

【 遺伝子情報の電子カルテへの取り込み 】

●電子カルテシステムからの参照イメージ

①電子カルテのインデックスをクリック

②秘匿レベルに応じてID/PW入力画面表示。レベルBのときは「電子カルテのパスワードを入力して下さい。」となります。

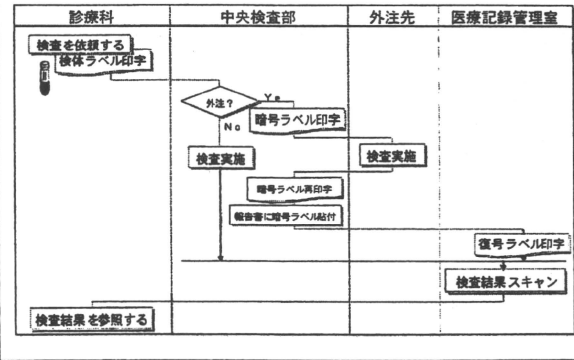
③認証OKとなれば内容表示

伝子関連検査結果

患者氏名：日立 太郎

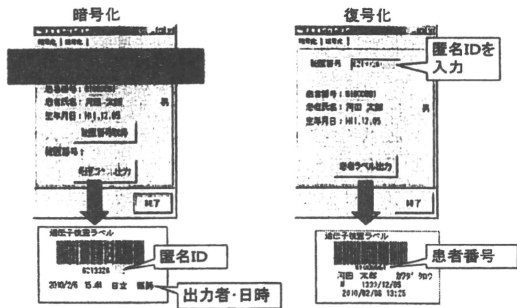
検査結果異常なし。

【 遺伝子検査依頼から結果参照まで 】



【 個人情報の暗号化・復号化について 】

●匿名化機能



【 匿名化ID検索ツール 】

●匿名化ID検索ツール

外送先から匿名IDで問い合わせがあった場合等の確認用(使用できる端末及び職員は限定)

Letter to the Editor

Entire *PTCH1* deletion is a common event in point mutation-negative cases with nevoid basal cell carcinoma syndrome in Japan

To the Editor:

Nevoid basal cell carcinoma syndrome [NBCCS (OMIM 109400)], also called Gorlin syndrome, is an autosomal dominant neurocutaneous disorder characterized by large body size, developmental and skeletal abnormalities, sensitivity to radiation, and an increased incidence of cancers such as basal cell carcinoma (BCC) and medulloblastoma (1). NBCCS is caused by inactivating mutations in the *Patched-1* (*PTCH1*) gene (2, 3). Heterozygous loss of *PTCH1* found in certain sporadic and familial cases of BCC indicates that *PTCH1* is also a tumor suppressor gene (4, 5).

Despite extensive efforts to detect mutations, they are still unidentified in 25–60% of patients (6–8). To date, we have analyzed 38 patients with NBCCS from 32 families. Eight of the families did not harbor any *PTCH1* mutations detectable by polymerase chain reaction (PCR)-based direct sequencing of the exons. To investigate the possibility of large deletions involving the *PTCH1* gene, we employed a high-resolution array-based comparative genomic hybridization technology. Consequently, we identified genomic deletions involving *PTCH1* in seven individuals from five of the eight point mutation-negative families (Fig. S1). These patients are listed in Table 1. Some of them have been reported previously by us (9) and one patient reported by others (NS6) (10) is also included in the table, all of which are of Japanese origin. To our knowledge, this table includes all the patients with *PTCH1* deletions in which the breakpoints have been identified at the nucleotide level. A schematic representation of each deletion's size together with the deleted genes is shown in Fig. 1a. Unlike in cases of Sotos syndrome and neurofibromatosis type 1, no recurrent breakpoints were observed in these patients (11, 12). Whereas deletions larger than 2.4 Mb were generated by non-homologous end joining, smaller ones (less than 1.2 Mb) were

produced by *Alu*-mediated nonallelic homologous recombination (Fig. S2).

G19 and G36 inherited the deletion from their mothers (G27 and G43, respectively), whereas the deletion in NS6 is of paternal origin. The breakpoint sequences in these cases were completely conserved through generations. Other patients (G35, G10 and G5) did not have a family history of NBCCS and, therefore, the deletions seemed to be *de novo*. Patients harboring deletions of less than 2.4 Mb did not exhibit any phenotypes atypical for NBCCS despite that up to 22 RefSeq genes (four disease genes) were included in the deleted region. This implies that hemizygous loss of these genes, except for *PTCH1*, might not have an influence on any observable phenotypes. In contrast, deletions larger than 5.3 Mb led to phenotypes unusual for NBCCS including severe mental and motor retardation, epilepsy, and hypotonia (Table 1).

Interestingly, each *Alu*-mediated deletion was mediated by a distinct path of rearrangement (Fig. 1b). G36/43 had a crossing over point within the *Alu* elements generating a hybrid *Alu* element. In G19/27, however, the crossing over occurred near the poly-A tail of the proximal *Alu* element (9). Therefore, the proximal *Alu* remained intact while the distal *Alu* was deleted. In the third case, NS6, crossing over occurred at the 5' end of the *Alu* elements and removed both *Alu* sequences leaving two short direct repeats flanking an *Alu* element on both sides called target-site duplications (10).

To date, we have analyzed 32 NBCCS families and identified entire deletions of *PTCH1* in 5 families. This implies that 16% of NBCCS families (five of the eight point mutation-negative families) can be explained by the entire loss of *PTCH1*. Mutations are not observed in the *PTCH1*-coding sequences in considerable numbers of NBCCS cases not only in Japanese but also in other ethnicities and, apart from *PTCH1*, only one *PTCH2* and one *SUFU* mutation in NBCCS have been

Table 1. NBCCS patients with gene deletions

Patient No.	Age (years)	Size	Deleted nucleotide No. ^a	Deleted RefSeq genes ^b	Deleted disease genes ^b	Predicted mechanism of deletion	Atypical phenotypes
G19 ^c	10	165 kb	97,187,146–197,350,058	1	1	Alu-mediated NAHR ^d	None
G27 ^e	40	165 kb	97,187,146–97,350,058	1	1	Alu-mediated NAHR	None
G36	8 M ^f	1.1 Mb	96,766,985–97,885,391	9	2	Alu-mediated NAHR	None
G43 ^g	32	1.1 Mb	96,766,985–97,885,391	9	2	Alu-mediated NAHR	None
NS6 ^h	NA ⁱ	1.2 Mb	96,070,054–97,646,323 ^j	13	3	Alu-mediated NAHR	None
G35	5	2.4 Mb	95,880,121–98,238,462	22	4	NHEJ ^k with 2-bp overlap	None
G10 ^c	8	5.3 Mb	94,898,311–100,101,915	58	6	NHEJ with 1-bp overlap	severe mental and motor retardation, epilepsy, hypotonia, inguinal hernia
G5 ^c	12	11 Mb	90,617,332–101,647,101	93	13	NHEJ with 7-bp addition	severe mental and motor retardation, epilepsy, hypotonia, webbed neck, hydronephrosis

^aNucleotide numbers are based on UCSC Genome Browser on Human March 2006 Assembly (hg18).

^bNumbers of the deleted genes are based on Database of Genomic variants (<http://projects.tcag.ca/variation/>).

^cFujii et al. 2007 (9).

^dnonallelic homologous recombination.

^eG19's mother.

^f8 months.

^gG36's mother.

^hTakahashi et al. 2009 (10).

ⁱNot available.

^jDistal breakpoint is ambiguous due to the complicated structure of the deletion (10).

^knon-homologous end joining.

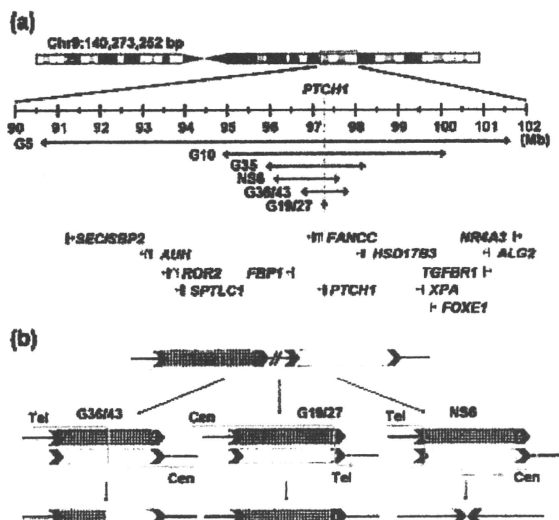


Fig. 1. Schematic representation of the deletions. (a) Architecture of the deleted region. Horizontal arrows represent the deleted regions in the six families listed in Table 1. Disease genes are depicted at the bottom. Vertical dotted lines indicate the positions of *PTCH1*. (b) Three different types of recombination between *Alu* elements observed in NBCCS patients. Black and gray lines represent flanking and intervening regions, respectively. Curved red arrows show the paths of recombination events. Red and blue arrowheads represent target-site duplications (TSDs) of the two elements, respectively. Cen, centromeric; Tel, telomeric.

reported (13, 14). Therefore, it is strongly advisable to investigate the possibility of the gene deletion in point mutation-negative cases.

Supporting Information

The following Supporting information is available for this article: Fig. S1. Microarray profile of two individuals with a copy number loss at 9q22. Probes are ordered on the x-axis according to physical mapping positions. Test over reference signal intensity ratios for each probe are given on the y axis. For clarity, data are smoothed over a 50-probe window. The position of *PTCH1* is indicated by a vertical dotted line. Disease genes lying in this region are schematically indicated at the bottom.

Fig. S2. DNA sequence of junction fragments. The DNA sequence for each deletion-specific junction fragment obtained by polymerase chain reaction (PCR) was aligned to the wild-type flanking genome sequence for both proximal and distal breakpoints. Alignments with the proximal boundary are shaded in light gray, and those with the distal boundary in dark gray. The estimated cross over points are shaded in red. (A) Sequence alignment in G36/43. Red lines surround *Alu* sequences. The precise length of polyT could not be determined due to the heterogeneity of the PCR product (A_{20–22}). (B) Sequence alignment in G35.

Additional Supporting information may be found in the online version of this article.

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Letter to the Editor

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