

through day 14 of development has been legalized.

The third material transatlantic difference concerns the relative weight assigned to public consultation on regulatory issues of substance. The UK public consultation process was an extensive outsourced multi-method (e.g., surveys and workshops) effort on a national scale lasting 6 months. The U.S. regulatory approach has thus far been largely limited to a conversation among experts, with relatively brief sessions open to the public (7).

A fourth transatlantic variance revolves around the framing of MRT as a beacon of national scientific prowess. For better or worse, the parliamentary debate has proceeded with an air of national pride. Even those opposed to MRT noted their admiration for the world-class work of the Newcastle group (2, 5). We

“This is not an academic question, because MRT represents but one of a growing complement of novel reproductive technologies, many of which will require expert regulatory adjudication.”

believe that this national sense of pride may have swayed some votes in support of MRT. No such sentiment has been sweeping the United States, even though U.S. scientists have made equally vital contributions to this field of inquiry (3, 4).

CONCLUSIONS. This examination of the different approaches taken to the regulation of MRT in the United Kingdom and the United States leads us to reexamine the wisdom of burdening the FDA with the regulatory adjudication of MRT, as opposed to adopting an HFEA-like paradigm (16). In the eyes of some, the regulatory oversight of reproductive technologies in the United States leaves much to be desired. Yet others are content with the status quo, in which reproductive technologies are not directly licensed (as in the United Kingdom) but instead are left to what can be characterized as self-regulation by the medical profession and its representative associations. However, with the MRT challenge looming and others not too far behind, it may be time to renew the national conversation as to the rules that should govern this terrain. Understandably, the outcome of such conversation is far from certain.

Because some forms of MRT involve embryo destruction, approval in the United States will be embroiled in the prolife/prochoice divide (17–19). It remains an open question whether an initiative to reform the regulatory oversight of reproductive technologies in the United States can be realized without capsizing under its own weight and the force of the political winds. ■

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DEVELOPMENT

Aneuploidy and mother's genes

A human genetic variant found at high frequency is associated with reduced fertility

By Samuel H. Vohr and Richard E. Green

Biological, ecology, and culture have shaped human genetic variation over thousands of generations. Technology now allows us to know the sequence of our genomes and to act on this knowledge. Which genes did a child inherit from either parent? With the direct-to-consumer genome scan products now available, this question can be answered at the cost of a few hundred U.S. dollars and a few milliliters of spit. Which fertilized embryo is free of genetic and genomic abnormalities? By combining in vitro fertilization, preimplantation genetic screening, and whole-genome scans, this is also now possible to assess (1, 2). But what if genes themselves select potential children? On page 235 of this issue, McCoy *et al.* (3) indicate that this may be the case. The authors describe paradoxical results of a genomic study of thousands of preimplantation human embryos and their parents. They turn up a maternal-effect genetic variant that occurs at high frequency in many populations, that was likely under positive selection in our recent past, and that dramatically decreases embryonic viability.

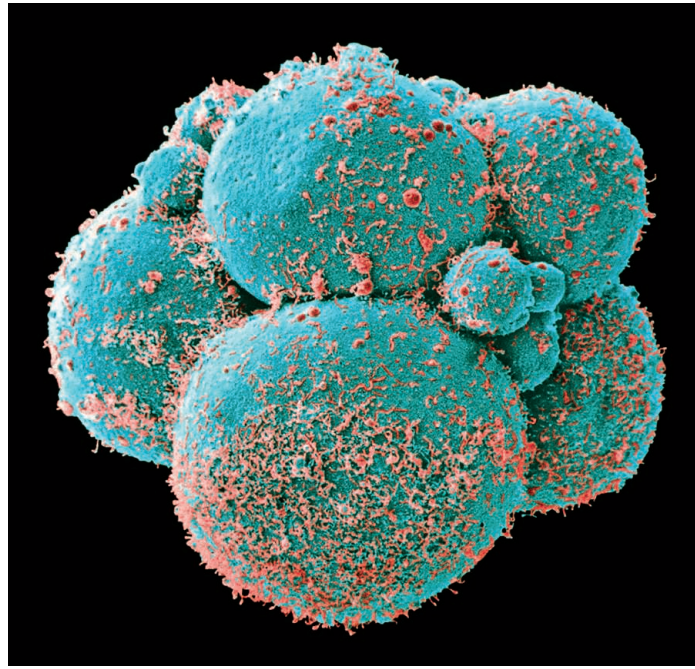
Since its first use in England in 1977, in vitro fertilization has become a mainstream reproductive technique, responsible for 2 to 3% of babies in developed countries (4). In vitro fertilization can be coupled with preimplantation genetic screening, wherein one or more genetic assays are performed on cells taken from an early-stage embryo before implantation (see the figure). This combination provides further options to many would-be parents. It allows a sneak peek at the genetic makeup of an embryo and is routinely used to screen for chromosomal abnormalities or disease-causing genetic defects when the parents are known or suspected carriers (2).

Recently, preimplantation genetic screen-

ing has been broadened to scan entire genomes of preimplantation embryos by means of whole-genome amplification and genotyping arrays (5). This allows for a hypothesis-free and more comprehensive genetic assessment of an early-stage embryo than was previously possible. But it also comes with data quality issues, such as “allelic dropout,” in which one or both alleles of a gene fail to be amplified in a whole-genome amplification step that is required when input DNA is limited to a single cell. This technical problem can be mitigated, however, by using genomic data from the parents together with that from the embryo. Using this approach, aneuploidies—the presence of an atypical complement of chromosomes—can be detected at fine resolution. It also becomes possible to determine which of the two parental chromosomes is aneuploid.

In both *in vitro* and *in vivo* fertilizations, aneuploidy is surprisingly common and often leads to early pregnancy loss (6). It has long been known that maternal age is positively correlated with aneuploidies (6) and that these are typically meiotic aneuploidies (i.e., present from the beginning, in the unfertilized egg of the mother). Against this background of common maternal meiotic aneuploidy, it has been difficult to detect and measure the rates of other types of aneuploidies such as paternal meiotic aneuploidies (present in the sperm that fertilized the egg) or later, mitotic-derived aneuploidies that arose in early cell divisions after fertilization.

To distinguish between the different sources of aneuploidy, McCoy *et al.* analyzed genotype data from sets of embryos and both parents to search for evidence of chromosome gain and loss. Reasoning that losses and gains that exclusively affect maternally inherited chromosomes in the embryo are meiotic in origin, they were able to identify these cases and confirm their known association with maternal age. Because there is a low rate of aneuploidy in sperm, the authors further reasoned that aneuploidies affecting paternally inherited chromosomes can generally be attributed to mitotic errors and focused on those. Tellingly, they found that these paternal aneuploidies often affect mul-



Preimplantation. A colored scanning electron micrograph of a human embryo at the eight-cell stage, 3 days after fertilization. At this stage, the embryo has not yet implanted in the uterus.

iple chromosomes and that their frequency of occurrence is not affected by the age of the mother. Given that some women produce aneuploid embryos more often than others (7) and that the mitotic machinery in early embryogenesis is largely maternally derived, is it possible that mitotic aneuploidies could be affected by the genes of the mother?

Armed with a large cohort to test this hypothesis, McCoy *et al.* searched maternal genomes for variants associated with various types of aneuploidy. They found no association between the mother’s genotype and rates of meiotic errors. However, they found a strong genetic association between the mother’s genotype and the rate of observed mitotic errors. Surprisingly, the variant most closely associated with high rates of embryonic mitotic errors, the single-nucleotide polymorphism rs2305957, is found at high frequency in populations across the world. Several genes are tightly linked to the high-risk variant, but the authors singled out the *Polo-like Kinase 4* (*PLK4*) as a candidate causal gene because of its known role in the centrosome cycle (8), a process whose disruption can cause aneuploidy. (Centrosomes are structures that organize microtubules into the mitotic spindle that orchestrates the separations of duplicated chromosomes during cell division). Underscoring the importance of the maternal genotype in this region, mothers with the high-risk variant contributed fewer later-stage (5-day) embryos, presumably because there is an elevated rate of embryonic

mortality associated with these aneuploidies.

How could a genetic variant so strongly associated with reduced fecundity have risen to such high frequency across the world? A possible clue is that this genomic region was previously identified in a scan for positive selection by contrasting genetic variation found in the Neandertal genome with that present in humans today (9). The scan has maximum power to identify episodes of positive selection that occurred in the time since human ancestors split from Neandertals but before human population differentiation—that is, between roughly 400,000 years ago and 100,000 years ago. McCoy *et al.* provocatively speculate that a genetic variant that reduces fecundity may provide a selective advantage by obscuring paternity. This interpretation may make sense in a species with

low fecundity and heavy parental investment, such as humans.

Around 30% of natural human conceptions do not go to full term (10). Armed with reproductive and genetic tools for inquiry, it is now possible to start unraveling this mystery. The results described by McCoy *et al.* are cause for both optimism and uncertainty about the future. If some human genomes carry a legacy of adaptive reduced fecundity, and people now have the means and motivation to select against these variants, will that happen? If the evolutionary driving force was indeed paternity confusion, does it make sense to purposefully select against this variant now that technology also exists to eliminate paternity confusion? What about the prospect of genetic screening or valuation of egg donors based on the genotype-predicted viability of the resulting embryos? Knowledge of the determinants of embryonic development and viability may add a new turn in the complicated trajectory of human evolution. ■

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IMAGE: YORGOS NIKAS/SCIENCE SOURCE



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