Preventing common hereditary disorders through time-separated twinning

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Abstract

Biomedical advances have led to a relaxation of natural selection in the human population in developed countries. In the absence of strong purifying selection, spontaneous and frequently deleterious mutations tend to accumulate in the human genome and gradually increase the genetic load; that is, the frequency of potentially lethal genes in the gene pool. It is not possible to assess directly the negative impact of the genetic load on modern society because it is influenced by many factors such as constantly changing environmental conditions and continuously improving medical care. However, gradual increase in incidence of many complex disorders suggests deleterious impact of the genetic load on human well being. Recent advances in *in vitro* fertilization (IVF) combined with artificial twinning and improved embryo cryoconservation offer the possibility of preventing significant accumulation of genetic load and reducing the incidence of hereditary disorders.

Many complex diseases such as type 1 and 2 diabetes, autism, bipolar disorder, allergies, Alzheimer disease, and some cancers show significantly higher concordance in monozygotic (MZ) twins than in fraternal twins (dizygotic, DZ) or parent-child pairs, suggesting their etiology is strongly influenced by genetics. Preventing these diseases based on genetic data alone is frequently impossible due to the complex interplay between genetic and environmental factors. We hypothesize that the incidence of complex diseases could be significantly reduced in the future through a strategy based on time-separated twinning. This strategy involves the collection and fertilization of human oocytes followed by several rounds of artificial twinning. If preimplantation genetic screening (PGS) reports no aneuploidy or known Mendelian disorders, one of the MZ siblings would be implanted and the remaining embryos cryoconserved. Once the health of the adult MZ sibling(s) is established, subsequent parenthood with the cryoconserved twins could substantially lower the incidence of hereditary disorders with Mendelian or complex etiology.

The proposed method of artificial twinning has the potential to alleviate suffering and reduce the negative social impact induced by dysgenic effects associated with known and unknown genetic factors. Time-separated twinning has the capacity to prevent further accumulation of the genetic load and to provide source of isogenic embryonic stem cells for future regenerative therapies.

Introduction

The failure of CuraGen and other similar startups demonstrated that prevention and cure of the complex diseases based on genomic information alone is elusive. Unlike simple Mendelian (single gene) disorders, many complex diseases are multi-locus, where minor compromises in multiple disease-associated genes combine through epistasis and trigger a disorder. Complex diseases such as diabetes type 1 and 2, all sorts of autoimmune disorders (allergies), autism spectrum disorder (ASD) and many others have been documented to have a strong genetic component in their etiology and frequently run in the families. Moreover, living standards in developed countries have improved to the point where natural selection is no longer a major driver of human evolution; thus, spontaneous *de novo* mutations are routinely passed on to the next generation. Mutations that might have been selectively eliminated in the past (Figures 1,2) now accumulate (Crow, 2000; Stephan and Henneberg, 2001) and increase the frequency of potentially lethal genes in the human gene pool, i.e. the "genetic load".

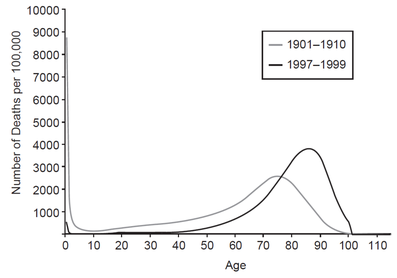

FIGURE 1: Mortality of the Australian human population by age for 1901-1910 and 1997-1999 (Image credit (Stephan and Henneberg, 2001)).

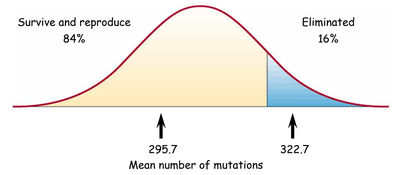

FIGURE 2: According to (Crow, 2000), the average number of 300 mutations per person follows roughly Poisson distribution. Elimination by natural selection of 16% of each generation with the highest genetic load is sufficient to offset the negative effect of 3 deleterious *de novo* variants per generation. This representation implies that there are few individuals with exceptionally low genetic load (Image credit (Crow, 2000)).

Incidence of many complex diseases has tendency to increase, which might be caused by the increasing genetic load:

- In Finland Type 1 Diabetes 32-year relative increase was 338% among children 1-4 yo (Karvonen *et al.*, 1999)
- In China, 23.46 million people currently have Type 2 Diabetes, and this number is projected to increase to 42.30 million by 2030 (Wang *et al.*, 2009)
- Nearly 5 times as many people have Celiac Disease in US today than during the 1950s (Rubio-Tapia *et al.*, 2009)
- The incidence of Autism among US children has reached a staggering 1% (110 out of 10,000) (Kogan *et al.*, 2009) and continues to grow
- The incidence of Asthma alone has at least tripled over the past 25 years and now affects more than 22 million people in US (rep, 2008)

Twin studies have long been recognized as a powerful technique for studying complex phenotypes (van Dongen *et al.*, 2012) consistently reporting significantly higher concordance rates in monozygotic (MZ) twins than in dizygotic (DZ) twins or parent-child pairs, suggesting a large genetic component to their etiology.

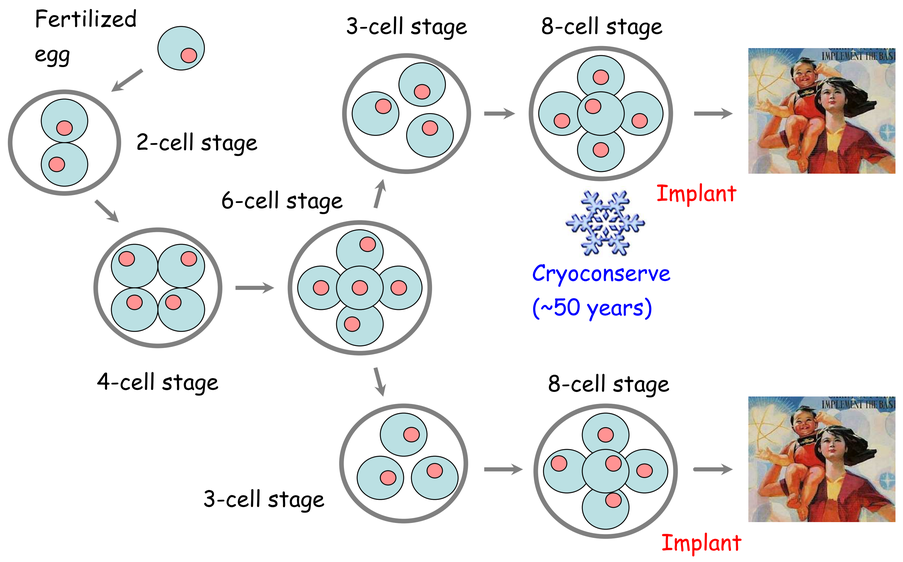

FIGURE 3: Time-separated artificial twinning

Based on this, the use of a time-separated twinning strategy guided by the health status of the adult siblings could not only prevent further accumulation of genetic load, but also significantly reduce the incidence of devastating complex diseases. This strategy involves the collection and fertilization of human oocytes followed by several rounds of artificial twinning (microsurgical splitting of an embryo at 6 or 8 cell stage) (Figure 3). If preimplantation genetic screening (PGS) reports no aneuploidy or known Mendelian disorders, one of the MZ siblings would be implanted and the remaining embryos cryoconserved. Once the good health of the adult MZ sibling(s) is established, subsequent parenthood with the cryoconserved twins (Figures 3,4) could substantially lower the incidence of hereditary disorders with complex etiology and virtually eradicate simple Mendelian disorders.

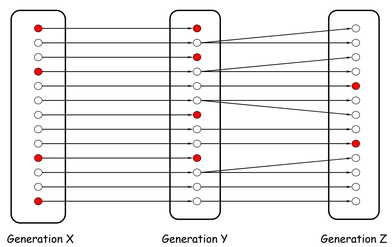

FIGURE 4: A simple model to explain our calculations. Red circles represent individuals affected by a certain disease and open circles represent healthy individuals in a population.

Methods and results

According to Bayesian rule probability of an individual becoming sick in the replicate population y (Figure 4) is $p(sick_y) = p(sick_y|\neg sick_x)\,(1 - p(sick_x)) + p(sick_y|sick_x)\,p(sick_x)$. Pairwise concordance between MZ twins $p(sick_y|sick_x)$ could be found in biomedical literature. Assuming that that $p(sick_x) = p(sick_y)$, $p(sick_y|\neg sick_x) = \frac{p(sick_x)\,(1-p(sick_y|sick_x))}{1-p(sick_x)}$. Under assumption that and $p(sick_z|\neg sick_y) = p(sick_y|\neg sick_x)$, $p(sick_z) = p(sick_z|\neg sick_y)\,p(\neg sick_y) = p(sick_y|\neg sick_x)$. Preventive odds for various complex diseases are shown in Table 1.

Conclusions

Time-separated twinning strategy and creation of demi-embryo repositories under government control will facilitate:

- Sustainable social development
- Prevention of further accumulation of undesirable mutations (genetic load)
- Significant reduction in incidence of complex diseases and virtual eradication of simple Mendelian disorders
- Future regenerative medicine with isogenic stem cells of total potency

Study	Type	Disease incidence	MZ twins pairwise concordance	Prevention odds
Diabetes type 2				
(Medici *et al.*, 1999)		7.67%-13.5%	76%	3.75
(Jap, 1988)			83%	5.29
(Kaprio *et al.*, 1992)			20%	1.12
(Newman *et al.*, 1987)			85.3%	6.12
Diabetes type 1				
(Jap, 1988)		0.01% - 0.034%	45%	1.82
(Kaprio *et al.*, 1992)			13%	1.15
(Hyttinen *et al.*, 2003)			27.3%	1.37
(Redondo *et al.*, 2001; Hyttinen *et al.*, 2003)	≤ 10 years old		50%	2.0
(Hyttinen *et al.*, 2003)	> 10 years old		16.7%	1.20
(Kyvik *et al.*, 1995)			38%	1.61
Cancer				
(Lichtenstein *et al.*, 2000)	Breast	1.92%	14%	1.14
	Colorectum	1.55%	16%	1.17
	Prostate	1.12%	21%	1.25
Autism spectrum disorder				
(Bailey *et al.*, 1995)		0.1%-1%	92%	12.37
(Steffenburg *et al.*, 1989)			91%	11.0
(Folstein and Rutter, 1977)			82%	5.5
Allergies				
(Sicherer *et al.*, 2000)	Peanut	0.4-0.6%	64.3%	2.79
(David *et al.*, 2001)	Astma past year ($< 50 \sim \geq 50$) yo	8%∼3%	29%∼0%	1.30∼0.97
	Hay fever ($< 50 \sim \geq 50$) yo	30%∼27%	39%∼30%	1.16∼1.05
	Seasonal rhinoconjunctivitis ($< 50 \sim \geq 50$) yo	15%∼11%	31%∼18%	1.23∼1.09
	Eczema ($< 50 \sim \geq 50$) yo	24%∼16%	34%∼30%	1.16∼1.20
	Pets ($< 50 \sim \geq 50$) yo	13%∼4%	39%∼7%	1.43∼1.03
	Pollen ($< 50 \sim \geq 50$) yo	21%∼14%	32%∼17%	1.17∼1.03
	Dust ($< 50 \sim \geq 50$) yo	22%∼12%	43%∼8%	1.37∼0.95
	Insect bites ($< 50 \sim \geq 50$) yo	10%∼11%	20%∼11%	1.12∼1.00
	Cat IgE+ ($< 50 \sim \geq 50$) yo	12%∼4%	28%∼44%	1.22∼1.74
	Grass IgE+ ($< 50 \sim \geq 50$) yo	21%∼10%	56%∼35%	1.77∼1.38
	Der p 1 IgE+ ($< 50 \sim \geq 50$) yo	22%∼9%	54%∼14%	1.69∼1.06
(Nisticò *et al.*, 2006)	Celiac disease	0.75%	71.4%	3.47

TABLE 1: Disease incidence and theoretically possible prevention odds.

The project is available at http://prevmed.big.ac.cn.