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Editorial

A single mutation causes a spectrum of cardiovascular defects: the potential role of genetic modifiers, epigenetic influences, and stochastic events in phenotypic variability

Keywords: CHF1; Hey2; Gridlock; Hrt2; Hesr2; Sox10; Tbx1; Tbx5; Epigenetic; Genetic modifiers; Ventricular septal defect; VSD; Outflow tract; Mouse; Developmental noise; Stochastic; BALB/c; C57BL/6; Hirschsprung; DiGeorge; Holt–Oram

How can an identical mutation result in distinct phenotypes in different individuals? This simple question underscores the importance of genetic background in disease severity and progression and highlights one of the challenges in understanding complex diseases. The role of genetic modifier genes in phenotypic variability and disease progression has long been appreciated, but the identification of modifiers has been difficult particularly in the highly variable human population [1]. There are numerous examples of variability in disease progression in humans, even in cases where identical causative mutations are present, indicating a strong influence of familial history and genetic background [1].

1. Hirschsprung disease: a congenital disorder with incomplete penetrance and phenotypic variability

A classic example of a variable human congenital disease phenotype is seen in the genetics of Hirschsprung disease. Hirschsprung disease is a disorder affecting the developing neural crest and is characterized by congenital intestinal aganglionosis with associated pigmentation defects and hearing loss in some cases [2]. Hirschsprung disease is clearly a genetic disorder with mutations in the genes encoding the RET receptor or its ligands or in the gene encoding the transcription factor Sox10 making up the majority of human cases [2,3]. Interestingly, however, for each of the Hirschsprung disease genes identified to date, incomplete penetrance and variable phenotypes have been observed, presumably due to modifier loci [2,3]. The variability ranges from no phenotype to severe aganglionosis in the presence of the same causative mutation [3]. However, the identification of these modifiers has been difficult. In this regard, the development of mouse models of human congenital anomalies has proven valuable. The ability to mutate genes in mice using reverse genetic strategies, combined with the availability of inbred strains, has allowed investigators to reduce phenotypic variability due to genetic background effects within a given strain and then to use differences in phenotype in different strains to map modifier loci. In the case of Hirschsprung disease, several modifiers of *Sox10* have been identified in mice, including *Sox8* and the endothelin receptor gene *Ednrb* [4,5]. Several additional loci have been identified as modifiers of *Sox10* by examining differences in the severity of the megacolon phenotype in two different inbred mouse strains by linkage analysis [6].

2. Several congenital cardiac disorders display phenotypic variability

Several examples of mutations that affect cardiovascular development and display significant variation in phenotype or disease severity have also been described, and a number of these mutations occur in genes encoding cardiac restricted transcription factors. A well-studied example is the microdeletion of human chromosome 22q11 or DiGeorge syndrome (DGS), which causes craniofacial and cardiovascular defects as well as several other abnormalities [7]. The most common deletion results in the loss of approximately 3 Mb and about 30 genes in the region [8]. DGS may be a contiguous gene deletion syndrome where multiple genes in the region contribute to the disease phenotype, or it may result primarily from the loss of a single gene *TBX1* [8]. Indeed, Yagi et al. [9] identified patients with mutations in *TBX1* that exhibited phenotypes characteristic of the complete syndrome, suggesting that mutations in *TBX1* may be the primary lesion in DGS. Interestingly, family members carrying the same *TBX1* mutation exhibited a highly variable phenotype ranging from mild to severe, implicating an important role for modifier genes [9]. Work in mice has suggested that *Crkl*, a gene commonly deleted in the DGS critical region on 22q11, may be responsible for some of the symptoms of DGS, which supports the idea of DGS being a contiguous gene deletion syndrome [10]. In addition, other work in mice has shown that deletion of *Fgf8*, which encodes a signaling molecule involved in pharyngeal arch development, results in a phenocopy of DGS

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[11]. *Fgf8* is not present in the DGS critical region, and it appears to be downstream of Tbx1 in the mouse, which suggests the strong possibility that *Fgf8* may be a modifier of *Tbx1* in mice and possibly in DGS in humans [11–13]. Additional work in mouse models will be important to define the role of other genes that are linked and unlinked to the DGS critical region for their role as modifiers of the DGS phenotype.

Mutations in the *TBX5* gene, which encodes another T box transcription factor related to Tbx1, cause Holt–Oram syndrome [14,15]. Holt–Oram syndrome is a haploinsufficiency disorder that results in congenital heart and forelimb defects and is characterized by a high degree of phenotypic variability, which is thought to be due in large part to the influence of genetic modifiers [15]. Again, *Tbx5* heterozygosity in mice recapitulates the majority of the Holt–Oram phenotype and provides the opportunity to identify modifier genes that influence the phenotype in mice and probably in humans as well [16]. Heterozygous mutations in the homeodomain transcription factor gene *NKX2-5* are associated with familial cases of atrial septal defects in humans [17]. In still another example, mice with a targeted null mutation in *Nkx2-5* also exhibit defects in the atrial septum, and the severity of these defects is dependent on genetic background and the likely effects of modifier genes [18].

3. Deletion of *CHF1*/Hey2 in mice results in variable cardiac defects depending on genetic background

Another excellent example of genetic background influencing phenotype in mice harboring a transcription factor gene mutation is observed with the *cardiovascular basic helix–loop–helix factor 1* (*CHF1*) gene. *CHF1* (also known as Hrt2, Hey2, and hesr2) encodes a basic helix–loop–helix (bHLH) transcription factor related to *Drosophila* Hairy and functions as a downstream effector of Notch signaling [19–21]. CHF1 is expressed in the developing ventricular myocardium from early in mouse development and appears to function as a transcriptional repressor via the recruitment of corepressors and histone deacetylases [20]. The *CHF1* ortholog in the zebrafish, *gridlock*, was shown to be essential for the initial formation of the aorta and suggested that the bHLH transcription factor encoded by *gridlock* was important for arterial endothelial cell specification [19,22]. Interestingly, several independent *CHF1* knockouts have been generated in mice and none displayed obvious vascular defects of the type seen in zebrafish with the *gridlock* mutation [23–26]. Furthermore, the null phenotype of each of the different *CHF1* knockouts was different. Each had a cardiac phenotype, but the range, type, and severity of the defects differed among the different knockouts. In one case, the primary defect was a fatal cardiomyopathy [25], while another group reported cardiomyopathy and an associated ventricular septal defect [23]. In another case, knockout mice exhibited a broader array of defects grossly resembling Tetralogy of Fallot, including pulmonic stenosis, right ventricular hypertrophy, and ventricular septal defects, as well as tricuspid atresia [24]. Finally, a more recent study has suggested that the primary defect in the absence of *CHF1* is in atrioventricular valve development [26].

As is the case for many mutations, variability in *CHF1* null phenotypes observed in mice has been explained as the likely influence of modifier genes due to variation in genetic background [20,27,28]. In this issue of the *Journal of Molecular and Cellular Cardiology*, Sakata et al. [27] present the first systematic study designed to determine the role of genetic background in the phenotypic variation observed in the absence of *CHF1* in mice by examining the loss of this gene in two different inbred strains of mice. The authors of the present study observe significant differences when *CHF1* is deleted in BALB/c compared to C57BL/6 backgrounds, and the phenotypes observed in each of these backgrounds are different from those observed in previous studies [23–27]. Mice lacking CHF1 in either the BALB/c or the C57BL/6 background are viable at birth, indicating that CHF1 is not required for development. However, by weaning, nearly all the homozygous null animals were dead, regardless of background, indicating a requirement for postnatal viability. Sakata et al. observe a spectrum of phenotypes resulting from loss of CHF1 in an inbred C57BL/6 background, including valve defects, large ventricular septal defects, and ventricular wall thinning. A spectrum of defects were also observed when *CHF1* was deleted in the BALB/c background, but the defects were different than those observed in the C57BL/6 background. *CHF1* deletion in the BALB/c background resulted in a moderate incidence of dysmorphic ventricular septum, small ventricular septal defects, valve defects, and occasional overriding aorta and immature right ventricle development. Ventricular septal defects were present in the absence of *CHF1* in both backgrounds, but the penetrance and severity differed with 100% penetrance and severe ventricular septal defects observed in the C57BL/6 background and much milder and only partially penetrant ventricular septal defects observed in the BALB/c background. Furthermore, ventricular wall thinning was only observed in the C57BL/6 background, and overriding aorta was only observed in the BALB/c background.

Mutation of the *CHF1* ortholog, *gridlock*, in the zebrafish results in defective outflow tract development, and those studies have suggested that the primary defects in the zebrafish mutants are vascular in origin [19,22]. Surprisingly, none of the previous studies of *CHF1* mutant mice has reported anatomical vascular defects [23–26]. Importantly, in their study, Sakata et al. [27] observed defective outflow tract development in the absence of *CHF1* in a C57BL/6 background. In that background, both the aorta and pulmonary artery have thinner walls, and this phenotype is probably due to decreased vascular smooth muscle proliferation [29]. The defects in vessel wall thickness indicate a role for CHF1 in vascular development in the mouse and reinforce the conservation of this transcription factor's function across divergent classes of vertebrates [27].

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