

Determine the Feasibility of Establishing a US National Twin Registry and Three Disease Specific Twin Registries

- Type 1 diabetes
 - 13-70% concordance in MZ twins, 0-14% in DZ twins
 - US prevalence is ~1.3 million
- Systemic lupus erythematosus
 - 24-69% concordance in MZ twins, 1-2% for DZ twins
 - US prevalence is ~1.4 million
- Multiple Sclerosis
 - 25-30% concordance in MZ twins, 2-5% in DZ twins
 - US prevalence is ~300,000

Background

- Powerful tool for investigating the relative contributions of genetic susceptibility and environmental influences to complex traits and disease
- Advantages
 - Increase study power due to sharing between co-twins
 - MZ pairs - eliminate genetic confounders
 - MZ/DZ pairs - eliminate environmental and age confounders
- Twin pairs needed for estimating genetic contribution

Martin, Boomsa, and Machin. Nature Genetics 1997;17:387-392.

 - 200 pairs for traits of high heritability
 - Several thousand pairs for traits of low to moderate heritability
- International (national population-based) Twin Registries
 - Limited access
 - Not representative of US population

Polycystic Ovary Syndrome (PCOS) Twin Study

- Major cause of infertility
 - Type 2 diabetes, high blood pressure, dyslipidemias, CVD, and CA
- Mid-Atlantic Twin Registry
- Cohort of MZ and DZ twins with PCOS
 - Concordance rates and heritability estimates
 - Identify environmental risk factors
 - Monitor discordant pairs for incident cases
 - Monitor discordant MZ twins over time to see whether concordance rates approach 100%
- Investigating other twin resources for the study

Maternofetomicrochimerism as a Risk Factor for Type 1 Diabetes

- Persistence of maternal cells in the child's circulation after birth
- British Diabetic Twins Study – Dr. David Leslie, St. Bartholomew's Hospital, London, UK
- Discordant MZ twins and their mothers
 - Nonshared HLA genotypes between mothers and their MZ twins (offspring)
 - Genotype CD3+ cells in the offspring to determine if there are any cells of maternal origin
 - Quantitate maternal DNA in offspring using standard real-time PCR techniques

Tasks 1 and 2 – Describe the Current US Twin Populations

- **Task 1** – Analyze and describe the current overall US twin population
 - No systematic attempt to estimate and analyze the US twin population to date
 - Total numbers of twins
 - Zygosity, age, gender, race/ethnicity, SES, region, etc.
 - Five year projection
- **Task 2** – Analyze and describe US twin populations with type 1 diabetes, SLE, and MS
 - Define phenotype(s) of each condition
 - Totals and demographics
 - Numbers justify the effort - cost/benefit point of view?
- Estimate numbers of twins that are currently enrolled in existing twin registries and/or research programs
 - Literature review
 - Survey existing twin registries, disease foundations, etc.

Survey of Existing Twin Registries

- Registry characteristics
- Registry experience
- Demographics of twin population
- Human Subjects Protections
- Data collection
- Tissue collection
- Retention
- Data sharing policies

- Survey for disease specific registries and disease foundations

- Estimate the willingness of twins to participate in registries and research programs

Task 3 – Ethical, Legal, and Social Issues

- Explore the ethical, legal and social issues (ELSI) that could impact establishing and operating a national US twin registry and the three disease-specific registries
- Separate panel of ELSI experts (twin research, minorities/underrepresented populations, privacy, genetic issues, other areas)
- Hold a special ELSI workshop (November 2005)
 - Privacy and confidentiality
 - Informed consent
 - Participation and recruitment – overall, children, minorities, underrepresented subgroups
 - Ethics review
 - Research
 - Genetics
- Focus groups of representative populations
- Literature reviews

Task 4 – Potential Size and Composition of the Proposed National Twin Registries

- Estimates from tasks 1 and 2
- Surveys of existing twin registries, foundations, studies, etc.
- Literature reviews
- Take current ELSI issues into account
- Methods for twin ascertainment, tracing, recruitment and retention
 - Overall twin population
 - Twins with disease
 - Minorities, children, underrepresented groups, etc.

Tasks 5, 6 and 7

- **Task 5 - Alternatives to a National US Twin Registry**
 - Consortium of already existing registries
 - One or more smaller population-based registries
 - Pilot registry
- **Task 6 - Alternatives to the disease-specific twin registries**
 - Expand existing resource
 - Subgroup twins within the National US Twin Registry
- **Task 7 - Compare alternatives with national registries**
 - Advantages and disadvantages of the various options
 - Draft summary report
 - Convene second panel expert meeting (June 2006)
 - Make recommendation to NIEHS Directors

Tasks 8, 9, and 10

- **Tasks 8 and 9** - Devise final methods and implementation plans for establishing the Twin Registries or their alternatives.
 - Ascertainment, tracing, recruitment and retention methods
 - Surveillance methods (disease specific registries)
 - Database development
 - Data and sample collection from twins
 - Registry policies
 - Timelines
- **Task 10** -Estimate infrastructure and costs
- Final Expert Panel Meeting (Oct 2006)
 - Final report and recommendations

Project Team

NIEHS - Co-Project Officers/ NIEHS Co-PIs

Patricia C. Chulada, PhD, MHS

Perry Blackshear, MD, DPhil

Virginia Commonwealth University

Linda Corey, PhD - Major PI

Phillip Morris USA

Lenn Murrelle, MSPH, PhD – Consultant

Alpha-Gamma Technologies, Inc.

Vani Vannappagari, PhD, MBBS – Lead
Epidemiologist

Teji Rakhra-Burris, MA - Project manager

Reese Howle, BA – Project director

Atif Hasan, MS – Database specialist

Tom Bensman, BA – Logistical support

Research Triangle Institute

Nedra Whitehead, PhD, MS – Medical Geneticist

Paul Levy, MA, Sc.D. – Biostatistician

Fengyu Zhang, PhD – Demographer, Statistician

Paul Pulliam, BS – Survey specialist

Ariana N. Napier, MA – Survey specialists

David Rein, PhD – Research economist

UNC School of Public Health

Robert C. Millikan, DVM, MPH, PhD – Consultant

University of Virginia

Paul Lombardo, JD, PhD, MA – Medical Bioethics

Twins Beget Twins

