In a population of patients with congenital heart defect (CHD) about 30% presents an association with genetic syndromes while about 70% have an isolated non-syndromic defect. Among these children with non-syndromic CHD the majority presents a sporadic defect while about 3-5% presents familial recurrence.

In 1968, Nora introduced the multifactorial model for the etiology of non-syndromic CHDs, suggesting that several genetic loci can interact together, in association with environmental factors. By following this hypothesis the genetic predisposition could be represented by several minor genes acting together, by one major gene acting with several minor genes or by a single major gene and the risk of recurrence could be estimated from 3 to 10 %, depending of the different CHD involved, the number of sibs affected, and the presence or absent of a CHD in the family.

In patients with AVCD for example, the frequency of cardiac defects corresponds to 3,6% in siblings and it is similar to that reported by the multifactorial hypothesis with prevalently an autosomal dominant concordant mechanism. A recurrence risk corresponding to about 10% for an affected parents could be estimated, but mothers seems to have a higher risk to transmit the defect in comparison to affected fathers perhaps because mitochondrial inheritance. In fact, the risk rate for offspring becomes 14% when the affected parent is the mother.

Two genes are recently involved in familiar AVCD: the p93 (chromosome 1p) and CRELD1 (chromosome 3p).

In patients with non syndromic tetralogy of Fallot, a recurrence risk of 3.1 % has been recognized with a model different from the vertical autosomal segregation of AVCD. This pattern is prevalently horizontal, showing recurrence in two or three sibs. No relation with non syndromic TOF and del22q11 has been reported supporting the hypothesis that non-syndromic TOF is not related to this chromosomal anomaly, but genes located on different chromosomes may be implicated.

Several genes have been identified as a cause of TOF, including Nkx2.5, JAGGED 1, and FOG2 but with a low penetrance.

Analyzing patients with familial transposition of the great arteries (TGA) has been demonstrated that familial recurrence is higher than previously thought, with a recurrence risk in sibs corresponding to 1.8 %.

It is important to note that, additionally to familial evidences, the pathogenetic link between TGA and laterality defects is also corroborated by molecular evidences showing mutations of genes related to laterality defects in mice and humans with complete TGA. So TGA should be considered, in the spectrum of laterality defects, as a cardiac anomaly limited at the conotruncal level.

An autosomal dominant transmission seems to be found analyzing familial cases of ASD. This genetic model is heterogeneous even thought a phenotype-genotype correlation could be identified in some families. In patients with ASD associated to AV block or pulmonary stenosis a link to mutations of the Nkx2.5 and GATA4 gene has been recognized.
In the group with left-sided heart defects, both vertical and horizontal transmissions have been found, suggesting the involvement of genes acting with an autosomal dominant mode and genes acting with an autosomal recessive transmission. This could be the reason for trying to explain as hypoplastic left heart syndrome, aortic coarctation, aortic stenosis and bicuspid aortic valve may segregate together in the same family.

In conclusion, the study of familial cases of CHD is particularly useful for:
- the practical clinical impact,
- the opportunity of making a correct genetic counselling for the families,
- for the possible pathogenetic links between CHDs,
- for new molecular studies and for the identifications of new genes
- and for the peculiar mechanisms of inheritance that we can not understand...... yet.

Bibliography

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