

# The St. Thomas' UK Adult Twin Registry

Tim D. Spector and Alex J. MacGregor

*Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London, UK*

The Registry consists of nearly 10,000 monozygous and dizygous adult caucasian twins aged 18–80 from all over the UK and was started in 1993. This is a volunteer sample recruited by successive media campaigns without selecting for particular diseases or traits. All twins receive a series of disease questionnaires. In addition over half the twins have been assessed in detail clinically for several hundred phenotypes related to common diseases or intermediate traits. The focus has been primarily on cardiovascular, metabolic, musculoskeletal, dermatological, and ophthalmological diseases. Over 3000 DZ twins have had a genome wide scan performed as well as many candidate genes allowing both linkage and association studies. The registry has led to many successful innovative research projects, particularly in common diseases previously thought to be predominantly environmental and helped positionally clone some novel genes for common diseases.

## History

A twin database was started in 1992 with a grant from the Arthritis and Rheumatism Campaign (ARC) medical charity to perform a classical twin study on osteoarthritis in females involving 250 twin pairs. Subsequent grants from the Wellcome Trust in 1993 to examine bone density for osteoporosis and then genetics of asthma and atopy and from the MRC to study disc disease led to the idea of combining phenotypes at the same visit and studying as wide a range of phenotypes as possible. From 1996 to 2001 the Twin unit received additional funding from a Genetics company Gemini Genomics which in addition to continued funding from charities allowed us to increase the size and depth of the clinical collection. Unlike other twin resources, ours has focussed on obtaining detailed and standardized clinical and biochemical phenotypes rather than record linkage and questionnaire data.

## The Collection

The twin database now includes over 8000 twins with an average age of around 45 and who are predominantly female and same sex, because the diseases we initially focussed on were more common in women. The ratio of identical to non-identical twins is approximately 50:50 and the volunteers come from throughout the UK and Ireland following multiple media campaigns for twins to help with research. The majority of twins have been seen clinically in the unit where as well as performing clinical tests, blood, urine and DNA is collected and stored at  $-45^{\circ}\text{C}$ . Approximately one third of twins have had multiple visits to the unit. The subjects are unpaid but are compensated for their travel and accommodation expenses. Zygosity is ascertained using the standard peas in the pod questionnaire, and if there is uncer-

tainty checked by genotyping. The average clinic visit is between 3–6 hours. Full ethical approval has been given and consent forms are updated annually and re-signed on every visit.

## Staff and Facilities

The unit is grant funded and has around 20 staff dealing with the twin registry, of whom 7 deal with statistical analysis. There is a lab that processes and stores the 60,000 samples and a molecular biology lab for candidate gene work and mutation detection. The unit produces regular newsletters for the twins and maintains a website.

## Aims

The overall objectives of the unit are:

1. To estimate heritabilities for common diseases and traits in adults.
2. Discover genes that influence these traits.
3. Provide a framework for epidemiologic studies using the twin design.
4. Develop statistical methodology to facilitate these aims.

## Major Research Findings to Date

The following groupings are examples of major research findings using the twin registry, but is not intended as an exhaustive list.

### Osteoporosis

- The following risk factors for osteoporotic fracture are strongly and independently genetic: bone density, bone quality (BUA), hip axis length, vitamin D levels, bone turnover markers, muscle strength.
- Vitamin D receptor genotypes are associated with bone density.
- TGF beta genotypes are linked and associated with bone density.
- Klotho genotypes are associated with bone density.
- Skeletal size is associated with birthweight.

### Osteoarthritis

- OA of knee, hand and hip all strongly heritable.

*Address for correspondence: Tim D. Spector, Twin Research & Genetic Epidemiology Unit, St Thomas' Hospital, London SE1 7EH, UK. Email: [tim.spector@kcl.ac.uk](mailto:tim.spector@kcl.ac.uk)*

- Some overlapping shared genes with osteoporosis.
- Most genes are site specific and not generalized.
- Vitamin D receptor genotype associated with knee disease.
- Obesity and OA genes are not shared.
- QT and PR interval and pulse shows genetic influence.
- Blood pressure in adults related to birth weight.
- Major clotting factors strongly heritable.
- Activated coagulation and fibrinolytic (prethrombotic) factors under genetic control.

#### Metabolic Syndrome

- Central fat deposition and body shape is genetic.
- HRT and cigarette use reduces central fat and total body fat.
- Leptin is correlated genetically with adiposity and body size.
- HbA1C levels reflect genetic susceptibility more than consequence of disease.
- Dietary fat levels not related to adiposity or fat distribution.

#### Cardiovascular disease

- Blood pressure shows low heritability compared to vascular resistance.

#### Skin Disease and Atopy

- Freckles and naevi strongly heritable with little environmental influence.
- Acne strongly genetic.
- Polymorphic light eruption (PLE) heritable.
- Eczema and hayfever heritable with some shared genes.
- Skin thickness changes in smokers.

#### Eye Disease

- Myopia and presbyopia heritable despite recent increases.
- Nuclear cataract shows major genetic component.

**Table 1**

Twin Research Unit, St.Thomas' Hospital

Name of register	St Thomas' UK Adult Twin Registry		
Country	United Kingdom		
Kind of ascertainment	Volunteers unselected		
Opposite sex twins (yes or no)	No		
Number of pairs (separated by birth range and sex)	1900–1920:	10 FF	3MM
	1920–1930:	144 FF	20 MM
	1930–1940:	670 FF	79 MM
	1940–1950:	1074 FF	115 MM
	1950–1960:	937 FF	193 MM
	1960–1970:	743 FF	193 MM
	1970–1980:	510 FF	157 MM
	1980–2000:	23 FF	3 MM
Totals		4104 FF	760 MM
Grand total	4864 pairs		
Major interests	Common complex diseases and traits		
Traits measured	Full questionnaires and clinical exam and testing on majority of twins for wide range of over 200 clinical and biochemical traits. Including: CVD, obesity, metabolic syndrome, respiratory disease, dermatology, osteoarthritis, osteoporosis, eye disease, back disease, coagulation system, immune function, cognitive function, GI system, Pain thresholds, allergy, atopy, pitch perception, sense of humour.		
DNA samples	6649		
Various samples	6700 serum, 6500 urine		
Contact	Tim Spector		
Address	Twin Research Unit, St. Thomas' Hospital, Block 4 A, 1st Floor, South Wing, London SE1 7EH		
Email	Tim.spector@kcl.ac.uk		
Web site	www.twin-research.ac.uk		
Main recent twin publications	Over 100 including: DeLange et al genetics of clotting. <i>Lancet</i> 2001, Drayna et al . Genetics of pitch perception. <i>Science</i> 2001, Hammond et al Genetics of cataract. <i>NEJM</i> 2000		
Main Sources of funding	Wellcome Trust, ARC, MRC, British Heart Foundation, CDRF, Sequenom inc		
Comments	MZ: DZ ratio approximately 1:1, database majority female. 1500 pairs with full genome scan information.		

- Pupil dilation under genetic control.
- Early macular degeneration heritable.

#### Immune and Haemopoetic System

- Levels of white and red cells and platelets heritable.
- Levels of circulating Haemoglobin F heritable and related to specific polymorphisms.
- CD4 and CD8 circulating T cells under genetic influence.
- X inactivation has genetic basis.

#### Miscellaneous

- Cognitive component of humour influenced by family environment.
- Pitch recognition is strongly genetic.
- Timing of menarche and menopause strongly genetic but not related.
- Back pain and disk disease measured by MRI strongly genetic.
- Raynauds syndrome and cold intolerance is genetic.
- Twins are comparable to singletons for most common traits measured.

#### Future Work

We plan to use the genetic information we have available on the twins which includes a genome wide scan on 1500 DZ twin pairs as well as a number of candidate genes genotyped in around 500 pairs. We will perform a combination of linkage and association studies to narrow down the loci of interest and use disequilibrium mapping to pin down the key genes. We have worked with a large number of different collaborators in the past and we are keen to encourage further and future collaborations particularly in areas where we can gain from additional clinical or technical expertise or where groups can add phenotypic or genotypic information.

#### Major Recent Twin Unit Publications

Arden, N. K., Baker, J., Hogg, C., Baan, K., & Spector, T. D. (1996). The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length — A study of postmenopausal twins. *Journal of Bone & Mineral Research*, *11*, 530–534.

Ariens, R. A., de Lange, M., Snieder, H., Boothby, M., Spector, T. D., & Grant, P. J. (2002). Activation markers of coagulation and fibrinolysis in twins: Heritability of the prethrombotic state. *Lancet*, *359*(9307), 667–671.

Bataille, V., Snieder, H., MacGregor, A. J., Sasieni, P., & Spector, T. D. (2000). Genetics and risk-factor significance of nevi and freckles in melanoma: An adult twin study. *Journal of National Cancer Institute*, *92*(6), 457–463.

Cherkas, L., Hochberg, F., MacGregor, A. J., Snieder, H., & Spector, T. D. (2000). Happy families: A twin study of humour. *Twin Research*, *3*(1), 17–22.

Cicuttini, F., Baker, J., & Spector, T. D. (1996). The association of obesity with osteoarthritis of the hand and knee in women: A twin study. *Journal of Rheumatology*, *23*, 1221–1226

de Lange, M., Snieder, H., Ariens, R. A., Spector, T. D., & Grant, P. J. (2001). The genetics of haemostasis: A twin study. *Lancet*, *357*(9250), 101–105.

Drayna, D., Manichaikul, A., de Lange, M., Snieder, H., & Spector, T. D. (2001). Genetic correlates of musical pitch recognition in humans. *Science*, *291*, 1969–1972.

Garner, C., Tatu, T., Reittie, J. E., Littlewood, T., Darley, J., Cervino, S., et al. (2000). Genetic influences on F cells and other hematological variables: A twin heritability study. *Blood*, *95*(1), 342–346.

Hall, M. A., Ahmadi, K. R., Norman, P., Snieder, H., MacGregor, A. J., Vaughan, R. W., et al. (2000). Genetic influence on peripheral blood T lymphocyte levels. *Genes and Immunity*, *1*, 423–427.

Hammond, C. J., Snieder, H., Gilbert, C. E., & Spector, T. D. (2001). Genes and environment in refractive error: The twin eye study. *Investigative Ophthalmology and Visual Science*, *42*(6), 1232–1236.

Hammond, C. J., Snieder, H., Spector, T. D., & Gilbert, C. E. (2000). Genetic and environmental factors in age-related nuclear cataracts in monozygotic and dizygotic twins. *New England Journal of Medicine*, *342*(24), 1786–1790.

Hunter, D., de Lange, M., Snieder, H., MacGregor, A. J., Swaminathan, R., Thakker, R. V., & Spector, T. D. (2001). Genetic contribution to bone metabolism, calcium excretion and vitamin D and parathyroid hormone regulation. *Journal of Bone and Mineral Research*, *16*(2), 371–378.

Hunter, D., Major, P., Arden, N., Swaminathan, R., Andrew, T., MacGregor, A. J., et al. (2000). A randomized controlled trial of vitamin D supplementation on preventing bone loss and modifying bone metabolism using identical twin pairs. *Journal of Bone and Mineral Research*, *15*(11), 2276–2283.

Keen, R. W., Snieder, H., Molloy, H., Daniels, J., Chiano, M., Gibson, F., et al. (2001). Evidence of association and linkage disequilibrium between a novel polymorphism in the transforming growth factor  $\beta$ 1 gene and hip bone mineral density: a study of female twins. *Rheumatology*, *40*, 48–54.

MacGregor, A. J., Antoniadou, L., Matson, M., Andrew, T., & Spector, T. D. (2000). The genetic contribution to radiographic hip osteoarthritis in women. *Arthritis & Rheumatism*, *43*(11), 2410–2416.

MacGregor, A. J., Snieder, H., Schork, N., & Spector, T. D. (2000). Novel uses of twins in studying the genetics of complex traits and diseases. *Trends in Genetics*, *16*(3), 131–134.

Millard, T. P., Bataille, V., Snieder, H., Spector, T. D., & MacGregor, J. M. (2000). The heritability of polymorphic light eruption. *Journal of Investigation in Dermatology*, *115*(3), 467–470.

Poulter, N. R., Chang, C. L., MacGregor, A. J., Snieder, H., & Spector, T. D. (1999). Association between birth weight and adult blood pressure in twins: Historical cohort study. *British Medical Journal*, *319*, 1330–1333.

Samaras, K., Spector, T. D., Nguyen, T. V., Baan, K., Campbell, L. V., & Kelly, P. J. (1997). Independent genetic factors determine the amount and distribution of fat in women after the menopause. *Journal of Clinical Endocrinology and Metabolism*, *82*(3), 781–785.

- Sambrook, P. N., MacGregor, A. J., & Spector, T. D. (1999). Genetic influences on cervical & lumbar disc disease: An MRI twin study. *Arthritis & Rheumatism*, *42*(2), 366–372.
- Snieder, H., Hayward, C. S., Perks, U., Kelly, R. P., Kelly, P. J., & Spector, T. D. (2000). Heritability of central systolic pressure augmentation. A twin study. *Hypertension*, *35*(2), 574–579.
- Snieder, H., MacGregor, A. J., & Spector, T. D. (1998). Genes control the cessation of a woman's reproductive life: A twin study of hysterectomy and age at menopause. *Journal of Endocrinology & Metabolism*, *83*, 1875–1880.
- Snieder, H., Sawtell, P. A., Ross, L., Walker, J., Spector, T. D., & Leslie, R. D. (2001). HbA(1c) levels are genetically determined even in type 1 Diabetes: Evidence from healthy and diabetic twins. *Diabetes*, *50*(12), 2858–2863.
- Spector, T. D., Cicuttini, F., Baker, J., Loughlin, J. A., & Hart, D. J. (1996). Genetic influences on osteoarthritis in females: A twin study. *British Medical Journal*, *312*(7036), 940–943.
- Spector, T. D., Keen, R. W., Arden, N. K., Morrison, N. A., Major, P. J., Nguyen, T., et al. (1995). Influence of vitamin D receptor genotype on bone density in postmenopausal women: A British twin study. *British Medical Journal*, *310*, 1357–1360.
- Strachan, D. P., Wong, H. J., & Spector, T. D. (2001). Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *Journal of Allergy and Clinical Immunology*, *108*(6), 901–907.
- Vickers, M. A., McLeod, E., Spector, T. D., & Wilson, I. J. (2001). Assessment of mechanism of acquired skewed X inactivation by analysis of twins. *Blood*, *97*(5), 1274–1281.
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