An Approach to Work-up of Dysmorphic Patients: Clinical, Cytogenetic, and Molecular Aspects

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Abstract. In view of recent advancement in the field of medical genetics, one approach to work-up a dysmorphic patient is to focus on how to study the patient clinically, cytogenetically, and molecularly. A clear understanding about major and minor anomalies, classification and terminologies of errors of morphogenesis, history taking, physical examination, laboratory studies including molecular cytogenetic techniques, genomic imprinting, uniparental disomy, and mosaicism is essential. Several clinical cases from my own experience are provided to illustrate my approach to work-up of dysmorphic patients. Case 1 was a newborn with multiple congenital anomalies (MCA) and a de novo dup (1) (pter→q25::q12→qter). Fluorescent in situ hybridization (FISH) unequivocally identified the duplicated region. Case 2 was a stillborn who had frontonasal dysplasia, arrhinencephaly, and other MCA with 46, XX, -7, +der(7), t(2;7) (q31;q36)mat. Her MCA were due to combined effect of trisomy 2q and monosomy 7q. This case helped to define the physical mapping of the critical region for a mild form of holoprosencephaly to 7q36. Case 3 had a classic de Lange phenotype with genital abnormality and sex reversal (46, XX male). Presence of SRY suggests X-Y interchange during paternal meiosis I. Case 4 was a female with primary amenorrhea, short stature, and 45,X/46,X,iddc(Y)/47,X,iddc(Y),iddc(Y). This case demonstrates the need for molecular analyses to confirm the cytogenetic interpretations and allowed the refinement of the breakpoint in the isodicentric Y and karyotype/phenotype correlations. Case 5 & 6 were half sibs with ambiguous genitalia, minor somatic abnormalities, and dup (X) (p21.2p22.11)mat. Limited extent of the Xp duplication in these cases allows assignment of the X-linked sex-reversal (SRVX) locus to Xp21.2→p22.11. (Keio J Med 43 (2): 98–107, June 1994)

Key words: major and minor anomalies, errors of morphogenesis, mosaicism, genomic imprinting, uniparental disomy

Introduction

To work-up a dysmorphic patient usually implies to make a specific diagnosis, given the symptoms and signs of the patient. In view of recent advancement in the field of medical genetics, my lecture, instead, focuses on how to study the patient clinically, cytogenetically, and molecularly. A clear understanding about major and minor anomalies, classification and terminologies of errors of morphogenesis, history taking, physical examination, laboratory studies including molecular cytogenetic techniques, genomic imprinting, uniparental disomy, and mosaicism is essential. Several cases from my own clinical experience are provided to illustrate my approach to work-up of dysmorphic patients.

Dysmorphology is the general term for the study of abnormal development as well as the extreme variability of normal physical features. One of the most difficult task in dysmorphology is to determine whether a particular feature is pathologic or a normal variant. To be a good syndromologist, we, trainers and trainees alike, can take note on Dr Robert Gorlin whose accomplishment in the field of syndromology was honored in a Festschrift issue of the American Journal of Medical Genetics. In that issue, Dr Victor McKusick commented that to make a syndromologist like Dr Gorlin, one has to have a phenomenal visual memory, tremendous humanity, syndrome sense, warm collegiality, strong linguistic skills, and curiosity and hard work.
**Major and minor anomalies**

About 160,000 infants will be born annually with anomalies and 120,000 infants will have mental retardation in the United States.\(^3\)\(^-\)\(^5\) Anomalies can be classified into major and minor. The major anomalies require medical and surgical intervention and have serious cosmetic impact whereas the minor anomalies are less significant and generally do not require medical intervention. Each year, 80,000 newborns, i.e. 2% of all liveborn infants, have major anomalies. Isolated anomalies, such as cleft lip/palate and polydactyly, are relatively common and often multifactorial in etiology. Presence of several minor anomalies increases the risk of the association of major defects. These structural defects are the most common reason for genetic evaluation (71%) during the first year of life at a general genetics clinic.\(^6\)

**Classification and terminologies of errors of morphogenesis\(^7\)**

**Malformation, disruptions, deformations, dysplasias:** Anomalies are commonly classified into malformations, disruptions, deformation, and dysplasia, depending on the presumed pathogenesis.\(^8\) Opitz in 1982\(^9\) clarified and expanded the concepts and terminology used in the classification so that phenotypes can be analyzed correctly, thereby providing the basis for accurate diagnosis and proper counseling. Malformations are structural defects caused by intrinsic or extrinsic insults during embryogenesis (e.g. holoprosencephaly). Most malformations are developmental field defects. A developmental field is a region or part of an embryo that responds as a coordinated unit to embryonic interaction and results in complex or multiple anatomic structures. Disruptions arise after formation of structures by destructive process (e.g. amniotic deformation-adhesion-mutilation complex). A deformation usually arise in late gestation and is caused by mechanical force on various structures (e.g. talipes equinovarus deformity or Potter syndrome caused by oligohydramnios). A dysplasia is an abnormal organization of cells into tissues and its morphologic results (e.g. hemangiomas).

**Sequence, disease, syndrome, association:** A sequence is a pattern of multiple anomalies derived from a single prior anomaly or mechanical factor. A sequence may be a malformation sequence (e.g. meningomyelecele produces lower limb paralysis, muscle wasting, clubfoot, incontinence, urinary tract infections, and other abnormalities), a disruption sequence (ADAM sequence caused by early amnion rupture), a deformity sequence (e.g. Potter sequence caused initially by oligohydramnios), and a dysplasia sequence (renal, pulmonary, CNS, and cardiac sequences in tuberous sclerosis). A disease is a condition of known cause in which there is progression and deterioration with time (e.g. Menkes disease). A syndrome is a given pattern of anomalies in which the components are known or thought to be pathogenetically related (e.g. Down syndrome). Association is a non-random occurrence of multiple anomalies in 2 or more individuals (e.g. VATER association).

**History taking essential for work-up\(^10\)**

**Family history:** The genetic information (e.g. name, sex, date of birth, age at onset of disease, medical data, and other essential information such as twinning and consanguinity) collected on family members in multiple generations can be summarized concisely in a pedigree. This will help to determine the inheritance pattern of a particular genetic disorder in the family. A family history of multiple spontaneous abortions or stillbirths may indicate a segregating structural chromosomal abnormality. Ethnic background may be important in certain genetic disorders (e.g. sickle cell anemia in blacks; Tay-Sachs disease in Ashkenazic Jews). Parental ages are important: an advanced maternal age is associated with an increased risk of having a child with a chromosomal anomaly (e.g. trisomy 21 syndrome); advanced paternal age may suggest an autosomal dominant new mutation (e.g. achondroplasia).

**Pregnancy and birth history:** Maternal risk factors (e.g. infections, drug administration, radiation, malnutrition, anoxia, trauma, diabetes, and other complications) during pregnancy should be recorded. It is also important to note fetal activity, fetal size, fetal presentation, the amount and appearance of amniotic fluid, gestational age, Apgar scores, and a description of the placenta, including the fetal membranes and the number of cord vessels.

**Medical information:** Adequate and essential information is needed for accurate diagnosis of a genetic disorder. Personal medical records, including biopsy slides, autopsy reports, and results of special studies such as radiographs, CT scans, MRI, and biochemical, cytogenetic, and molecular studies should be requested and reviewed if necessary. Permission to contact relatives and to acquire photographs may need to be obtained.

**Physical examination**

Major anomalies are obvious on physical examination; minor anomalies, however, require careful observation, including measurements and comparisons to normal growth charts, since they often provide important clues to diagnosis. When there are three or more minor anomalies, one should look for occult major anomalies.
Physical examinations should include anthropometric measurements (height, weight, head circumference, other pertinent measurements of features that appear unusual or abnormal), and an estimate of the developmental status (e.g. speech delay, mental retardation). Repeat observations over a period of years may ultimately lead to a diagnosis not initially obvious or revision of a previously incorrect diagnosis.\textsuperscript{11} Comparison of minor features, particularly facial characteristics, with those of the parents and siblings often permits separation of family traits from those that may be of diagnostic importance.

Natural histories of various syndromes are important to keep in mind. For examples, in the fragile X syndrome, one expects large size at birth; developmental delay, especially in speech, during the early childhood; and facial characteristics and macroorchidism in the post-pubertal years.\textsuperscript{11} Infants with 45,X Turner syndrome have lymphedema, excess nuchal skin, and coarctation of the aorta at birth; stunted growth during childhood; and failure to mature sexually at adolescence.\textsuperscript{12}

\textbf{Laboratory studies}

In most cases, laboratory studies include blood, urine, and biopsied samples. Fibroblast and lymphoblastoid cell lines are important for the studies of certain conditions, especially chromosomal and metabolic disorders.

\textbf{Imaging techniques}

The radiographic examination is probably the most useful means of studying skeletal dysplasia. The short stature can be predominantly in the trunk or in the limbs. Diagnosis of the short limb variety depends on the segment of the long bone most severely affected (e.g. rhizomelic, mesomelic, acromelic, and acromesomelic shortenings). Diagnosis can also be based on the affected anatomical part of the skeleton that can be detected radiologically (e.g. epiphyseal, metaphyseal, diaphyseal, spondyloepiphyseal, spondylometaphyseal, and spondyloepimetaphyseal dysplasias).

\textbf{Cytogenetic studies}

Chromosome analysis plays an important role in evaluating dysmorphic patients. Indications for cytogenetic studies include: (1) Clinical features suggestive of recognizable chromosomal syndromes. (2) Patients with idiopathic multiple congenital anomalies and mental retardation (MCA/MR) syndrome, especially when patients have an unusual facial appearance, microcephaly, prenatal and postnatal growth deficiency, or several minor anomalies, and there is a lack of familial resemblance. (3) Abnormality of sexual development, including ambiguous or hypoplastic genitalia and failure of sexual maturation at puberty. (4) Unexplained abnormalities of growth. (5) Features of mosaicism (hypomelanotic spots, streaky pigmentary disturbance, asymmetry). (6) Spontaneously aborted embryos, unexplained stillborn fetuses, and hydropic placentas. (7) Family members of an individual with an inherited chromosome duplication, deletion or other rearrangement.

\textbf{Fluorescence in situ hybridization (FISH)}\textsuperscript{13,14}

FISH has become an important tool for analysis of the number, size, and location of specific DNA sequences. Chromosome specific probes are of 3 types; chromosome specific repeat-sequence (centromere) probes, whole chromosome "painting" probes, and locus-specific probes. The ability to detect and characterize numerical and structural aberrations in metaphase spreads and in interphase nuclei has substantial clinical value.

\textbf{Molecular cytogenetics}

The first successful mapping of a mendelian disorder by chromosome rearrangements was mapping of the Duchenne muscular dystrophy locus to Xp21.\textsuperscript{15} Other chromosome rearrangements (e.g. deletions, translocations) not only helped the mapping of certain disease genes but also contributed to rapid isolation of disease genes by positional cloning strategies.\textsuperscript{16}

\textbf{Mosaicism}

Mosaicism denotes the presence of at least two cell lines differing in genotype or karyotype, in a single individual or tissue, derived from a single zygote. Current evidence suggests that mosaicism is a common, possibly universal phenomenon.\textsuperscript{17} Functional mosaicism has been produced regularly by X-inactivation and tissue differentiation. Mosaicism can be found both in somatic cells and germ cells. For instance, a parent with a patchy or segmental neurofibromatosis (appears to be somatic mosaics) with fully affected children would suggest that the parent has both germ line and somatic mosaicism.\textsuperscript{18} Patchy or streaky pigment indicates gene or chromosomal mosaicism. For examples, patients with McCune-Albright syndrome, which is characterized by sexual precocity, osteolytic lesions, and hyperpigmentation, are mosaic for genes (mutations of a subgroup of the G\textsubscript{1} protein) in the affected areas.\textsuperscript{19} Patients with hypomelanosis of Ito,\textsuperscript{20} which is characterized clinically by patchy depigmentation and CNS deterioration, and many patients who have asymmetric growth\textsuperscript{21} have been found to be chromosomally mosaic.
Nontraditional inheritance (genomic imprinting, uniparental disomy)\textsuperscript{22-25}

Mendelian genetics implies that identical genes inherited from each parent have an equal effect on the development of their offspring, i.e. the parental source of the genetic information does not influence gene expression. During the last decade evidence has accumulated in mammalian genetics that certain genetic phenomena cannot be explained by traditional mendelian concepts. Genomic (parental) imprinting and uniparental disomy, two important phenomena and interrelated concepts, have been described recently.

Genomic imprinting: Genomic imprinting is defined as the differential influence of genetic material, being transferred to the embryo from the mother or father, on development of the embryo. Deficient or excessive maternal or paternal influence (imprinting) modifies the phenotype of the placenta or embryo. Genomic imprinting on the placenta is dominated by paternal chromosomal influence; genomic imprinting on the embryo by maternal chromosomal influence. When there is only paternally derived chromosome material, there is relatively normal development of the placenta with poor development of the embryonic structures; when there is only maternally derived chromosome material, there is reasonable development of the embryo with poor placental development. The following two clinical examples reflect these phenomena: hydatidiform moles, a placental tumor, have both sets of paternally derived chromosomes while ovarian tumors, which consist of embryonic tissue, have only maternally derived chromosomes.

In humans, examples of genomic imprinting\textsuperscript{26} are: Angelman and Prader-Willi syndrome (15q11-13), fragile X syndrome (Xq27.3), Huntington disease (distal 4p), myotonic dystrophy (19q13.3), teratomas and hydatidiform moles (all chromosomes), and Wilms tumor (11p13-15). The most compelling evidence that genomic imprinting exists in humans and plays an etiological role in causing anomalies came from the Angelman and Prader-Willi syndrome. Both syndromes have strikingly different neurobehavioural characteristics but share a common chromosomal deletion in 15q11-q13.

Prader-Willi syndrome (PWS) is characterized by profound obesity secondary to hyperphagia, hypogonadism, mild to moderate mental retardation, profound hypotonia in infancy, small hands and feet, and picking at skin sores. Using high resolution chromosome analysis, Ledbetter \textit{et al}\textsuperscript{27} demonstrated for the first time a small deletion at 15q11-q13 in PWS patients.

Angelman syndrome (AS) is characterized by unusually happy disposition, inappropriate laughter, affectionate behavior, ataxic, unsteady gait with upraised hands (puppet-like motion), severe mental retardation especially absence of speech, microbrachycephaly, and uncontrollable seizures. Deletion of the same chromosome region 15q11-13 also occurred in AS patients.\textsuperscript{28,29}

The parental origin of the deletion distinguishes PWS and AS; paternal deletion in the former\textsuperscript{30,31} and maternal deletion in the latter.\textsuperscript{32,33} Fig. 1\textsuperscript{25} (modified from Driscoll, 1993) shows the parental origin of the deletion in the AS and PWS using Southern blotting technique, digested with the restriction enzyme TagI and hybridized with the probe 189-1 from the 15q11-13 region.\textsuperscript{31} The maternal allele (3.8kb) was absent in the AS patient and the paternal allele (3.8kb) was absent in the PWS patient. A parent-of-origin DNA methylation (D15S9 and D15S63 loci), DNA replication asynchrony between maternal and paternal derived chromosomes, DNA binding proteins and chromatin structure have all been implicated in the imprinting process.\textsuperscript{34}

Uniparental disomy (UPD): A significant number of non-deletion cases of AS and PWS patients exist. Nicholls \textit{et al}\textsuperscript{31} demonstrated two maternal copies of chromosome 15 and no paternal copy as a mechanism in causation of the PWS. This phenomenon is called uniparental disomy. UPD originates when 2 copies of a particular chromosome come from one parent and none from the other parent. Uniparental isodisomy occurs where 2 copies of exactly the same chromosome originated from one parent; uniparental heterodisomy occurs where both homologs of a chromosome pair originated from one parent. Later, UPD was also demonstrated to be a mechanism in the AS.\textsuperscript{35} Dependent upon which parental chromosome region (15q11-13) is missing, there is a significant difference in the phenotype. Lack of a paternal region, either by deletion or UPD, leads to
PWS; lack of a maternal region by the same mechanisms leads to AS.

Molecular classes of AS and PWS patients are given in the Fig 2.25 Molecular deletions are seen with similar frequencies in both conditions (72% AS vs 74% PWS). The incidence of UPD is frequent in PWS (29%) but infrequent in AS (5%). The biparental class of AS (23%) (neither deletion nor UPD) is probably due to mutation in a single maternal gene. The gene(s) responsible for AS and PWS undoubtedly are in close proximity but must be separate loci.

Possible mechanisms for the origin of UPD are; 1) simultaneous nondisjunction in maternal and paternal gametogenesis (one parent contributes two chromosome 15's and the other parent contributes none), 2) nondisjunction in one parent with two chromosome 15's leading initially to a trisomic state with subsequent reduction by selection to a disomic state.

Patterns of inheritance of imprinted genes

It is important to re-examine pedigrees in known disorders for possible imprinting effects since imprinting appears to be a common phenomenon in humans. There may be differences in phenotypic expression depending on who is the parent transmitting the gene. If a gene is imprinted, it is “silenced” or “turned off” when it has been inherited from one particular parent, mother or father.

Hypothetical pedigrees are shown for paternal (Fig 3) and maternal (Fig 4) imprinting. The term paternal imprinting is used to imply that there will be no phenotypic expression when inherited from the father; the term maternal imprinting is used to imply that there will be no phenotypic expression when inherited from the mother.

Case Illustrations

Case 1

A newborn with multiple congenital anomalies (Fig 5) died shortly after birth. Clinical features were characterized by micro/brachycephaly, hydrocephalus, small temporal lobes, cardiac defects consisting of patent ductus arteriosus and foramen ovale, pulmonary hypoplasia, evagination of left hemidiaphragm, cryptorchidism, sacral dimple, flexion contractures of fingers/knees, and talipes equinovarus deformities. Chromosome analysis revealed de novo dir dup(1) (pter→q25::q12→qter) (Fig 6).

Most cases of dup(1q) involve distal 1q and usually associated with monosomy of other chromosomal segments. Pure proximal dup(1q) are extremely rare. FISH technique is essential to accurately define the duplication segment of this case although C-banding pattern did suggest possible duplication of chromosome 1. This is the first case with unequivocal identification of proximal duplication of 1q, using a chromosome
The FISH technology is, therefore, essential for accurate karyotypic diagnosis and should help in further karyotypic-phenotypic correlation of partial 1q trisomy.

**Case 2**

Fetal blood sampling was performed because of abnormal ultrasound findings (oligohydramnios and fetal ocular hypertelorism). The karyotype revealed 46,XX,−7,+der(7), t(2;7)(q31;q36)mat (Fig 8). The mother & maternal grandmother both had balanced t(2;7)(q31;q36). The stillborn (Fig 9) had intrauterine growth retardation, frontonasal dysplasia, arrhinencephaly and other CNS abnormalities, pulmonary hypoplasia, cartilaginous deficiency of trachea and bronchus, severe tetralogy of Fallot, gastrointestinal tract anomalies (Meckel diverticulum, colon malrotation), genitourinary tract anomalies (renal and ureteral aplasia, bladder hypoplasia, imperforate anus), and flexion contractures of joints with webbings.

This is an important case. Frontonasal dysplasia has not been reported to be associated with chromosome anomaly. Multiple congenital anomalies of this patient

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**Fig 5** Frontal (a) and lateral (b) view of the patient.

**Fig 6** Idiogram (a) and partial G-banded (b) and C-banded (c) karyotypes illustrating the normal (left) and the duplicated (right) chromosome 1.

**Fig 7** Partial chromosome spread counterstained with DAPI (a) and hybridized with the chromosome 1 painting probe labeled with Texas red (b).

**Fig 13** FISH analysis. The sites are separated by the combined length of most of the short arms of Y. A chromosome spread shows 2 idic(Y).
Fig 8 Partial karyotypes of the patient, mother and maternal grandmother and an idiogram illustrating t(2:7)(q31;q36).

may be due to partial trisomy 2q, but effect of the monosomy of 7q cannot be overlooked. Recently, the gene for a form of holoprosencephaly has been suggested at 7q36. This case further supports the physical mapping of the critical region for a mild form of holoprosencephaly to 7q36. We have also defined the minimal critical region of holoprosencephaly to be in 7q36 between DNA markers D7S92 and D7S392.37

Fig 9 Whole view of the patient showing characteristic craniofacial features along with flexed elbows and wrists, flexed fingers with interphalangeal webbings, fixed hips, extended knees, and rotational deformities of the ankles and feet.

Case 3

An infant (Fig 10) was referred for evaluation because of small for gestational age, hirsutism, microcephaly, synophrys, long/curled eyelashes, small nose, a carp-like upper lip with a receding chin, low set ears, micropenis with hypospadias, and oligodactyly (ectrodactyly). The diagnosis suggests Cornelia de Lange syndrome. Genital abnormality in the de Lange syndrome is quite rare. This prompted chromosome analysis which revealed 46,XX. Since the cytogenetic finding (46,XX) did not correspond to the phenotypic sex (male), further molecular studies were performed.

PCR analysis using Y97 alphoid repeat sequence revealed no presence of Y centromeric repeat sequence. This implies that there is no free Y chromosome present in the patient. PCR analysis using SRY primers revealed a 609 bp fragment (Fig 11), indicating the presence of SRY. Speculation is that the tip of one of the X chromosome contains SRY, which originated from X−Y interchange during meiosis I of the father. This could be demonstrated by FISH with SRY probe to hybridize the tip of the short arm of an X chromosomes.

Case 4

An 18 year old female was evaluated for primary amenorrhea and short stature. There was hypoplastic labia majora with clitoromegaly. Cytogenetic studies

Fig 10 (a) Frontal view of the patient showing characteristic craniofacial features and ectrodactyly of Cornelia de Lange syndrome. (b) Genitalia showing micropenis with hypospadias and cryptorchidism.
Fig 11 PCR analysis using SRY primers revealed a 609 bp fragment in lanes 2 and 3; lanes 4 and 5 are male controls; lanes 6 and 7 are female controls. Lane 1 is a standard DNA marker.

were carried out. Three cell lines were present: 45,X/46.X,idic(Y)/47.X,idic(Y),idic(Y). The isodicentric Y chromosome was described as idic(Y) (qter→p11; p11→qter) (Fig 12). The results of cytogenetic analysis were variable in different tissues (blood, skin, right and left gonad). Internal genital organs were characterized by a rudimentary uterus, left vestigial Wolffian structures in the left streak gonad, left fallopian tube, and right dysgerminoma.

A total of 38 cases of dic(Y) with breakpoint in the Yp have been reported in the literature; 38 ambiguous external genitalia with streak gonads, undescended testes, and ovotestes (31.6%), female external genitalia (44.7%) with some degree of gonadal dysgenesis, and phenotypic male (mostly infertility) (23.7%). Short stature, features of Turner syndrome, and gonadoblastoma were reported in 63%, 26%, and 18% respectively.

To further define the idic(Y), FISH was performed. The binding sites of biotin-labeled α-satellite probe of Y are seen at the 2 centromeric regions of the dicentric Y. The sites are separated by the combined lengths of most of the 2 short arms of the Y chromosome (Fig 13). The probe is detected with fluorescein and chromosomes are counterstained with propidium iodide. FISH also confirmed the presence of the 2 idic(Y).

The following molecular studies were performed. PCR analysis using ZFY primers amplified a Y-linked zinc finger fragment (340 bp) in the proband. PCR analysis was also performed using SRY primers. Amplified SRY fragment (609 pb) was absent in left gonad but present in right gonad, skin, and blood (Fig 14). Results of the molecular analysis were compatible with the cytogenetic analyses.

FISH analysis confirmed the presence of the third cell line with 2 dic(Y). The entire long arm and most of the Yp were duplicated. ZFY and SRY which map near the pseudoautosomal boundary are both present, placing the breakpoint at Yp11.32. PCR analysis confirmed the cytogenetic results of tissue distribution of the idic(Y).

Cases 5 and 6

Phenotypically normal mother was found to have 46,X.dup(X) (p21.2→p22.11) (Fig 15). Her two children (half sibs) have 46,X.dup(X) (p21.2→p22.11)mat,Y (Fig 15). Both children have ambiguous genitalia (Fig 16) and gonads resembling epididymis without germ cells and no mullerian derivatives. The older child had mild developmental delay; the younger child had trigonocephaly.

Female differentiation of XY embryos may be caused by mutation in at least the following genes: 1) SRY, the Y-linked testis-determining gene; 2) SRA1 (17q24.3–
Fig 15  a: An idiogram showing the duplication of X chromosome in the mother and half-siblings [dup(X)(p21.2→p22.11)]. The normal X on the left shows break points at p21.2 and p22.11; the dup(X) on the right shows duplication of the band p21.3. b: Normal (left) and duplicated (right) X of the mother. c: Duplicated X and Y in younger sib.

Fig 16  Closed up of the external genitalia of younger sib (a, b).

q25.1), the autosomal sex reversal gene associated with campomelic dysplasia; an X-linked gene, indicated by certain familial cases of XY gonadal dysgenesis and in sex-reversed XY females with duplications in Xp including this family. We have now mapped the X-linked gene, SRVX, based on our study of two families with XP21 duplication; the first family in which dup(Xp21→pter) was found in a XY male with severely retardation and MCA (Gardner-Silengo-Wachtel syndrome) and her similarly affected fetal sibling; the second family in which the duplication involved Xp21 2→p22.11 in sex reversed maternal half siblings with only minor somatic abnormalities. The limited extent of the Xp duplication in the second family allows assignment of the SRVX locus to Xp21.2→p22.11, spanning about 6 or 7 megabases distal to the OTC locus and including DMD. When the duplication does not include Xp21.3, the genitilia are those of a normal male, suggesting that the region containing SRVX may be further localized to Xp21.1→p21.3.

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