *FGFR2* mutation was inherited from the father. Furthermore, they found that an increase in paternal age was associated with an increased likelihood of inheriting an *FGFR2* mutation[3]. Further work by the Clinical Genetics Laboratory revealed that while *FGFR2* mutations can be detrimental to an embryo, they are advantageous to the cells that generate sperm[4]. These findings showed that sperm-generating cells with an *FGFR2* mutation could outcompete their non-mutant counterparts in the testes, leading to an increased proportion of sperm carrying the *FGFR2* mutation[4]. This research established the general principle that deleterious mutations can have competitive advantage, and the group went on to show a similar paternal age-effect mechanism for mutations in other genes, responsible for testicular tumors and other craniofacial disorders[5]. The Oxford researchers have argued that these findings will have broad implications for the origins of many inherited genetic diseases[4-5]. They recently showed how spermatogonial selection combines with mutation rates to cause an increased burden of HRas mutations in the sperm of healthy older men[6].

The research has shown, unambiguously, that paternal age is a risk factor for the occurrence of mutations, and has identified a mechanism by which this risk can be amplified with age, causing serious and unexpected disorders in offspring.

References to the research:

1. Wilkie, A. O. *et al.* Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nat. Genet.* **9**, 165–172 (1995) doi:10.1038/ng0295-165. ***Primary paper describing the FGFR2 gene mutation in Apert Syndrome.***

2. Risch, N., Reich, E. W., Wishnick, M. M. & McCarthy, J. G. Spontaneous mutation and

parental age in humans. *Am. J. Hum. Genet.* **41**, 218–248 (1987). ***Inconclusive statistical analysis study of parental age and the incidence of new mutations.***

3. Moloney, D. M. *et al.* Exclusive paternal origin of new mutations in Apert syndrome. *Nat. Genet.* **13**, 48–53 (1996) doi:10.1038/ng0596-48. ***Study showing that an increase in paternal age is associated with an increased likelihood of inheriting an FGFR2 mutation.***

4. Goriely, A., McVean, G. A. T., Röjmyr, M., Ingemarsson, B. & Wilkie, A. O. M. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. *Science* **301**, 643–646 (2003) doi: 10.1126/science.1085710. ***The first paper to describe the accurate measurement of any individual mutation in human sperm.***

5. Goriely, A. *et al.* Activating mutations in FGFR3 and HRAS reveal a shared genetic origin for congenital disorders and testicular tumors. *Nat. Genet.* **41**, 1247–1252 (2009) doi: 10.1038/ng.470. ***Paper outlining the implications for the inheritance of craniosynostosis syndromes and other disease-causing mutations in sperm.***

6. Giannoulatou E, McVean G, Taylor IB, McGowan SJ, Maher GJ, Iqbal Z, Pfeifer SP, Turner I, Burkitt-Wright EMM, Shorto J, Itani A, Turner K, Gregory L, Buck D, Rajpert-De Meyts E, Looijenga LHJ, Kerr B, Wilkie AOM* & Goriely A* (2013). Contributions of intrinsic mutation rate and selfish selection to levels of de novo HRAS mutations in the paternal germline. Proc Natl Acad Sci USA in press. ***Shows how selfish spermatogonial selection combines with mutation rate to cause the increased burden of mutations in the sperm of healthy older men.***

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Details of the impact:

Research carried out by the University of Oxford's Clinical Genetics Laboratory has directly influenced changes in sperm donor guidelines in the UK and abroad. The research has also received significant media attention, contributing to improved social awareness of paternal age effect mutations, as well as public awareness of genetic diagnostic testing.

Changes to Practice Guidelines

Oxford University's 1996 discovery of the paternal age effect on mutations in Apert syndrome was a major contributor to the 1999 decision of the British Andrology Society to introduce an upper age limit of 40 years for sperm donors[7]. The University of Oxford's 1996 paper[3] was one of two studies from the same year that were cited as primary evidence for imposing the age limit to prevent the transmission of somatic mutations (the other describing an association of increase in parental age with cases of dyskinetic cerebral palsy). In a review of sperm donor guidance in 2004[8], the UK Human Fertilisation and Embryology Authority confirmed the British Andrology Society's recommendations for an upper age limit, again citing the group's 1996 paper[3].

This upper age limit for sperm donors was upheld in the British Andrology Society's 2008 guidance[9]. The Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology have since introduced an upper age limit for sperm donors[10].

Public Awareness of Paternal Age Effect

In October 2009, the Clinical Genetics Laboratory's description of selective advantage due to deleterious mutations in the testes[5] received wide coverage in national newspapers. Articles featuring commentary from Professor Wilkie were published in The Times[11], The Telegraph[12], and the Daily Mail Online[13]. These articles and the associated research have increased public consciousness and understanding of the parental age effect. The impact this research has had on

society is illustrated in a recent feature article on late fatherhood, published in the Daily Mail[14]. The article received over 70 comments from readers[14].

Sources to corroborate the impact:

7. British Andrology Society. British Andrology Society guidelines for the screening of semen donors for donor insemination (1999). *Hum. Reprod.* **14**, 1823–1826 (1999) doi: 10.1093/humrep/14.7.1823. ***Guidelines recommending the upper age limit of 40 years for all sperm donors within the UK. Guidelines directly cite the Moloney et al. (1996) paper from Oxford as key evidence to support the upper age limit of 40 years***.

8. Human Fertilisation & Embryology Authority: Seed Review: (SCAG/ELC (06/04) 02 – ANNEX A)(2004, June 17). (Accessed 2013), Available from http://www.hfea.gov.uk/docs/ELC_Annex_A_Audit_June04.pdf. ***The Human Fertilisation and Embryology Authority sperm donor guidance review, confirming recommendations for an upper age limit of 40 years for sperm donors. This audit directly cites Moloney, et al (1996) as key evidence.***

9. Association of Biomedical Andrologists; Association of Clinical Embryologists; British Andrology Society; British Fertility Society; Royal College of Obstetricians and Gynaecologists UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors (2008) *Human Fertility*,**11**:4,201 — 210 (2008) doi: 10.1080/14647270802563816. Also available from *http://www.britishandrology.org.uk/BAS/Policy/New%202008%20Donor%20Guidelines.pdf (Accessed 2013)* ***British Andrology Society guidelines confirming the upper age limit of 40 for all sperm donors within the UK.***

10. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Recommendations for gamete and embryo donation: a committee opinion *Fertil Steril*. Jan;99(1):47-62 (2013). doi: 10.1016/j.fertnstert.2012.09.037. Also available from http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Guidelines_and_Minimum_Standards/2008_Guidelines_for_gamete(1).pdf (Accessed 2013) ***Guidelines from the Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology recommending an upper age limit of 40 for all sperm donors within the US.***

11. Scientists discover link between older dads and genetic diseases - *The Times* (*October 26th* 2009) (Accessed 2013). Available from http://www.thetimes.co.uk/tto/science/genetics/article1844016.ece ***Article reporting findings from Goriely et al (2009) paper featuring commentary from Professor Andrew Wilkie.***

12. Older fathers linked to genetic disease due to testicular tumours – *The Telegraph (October 26th 2009) (Accessed 2013)*. Available from http://www.telegraph.co.uk/health/healthnews/6435802/Older-fathers-linked-to-genetic-disease-due-to-testicular-tumours.html ***Article reporting findings from Goriely et al (2009) paper featuring commentary from Professor Andrew Wilkie.***

13. Why older fathers are more likely to have children with genetic disorders - *Mail Online* (October 26th 2009) (Accessed 2013) Available from http://www.dailymail.co.uk/health/article-1223025/Why-older-fathers-likely-children-genetic-disorders.html ***Article reporting findings from Goriely et al (2009) paper featuring commentary from Professor Andrew Wilkie.***

14. We all know late-life motherhood poses risks for babies. But worrying new research reveals how having an older father can damage a child's health too. - *Mail Online* (February 21st 2013) (Accessed 2013) Available from http://www.dailymail.co.uk/femail/article-2282033/We-know-late-life-motherhood-poses-risks-babies-But-worrying-new-research-reveals-having-older-father-damage-childs-health.html ***Article reviewing the risks of late fatherhood, quoting Professor Wilkie and his work.***