

The role of the geneticist and genetic counselor in an ACHD clinic

Ashley Parrott, Stephanie M. Ware*

The Heart Institute, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, 240 Albert Sabin Way, MLC 7020, Cincinnati, OH 45229-3039, USA

ARTICLE INFO

Keywords:

Genetics
Genetic counseling
Recurrence risk
Syndrome

ABSTRACT

There is a growing population of adults surviving with congenital heart disease due to the advancements in surgical repair and medical management. At the same time, the understanding of the genetic basis of both syndromic and isolated congenital heart disease has grown tremendously and is being rapidly translated into changes in clinical care, resulting in an increasing need for incorporation of genetic expertise into the care of adult congenital heart disease patients. Here we review the importance of delivery of genetic information to the adult congenital heart disease population and highlight the shared and distinct roles of clinical geneticists and genetic counselors in provision of services. The adult congenital heart disease patient population has unique needs and clinical geneticists and genetic counselors can play an important role in the diagnostic evaluation and assessment of these patients to provide an accurate etiologic diagnosis and to counsel regarding genetic testing, recurrence risk, family screening, and prenatal diagnosis.

© 2012 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

There is a growing population of adults surviving with congenital heart disease due to the advancements in surgical repair and medical management. At the same time, the understanding of the genetic basis of both syndromic and isolated congenital heart disease has grown tremendously. Advancements in genetic technologies now allow more precise diagnosis. Furthermore, an improved understanding of epidemiology, human genetics, and cardiac development has identified subclasses of cardiovascular malformations with increased heritability. Therefore, at a time when many patients with congenital heart disease are reaching childbearing age, there are substantial new insights into causation that may be relevant to their own medical condition as well as their recurrence risk. Medical genetics professionals can play an important role in the diagnostic evaluation and assessment of ACHD patients to provide an accurate etiologic diagnosis and to counsel regarding genetic testing, recurrence risk, family screening, and prenatal diagnosis.

2. Genetics care providers in the clinic

A clinical geneticist is a physician who has specific subspecialty training in medical genetics. In the United States, clinical geneticists are board certified through the American Board of Medical Genetics. Physicians must have 2 years of training in an ACGME accredited

residency program in another specialty and 2 years in an ACGME-accredited residency in clinical genetics. Training may also be accomplished as a residency combined with pediatrics, internal medicine, or obstetrics and gynecology (www.abmg.org). Most clinical geneticists obtain board certification in two specialties, most commonly pediatrics and clinical genetics. Clinical geneticists receive training in the diagnostic evaluation, management, and genetic counseling of patients with genetic disorders and their families.

A genetic counselor is a graduate level trained healthcare professional who receives training in both medical genetics and counseling. The National Society of Genetic Counselors describes genetic counseling as the process of helping people understand and adapt to medical, psychological, and familial implications of genetic contributions to disease. This process integrates: 1) interpretation of family and medical histories to assess the chance of disease occurrence or reoccurrence, 2) education about inheritance, testing, management, prevention, resources and research and 3) counseling to promote informed choices and adaptation to the risk or condition [1].

3. Rationale for involvement of genetics

The 2007 American Heart Association Scientific Statement on the genetic basis for congenital heart defects outlined four important reasons for making a genetic diagnosis in patients with congenital heart disease [2]. First, there may be other important organ system involvement for which screening or surveillance is indicated and which can be proactively managed. Second, there may be prognostic information for clinical outcomes. Third, there may important genetic reproductive risks. Fourth, there may be other family members for whom genetic testing (or other medical surveillance) is appropriate. The first reason presented in the AHA statement may appear to be geared

* Corresponding author at: Cincinnati Children's Hospital Medical Center, 240 Albert Sabin Way, MLC 7020, Cincinnati, OH 45229-3039, USA. Tel.: +1 513 636 9427; fax: +1 513 636 5958.

E-mail address: stephanie.ware@cchmc.org (S.M. Ware).

toward a pediatric population and less relevant for the ACHD patient population. However, it is not uncommon to encounter ACHD patients for whom diverse medical problems have never had a unifying diagnosis. Providing this information not only guides future management and therapy but is also frequently a source of relief for patients and allows increased understanding and engagement in their health care needs.

Current ACHD patients may not have been evaluated by genetics at the time of diagnosis. Those who were evaluated did not have access to the significant advances that have occurred in genetic testing in the interim. As described in more detail in the section on genetic testing, chromosome microarray analysis, fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), and the majority of single gene sequencing tests have only been available within the last 5–15 years. In many centers, newborns with complex cardiovascular malformations now routinely undergo genetic testing. For example, the 2007 AHA consensus statement advocates FISH testing for 22q11.2 deletion syndrome for all infants with interrupted aortic arch type B or truncus arteriosus; tetralogy of Fallot associated with absent pulmonary valve, aortic arch anomalies (including right aortic arch), pulmonary artery anomalies, or aortopulmonary collaterals; perimembranous ventricular septal defect and associated aortic arch abnormalities; or infants with isolated aortic arch abnormalities [2]. Recommendations for testing in the ACHD population have not been developed, but it is clear that the genetic testing now considered standard of care was not available when this patient population was first diagnosed.

The accuracy of genetic counseling about recurrence risk is determined by the accuracy of the patient's diagnosis. Based on epidemiologic studies such as the Baltimore–Washington infant study and the Danish National epidemiologic study, syndromic cardiovascular malformations comprise at least 25% of all cardiovascular malformations [3–5]. With the improvements in diagnostic yield with more sophisticated genetic testing, it is possible to identify a higher percentage. To our knowledge, no specific study on the yield of genetic testing in an unselected ACHD population has been performed. However, it is not rare to make a syndromic diagnosis in an adult. Geneticists are well trained to evaluate patients for possible genetic syndromic conditions including those conditions with markedly variable expressivity or decreased penetrance. In addition, geneticists can evaluate family members for other syndromic features and facilitate appropriate genetic testing or referrals.

Recent human genetic studies have also identified subclasses of cardiovascular malformations which show familial clustering and are highly heritable or more likely associated with underlying genetic causes [3,6]. Multiple epidemiologic studies show that isolated cardiovascular malformations show familial clustering and have high heritability. A recent Danish population-based study investigating absolute and relative recurrence risk of congenital heart disease strongly suggests that gene mutations are the underlying cause [3]. Three of the classes of defects with the highest relative risk of recurrence of the same heart defect phenotype were heterotaxy, with a relative risk of 79.1 (95% CI 32.9–190), right ventricular outflow tract defects, with a relative risk of 48.6 (95% CI 27.5–85.6) and left ventricular outflow tract obstructive (LVOTO) defects, with a relative risk of 12.9 (95% CI 7.48–22.2). Familial clustering of dissimilar types of heart defects also had an elevated relative risk of 3.02 [7], suggesting that common pathways that involve shared susceptibility genes may underlie a continuum of heart defects.

These findings are important because they alter information on recurrence risk based on type of cardiovascular lesion. Further, they suggest the importance of additional screening in first degree family members. For example, LVOTO defects including bicuspid aortic valve (BAV), aortic valve stenosis (AVS), coarctation of the aorta (CoA), and hypoplastic left heart syndrome (HLHS) have been shown to be highly heritable and multiple genetic loci have been

mapped [8–10]. The presence of an LVOTO lesion increases the risk of identifying BAV in a parent or children (relative risk 5.05) [11]. The high heritability of these malformations has been established with recurrence risks ranging from 5% risk of BAV in first degree family members of individuals with AVS, CoA, or HLHS to 22% recurrence risk of cardiovascular malformations in siblings of patients with HLHS [8,11,12]. These findings lead to a recommendation for echocardiographic screening in first degree relatives of an individual with AVS, CoA, or HLHS.

Current guidelines recommend counseling about recurrence risk for patients with ACHD. One recent study addressed the knowledge of ACHD patients regarding their diagnosis, family risk, and recurrence risk [13]. Over 50% of patients did not estimate recurrence risk in the correct range of magnitude. Additional information about inheritance of CHD was desired by 41% of patients. One-third of patients recalled receiving information from their cardiologists whereas 13% had been evaluated by a clinical geneticist. Approximately 60% of patients seen by a geneticist reported that the information was clear as compared to 29% receiving information from a cardiologist or nurse. Likewise, 60% reported receiving information about recurrence risk of CHD as compared to 28% receiving information from a cardiologist or nurse. While additional data are needed, these results indicate that genetic evaluation and genetic counseling are important components of ACHD care and developing improved methods for communicating genetic information and education in this patient population is important.

4. Role of the genetic counselor in the ACHD population

In the adult congenital heart disease clinic, the genetic counselor functions in several capacities, including obtaining a detailed family and medical history and interpreting that history for risk assessment; counseling the patient on recurrence risk associated with congenital heart disease and/or on risk for a specific genetic syndrome; facilitation of genetic testing and interpretation of results; and finally providing psychosocial support and counseling related to this genetic information. In the ACHD clinic, a genetic counselor may take on an additional role of triaging patients that should be referred for a complete genetic evaluation with a geneticist as well as suggesting other subspecialty referrals based on medical history.

4.1. Family and medical history

Genetic counselors aid in the process of genetic evaluation by obtaining detailed family and medical histories, beyond those histories routinely obtained due to time constraints of physicians involved in the care of patients seen in the ACHD clinic. This information should include focus on congenital heart disease as well as other possible associated non-cardiac concerns. Evaluation of a family history should begin with obtaining a pedigree. Standard pedigrees should include at least 3 generations and document family history of not only congenital heart disease but also other birth defects, learning disabilities, multisystem disease, and consanguinity. The detailed patient medical history obtained should include documentation of non-cardiac disease, particularly those which may be associated with genetic syndromes (Tables 1 and 2).

4.2. Counseling on recurrence risk and risk for a genetic syndrome

Interpretation of the family and medical history for assessment of recurrence risk or risk for a genetic syndrome is a key component of the genetic counseling process. One role of the genetic counselor in this patient population, after interpretation of the obtained family and medical history, is to explain inheritance patterns to a family. Possible inheritance patterns associated with congenital heart disease, both isolated and syndromic, include autosomal dominant, autosomal recessive, X-linked, and multifactorial. Genetic conditions following

Table 1
Characteristics of ACHD patients who benefit from genetics referral and evaluation.

Reason for referral	Examples/features
Suspicion of an underlying genetic syndrome	Intellectual disability; learning disability; autism; other cognitive impairment Dysmorphic features Short stature Congenital anomalies Endocrine abnormalities Sensory deficits such as hearing loss or visual impairment Neurological deficits or psychiatric illness Unexplained medical conditions
Family history of CHD, other malformations, learning disability, or multiple miscarriages	Family member with congenital heart defect (concordant or discordant) Family member with autism
Isolated CHD highly associated with specific syndromes	Interrupted aortic arch, truncus arteriosus etc.
Preconception or prenatal genetic counseling regarding recurrence risk	Parent with CHD interested in discussing recurrence risk for offspring before pursuing pregnancy Parent with 22q11.2 deletion syndrome for discussion of genetic testing in a future or current pregnancy
Facilitation of genetic testing; pre- or post-test genetic counseling	Provision of educational resources and anticipatory guidance after a positive genetic test result

these inheritance patterns each have their own recurrence risk which should be described to the family. For example, Noonan syndrome and Holt–Oram syndrome each follow an autosomal dominant pattern, with 50% risk of recurrence in offspring. Chromosomal deletion syndromes including 22q11.2 deletion syndrome also have a 50% risk of recurrence. Autosomal recessive conditions associated with congenital heart defects such as Primary Ciliary Dyskinesia generally have a low risk of recurrence for an individual's offspring, due to the fact that the patient's partner would also need to be a carrier in order for the offspring to have a 25% chance of being affected. X-linked inheritance typically appears in a family as males with the gene mutation being affected and females with the mutation being silent carriers. However in some cases, such as heterotaxy caused by ZIC3 mutations, the gene mutation may also more rarely result in heart defects in “carrier” females [14]. Therefore, specific knowledge of the disease causing gene is required for accurate counseling and testing.

It is well known that adults with congenital heart disease have an increased risk of recurrence of congenital heart disease in their offspring, whether the CHD in the family is isolated or syndromic. Recurrence risk for isolated CHD should be provided to patients based on cardiac lesion as discussed previously as well as gender of the patient. For mothers and fathers with isolated congenital heart disease, different empiric

recurrence risk information is available in the literature and should be called upon to provide the most accurate recurrence risk possible [3,7,11,15–17]. Knowledge of genes associated with isolated congenital heart disease is increasing. In some families mutations in genes important for cardiac development may cause autosomal dominant inheritance of isolated CHD and may be associated with reduced or incomplete penetrance. For example, *GATA4* is a gene implicated in non-syndromic CHD including septal defects and tetralogy of Fallot [18].

An additional component of risk assessment is determining the risk for a possible associated genetic condition related to the diagnosis of congenital heart disease. Information obtained by a genetic counselor through a family or medical history that is suggestive of a genetic syndrome should be considered as an impetus for evaluation by a medical geneticist. Additionally, some types of congenital heart disease with high correlation with a genetic syndrome may be sufficient to trigger genetic testing, as described above for specific conotruncal defects with correlation with 22q11.2 deletion syndrome. Genetic counselors are able to discuss with a family the concerning aspects of their family or personal medical history which indicate need for additional evaluation and/or genetic testing.

4.3. Facilitation of genetic testing and interpretation of results

Education and counseling regarding genetic testing options are an additional key component of the genetic counseling process. In an adult congenital heart disease clinic, genetic testing may need to be addressed in several areas. This includes discussion of testing options for individuals considering their reproductive options. Ideal genetic counseling is provided prior to pregnancy. For families with known genetic conditions with positive genetic test results, counseling includes testing options such as preimplantation genetic diagnosis, chorionic villus sampling (CVS), amniocentesis, and postnatal testing. Additionally, fetal echocardiography during pregnancy should be discussed for families with isolated or non-isolated CHD.

Adults with concern for genetic syndrome who are recommended to undergo genetic testing also benefit from genetic counseling. Counselors aid in identifying appropriate laboratories suitable for the genetic test of interest. Genetic counselors review benefits and limitations of genetic tests and explain testing to the patient in a detailed consent process including review of clinical sensitivity of testing, insurance coverage and cost of testing, timeline of expecting results, and explanation of basic science behind the testing technology at a level appropriate to the patient's developmental and educational background. Possible results from genetic testing are also reviewed including implications of a positive or negative test result, as well as the possibility of identifying a finding with unknown significance.

Finally, upon receipt and interpretation of genetic test results by providers involved in a patient's care, it is often the genetic counselor who discloses test results to the patient. Disclosure of results is an integral component of the testing process and the genetic counselor will

Table 2
Common genetic disorders in the ACHD population.

Syndrome	Cause	Diagnosis
22q11.2 Deletion syndrome (DiGeorge, velocardiofacial syndrome)	Deletion chromosome 22q11.2	FISH or MLPA for 22q11.2; chromosome microarray
Williams syndrome	Deletion chromosome 7q11.23	FISH for Williams or chromosome microarray
Jacobsen syndrome	Deletion chromosome 11q23	Chromosome analysis or chromosome microarray
1p36 Deletion syndrome	Deletion chromosome 1p36	Chromosome microarray; chromosome analysis in some cases
Turner syndrome	45, X karyotype, mosaicism, or other X chromosome abnormality	Chromosome analysis or chromosome microarray
Noonan syndrome	> 10 genes known to be causative	Single gene testing (<i>PTPN11</i> gene mutations in 50%); gene panel testing available
Alagille syndrome	Mutation in <i>JAG1</i> gene; rare mutations in <i>NOTCH2</i>	Single gene testing (<i>JAG1</i> mutations in 70–95%; <i>NOTCH2</i> mutations in <1%)
Holt–Oram syndrome	Mutation in <i>TBX5</i> gene	Single gene testing

help to ensure patient understanding, coping, and plan for follow-up. This often includes patient phone calls as well as patient counseling letters summarizing important test results. In instances where testing will be recommended for additional family members based on the patient's results, genetic counselors aid in facilitating evaluation for these relatives.

4.4. Psychosocial counseling and support

Finally, genetic counselors function in providing psychosocial support to patients with or at risk for genetic disease. In the ACHD population, this support may come for patients dealing with feelings of worry or guilt regarding risk of recurrence of CHD or a genetic syndrome in their offspring. Those individuals with a newly diagnosed genetic condition may benefit from support provided with additional resources including educational materials and information on support groups as well as anticipatory guidance that a genetic counselor can provide. Adults with congenital heart disease may face difficult decisions regarding personal and reproductive genetic testing options, and counselors serve to facilitate the decision-making process in a non-coercive manner [19].

5. Genetic evaluation

ACHD clinics have the opportunity to play an important role in identifying patients who would benefit from additional genetic evaluation or genetic counseling. In a non-scientific poll of the audience at the 21st Annual International Adult Congenital Heart Disease Course, nearly 25% reported functioning with genetics professionals as part of a multidisciplinary clinic (Fig. 1). However, of the remaining practitioners, only 18% reported regular referral to genetics, defined as a protocolized referral pattern in which specific features such as cardiac lesion, extra-cardiac findings, or family history automatically trigger referral.

Identifying patients who should undergo further assessment may require a high level of suspicion. In a 2005 study of 103 consecutive adult patients with conotruncal malformations, Beauchesne et al. identified a prevalence of 22q11.2 deletion of 5.8% [20]. Half of those patients reportedly did not have physical features of 22q11.2 deletion. When should a referral to a geneticist be considered? The answer may vary depending on the knowledge and comfort-level of the ACHD physician with genetic disorders and testing, clinic structure, and access to genetic expertise and local resources. Certainly any patient with multiple congenital anomalies or CHD and intellectual disability should have a comprehensive examination by a geneticist (Table 1). Likewise,

any patient with a known genetic diagnosis should be re-referred to genetics if they have been lost to follow-up or if they are having non-cardiac medical problems. There are a number of new health supervision guidelines for syndromes such as Turner syndrome, Noonan syndrome, and 22q11.2 deletion syndrome that take into account newer longitudinal patient information and would benefit the medical care of ACHD patients [21–24]. Thirdly, screening for patients who have a family history that could impact management and education should be undertaken. Those individuals with a positive family history should be further evaluated by a clinical geneticist. As discussed above, all ACHD patients should be counseled regarding their recurrence risk. The ability to provide lesion-specific and gender-specific recurrence risks is improving. Since the accuracy of genetic counseling about recurrence risk is determined by the accuracy of the patient's diagnosis, in some cases genetic testing may be warranted in order to provide the most comprehensive information. Evidence is lacking regarding the best methods for communicating recurrence risk and counseling information to ACHD patients, but recent data indicate that the patients would like more information than is routinely provided [13]. Reasons for referral to a geneticist are summarized in Table 1.

6. Genetic testing

Recent advances in genetic technology have had a significant impact on the practice of clinical genetics and the diagnosis of genetic syndromes associated with cardiac malformations as well as sporadic congenital heart disease (Table 2). Advancements in both chromosome-based testing as well as sequencing has led to expansion of the spectrum of well described genetic syndromes since individuals with non-classic features are increasingly being given a genetic diagnosis. Chromosome-based testing evaluates chromosome number and structure. Gene-based testing evaluates the individual DNA nucleotides (letters) to determine whether a mutation (misspelling) is present. The audience at the 21st Annual International Adult Congenital Heart Disease Course reported distinct approaches to their use of genetic testing (Fig. 2).

6.1. Chromosome based testing

Chromosome analysis (karyotype) is the most well-known genetic test. This testing identifies abnormalities in chromosome number and structure. It is the test of choice for suspicion of aneuploidies such as Turner syndrome, Down syndrome, Trisomy 13, and Trisomy 18. Less common large chromosomal rearrangements and deletions are also detected. Chromosome analysis has a low yield in patients with apparently isolated heart defects.

Chromosome microarray testing is a relatively new method that allows for comprehensive interrogation of hundreds or thousands of discrete genomic locations. The development of chromosome microarray

ACHD Clinic use of Genetics Professionals

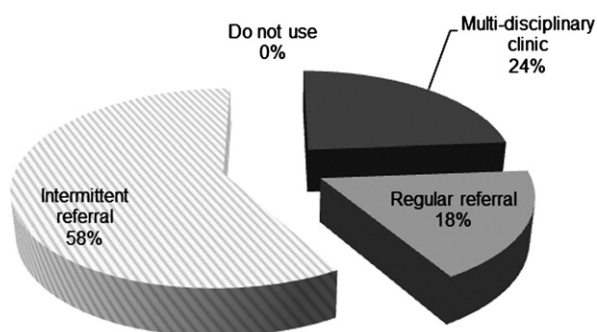


Fig. 1. Representation of mechanisms by which ACHD clinics access genetics expertise. Regular referral is defined as a protocolized referral pattern based on specific medical history or physical exam findings.

Genetic Testing by ACHD Physicians

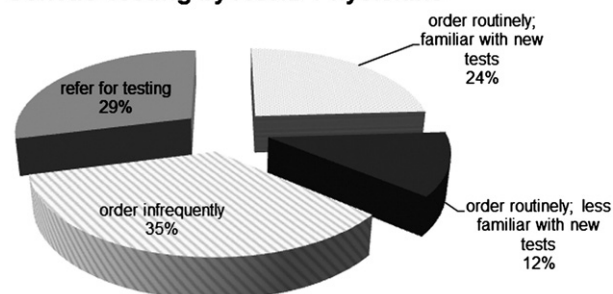


Fig. 2. Use of genetic testing by ACHD physicians.

technology has largely replaced routine chromosome analysis and has led to the identification of a number of new genomic disorders resulting from microdeletions or microduplications of genetic material. Chromosome microarray will detect common conditions associated with CHD such as 22q11.2 deletion and Williams syndrome. Several studies have analyzed the diagnostic yield of microarray testing specifically in patients with CHD and have shown abnormalities in 15–25% [25–28]. The yield is higher in patients with multiple congenital anomalies. No studies have been performed to determine the yield of microarray testing specifically in the ACHD population. A recent consensus statement recommends microarray as standard of care genetic analysis for patients with intellectual disability, developmental delay, autism spectrum disorders, and multiple congenital malformations [29].

Multiplex ligation-dependent probe amplification (MLPA) provides targeted analysis of a specific region of the genome. It is technically similar to microarray but rather than providing information across the genome, it analyzes only a specific region of interest. MLPA has been used widely by some centers for diagnosis of 22q11.2 deletion syndrome. MLPA allows precise detection of the size of the deletion, a feature not available by FISH testing.

Like MLPA, FISH testing is targeted testing for deletions or duplications that would be missed by routine chromosome analysis because of their relatively small size. Microarray technology is capable of detecting any condition identifiable by FISH. For example, FISH for 22q11.2 deletion syndrome is greater than 95% sensitive. However, it may miss smaller deletions that can be detected by MLPA or microarray. When strongly suspicious of a specific genetic diagnosis, FISH testing is a fast and economical approach to diagnosis.

6.2. Gene based testing

Many cardiovascular malformations are caused by mutations in a specific gene rather than chromosomal or submicroscopic chromosomal abnormalities. Genetic syndromes such as Noonan syndrome exhibit marked locus heterogeneity with causative mutations occurring in several different genes. Importantly, chromosome-based testing methods will not detect these mutations. Isolated cardiovascular malformations are also frequently caused by single gene defects, and clinical testing is becoming increasingly available.

7. Common genetic syndromes in the ACHD population

Several recent publications highlight important syndromic conditions that are common in the ACHD population [2,22,30]. Lin et al. specifically highlight the longitudinal history and management problems that typify specific syndromic diagnoses including the importance of extra-cardiac management [22]. An overview of the most common syndromes likely to be identified in the ACHD clinic, not including aortopathy, is presented in Table 2.

8. Conclusions

ACHD patients have unique needs for genetic evaluation, testing, and counseling. New advances in diagnosis of isolated and syndromic CHD are being translated into changes in clinical care. Emerging information on inheritance and recurrence risk allow the opportunity to provide better education and counseling to ACHD patients about recurrence risk. Identifying adult patients that benefit from additional genetic evaluation and testing and providing appropriate information and education are important for providing optimal care for the patient and family. The model for provision of genetic services to the ACHD population may vary depending on patient population, ACHD provider expertise, and local genetic services. Preliminary studies indicate that the ACHD patient population desires more education and information regarding the genetic basis of their CHD. Clinical

geneticists and genetic counselors should play an increasing role in the delivery of care to this patient population.

Acknowledgments

S.M.W. is supported by grant funding from the NIH/NHLBI, March of Dimes, Burroughs Wellcome Fund, and Children's Cardiomyopathy Foundation.

References

- [1] Resta R, Biesecker BB, Bennett RL, et al. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns* 2006;15:77–83.
- [2] Pierpont ME, Basson CT, Benson Jr DW, et al. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007;115:3015–38.
- [3] Oyen N, Poulsen G, Boyd HA, et al. Recurrence of congenital heart defects in families. *Circulation* 2009;120:295–301.
- [4] Ferencz C, Boughman JA, Neill CA, Brenner JJ, Perry LW. Congenital cardiovascular malformations: questions on inheritance. Baltimore–Washington Infant Study Group. *J Am Coll Cardiol* 1989;14:756–63.
- [5] Ferencz C, Neill CA, Boughman JA, et al. Congenital cardiovascular malformations associated with chromosome abnormalities: an epidemiologic study. *J Pediatr* 1989;114:79–86.
- [6] Burn J, Brennan P, Little J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. *Lancet* 1998;351:311–6.
- [7] Oyen N, Poulsen G, Wohlfahrt J, et al. Recurrence of discordant congenital heart defects in families. *Circ Cardiovasc Genet* 2010;3:122–8.
- [8] Hinton Jr RB, Martin LJ, Tabangin ME, et al. Hypoplastic left heart syndrome is heritable. *J Am Coll Cardiol* 2007;50:1590–5.
- [9] Martin LJ, Ramachandran V, Cripe LH, et al. Evidence in favor of linkage to human chromosomal regions 18q, 5q and 13q for bicuspid aortic valve and associated cardiovascular malformations. *Hum Genet* 2007;121:275–84.
- [10] McBride KL, Zender GA, Fitzgerald-Butt SM, et al. Linkage analysis of left ventricular outflow tract malformations (aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart syndrome). *Eur J Hum Genet* 2009;17:811–9.
- [11] Lewin MB, McBride KL, Pignatelli R, et al. Echocardiographic evaluation of asymptomatic parental and sibling cardiovascular anomalies associated with congenital left ventricular outflow tract lesions. *Pediatrics* 2004;114:691–6.
- [12] McBride KL, Pignatelli R, Lewin M, et al. Inheritance analysis of congenital left ventricular outflow tract obstruction malformations: segregation, multiplex relative risk, and heritability. *Am J Med Genet A* 2005;134A:180–6.
- [13] van Engelen K, Baars MJ, van Rongen LT, et al. Adults with congenital heart disease: patients' knowledge and concerns about inheritance. *Am J Med Genet A* 2011;155A:1661–7.
- [14] Ware SM, Peng J, Zhu L, et al. Identification and functional analysis of ZIC3 mutations in heterotaxy and related congenital heart defects. *Am J Hum Genet* 2004;74:93–105.
- [15] Nora JJ. From generational studies to a multilevel genetic-environmental interaction. *J Am Coll Cardiol* 1994;23:1468–71.
- [16] Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. *Am J Med Genet* 1988;29:137–42.
- [17] Whittemore R, Wells JA, Castellsague X. A second-generation study of 427 probands with congenital heart defects and their 837 children. *J Am Coll Cardiol* 1994;23:1459–67.
- [18] Wessels MW, Willems PJ. Genetic factors in non-syndromic congenital heart malformations. *Clin Genet* 2010;78:103–23.
- [19] Veach PM, LeRoy B, Bartels DM. Facilitating the genetic counseling process: a practice manual. New York: Springer; 2003. xii, 308 pp.
- [20] Beauchesne LM, Warnes CA, Connolly HM, et al. Prevalence and clinical manifestations of 22q11.2 microdeletion in adults with selected conotruncal anomalies. *J Am Coll Cardiol* 2005;45:595–8.
- [21] Bassett AS, McDonald-McGinn DM, Devriendt K, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. *J Pediatr* 2011;159:332–9 [e331].
- [22] Lin AE, Basson CT, Goldmuntz E, et al. Adults with genetic syndromes and cardiovascular abnormalities: clinical history and management. *Genet Med* 2008;10: 469–94.
- [23] Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* 2010;126:746–59.
- [24] Saenger P, Wikland KA, Conway GS, et al. Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001;86:3061–9.
- [25] Erdogan F, Larsen LA, Zhang L, et al. High frequency of submicroscopic genomic aberrations detected by tiling path array comparative genome hybridisation in patients with isolated congenital heart disease. *J Med Genet* 2008;45:704–9.
- [26] Breckpot J, Thienpont P, Peeters H, et al. Array comparative genomic hybridization as a diagnostic tool for syndromic heart defects. *J Pediatr* 2010;156:810–7 [817 e811–817 e814].

- [27] Lu XY, Phung MT, Shaw CA, et al. Genomic imbalances in neonates with birth defects: high detection rates by using chromosomal microarray analysis. *Pediatrics* 2008;122:1310–8.
- [28] Richards AA, Santos LJ, Nichols HA, et al. Cryptic chromosomal abnormalities identified in children with congenital heart disease. *Pediatr Res* 2008;64:358–63.
- [29] Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86:749–64.
- [30] Bernier FP, Spaetgens R. The geneticist's role in adult congenital heart disease. *Cardiol Clin* 2006;24:557–69 [v–vi].