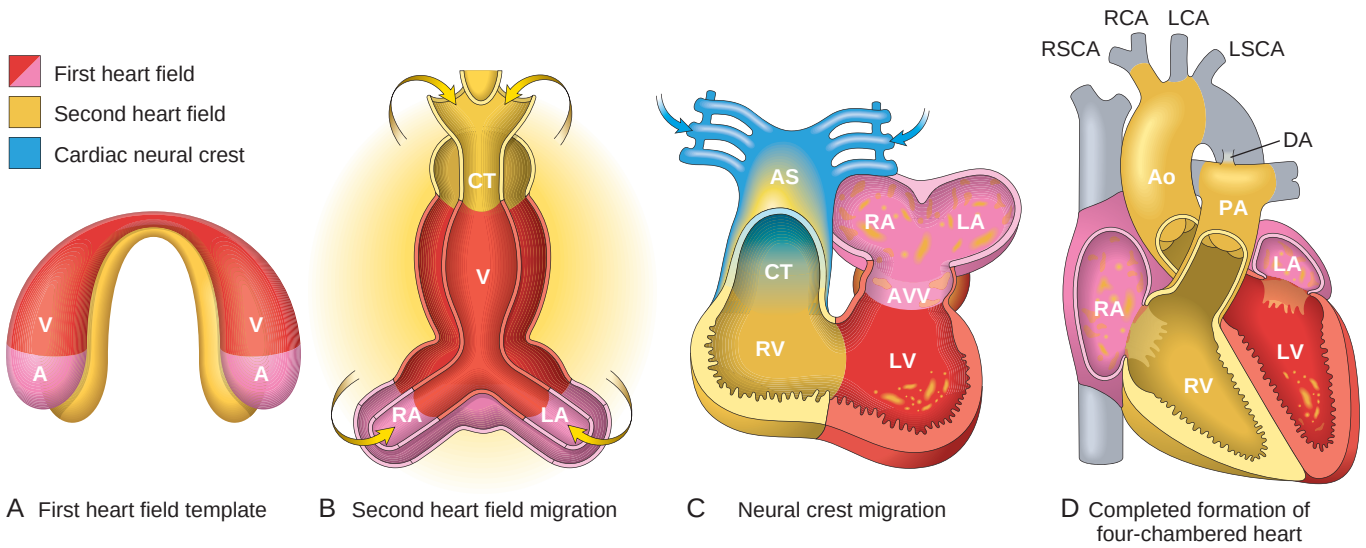

Figure 12-3 Human cardiac development, emphasizing three main sources of cells. **A,** Day 15. First heart field (FHF) cells (shown in red) form a crescent shape in the anterior embryo with second heart field (SHF) cells (shown in yellow) near the FHF. **B,** Day 21. SHF cells lie dorsal to the straight heart tube and begin to migrate *(arrows)* into the anterior and posterior ends of the tube to form the right ventricle, conotruncus (CT), and part of the atria (A). **C,** Day 28. Following rightward looping of the heart tube, cardiac neural crest cells (shown in blue) also migrate *(arrow)* into the outflow tract from the neural folds to septate the outflow tract and pattern the bilaterally symmetric aortic arch arteries. **D,** Day 50. Septation of the ventricles, atria, and atrioventricular valves (AVV) results in the appropriately configured four-chambered heart. Ao, Aorta; AS, aortic sac; DA, ductus arteriosus; LA, left atrium; LCA, left carotid artery; LSCA, left subclavian artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RCA, right carotid artery; RSCA, right subclavian artery; V, ventricle. (Modified with permission from Srivastava D: Making or breaking the heart: from lineage determination to morphogenesis. Cell 126:1037, 2006.)

Many of the inherited defects that affect heart development involve genes that encode transcription factors; these typically cause partial loss of function and are autosomal dominant (discussed later). Even relatively minor decrements in activity can result in significant defects. Moreover, transient environmental stresses during the first trimester of pregnancy that alter the activity of these same genes could conceivably lead to acquired defects that mimic those produced by heritable mutations.

Etiology and Pathogenesis. **Sporadic genetic abnormalities are the major known causes of congenital heart disease.** They can take the form of single gene mutations, small chromosomal losses, and additions or deletions of whole chromosomes (trisomies and monosomies). In the case of single gene mutations, the affected genes encode proteins belonging to several different functional classes (Table 12-3); as noted earlier, many of these involve transcription factors. Since affected patients are heterozygous for such mutations, it follows that a 50% reduction in the activity of these factors (or even less) may be sufficient to derange cardiac development.

Moreover, many of the transcription factors interact in large protein complexes, providing a rationale for why mutations in any one of several genes can produce similar defects. Thus, GATA4, TBX5, and NKX2-5, three transcription factors that are mutated in some patients with atrial and ventricular septal defects, all bind to one another and co-regulate the expression of target genes required for proper cardiac development. Of further interest, GATA4 and TBX20 are also mutated in rare forms of adult-onset cardiomyopathy (discussed later), indicating important roles not only in development but also in maintaining normal function of the postnatal heart.

Table 12-3 Selected Examples of Gene Defects Associated with Congenital Heart Disease*

Disorder	Gene(s)	Gene Product Function
Nonsyndromic		
ASD or conduction defects	*NKX2.5*	Transcription factor
ASD or VSD	*GATA4*	Transcription factor
Tetralogy of Fallot	*ZFPM2* or *NKX2.5*	Transcription factors
Syndromic†		
Alagille syndrome—pulmonary artery stenosis or tetralogy of Fallot	*JAG1* or *NOTCH2*	Signaling proteins or receptors
Char syndrome—PDA	*TFAP2B*	Transcription factor
CHARGE syndrome—ASD, VSD, PDA, or hypoplastic right side of the heart	*CHD7*	Helicase-binding protein
DiGeorge syndrome—ASD, VSD, or outflow tract obstruction	*TBX1*	Transcription factor
Holt-Oram syndrome—ASD, VSD, or conduction defect	*TBX5*	Transcription factor
Noonan syndrome—pulmonary valve stenosis, VSD, or hypertrophic cardiomyopathy	*PTPN11, KRAS, SOS1*	Signaling proteins

ASD, Atrial septal defect; CHARGE, posterior *c*oloboma, *h*eart defect, choanal *a*tresia, *r*etardation, *g*enital and *e*ar anomalies; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
*Different mutations can cause the same phenotype, and mutations in some genes can cause multiple phenotypes (e.g., *NKX2.5*). Many of these congenital lesions also can occur sporadically, without specific genetic mutation.
†Only the cardiac manifestations of the syndrome are listed; the other skeletal, facial, neurologic, and visceral changes are not.