GENEReviews

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Emanuel Syndrome

[*Supernumerary der(22)t(11;22) Syndrome*]

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Summary

Disease characteristics. Emanuel syndrome is characterized by severe mental retardation, microcephaly, failure to thrive, preauricular tag or sinus, ear anomalies, cleft or high-arched palate, micrognathia, kidney abnormalities, congenital heart defects, and genital abnormalities in males.

Diagnosis/testing. Emanuel syndrome is caused by a chromosome imbalance consisting of either (1) a derivative chromosome 22 [der(22)] as a supernumerary chromosome with the following karyotype: 47,XX,+der(22)t(11;22)(q23;q11) in females or 47,XY,+der(22)t(11;22)(q23;q11) in males or, rarely, (2) a balanced (11;22) translocation as well as the supernumerary derivative chromosome. The supernumerary der(22) chromosome is easily identified by routine G-band analysis at the 500-550 band level.

Management. *Treatment of manifestations:* Care by a multidisciplinary team is usually necessary; standard management of gastroesophageal reflux, anal atresia (or stenosis), inguinal hernias, cardiac defects, cleft palate, hip dysplasia, other skeletal complications, hearing loss, cryptorchidism and/or hypoplastic genitalia, refractive errors, strabismus or other ophthalmologic issues; ongoing physical, occupational and speech therapies; alternative communication methods to facilitate communication. *Prevention of secondary complications:* attention to the airway during sedation and/or operative procedures in an institution with pediatric anesthesiologists. *Surveillance:* follow-up as needed based on the extent of systemic involvement in each individual case; regular developmental assessments; periodic reevaluation by a medical geneticist.

Genetic counseling. In greater than 99% of cases, one of the parents of a proband with Emanuel syndrome is a balanced carrier of a t(11;22)(q23;q11.2) and is phenotypically normal. In most cases, a carrier parent has inherited the t(11;22) from one of his or her parents. Each sib of a proband with a carrier parent will either (1) have supernumerary der(22) syndrome, (2) be a balanced t(11;22) carrier, or (3) be spontaneously aborted as a result of supernumerary der(22) or another meiotic malsegregant. Risks vary depending on whether the mother or father of a proband is the balanced translocation carrier. Prenatal diagnosis is available.

Diagnosis

Clinical Diagnosis

Emanuel syndrome is characterized by:

- **A distinct phenotype** consisting of the following [Fraccaro et al 1980, Zackai & Emanuel 1980, Lin et al 1986]:
  - Severe mental retardation
  - Microcephaly
  - Failure to thrive
  - Preauricular tag or sinus
  - Ear anomalies
  - Cleft or high-arched palate
  - Micrognathia
  - Kidney abnormalities
  - Congenital heart defects
  - Genital abnormalities in males
- **A chromosomal imbalance** consisting of either of the following:
  - Most commonly, a derivative chromosome 22[der(22)] (Figure 1A) as a supernumerary chromosome with the following karyotype: 47,XX,+der(22)t(11;22)(q23;q11) in males **or** 47,XY,+der(22)t(11;22)(q23;q11) in females
  - Rarely, a balanced (11;22) translocation as well as the supernumerary derivative chromosome. Figure 1B shows a karyotype of a balanced t(11;22) carrier.

Affected individuals are usually identified in the newborn period as the offspring of balanced (11;22) translocation carriers. The progeny affected with Emanuel syndrome are genotypically unbalanced because the der(22) is a supernumerary chromosome.

Testing

Cytogenetic testing. When a chromosomal abnormality is suspected, routine cytogenetic analysis is recommended. The supernumerary der(22) chromosome is easily identified by routine G-band analysis at the 500-550 band level in individuals with the disorder.

- Parental karyotypes should be performed to determine whether one parent is a carrier of the balanced translocation, t(11;22).
- In the rare instance in which one of the parents is not a balanced translocation carrier, commercially available FISH probes for the 22q11.2 deletion and for the telomere of 11q can identify the supernumerary chromosome in the karyotype as being derived from chromosomes 11 and 22.

The combined use of these testing modalities identifies 100% of the small acrocentric chromosomes resulting in Emanuel syndrome.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US*

clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Genes. Duplication of genes on the supernumerary derivative chromosome 22 is the only genetic defect known to be associated with Emanuel syndrome. The clinical phenotype arises from duplication of 22q10-22q11 and duplication of 11q23-qter on the supernumerary der(22).

Note: Duplication of the short (p) arm of chromosome 22 is clinically insignificant, as chromosome 22 is an acrocentric chromosome with the p arm containing heterochromatin.

Clinical testing

- **Chromosome analysis** with G banding identifies the supernumerary der(22).
- **FISH testing** is accomplished using probes N25 or TUPLE1 mapping to 22q11.2 and using 11q subtelomeric probe.
- **Whole chromosome paint (WCP)** using chromosome 11 and 22 probes would show that the supernumerary chromosome is derived from chromosome 22 and 11. This method is not routinely used and FISH testing readily confirms the origin of the supernumerary der(22) observed on chromosome analysis.
- **Comparative genomic hybridization (CGH) microarray analysis** would detect the supernumerary der(22) as all commercial kits include pericentromeric, subtelomeric, and 22q11.2 region BAC clones.

Research testing

- **Breakpoint-specific PCR-based testing.** Using PCR, primer pairs that amplify across the breakpoints can confirm the typical recurrent translocation breakpoint [Kurahashi, Shaikh, Emanuel 2000; Kurahashi, Shaikh, Zackai et al 2000].
- **MLPA (multiplex ligation-dependent probe amplification) assay** has been developed to detect duplication of 22q. MLPA is a quantitative multiplex PCR approach for determining the relative copy number of a genomic target sequence. It has been successful in identifying supernumerary der(22) [Vorstman et al 2006].
- **Oligonucleotide-based array CGH (aCGH)** should prove extremely sensitive for the purpose of copy number detection and will detect the duplications of 22q and 11q of the supernumerary der(22).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Emanuel Syndrome

Test Methods	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Chromosome analysis	Supernumerary der(22)	100%	Clinical
FISH	Duplication 22q11 and 11q23	100% when both probes are used	Clinical Testing
CGH	Copy number variations of chromosome 11 and chromosome 22 BAC clones	100%	Clinical Testing
MLPA	Duplication 22q11	100%	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

Testing Strategy

To establish the diagnosis in a proband. When supernumerary der(22) is suspected, perform routine cytogenetic analysis since the additional chromosome is easily identified as an additional small acrocentric chromosome.

- Use FISH probes for 22q to determine that the extra chromosome is partially derived from chromosome 22.
- Use FISH probes for the 11q telomere to confirm that the translocation is between 11q and 22q.

Carrier testing for at-risk relatives requires prior identification of the translocation in a family member. (Balanced translocation carriers are typically asymptomatic.)

Prenatal diagnosis for at-risk pregnancies requires prior identification of the translocation in a family member.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with supernumerary der(22).

Female carriers of a balanced t(11;22) may have a somewhat increased risk for premenopausal breast cancer. This possible association was first proposed by Lindblom et al (1994), who noted one woman with breast cancer in five of the eight families studied. More recently, two unrelated families have been reported with multiple instances of breast cancer cosegregating with the balanced t(11;22) across several generations [Jobanputra et al 2005, Wieland et al 2006]. However, other studies looking at a larger number of families have not confirmed this association [Kurahashi, Shaikh, Zackai et al 2000]. Additional and appropriately designed studies are needed to better evaluate this possible association. In the meantime, increased breast cancer surveillance may be warranted in female carriers of a balanced t(11;22), especially if there is a family history of breast cancer.

Clinical Description

Natural History

Well over 100 individuals with supernumerary der(22) have been reported [Kessel & Pfeiffer 1977, Fraccaro et al 1980, Zackai & Emanuel 1980, Schinzel et al 1981, Iselius et al 1983, Lin et al 1986]. Significant mortality is associated with life-threatening congenital malformations such as congenital heart defects, diaphragmatic hernia, or renal insufficiency. The highest mortality rate is in the first months of life. With improved palliative care and time, survival chances improve and survival into adulthood has been well documented.

Affected children are usually identified in the newborn period as the offspring of balanced (11;22) translocation carriers.

Constitutional. Most individuals have pre- and postnatal growth retardation and associated dysmorphic features.

Craniofacial. Observed dysmorphic features include micro-brachycephaly, prominent forehead, epicanthal folds, downslanting palpebral fissures, broad and flat nasal bridge, long and pronounced philtrum, microretrognathia, and abnormal auricles (ranging from microtia to large ears) often associated with preauricular ear pits and/or tags (see Figure 2).

Cardiac. Congenital heart defects, seen in approximately 60% of individuals with supernumerary der(22), contribute to morbidity and mortality. Heart defects include atrial

septal defect, ventricular septal defect, tetralogy of Fallot, truncus arteriosus, tricuspid atresia, coarctation of aorta, aberrant subclavian artery, persistent left superior vena cava, and patent ductus arteriosus.

Genitourinary. Renal malformations, seen in approximately 30% of affected individuals, range from complete renal agenesis to various degrees of renal hypoplasia. Males often have genital hypoplasia with cryptorchidism, small scrotum, and micropenis. Uterine malformations can occasionally be observed in females.

Gastrointestinal. Diaphragmatic hernia and hypoplasia or eventration of the diaphragm have been observed.

Anal atresia with or without fistula is seen in about 20% of affected individuals. Anal stenosis without complete atresia is observed as well.

Inguinal hernias are uncommon but well documented.

Biliary atresia, Hirschsprung disease, abnormal liver lobation, extrahepatic biliary ducts, absent gallbladder, and polysplenia have been observed occasionally.

Poor weight gain is common. While specific feeding problems are often not described, gastroesophageal reflux and difficulties with suck and swallow are common.

Musculoskeletal. All affected individuals have significant centrally based hypotonia. Congenital hip dislocation or subluxation is common and requires orthopedic interventions such as a harness or surgery.

Arachnodactyly and tapering fingers are characteristic.

Club foot and joint contractures can be congenital or develop later in life. Curvature of the spine is most likely a secondary complication of severe hypotonia and resulting motor delays.

Other, less frequently observed skeletal malformations include 13 pairs of ribs, hypoplastic clavicles, cubitus valgus, radio-ulnar synostosis, and 4-5 syndactyly of the toes. Lumbar myelomeningocele has been reported once [Najafzadeh & Dumars 1981]. Sacral dimple is common.

Delayed bone age is mentioned in a few case reports.

Palate. Cleft palate is seen in approximately 50% of affected individuals.

Eyes. Most persons with Emanuel syndrome have normal vision. Although uncommon, eye abnormalities have included strabismus and myopia. Ptosis and degenerative retinal changes are rarer.

Ears, nose and throat. The external ear auricle is typically malformed and preauricular ear pits and/or tags are characteristic. Severe microtia with atresia of the external auditory canal and deafness have been reported. Hearing loss is uncommon, but milder forms may be underestimated because of the difficulties associated with accurate hearing evaluation in individuals with severe developmental delay.

Angular mouth pits or clefts, cleft maxilla, laryngomalacia, and branchial sinuses have been reported. Bifid uvula is also associated.

CNS. Microcephaly is present in all affected individuals.

The incidence of structural brain abnormalities is not known as brain imaging is not required to establish the diagnosis. Reported malformations have included Dandy-Walker malformation, agenesis of the corpus callosum, arrhinencephaly, and absent olfactory bulbs and tracts.

Seizures are reported in a few affected individuals and abnormal EEGs without clinical seizures in another small subset.

Development. All children with Emanuel syndrome have severe global developmental delays and adults function in the spectrum of severe to profound mental retardation. Most individuals can sit unsupported and only a small number learn to walk. Walking is often difficult because of poor motor coordination. Speech and language development is significantly delayed. Receptive language is better than expressive language and some individuals are able to use single words to communicate.

Other. Congenital immunoglobulin deficiency; thymic-dependent immunodeficiency; dysplastic teeth.

Genotype-Phenotype Correlations

All individuals with Emanuel syndrome have the supernumerary der(22), which results from almost identical breakpoints on both 11q23 and 22q11. The breakpoints differ by only a few nucleotides [Shaikh et al 1999; Kurahashi, Shaikh, Hu et al 2000; Kurahashi & Emanuel 2001]. Genotype-phenotype correlation, however, is difficult as the clinical findings result from duplicated genetic material. While systemic involvement can vary, developmental outcome is uniformly in the spectrum of severe to profound mental retardation.

Penetrance

Penetrance is complete in individuals with the supernumerary der(22).

Anticipation

Anticipation is not associated with the supernumerary der(22).

Nomenclature

Supernumerary der(22) syndrome almost always results from 3:1 malsegregation of a balanced t(11;22) in an unaffected parent [Lindenbaum & Bobrow 1975, Shaikh et al 1999].

Older case reports published prior to G banding described this chromosome abnormality as "partial trisomy 22" [Uchida et al 1968, Emanuel et al 1976] or "partial trisomy 11" [Tusques et al 1972, Aurias & Laurent 1975].

In 2004, supernumerary der(22) syndrome was named Emanuel syndrome.

Prevalence

Supernumerary der(22) is a rare chromosomal disorder; its prevalence is unknown.

The prevalence of balanced t(11;22) carriers is unknown in the general population.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Clinical features that overlap with Emanuel syndrome can be seen in the syndromes listed below. Chromosome analysis always confirms the diagnosis of Emanuel syndrome and rules out other diagnoses.

- Fryns syndrome
- Smith-Lemli-Opitz syndrome
- Pallister-Killian syndrome
- Kabuki syndrome
- Wolf-Hirschhorn syndrome
- Other chromosomal abnormalities

Management

Evaluations Following Initial Diagnosis

No current guidelines to evaluate the clinical manifestations that contribute to morbidity and mortality have been published. The following recommendations to establish the extent of disease in an individual diagnosed with Emanuel syndrome are based on the literature and the authors' experience:

- Cardiac evaluation with an echocardiogram to screen for cardiac defects. ASDs are the most common and may not be detected by auscultation alone.
- Renal ultrasound examination to evaluate for structural kidney anomalies; if indicated, vesicoureterogram (VCUG) to evaluate for vesicoureteral reflux
- Palatal evaluation for cleft palate
- Gastrointestinal evaluation with appropriate radiologic studies for structural anomalies of the gastrointestinal (GI) tract, in particular anal stenosis or diaphragmatic abnormalities, gastroesophageal reflux
- Feeding and swallowing assessment
- Orthopedic evaluation with appropriate radiologic studies for hip dysplasia as well as joint contractures, club foot, curvature of the spine, and radio-ulnar synostosis
- Otolaryngology (ENT) evaluation for stenosis or atresia of ear canals
- Audiology evaluation with auditory brainstem response testing and otoacoustic emission testing
- Ophthalmologic evaluation, including dilated fundoscopic examination, to assess visual acuity and to evaluate for strabismus
- Urologic evaluation in males with cryptorchidism and/or genital hypoplasia
- Evaluation by a developmental pediatrician and therapists to develop educational/ therapeutic intervention with emphasis on communication skills
- Genetics evaluation for genetic counseling and to identify at-risk relatives (The +der (22) is almost always inherited from a carrier parent.)

Treatment of Manifestations

Depending on the age and extent of systemic involvement of the individual with Emanuel syndrome, evaluations involving healthcare providers from multiple specialties are necessary.

In some cases, palliative care is appropriate when there are severe structural defects and/or renal failure.

- Standard management of gastroesophageal reflux; supplementary formulas and consideration of enteral feeds if there is failure to thrive
- Surgical correction for anal atresia (or stenosis if indicated) and inguinal hernias
- Standard interventions for:
  - Cardiac defects
  - Cleft palate
  - Hip dysplasia and other skeletal complications; assistive devices such as walkers are often required for ambulation
  - Hearing loss
  - Cryptorchidism and/or hypoplastic genitalia
  - Refractive errors, strabismus, or other ophthalmologic issues
  - Seizures, if present
- Ongoing physical, occupational, and speech therapies to optimize developmental outcome
- Alternative communication methods to facilitate communication as verbal skills are often very limited

Prevention of Secondary Complications

Care during sedation and/or operative procedures should be provided by a pediatric anesthesiologist as small airways, various palatal abnormalities, and laryngomalacia can be seen in children with Emanuel syndrome.

Surveillance

- Follow-up as needed based on the extent of systemic involvement in the affected individual
- Regular assessment of developmental progress to guide therapeutic interventions and educational modalities
- Periodic reevaluation by a medical geneticist to apprise the family of new developments and/or recommendations

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Patients and their families should be informed regarding natural history, treatment, mode of inheritance, genetic risks to other family members, and consumer-oriented resources.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Emanuel syndrome is an inherited chromosome abnormality. It is the result of 3:1 meiotic segregation of the balanced translocation t(11;22)(q23;q11). This rearrangement is the only known recurrent, non-Robertsonian translocation in humans.

Risk to Family Members

Parents of a proband

- In greater than 99% of cases, one of the parents of a proband with Emanuel syndrome is a balanced carrier of a t(11;22)(q23;q11.2) and is phenotypically normal. There is a single case report of supernumerary der(22) arising from *de novo* (11;22) translocation in the paternal germline with probable unbalanced adjacent 1 segregation and maternal non-disjunction of chromosome 22 in meiosis I [Dawson et al 1996].
- Parents of a proband with Emanuel syndrome should be offered chromosome analysis.
- Statistically, the mother of a proband with supernumerary der(22) is more likely than the father to be a carrier of the balanced t(11;22).
- In most cases, a carrier parent has inherited the t(11;22) from one of his or her parents.

Sibs of a proband

- Sibs of a proband who have no findings of Emanuel syndrome:
  - Are not at risk for Emanuel syndrome.
  - Have almost no chance of having a different unbalanced chromosome abnormality.
  - Have an estimated 50% chance of having a balanced translocation (see Table 2). The offspring of sibs identified as balanced t(11;22) carriers have the same risks as described below (see When one of the parents..).
  - Have an estimated 50% chance of having normal chromosomes.

- Sibs of a proband who have findings of Emanuel syndrome (e.g., severe developmental delays, poor growth, and multiple congenital anomalies) almost always have supernumerary der(22).
- When one of the parents of a proband is a carrier of the balanced t(11;22), future pregnancies of the parents are at an increased risk of one the following:
  - Supernumerary der(22) syndrome
  - Balanced t(11;22) carrier
  - Spontaneous abortion with supernumerary der(22) or another meiotic malsegregant
- Several studies have calculated the risks in Table 2 based on the reproductive history data of families studied. Risks vary depending on whether the mother or father of a proband is the balanced translocation carrier [Fraccaro et al 1980,Zackai & Emanuel 1980,Iselius et al 1983].

Offspring of balanced t(11;22) carriers. See Table 2.

Table 2. Pregnancy Outcomes of Balanced t(11;22) Carriers

	Female Carrier	Male Carrier	Overall
Liveborn with supernumerary der(22)	5.7%-6.1%	2.2%-5%	1.8%-5.6%
Liveborn with balanced t(11;22)	55.4%	41.2%	
Spontaneous abortion	23%-37%		

Offspring of a proband. Individuals with Emanuel syndrome are unlikely to reproduce because of severe cognitive impairment.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. Family members of the parent carrying the balanced t(11;22) are at risk of being carriers or having Emanuel syndrome. Those identified as carriers would have the same risks as described above (see Table 2). Chromosome analysis should be offered to the at-risk family members.

Carrier Detection

At-risk family members can be tested by chromosome analysis. Carrier testing is not routinely performed in at-risk family members when they are minors, but rather when they are adults and can understand the reproductive implications of being a balanced translocation carrier.

Unaffected siblings are typically tested for carrier status when they are legal adults, of reproductive age and able to understand the reproductive implications of being a carrier.

Related Genetic Counseling Issues

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are or are at risk of being balanced translocation carriers.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by chromosome analysis of fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation. The two methods are equally sensitive in detecting the supernumerary der(22).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD), which has been successfully performed on several occasions [Van Assche et al 1999], may be available for families at increased risk. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. OMIM Entries for Emanuel Syndrome

609029	EMANUEL SYNDROME

Molecular Genetic Pathogenesis

Molecular genetic pathogenesis is not known as Emanuel syndrome results from duplicated genomic segments of chromosomes 11q and 22q, which include a significant number of genes.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Chromosome 22 Central
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Phone: 705-268-3099
Email: c22c@ntl.sympatico.ca
www.c22c.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Web: humangenetics.chop.edu

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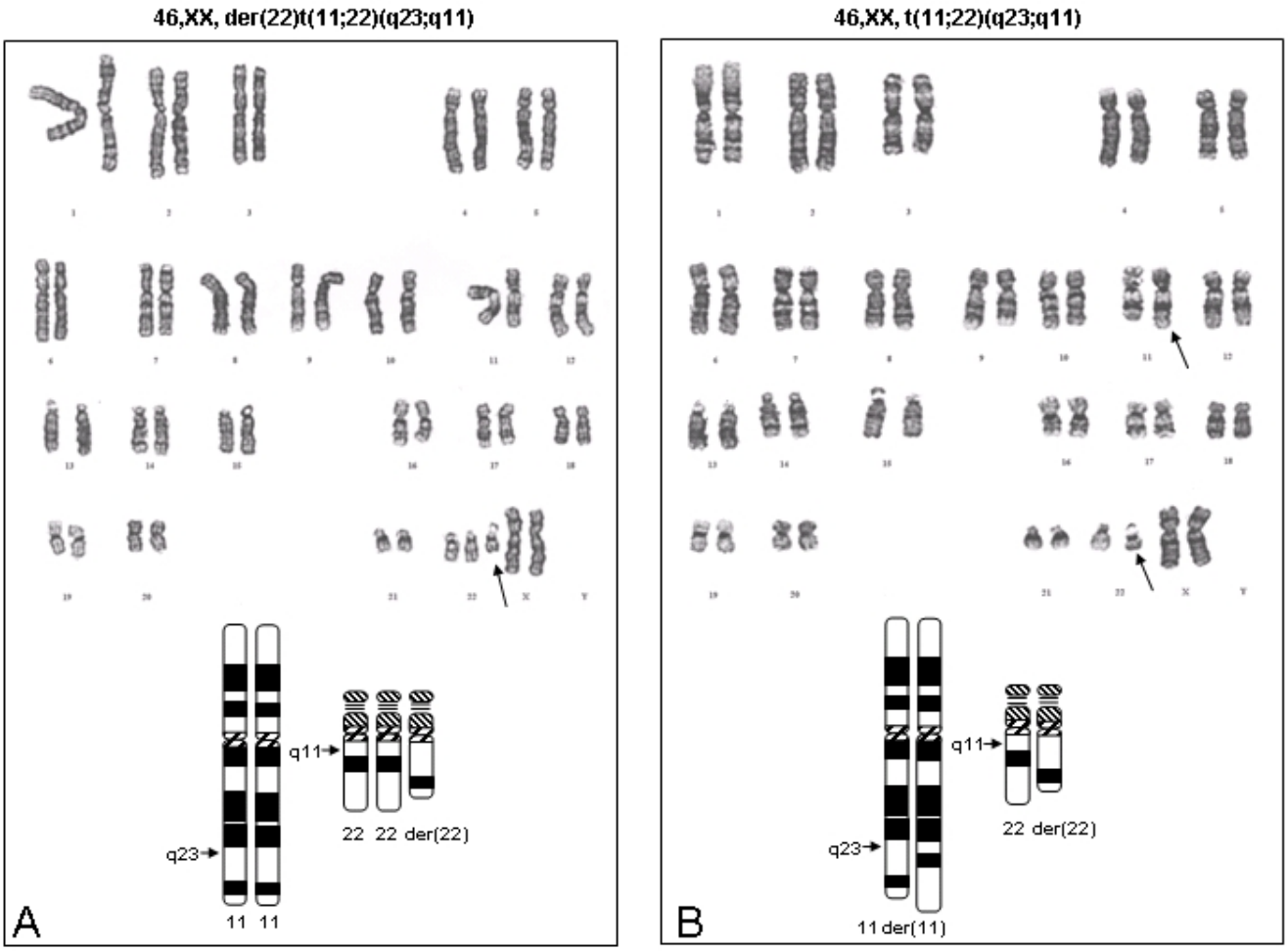

Figure 1
A. Karyotype and schematic ideogram showing the supernumerary derivative chromosome 22, which results in trisomy of chromosome 11q23-qter and 22q cen-q11
B. Karyotype and schematic ideogram showing a balanced translocation carrier.

Figure 2. Four individuals with Emanuel syndrome. Note the round face, deep-set, round eyes, and prominent forehead in young individuals A (age ~6 months) and B (age 3 years). Note the coarsening of facial features over time in individual D; photos are taken at age one year (D-1) and ten years (D-2). Facial features are significantly similar in the two older individuals, C (age 17 years) and D-2.