Detection of Gene Deletions in Children with Chondrodysplasia Punctata, Ichthyosis, Kallmann Syndrome, and Ocular Albinism by FISH Studies

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Background: Contiguous gene syndrome (CGS) is characterized by a series of clinical features resulting from interstitial or terminal deletions of various adjacent genes. Several important genes have been identified in the Xp22.3 region to be responsible for genetically heterogeneous diseases. In this study, fluorescence *in situ* hybridization (FISH) methods were used to detect the extent of gene deletion related to the phenotypes of patients with Xp-CGS.

Methods: The molecular cytogenetic statuses of 23 boys with at least 1 apparent feature of chondrodysplasia punctata (CDP), ichthyosis, Kallmann syndrome, or type 1 ocular albinism and those of their family members were investigated. High-resolution banding and FISH studies were performed using the probes of steroid sulfatase (STS), KAL1 and OA1, to detect the deleted status on Xp22.3 in these patients along with their mothers and/or sisters or maternal grandmothers.

Results: All of these boys had normal karyotypes. FISH study showed nullisomy in 9 of the 23 male patients and hemizygosity in all female carriers in the genes on Xp22.3. The existence of 2 or more diseases in the same individual indicates a CGS. In addition, a putative mental retardation-related gene on Xp22.3 locus was considered to be located between X-linked CDP and STS.

Conclusions: The use of FISH probes for the Xp22.3 region allowed us to identify X-linked CGSs, especially in those patients with 2 or more distinct clinical entities or an obvious X-linked disorder.

(Chang Gung Med J 2005;28:643-50)

Key words: contiguous gene syndrome, Kallmann syndrome, chondrodysplasia punctata, ichthyosis, ocular albinism, fluorescence *in situ* hybridization.

Contiguous gene syndrome (CGS) is caused by interstitial or terminal deletions of several adjacent genes.[1] The phenotype results in a combination of 2 or more monogenic disorders, and clinical findings are correlated with corresponding genotypes.[1] Several disease gene loci over the human Xp22.2-p22.3 region have been identified by deletion and linkage studies, including the genes responsible for Léri-Weill syndrome and some cases of short stature,[2] X-linked recessive chondrodysplasia punc-

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Received: Dec. 17, 2004; Accepted: Feb. 21, 2005
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tata (CDP and CDPX1),[3] X-linked nonspecific mental retardation (MR and MRX),[4] X-linked ichthyosis (ICH and XLI),[5] Kallmann syndrome (KS),[5,6] and ocular albinism (OA and OA1).[7] KS is a clinical entity characterized by hypogonadotropic hypogonadism with anosmia or hyposmia.[6,8] CDP shows a clinically distinct phenotype represented by dysplasia and shortening of the long bones, particularly with calcification and cataracts.[3,9] Albinism is a generic designation that covers various clinical syndromes exhibiting hypomelanosis.[7,10] The genotypes and phenotypes are heterogeneous in all of these syndromes. However, 2 or more of them may coexist in the same male individual, indicating a CGS on the X chromosome.[11] Among these genes, only that for short stature resides within the pseudoautosomal region 1 (PAR1) and is identical on both the X and Y chromosomes.[2] Several reports have described the features of X-linked KS to be part of a complex phenotype.[12-14] These patients were associated with other X-linked diseases, such as XLI, CDPX1, MRX, short stature, and OA1. This complex phenotype is due to a deletion in the Xp22.3 region, which involves an adjacent disease gene, causing a contiguous gene syndrome. This study illustrates that Xp22.3 region-related CGSs may have various clinical presentations, hence it is useful to combine clinical, metabolic, and molecular cytogenetic studies in their diagnosis. Using a FISH study, a more-explicit differential diagnosis of X-linked CGS (CPDX1, XLI, KS, and OA1) patients can be achieved compared to those with similar phenotypes but with other inherited forms.

METHODS

Patients

Children with at least 1 of the following disorders were enrolled in this study. (1) CDP: Punctate calcifications, due to abnormal calcium deposition in areas of enchondral bone formation, have been described for a variety of osteodysplasias referred to by the term chondrodysplasia punctata[3] (Fig. 1A). Different forms of CDP are classified based on the clinical features and on different inheritance patterns. The X-linked recessive CDP (CDPX1) is characterized by facial anomalies with severe nasal hypoplasia, short stature, and distal phalangeal hypoplasia in male patients. Five male patients with CDP were recruited. (2) ICH: Inherited ichthyoses represent a heterogeneous group of skin disorders characterized primarily by visible scales but often involving other organ systems (Fig. 1B). The most common and best defined is X-linked ICH (XLI) caused by a steroid sulfatase (STS) deficiency.[5] Fifteen male patients with ICH were enrolled. (3) KS: KS is characterized by hypogonadism caused by a hypothalamic gonadotropin-releasing hormone deficiency and anosmia secondary to an absence of olfactory bulbs and tracts.[5,6] Five male patients without affected female siblings were recruited. (4) OA: The clinical recognition of oculocutaneous albinism or ocular albinism is usually obvious because of the cutaneous hypopigmentation in the former and its absence in the latter. Both types of albinism are associated with nystagmus, foveal hypoplasia with little retinal melanin pigmentation, reduced visual acuity, and strabismus.[7] Five patients with OA were also enrolled.

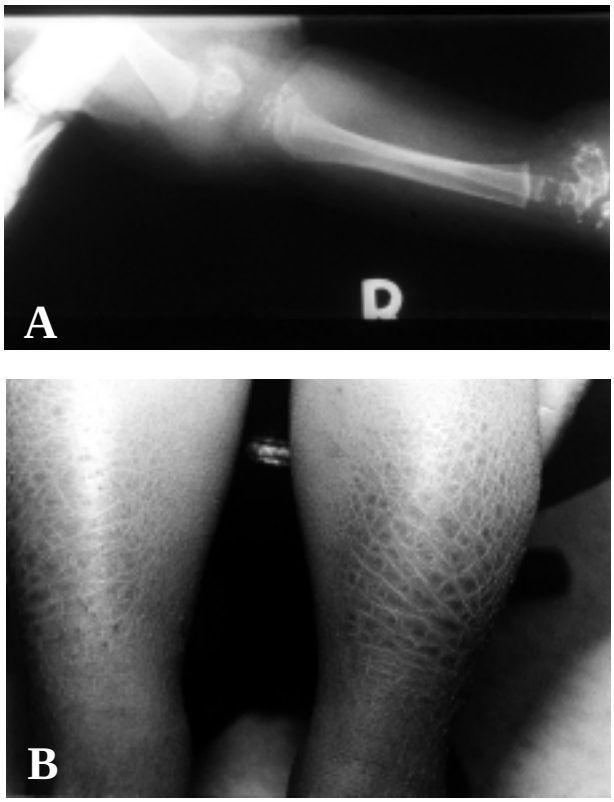

Fig. 1 Patient 1. (A) Several punctate calcifications compatible with CDP, (B) ichthyosis over the lower leg.

Methods

Clinical evaluations included growth parameters; a physical examination (especially for a micropenis, cryptorchidism, and a hypoplastic scrotum); a family study especially a maternal uncle with cryptorchidism, lack of secondary sexual characteristics, and anosmia or hyposmia; neurological examination (mentality and neurological disorders including mirror movements of the bilateral hands and nystagmus); IQ test; long bone study; eye examination; and the response to LHRH (luteinizing hormone releasing hormone) to evaluate the status of hypogonadotropic hypogonadism.

In the molecular cytogenetic studies,[14,15] the molecular cytogenetic status of the 23 boys with at least 1 apparent feature of CDP, ICH, KS, or OA but with normal karyotypes, and those of their family members were investigated. High-resolution G-banded chromosome analysis was first used to detect any structural abnormalities of the X chromosome. To further elucidate deletions in Xp22.3, FISH was performed according to procedures described previously.[15] Specific probes were applied to the metaphase chromosome preparations including X chromosome paint, and those from the distal Xp region known to be associated with the following clinical phenotypes: for X-linked ichthyosis-TS (locus Xp22.32), for KS-KAL (locus Xp22.32), and for X-linked OA-OA1 (locus Xp22.31) (Fig. 2). Twenty cells from each preparation were scored for the presence or absence of signals, i.e., to show nullisomy in males or hemizygosity in females over the 3 loci (Fig. 3).[14]

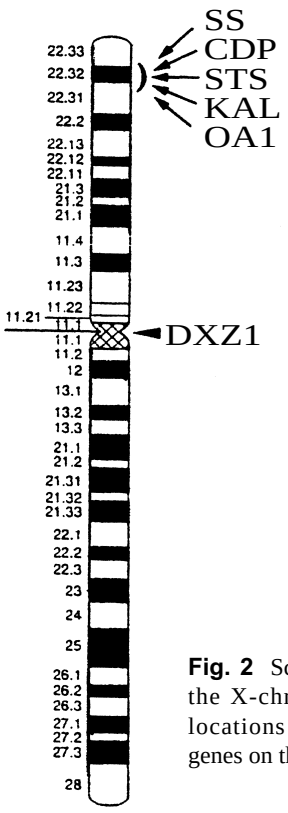

Fig. 2 Schematic representation of the X-chromosome with relative locations of the major identified genes on the Xp22.3 locus.

RESULTS

Physical examinations of the 23 children and their family members showed that 3 male patients with CDP had and 2 did not have associated syndromes, 10 with isolated ICH and 5 with syndromic ICH had associated syndromes, and 2 with isolated KS and 3 with syndromic KS had associated syndromes. One boy with sporadic OA, another family in which 2 short brothers had moderate attention deficit-hyperactivity disorder (ADHD) and mild OA inherited from their mother (very mild), and a further 2 syndromic OA patients were also noted. The combination of the clinical entities was suggestive of CGS (Table 1), including a short stature (SS)+CDP+MR+ICH+KAL+OA (patient 1), SS+CDP+MR+ICH (patient 2), MR+ICH+KAL (patient 3), MR+ICH+KAL+OA (patient 4), MR+ICH (patient 5), and SS+CDP+MR+ICH (patient 7). MR was seen in all children with CDP

Table 1. Classification of Patients

Disorders	Number (n = 23)	Xp^- (FISH) (n = 9)
OA only	3	2
KS only	2	0
ICH only	10	1
CDP only	2	0
ICH+MR	1	1
KS+ICH+MR	1	1
ICH+MR+CDP+SS	1	1
OA+KS+ICH+MR	1	1
ICH+MR+CDP+SS	1	1
OA+KS+ICH+MR+CDP+SS	1	1

Abbreviations: OA: ocular albinism; KS: Kallmann syndrome; ICH: ichthyosis; CDP: chondrodysplasia punctata; MR: mental retardation; SS: short stature.

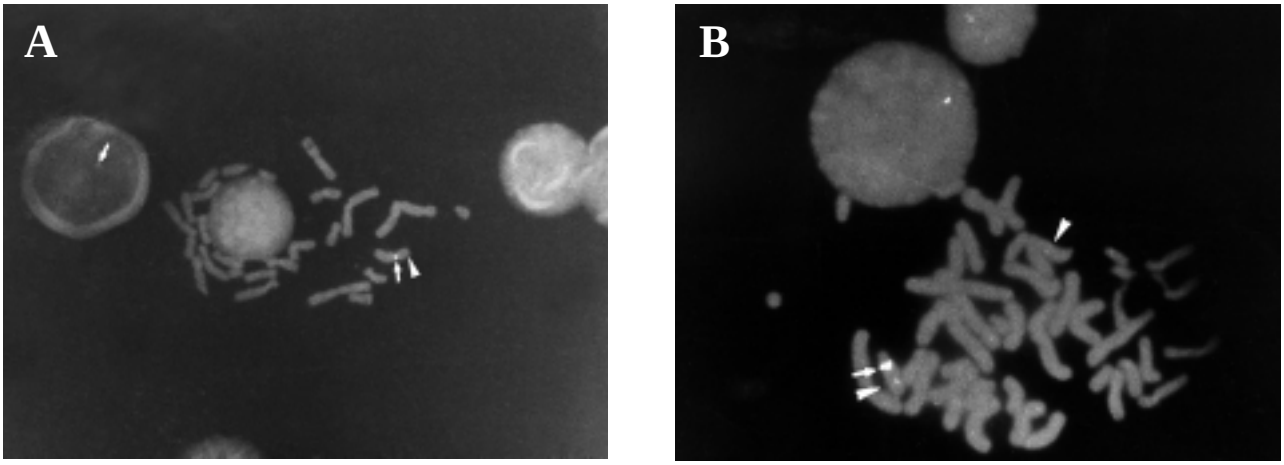

Fig. 3 Patient 4. FISH studies using a cosmid containing the human gene for STS showing nullisomy (A) and hemizygosity (arrow) in a female carrier (B). An X-specific centromeric probe (DXZ1) was used as a control (arrowhead).

(patients 1, 2, and 6). Two brothers had inherited OA from their mother (patients 8 and 9). Both of them were also suffering from growth hormone deficiency as confirmed by insulin tolerance and clonidine provocative tests. A homozygous point mutation over the GH-1 gene was detected. Patient 4 had a positive family history. His maternal uncle also presented with a tall slender habitus, cryptorchidism, no development of secondary sexual characteristics, and anosmia. Their responses to LHRH and hCG (human chorionic gonadotropin) were subnormal. His older sister, mother, and maternal grandmother all showed borderline intelligence (with IQs of 70~80), but no disorder of smell, ichthyosis, or nystagmus. MR occurred in 3 boys with CDP (patients 1, 2, and 6) and also in 6 of 7 ICH patients.

High-resolution G-banded chromosome analysis detected no structural abnormalities of the X chromosome. FISH with a human X chromosome paint probe detected no cryptic translocations involving the Xp region. Nonetheless, the FISH study with the probes STS (locus Xp22.32), KAL (locus Xp22.32), and OA1 (locus Xp22.31) all showed nullisomy over 1, 2, or 3 of the above 3 loci in 9 boys, while their mothers and older sisters exhibited hemizygosity (Fig. 3A, B).[14] These included 2 patients with OA (patients 8 and 9), and 1 with ICH (patient 7), and those with 2 or more diseases in the same individual (patients 1 to 6) (Tables 1, 2). The final karyotypes were as follows: patient 1: 46, XY, ish del(X)(p22.3)(DXZ1+, STS-, KAL-, OA1-)mat; patient 2: 46, XY, ish del(X)(p22.3) (DXZ1+, STS, KAL+, OA1+)mat; patient 3: 46, XY, ish del(X)(p22.3) (DXZ1+, STS-, KAL-, OA1+)mat; patient 4: 46, XY, ish del(X)(p22.3) (DXZ1+, STS, KAL-, OA1-)mat; patients 5, 6, and 7: 46, XY, ish del(X)(p22.3) (DXZ1+, STS-, KAL+, OA1+)mat; and patients 8 and 9: 46, XY, ish del(X)(p22.3) (DXZ1+, STS+, KAL+, OA1-)mat.

DISCUSSION

The distal part of Xp is a region of the human genome with several very peculiar features. Several important genes have been identified in the Xp22.3 region, including 6 contiguous disease genes (Fig. 2, from distal to proximal) for short stature (SS, P-growth gene), X-linked recessive chondrodysplasia punctata (CDPX1), X-linked nonspecific mental retardation (MRX), X-linked ichthyosis (XLI), Kallmann syndrome (KAL1), and type 1 ocular albinism (OA1).[3-5,7,11,14,16,17] These genes may escape X inactivation and may share homology with both the short and long arms of the Y chromosome.[2,7,11] Deletions of adjacent genes may cause various clinical entities (CGS) with a Mendelian inheritance.[1]

In the present study, features of SS, CDP, MR, ICH, and KS were found to be an isolated entity or to be associated in various combinations in 9 of 23 boys with interstitial deletions involving the distal

Table 2. Clinical Features and FISH Study Results

Patient/Feature	SS	CDP	MR	ICH	KS	OA	(del) STS	KAL	OA-1
1	+	+	+	+	+	+	+	+	+
2	+	+	+	+	—	—	+	—	—
3	—	—	+	+	+	—	+	+	—
4	—	—	+	+	+	+	+	+	+
5	—	—	+	+	—	—	+	—	—
6	+	+	+	+	—	—	+	—	—
7	—	—	—	+	—	—	+	—	—
8*	+	—	—	—	—	+	—	—	+
9*	+	—	—	—	—	+	—	—	+

Abbreviations: SS: short stature; CDP: chondrodysplasia punctata; MR: mental retardation; ICH: ichthyosis; KS: Kallmann's syndrome; OA: ocular albinism; del: deleted in FISH; STS: steroid sulfatase; KAL: Kallmann; OA1: X-linked ocular albinism.

short arm of the X chromosome by FISH studies in an X-linked recessive inheritance. The existence of 2 or more diseases in the same individual indicates a CGS. Female heterozygotes for these X-linked CGSs may show a normal phenotype or less-severe disease such as only reduced fertility or hyposmia in KS,[11-13] as seen in the present series. Deletion of the KAL1 gene together with genes mapping more distally on X has been observed in males with ICH, owing to STS deficiency, CDP, MR, and KS.[11,16,17] Contiguous gene syndromes composed of those clinical entities and/or short stature due to interstitial Xp22.3 or terminal Xp22.31-pter deletions have been reported.[14,16,17] Chromosome abnormalities in these diseases are rare evident even after high-resolution banding or are easily confirmed by FISH studies.[7,11,14] An isolated disease may imply an autosomal dominant, X-linked recessive, or point gene mutation of each candidate gene.

Retarded growth was noted in patients 1, 2, 7, 8, and 9. Both environmental factors and genetic background may contribute to the development of stature. It has been proposed that a locus affecting height might be located on the distal portions of Xp and Yp (PAR1).[2] Growth failure may have been a result of skeletal dysplasia in CDP, or deletion of the neighboring P-growth gene around the CDPX1 locus in patients 1, 2, and 7. In patients 3 to 6, there were interstitial deletions over Xp22.3 involving at least from the MRX locus to XLI but not the P-growth gene or CDPX1, because the boys did not have the phenotype of short stature or bone lesions. CDPX1, due to mutations of the arylsulfatase E gene, is a congenital disorder characterized by abnormalities in cartilage and bone development.[9,17,18] It is characterized by facial anomalies with severe nasal hypoplasia, short stature, and distal phalangeal hypoplasia. Other CDPs such as the X-linked dominant form (Conradi-Hunermann syndrome) and the autosomal recessive form (PEX7 gene), need to be differentiated from X-linked CDPX1.[3,18]

X-linked ICH, due to a defect in the enzyme steroid sulfatase (STS), affects males with generalized scaling that usually begins soon after birth.[5] Most (85%~90%) patients with STS deficiency have submicroscopic deletions spanning the entire STS gene and flanking markers,[17,18] which can easily be confirmed by a FISH study as shown in patients 1 to 7 (Table 2). Some patients may have point mutations in the STS genes, and a few have a complex phenotype resulting from the presence of a CGS involving a deletion of an additional disease gene located in the Xp22.3 region.[18]

Kallmann syndrome is the most-common form of gonadotropin deficiency,[13,19] in which the autosomal dominant, autosomal recessive, and X-linked recessive patterns of inheritance have been described.[19] Patients with X-linked KS who carry the KAL1 gene deletion all have CGS displaying the phenotype of several X-linked disorders as in patients 1, 3, and 4 (Table 2). Isolated KS (Table 1) in patients may have been the result of certain point

mutations in the KAL1 gene or in other autosomal genes.[19] Albinism is a generic designation that covers several heritable metabolic defects of the pigment cell (melanocyte) system of the eyes and skin. X-linked ocular albinism type 1 (OA1) is caused by mutations in the OA1 gene, which encodes a membrane glycoprotein localized to melanosomes.[7,10,20] Optic changes in OA1 patients lead to nystagmus, strabismus, and reduced visual acuity in affected males. Submicroscopic and intragenic deletions, or missense mutations of the OA1 gene have been described in most patients with X-linked OA,[10,20] such as in patients with isolated OA (patients 8 and 9) and CGS-OA (patients 1 and 4) (Tables 1, 2). In patients 8 and 9, the deleted status of the OA1 gene was confirmed by the FISH study. In addition, a GH deficiency in these 2 brothers was caused by another autosomal recessive GH-1 gene mutation within their family instead of the distal P-growth gene. A possible CGS in this chromosomal segment may be present because the phenotype of ADHD was also described in Xp-CGS.[21]

Combinations of X-linked recessive disorders such as CDP, ICH, KS, OA, or other associated diseases such as MR, SS, epilepsy, and ADHD in males present as a form of CGS, in which the co-deletion of adjacent genes on a chromosome is responsible for a complex phenotype.[1,11,14,16,17,21] These clinical entities may be a result of a terminal deletion with a breakpoint at Xp22.31 or an interstitial submicroscopic deletion of Xp22.3, inherited maternally or sporadically.[4,11,14,16,17,22] Another important manifestation in these patients was moderate MR. This indicates that 1 or more MRX (X-linked MR) gene(s) nearby may have been deleted or disrupted. It was suggested that deletions or mutations of X chromosome loci may cause MRX.[4,11,22] X-linked MR occurs in about 1 in 600 male births, and fragile X syndrome accounts for only 1/4 of them.[11] From Table 2, a correlation between the deletion of a specific X chromosomal region and the presence of MR as an additional sign in patients 1 to 6 was identified. One or 2 possible X-linked non-syndromic MR genes have tentatively been assigned to a specific interval between CDPX1 and XLI, or around them.[11,22]

FISH is a convenient and rapid screening method for patients with features of such combinations. However, small deletions or point mutations in related gene loci may be missed by FISH analysis.[14,21] Further PCR sequencing studies of all of their coding sequences will elucidate those problems. Thus, for X-linked CGS, multiplex PCR or FISH analysis of nullisomic males and FISH analysis of carrier females are efficient strategies for deletion detection. Submicroscopic maternal deletions have important implications for genetic counseling.

Acknowledgments

This work was partly supported by a grant from Chang Gung Memorial Hospital (CMRP-900).

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以螢光原位雜交法偵測斑點性軟骨形成不良、魚鱗癬、Kallmann 氏症及眼白化症兒童之基因缺損

侯家瑋

背 景： 相鄰基因症候群 (CGS) 是在染色體間質或末端一組相鄰基因缺損而有特殊的臨床症狀。在染色體 Xp22.3 區域上有一些重要基因對應一系列不同疾病。本研究利用螢光原位雜交法 (FISH) 來偵測 Xp- 相鄰基因症候群之基因缺損範圍。

方 法： 共有二十三名男性病人及其家人接受分子細胞遺傳學研究，病人帶有至少下列一種症狀：斑點性軟體形成不良 (CDP) 、魚鱗癬、Kallmann 氏症及／或眼睛白化症症狀。應用高解析度染色體分帶及 FISH 技術（探針有 STS、KAL1、OA1）來偵測 Xp22.3 區域基因缺損程度。

結 果： 所有病人均有正常染色體核型，以 FISH 方法可發現九名男性不同程度的 nullisomy，與女性帶病者（母親）的 hemizygosity，病人帶有兩種或兩種以上的症狀顯示 CGS 情況。同時一個與性連鎖智障有關的基因可能位於 CDP 與 STS 之間。

結 論： FISH 是一種檢查 Xp-CGS 病症的有效方法，尤其在病人帶有兩種或兩種以上的症狀顯示 CGS 情況。

(長庚醫誌 2005;28:643-50)

關鍵字： 相鄰基因症候群，斑點性軟骨形成不良，魚鱗癬，Kallmann 氏症，眼白化症，螢光原位雜交法。

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受文日期：民國93年11月17日；接受刊載：民國94年2月21日
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