

CONGENITAL CARDIAC DEFECTS

CHROMOSOMAL & GENETIC ABNORMALITIES

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CONGENITAL CARDIAC DEFECTS

- Congenital anomalies are present in ~3% of live births
- Congenital heart disease (CHD) are the most common single group of congenital anomalies
 - *30% of the total abnormalities*

CONGENITAL CARDIAC DEFECTS

- Incidence is varying from 4-50/1000 live births
- 10% of spontaneously aborted fetus
- CHD occur as an isolated malformation in most patients
- But also about 33% have associated anomalies

ETIOLOGY

- Isolated heart defect
 - *Chromosomal abnormalities (numerical & constitutional)*
 - *Microdeletion syndromes*
 - *Single gene disorders (syndromic and nonsyndromic)*
- Maternal diabetes
- Teratogenic agents

PRENATAL DIAGNOSIS

- CHD can be identified in prenatal period by
 - *Detailed US*
 - *Amniocentesis, CVS and cordocentesis (karyotype)*
- Second anomaly is very important to diagnosis
- The family history can be the key for diagnosis

PRENATAL DIAGNOSIS

- Precise and correct diagnosis is important for determining of
 - *Etiology*
 - *Prognosis*
 - *Recurrence risk*
 - *Prevention**

* Prenatal diagnosis & preimplantation genetic diagnosis options in future pregnancies

CHROMOSOME ANALYSIS (KARYOTYPE)

- Chromosome abnormalities account for about 20% of all genetic diseases
- 1 in 156 live births were found to have a major chromosome abnormality*

* Combining surveys from 1969 to 1982 of 68,159 liveborn babies

CHROMOSOME ANALYSIS (KARYOTYPE)

- Structural heart abnormalities are a well-established risk factor for chromosome abnormalities
- Prenatal data indicate that up to 32-48% of fetuses with cardiac abnormalities are chromosomally abnormal
- The presence of extracardiac abnormalities increases the risk of a chromosome abnormality from 32-48% to 50-71%

FISH ANALYSIS

- Specific fluorescent probes can be located on the microscope and will recognize microdeletion syndromes
 - 22q11 syndrome (DiGeorge / VCF)
 - Williams-Beuren syndrome
 - Alagille syndrome
- This technology that is widely performed in cytogenetics laboratory for the diagnosis

22q11 DELETIONS

- Characterized by
 - *Dysmorphic features*
 - *CHDs*
 - *Absence or hypoplasia of the thymus*
 - *Growth failure*
 - *Cognitive deficits*

22q11 DELETIONS

- Cardiac and vascular abnormalities include
 - *Tetralogy of fallot and variants (35%)*
 - *Interrupted aortic arch type B (19%)*
 - *Ventricular Septal Defect (VSD) (16%)*
 - *Truncus arteriosus (19%)*

 - *Right aortic arch (35%)*
 - *Aberrant origin subclavian artery (16%)*
 - *Left superior vena cava (9%)*
 - *Vascular ring (5%)*

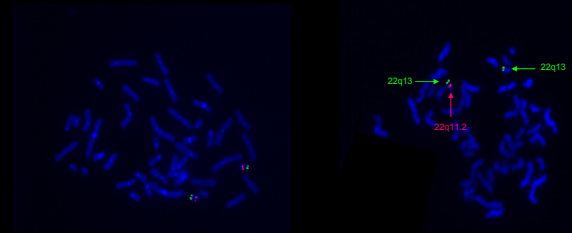
22q11 DELETIONS

- Prevalance 1/5950 live births
- 5-10% of prenatally diagnosed heart defects
- 10-20% cytogenetically visible
- 90% of patients have a microdeletion (22q11)

22q11 DELETIONS

- Different other microdeletions syndromes
 - *Inherited in about 10% of the cases*
 - *Autosomal dominant pattern*
- This has significant implications for future pregnancies
 - *Because there is a 50% chance from an affected parent will be transmitted to the offspring*

FISH analysis for DiGeorge syndrome



LSI DiGeorge probe [22q11.2 (Spectrum Red)(test probe), 22q13 (Spectrum Green)(control probe)]

Microdeletion Syndromes Associated with CHDs

| Microdeletion Syndromes | Congenital Heart Defect | Percentage |
|--|---|------------|
| Wolf-Hirschhorn syndrome (4p deletion) | ASD, VSD, PDA, LSVG, aortic atresia, dextrocardia, TOF, tricuspid atresia | 50-65 |
| Cri-du-chat syndrome (5p deletion) | VSD, ASD, PDA | 30-60 |
| Williams-Beuren syndrome (7q11.23 deletion) | Supravalvar AS and PS, PPS | 53-85 |
| Deletion 8p syndrome | AVSD, PS, VSD, TOF | 50-75 |
| Deletion 10p | BAV, ASD, VSD, PDA, PS, CoA, truncus arteriosus | 50 |
| Jacobsen syndrome (11q deletion) | HLHS, valvar AS, VSD, CoA, Shone's complex | 56 |
| Alagille syndrome (20p12 deletion) | Peripheral PA, hypoplasia, TOF, PS, (left-sided heart lesions and septal defects less common) | 85-94 |
| DiGeorge/VCF syndrome (22q11 deletion) | IAA-B, truncus arteriosus, isolated aortic arch anomalies, TOF, conoventricular VSD | 75 |
| Subtelomeric rearrangement | Aortic arch anomalies, VSD, atrial septal defect, mitral valve insufficiency, and concomitant pulmonary stenosis with VSD | - |

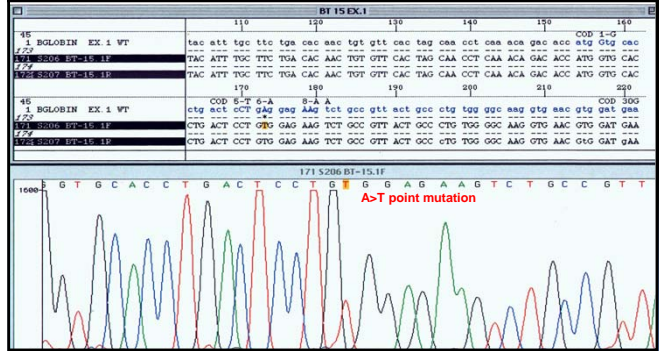
DNA ANALYSIS

- The chromosome and FISH methods described above identify many changes in chromosome number and structure
- However, some abnormalities must be defined by different techniques
- Because, this changes occur at the level of a single gene, and called mutation

DNA ANALYSIS

- DNA mutation analysis identifies sequence alterations of the gene
- This alterations include
 - *Small deletions*
 - *Insertions*
 - *Substitutions*
- Most techniques depend from polymerase chain reaction based assays

Mutation analysis for Single Gene Disorders



Single Gene Disorders Associated with CHDs

| Single Gene Disorders | Congenital Heart Defect | Gene |
|-------------------------------|---|------------------------------|
| Holt-Oram syndrome | Septation (atrial and/or ventricular) defects and/or progressive atrioventricular conduction disease | TBX5 |
| Alagille Sendromu (PPS) | Pulmonary artery stenosis or hypoplasia, Tetralogy of Fallot, Valvar pulmonary stenosis, ASD | JAG1 |
| Char syndrome | PDA | TFAP2B |
| Noonan syndrome | Pulmonic stenosis, Aortic coarctation, Secundum ASD, Mitral valve defects, Tetralogy of Fallot, VSDs, Patent ductus arteriosus, Hypertrophic cardiomyopathy | PTPN11 KRAS SOS1 |
| CHARGE association | Tetralogy of Fallot, ASD, VSD, Double-outlet right ventricle, PDA, Pulmonary valve stenosis | CHD7 |
| Ellis-van Creveld syndrome | Single atrium | EVC EVC2 |
| Marfan syndrome | Aortic regurgitation, Mitral regurgitation, Mitral and tricuspid valve prolapse, Congestive heart failure | FBN1 |
| Cardiofaciocutaneous syndrome | ASD, Pulmonic stenosis, Hypertrophic cardiomyopathy | KRAS BRAF MEK1 MEK2 |
| Costello syndrome | Pulmonary valve stenosis, ASD, VSD, Mitral valve prolapse, Hypertrophic cardiomyopathy | HRAS |

GENETIC COUNSELING

| Disorders | RR | Management |
|--|----------|---|
| Isolated CHDs | ~6% | • Echocardiography |
| Numerical Chromosomal Abnormalities | ~6% | • Prenatal Diagnosis • Preimplantation Genetic Diagnosis |
| Constitutional Chromosomal Abnormalities | variable | • Prenatal Diagnosis • Preimplantation Genetic Diagnosis |
| Single Gene Disorder (AD) | ~65% | • Prenatal Diagnosis • Preimplantation Genetic Diagnosis |
| Single Gene Disorder (AR) | ~62% | • Prenatal Diagnosis • Preimplantation Genetic Diagnosis |

RR, recurrence risk; AD, autosomal dominant; AR, autosomal recessive