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ORIGINAL ARTICLE

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Patients with congenital heart defect and their families support genetic heart research

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Abstract

Background: Congenital heart disease (CHD) affects up to 1% of live births the etiology remains relatively poorly understood. Thus, cardiac research is needed to understand the underlying pathomechanisms of the disease. About 51 000 CHD patients are registered in the German National Register for Congenital Heart Defects (NRCHD). Patients and relatives were interviewed online about their willingness to support genetic heart research in order to donate a biological sample.

Methods: Study participants were recruited via the database of the NRCHD. Seven thousand nine hundred eighty-nine patients were invited to participate in the study. Participants have been asked to rate three questions on a ten-staged Likert scale about their willingness to provide a saliva/blood sample and their motivation to ask family members to support genetic heart research.

Results: Overall, 2035 participants (patients/relatives) responded the online survey (25.5%). Two-thirds of the participants are willing to donate a saliva sample. Whereas the motivation to provide a blood sample is slightly lower (patients: 63.8%, relatives: 60.6%). Female relatives are more fain to provide a saliva sample as well as a blood sample compared to men (saliva sample: $P < .001$, blood sample: $P < .01$). The motivation to ask an additional family member for a biological sample was significantly higher in relatives (59.2%) compared to patients (48.4%).

Conclusions: The motivation to provide biological samples is high reflecting the need for genetic research to unravel the pathomechanism of CHD. A future aim should be to offer an individual risk assessment for each patient based on the underlying genetics.

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1 | BACKGROUND

Congenital heart disease (CHD) is the most common birth defect (0.8%–1%) and a leading cause for infant morbidity and mortality.[1,2] While much progress has been made regarding the management of children and adults with CHD, a better understanding of the underlying genetics will lead to further advances in preventive care and therapeutic strategies.[3]

Several explanations have been put forward to explain the complexity and heterogeneity observed among CHD cases, such as a polygenic model complicated by de novo mutations, incomplete penetrance, and environmental factors.[4] Technological advances such as next generation sequencing (NGS) opened a new field to discover monogenetic causes of CHD in both syndromic and nonsyndromic patients.[5] De novo mutations are a major cause of syndromic occurrences of CHD, but they are also observed among nonsyndromic cases.[5] In addition, nonsyndromic patients present with inherited high-risk variants with incomplete penetrance.[5] Although, a substantial proportion of CHD can be explained by these new techniques, the majority in particular among nonsyndromic remains unsolved. To fully unravel the underlying genetic architecture and its modifiers on the genetic and environmental level, large cohorts need to be analyzed. For example, to discover most dominant CHD-associated genes in syndromic patients power calculation point to a sample size of ~10 000 patients and their parents. For nonsyndromic patients, this challenge is even greater for identifying most genes harboring variants with incomplete penetrance. Therefore, multicenter register-based studies in combination with detailed phenotyping will be required to reach these numbers of cases for a powerful analysis. Unfortunately, genetic testing for CHD has not yet been implemented into routine diagnostic in Germany limiting its applicability.

To address this need for multicenter register-based studies in genetic cardiac research a biobank was established in the German National Register of Congenital Heart Defects (NRCHD) in 2009.[6] Beside the collection of DNA from patients with CHD and their biological relatives (eg parents, siblings), medical records and clinical data such as cardiac MRI and echo data are assembled. Phenotypic information on cardiac and noncardiac features is recorded using both the International Paediatric and Congenital Cardiac Code (IPCCC)[7] and HPO terms.[8] Therefore, the biobank provides extraordinary patient information to generate better genotype-phenotype correlations. By now, DNA of approximately 4200 patients with different types of CHD is stored in the biobank including DNA from over 430 trios (CHD-child + parents) and 120 families with more than one affected CHD patient. Additionally, the biobank comprises 1143 tissue samples from 556 patients after heart surgery.

Although the NRCHD with its 51 000 registered CHD patients is the largest register for CHD in Europe,[9] the main challenge remains the willingness of patients and their relatives to provide biological samples (saliva, blood) for genetic research. Since routinely genetic diagnostics is not applicable for all patients with CHD, genetic research needs to step in to unravel etiological mysteries that underpin CHD and provide new insights in the pathomechanism of CHD. In addition, the identification of the underlying genetics offers the potential to counsel families regarding future offspring and assists in risk assessment of each individual patient with CHD.

Therefore, the aim of the present study was to survey CHD patients and their family members about the willingness to provide a biological sample (saliva or blood) for genetic cardiac research.

2 | MATERIAL AND METHODS

In a primarily quantitative cross-sectional survey, patients and their relatives were asked about their willingness to donate a biological sample for genetic heart research. The survey was available online for a period of 30 days. The study participants were recruited through the database of the NRCHD. The inclusion criterion for study participation was the presence of a current email address. Seven thousand nine hundred eighty-nine patients were invited to participate in the study (4100 patients ≥18 years, 3889 patients <18 years). If the patient was too young or too sick to answer the survey, a family member was allowed to help out. The survey was carried out anonymously. An overview of the patient population and the cardiac diagnoses within the NRCHD is given by Helm et al[9] and Pfitzer et al.[10]

Eligible participants were first asked to indicate whether they had a CHD or whether they were a nonaffected family member (patient: "I have a congenital heart defect," relative: "I have no congenital heart defect, but someone in my family has a congenital heart defect"). Additionally, study participants had to state their age and gender.

The study participants were asked to answer three questions to assess the willingness to donate a biological sample:

1. Imagine the National Register for Congenital Heart Defects asks you for your help in heart research. How likely is it that you donate a saliva sample for genetic heart research (1 = very unlikely, 10 = very likely)?
2. Imagine the National Register for Congenital Heart Defects asks you for your help in heart research. How likely is it that you donate a blood sample for genetic heart research (1 = very unlikely, 10 = very likely)?
3. Imagine the National Register on Congenital Heart Defects asks you for your help in genetic heart research. How likely is it that you ask family members to support genetic heart research with a saliva or blood sample (1 = very unlikely, 10 = very likely)?

The ten-staged Likert scale has been divided into three categories:

1-6 = unlikely
7-8 = neutral
9-10 = likely

Statistical analysis was performed using the statistical software SPSS (version 22; IBM, Armonk, New York). Mean values were compared with *t* test. The online questionnaire was created using the software EFS-Survey.

3 | RESULTS

3.1 | Sample composition

Out of the initial 7989 invited patients, 2035 probands participated in the survey (response rate: 25.5%). Accounting all respondents, 52.9% had a CHD. 63.4% of the participants were women and the average age was 32.8 ± 14.2 years (men: 31.4 ± 16.1 years, women: 33.6 ± 12.9 years). Two hundred sixty-four participants were younger than 18 years. A detailed descriptive statistics on the sample composition is shown in Table 1.

TABLE 1 Sample composition

		Sample size	Average age
Study participants	Total	2035	32.8 ± 14.2 years
	Male	745 (36.6%)	31.4 ± 16.1 years
	Female	1290 (63.4%)	33.6 ± 12.9 years
Patients	Total	1076	29.6 ± 13.3 years
	Male	475 (44.1%)	30.3 ± 14.7 years
	Female	601 (55.9%)	29.1 ± 12 years
Relatives	Total	959	36.3 ± 14.4 years
	Male	270 (28.2%)	33.4 ± 18.3 years
	Female	689 (71.8%)	37.5 ± 12.4 years

3.2 | Willingness to donate a biological sample

Our data show that approximately two-thirds of eligible patients (67.7%) and relatives (66.9%) are willing to donate a saliva sample (Figure 1). Thereby, women (mean value = 8.6 ± 2.3) are significantly more fain to provide a saliva sample ($P < .001$) compared to men (mean value = 8.1 ± 2.7). These gender differences are apparent in both patients with CHD and interviewed family members (Figure 1).

The willingness to donate a blood sample is lower in both patients (63.8%) and relatives (60.6%) compared to saliva samples (Figure 1). In general, the alacrity of participating women (mean value = 8.3 ± 2.5) to contribute a blood sample is significantly higher ($P < .01$) than compared to men (mean value = 7.9 ± 2.8). In contrast to the willingness to provide a saliva sample, there are no gender differences among patients. Within the group of relatives, significant differences ($P < .001$) between women (mean value = 8.3 ± 2.6) and men (mean value = 7.5 ± 2.9) can be found (Figure 1).

Interestingly, the willingness to ask a family member for a biological sample is significantly higher in relatives (59.2%) compared to patients (48.4%) (Figure 1). As seen before, women are more willing to trouble a family member to donate a saliva or blood sample in comparison to men. Female patients are more fain to approach somebody within the family compared to male patients. These differences are not so evident between female and male relatives (Figure 1).

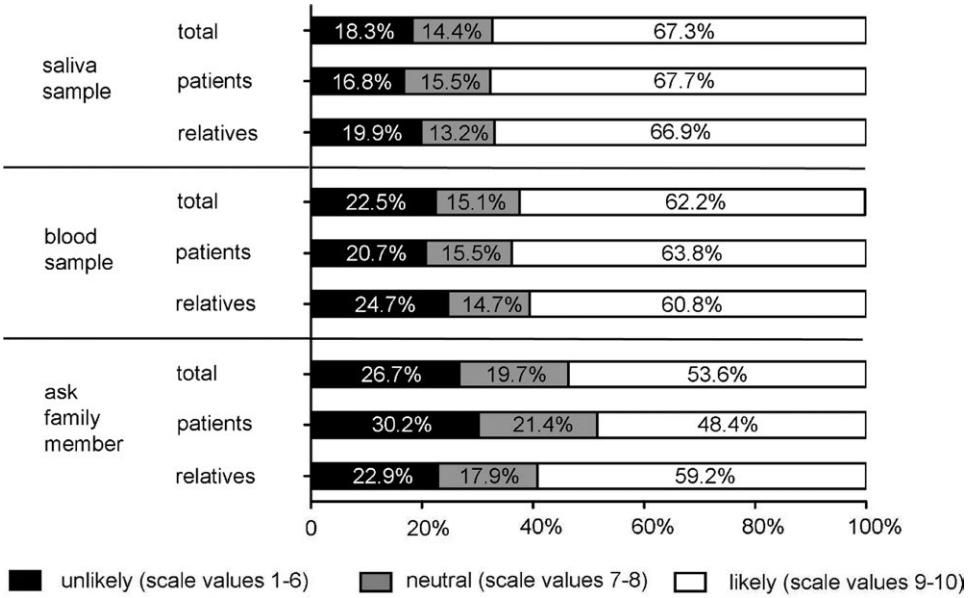

FIGURE 1 Assessment of questionnaire. Study participants were asked to answer three questions on a ten-tiered Likert scale (1-6 = unlikely, 7-8 = neutral, 9-10 = likely). Study participants were grouped into patients or relatives. Significant differences were found between male and female to provide a saliva sample (total (male vs female): $P < .001$; patients (male vs female): $P < .01$; relatives (male vs female): $P < .001$). The willingness to provide a blood sample was significantly higher in female relatives compared to male (total (male vs female): $P < .01$; relatives (male vs female): $P < .001$). The motivation to ask another family member to donate a biological sample was significantly higher for relatives compared to patients as well as for females compared to males (total (patients vs relatives): $P < .001$; total (male vs female): $P < .001$; patients (male vs female): $P < .001$; relatives (male vs female): $P < .05$

4 | DISCUSSION

We conducted a survey to investigate the willingness of patients with CHD and their relatives to donate a biological sample for genetic cardiac research. The participants were registered in the German National Register of Congenital Heart Defects (NRCHD). Due to the anonymous character of the survey, there is no information on the specific cardiac diagnoses but we assume that the distribution of CHD reflects the patient population of the NRCHD, which is representative for frequency scale in Germany and Europe.[9,10]

Approximately one-quarter of the invited probands responded to our survey. These results are in accordance with other email surveys.[11,12] We presume that the quality of the survey is still high taking in account that it has been shown that surveys with a return rate of 20% have the same informative value than surveys with response rates up to 70%.[13] In addition, Keeter et al found similar results by comparing two surveys with response rates of 25% and of 50%. The differences between these two surveys ranged from 4%–8%.[14] Other studies also support these findings.[15–17]

We observed that 26.8% more women took part in the questionnaire than men. The readiness of women to participate in online surveys has been described before.[17–20] The higher response rate in the patient group might be evoked by the interest to find out more about the underlying cause of their disease. In addition, patients might expect to benefit from new therapies, which might come out of genetic research. Both patients and their relatives suffer from a high psychological strain due to the chronic illness of the patient. The expectation in cardiac research might be considerable and therefore the willingness to donate a biological sample for genetic research is high in patients as well as in family members. Due to lifelong medical care patients are more frequently involved in research studies compared to healthy probands. This might strengthen the attitude toward research projects and lead to an increased willingness to provide a biological sample.[21–24] Approximately two-thirds of the participants are disposed to donate a saliva sample. The alacrity for a blood sample is slightly lower, which might be affected by the fact that a blood withdrawal is more invasive than the donation of a saliva sample. This observation has been described in several other studies before.[25,26] In Germany, the publicity of the German National Bone Marrow Donor Registry and related organizations to register as a stem cell donor by providing a saliva or blood sample, has evoked both the awareness and willingness to donate biological samples for medical purposes and research. Consequently, the attitude toward the donation of biological samples has changed within the population and a great number of people are willing to donate, which can also be depicted in our study.

The observation, that women are more fain to donate a saliva or blood sample than men regardless of whether they are patients or relatives might be explained by the higher willingness to participate in (online) studies in general[17–20] as well as by the fact that in the group of female relatives mothers were overrepresented. In the care of chronically ill patients mothers might be more involved than fathers and consequently the differences in willingness to donate a biological sample between male and female participants might be due to gender-specific coping and compliance strategies.

Interestingly, relatives showed a significantly higher motivation to ask additional family members for participation in genetic heart research by donating a biological sample than patients. One reason might be the desire to support the patient in order to ascertain the underlying cause of the disease and thus asking more people to participate. Otherwise, the patient might be afraid to impose additional burden on the family members besides the own disease and the accompanying challenges. The significantly higher willingness of women to approach a family member in order to donate a biological sample might be explained by a more open social behavior and cooperativeness as well as the easiness overcoming their inhibitions to ask for assistance.

5 | LIMITATIONS

The survey was a primarily quantitative descriptive cross-sectional study. It is not possible, therefore, to make statements about the constant stability of willingness to donate a biological sample in the future. We did not perform an alpha error correction in multiple tests because it was an explorative and descriptive study and we did not want to miss any possible group differences. Due to the ethically controversial topic of genetic research in the context of congenital chronic diseases, the survey was carried out anonymously in order to prevent socially desirable response behavior. Thus no cardiac main diagnosis or any other medical information is available.

6 | CONCLUSIONS

Despite much progress in the treatment of patients with CHD the underlying cause of the disease remains unknown in most of the cases. Therefore genetic heart research is mandatory and patients are asked to participate by donating a biological sample. Overall, our study showed that the willingness to donate a biological sample is high and patients as well as their relatives are motivated to recruit further family members. The positive attitude toward genetic heart research and the motivation to provide a biological sample by patients and their relatives support the need for genetic diagnostics to counsel families regarding recurrences risks of future offspring and to offer a risk assessment of each individual patient with CHD.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Conception and design of study: Helm, Bauer, Kahlert, Hitz

Acquisition of data: Helm, Bauer, Pickardt

Analysis and/or interpretation of data: Helm, Bauer, Kahlert, Hitz.
Drafting the manuscript: Helm

Critical revising of the manuscript: Abdul-Khaliq, Baumgartner, Kramer, Schlensak, Pickardt

ETHICS

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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