

HealthTwiSt: The Berlin Twin Registry for Health Research

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The Berlin Twin Registry has its focus on health research. It is operated as a private company, making twin studies available to academic institutions as well as commercial partners in the area of biotechnology and nutrition. Recruitment is based on invitation in the context of mass media coverage of scientific results. Phenotyping in the unselected twin subjects is directed toward intermediate phenotypes that can bear on common diseases. These phenotypes include proteomic approaches and gene expression. Some results are briefly described to give an impression of the range of research topics and related opportunities for retrospective and prospective collaborative research.

■ **Keywords:** twins, health research, nutraceuticals, cardiovascular, metabolic, DNA

In 2003, HealthTwiSt was established as a spin-off from the Medical Faculty of the Charité and Max Delbrück Center for Molecular Medicine as the legal entity operating the Berlin Twin Registry (BTR). Both retrospective data analyses as well as prospective studies from the BTR sample are offered to academic and commercial institutions.

Recruitment

Our main recruitment strategy is to increase awareness of the twin registry's existence, along with the uniqueness of twins in research. This includes mass media advertisements for specific projects as well as publication of results in non-scientific newspapers. Motivation comes from demonstrating value for the general population as well as the individual benefits for the twins who participate. As an incentive for participation, we provide a free health checkup and free zygosity testing to twins. Aside from recruiting new twin pairs, keeping in contact with the current registry members is the second important part of maintaining a vibrant twin registry. While some twins will have been participating in ongoing studies, a larger portion may either not be suitable for the current projects or currently not available. It is crucial to keep ties and maintain involvement even if no immediate participation is possible. Regular newsletters and participation in local twin conventions are currently our main activities; extensions to our Web site for interaction between twins are under development.

Data and Samples

Data storage is accomplished in a MySQL database with Web front end. This includes all personal as well as phenotypic information. A major part of our internal resources are devoted to the continuing database development.

In most projects, complex measurement schemes are applied to balance effort in recruitment, time strain for the twins, and scientific value. As long as there is a balance between research interest and burden to the twins, combining studies is a suitable strategy to maximize the power of phenotyping in twins.

Our twin sample is a self-selected adult sample with a wide age range (38 ± 15 years) (Table 1) without specific diseases; we have directed our phenotyping at intermediate traits and studied the influence of genetic variability on normal physiological variation. Direct measurements of traits like blood pressure were extended by functional assays to determine venous function (e.g., Brinsuk et al., 2004). Molecular phenotyping has been included in one study in which we counted the percentage of neutrophils expressing Proteinase 3 on their cell surface as a potential risk factor for Wegener granulomatosis, finding a heritability of 0.99

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TABLE 1
Number of Twin Pairs by Age, Sex, and Zygosity

Age group	MZ female	MZ male	DZ female	DZ male	DZ opposite sex	Ambiguous female	Ambiguous male
Under 11	0	0	0	0	1	9	15
11–20	0	5	1	0	16	27	29
21–30	13	23	5	4	81	130	63
31–40	33	32	10	3	148	261	165
41–50	35	25	17	8	58	160	54
51–60	19	6	7	4	18	74	19
61–70	11	7	5	2	7	44	6
Over 71	18	13	5	3	5	33	7
Total	129	111	50	24	334	738	358

with strong indication of epistatic effects (Schreiber et al., 2003). Gene expression assays to measure gene activity as an intermediate phenotype are currently under way.

While our past studies were based on status variables, we have started intervention studies, looking at changes in response to nutraceuticals. Using the monozygotic (MZ) co-twin control design, a decrease in blood pressure after an 8-week period of supplementation with an olive tree leaf extract was found (Perrinjaquet-Moccetti et al., 2008).

Major Research Focus and Findings

Our main focus has been on the cardiovascular system. The heritability analysis of blood pressure response to stress (Busjahn et al., 1996) was extended to linkage and association with candidate genes (Li et al., 2001). For resting blood pressure, with its well-established genetic variance (Williams et al., 1990), a number of candidate genes were tested based on findings from animal studies, cell-based assays, or case–control studies in hypertension (Busjahn et al., 2000, 2002b; Firouzi et al., 2006; Gollasch et al., 2002; Nagy et al., 1999).

Other cardiovascular traits of interest included baroreflex sensitivity (Gollasch et al., 2002; Tank et al., 2001), the electrocardiographic QT interval (Aydin et al., 2005; Bezzina et al., 2001, 2003; Busjahn et al., 1999b, 2004;), lipid metabolism (Al-Kateb et al., 2002; Knoblauch et al., 1997, 1999, 2000), and cardiac function as well as morphology as determined by echocardiography (Busjahn et al., 1997, 2000, 2009).

We have also included obesity-related measurements. New heritability estimates have been obtained for free ($h^2 = 0.28$) and bound leptin ($h^2 = 0.72$) concentrations, together with the leptin receptor ($h^2 = 0.56$; Jordan et al., 2005). Candidate genes for obesity have also been studied (Dieter et al., 2004; Knoblauch et al., 1999). A recent major project focused on the impact of dietary changes on hormones as well as gene expression; following 2 years of data collection, analyses are currently being conducted.

Pharmacogenetic studies have been attempted too, but recruitment proved to be less successful compared to non-interventional studies (Birkenfeld et al., 2009). Radiosen-

sitivity, a trait of utmost relevance for cancer in terms of causality as well as therapy, was studied based on cultured blood cells from MZ twins (Borgmann et al., 2007, 2010).

Psychological traits are not our main focus; however, we have studied ‘stress coping’ because stress has been implicated as a risk factor for various mental and physical diseases (von Känel, 2012). Heritability estimation and gene identification studies for stress coping have been carried out, showing heritability estimates between 0.21 and 0.52 for four major coping factors, as well as a significant association with the beta-2 adrenergic receptor gene (Busjahn et al., 1999a, 2002a).

Collaborations

The BTR is open to collaboration with national as well as international networks. Beside common scientific endeavors, this may include the establishment of data management structures for newly emerging twin registries, based on our in-house framework. Hosting of our twin registry by a private company has added great flexibility for collaborations, academic as well as industrial. Traditionally, there have been close ties with the Medical Faculty of the Charité, where most of the clinical phenotyping takes place, and the Max-Delbrück–Center for Molecular Medicine. Other collaborations have included the University Hospital Eppendorf in Hamburg, Tübingen University, the Max-Planck Institute for Psychiatry in Munich, the Dr Margarete Fischer-Bosch Institute for Clinical Pharmacology in Stuttgart, University Hospital Jena, and the Academic Medical Center of the University of Amsterdam.

Collaborative research may include access to clinical data and DNA from earlier studies in the context of candidate gene studies, as well as prospective studies to obtain new data and biological samples. Prospective studies may include intervention studies in the context of nutraceuticals/cosmeceuticals, but not clinical trials in phase I or II.

Depending on the background of the collaboration, development and fine-tuning of methodology can be done by either party or in close collaboration. If necessary, we can involve our local partners in phenotyping and/or genotyping.

Ethical Responsibilities

All our projects have been approved either by the Ethics Committee of the Charité or the partnering research institution. There is no direct access to non-anonymized data or twin addresses. The subjects have the option of withdrawing at any time. Participants receive feedback on clinical measurements — for example, blood pressure or cholesterol — but not on gene variants.

Conclusions and Future Directions

In conclusion, the BTR has already managed to revive interest in twin research in Germany and will continue to serve a broad range of research interests. We believe that twin research is a novel approach to complicated problems. Moreover, since the healthy are the harbinger of traits that cause disease, studies of the healthy are an underutilized resource. The purpose of the BTS is to answer fundamental questions regarding complex, common diseases.

It is our vision to set up a regional, population-based twin registry in the Berlin and Brandenburg areas in the future. Furthermore, we strive toward greater ties with international partners within various initiatives; a major step was the recent establishment of the Web site worldwidetwins.net as a platform for collaboration between twin registries.

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