New mutations and an updated database for the patched-1 (PTCH1) gene

Marie G. Reinders1,2* | Antonius F. van Hout1* | Betül Cosgun1,2 | Aimée D. Paulussen2,3 | Edward M. Leter3 | Peter M. Steijlen1,2 | Klara Mosterd1,2 | Michel van Geel1,2,3 | Johan J. Gille4

1Department of Dermatology, Maastricht University Medical Center, Maastricht, The Netherlands
2GROW Research School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands
3Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands
4Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands

Correspondence
Marie G. Reinders, Maastricht University Medical Centre, Maastricht, The Netherlands.
Email: marieke.reinders@mumc.nl

Abstract

Background: Basal cell nevus syndrome (BCNS) is an autosomal dominant disorder characterized by multiple basal cell carcinomas (BCCs), maxillary keratocysts, and cerebral calcifications. BCNS most commonly is caused by a germline mutation in the patched-1 (PTCH1) gene. PTCH1 mutations are also described in patients with holoprosencephaly.

Methods: We have established a locus-specific database for the PTCH1 gene using the Leiden Open Variation Database (LOVD). We included 117 new PTCH1 variations, in addition to 331 previously published unique PTCH1 mutations. These new mutations were found in 141 patients who had a positive PTCH1 mutation analysis in either the VU University Medical Centre (VUMC) or Maastricht University Medical Centre (MUMC) between 1995 and 2015.

Results: The database contains 331 previously published unique PTCH1 mutations and 117 new PTCH1 variations.

Conclusion: We have established a locus-specific database for the PTCH1 gene using the Leiden Open Variation Database (LOVD). The database provides an open collection for both clinicians and researchers and is accessible online at http://www.lovd.nl/PTCH1.

Keywords
Basal cell nevus syndrome, BCNS, Gorlin syndrome, mutation database, PTCH1

1 | INTRODUCTION

Basal cell nevus syndrome (BCNS, MIM#109400) or Gorlin syndrome is a rare autosomal dominant disorder characterized by multiple basal cell carcinomas (BCCs), maxillary keratocysts, and cerebral calcifications (John & Schwartz, 2016). The incidence of BCNS is estimated at 1 in 50,000 to 256,000 (Lo Muzio, 2008). Diagnostic criteria for BCNS were first established by Evans et al., (1993); modified by Kimonis et al., (1997) and revised in 2011 by Bree & Shah, (2011). Diagnosis is based on two major criteria, one major criterion and two minor criteria or one major criterion and genetic confirmation (Table 1).

Most frequently occurring symptoms are multiple basal cell carcinomas, maxillary keratocysts, palmoplantar pits, and calcification of the falx cerebri. About 60% of patients...
have a typical phenotype with macrocephaly, frontal bossing, coarse facial features, and hypertelorism (Evans et al., 1993; Kimonis et al., 1997), 3%–5% of patients develop medulloblastoma in childhood (Evans, Farndon, Burnell, Gattamaneni, & Birch, 1991).

In 1996, the patched-1 (PTCH1) gene (MIM#601309) was first reported as a candidate gene for BCNS. Two different heterozygous mutations in the PTCH1 gene were identified in two patients with Gorlin syndrome (Johnson et al., 1996). Another disorder that is caused by a germline mutation in the PTCH1 gene is holoprosencephaly-7 (MIM#610828), a structural anomaly of the brain in which there is failed or incomplete separation of the forebrain early in gestation. In addition, the vast majority of sporadic BCCs have somatic mutations in PTCH1 (Bonilla et al., 2016; Reifenberger et al., 2005).

1.1 | The PTCH1 gene

PTCH1 (NCBI Reference Sequence NM_000264.3) is the human homolog of the Drosophila patched-1 gene and is located on chromosome 9q22.3. It contains 24 exons with the transcriptional start site in exon 1 and the termination site in exon 23. PTCH1 encodes a 1447-amino acid transmembrane glycoprotein, which is part of the hedgehog (Hh) pathway. The Hh pathway is a key regulator in embryonic development and tumorigenesis controlling cell differentiation, tissue polarity, and cell proliferation.

The function of the PTCH1 protein is inhibition of the transmembrane protein Smoothened (SMO). Extracellular Hh ligands can bind to the PTCH1 receptor, releasing this inhibition, allowing SMO to signal downstream and activate GLI transcription factors. Based on this role in preventing cells from uncontrolled proliferation, PTCH1 is seen as a tumor suppressor gene. SMO on the other hand acts as an oncogene (Kogerman et al., 2002).

The typical congenital features of BCNS seem to occur due to haploinsufficiency (Wicking et al., 1997), while tumors in BCNS are believed to develop according to the two-hit hypothesis described by Knudson, (2001)and Pan, Dong, Sun, & Li, (2010). In the latter, either both alleles of the gene harbor a mutation, or one mutated allele is accompanied by allelic loss of the remaining wild-type allele. Recent mouse model studies show that haploinsufficiency of PTCH1 may be sufficient for the development of medulloblastoma and rhabdomyosarcoma, so tumor formation not always follows the two-hit hypothesis (Calzada-Wack et al., 2002; Zurawel, Allen, Wechsler-Reya, Scott, & Raffel, 2000). With DNA sequencing analysis of the PTCH1 gene, mutation detection frequency ranges from 50% to 85% in individuals with typical findings of BCNS (Lam, Ou, & Billingsley, 2013). Mosaic presentations of BCNS can occur (Reinders et al., 2016; Torrelo et al., 2013).

1.2 | Ethical compliance

Our study was approved by the independent ethics committee of our hospital.

1.3 | The PTCH1 database

We have established a database for PTCH1 using the Leiden Open Variation Database (LOVD) version 3.0 (Variants of patched 1 (PTCH1), 2004). The purpose of this database is to assemble molecular variants of the PTCH1 gene in a standardized format. The database provides an open collection for both clinicians and researchers containing published and unpublished PTCH1 mutations.

For each mutation, information is provided at the molecular level: DNA change, predicted protein change, RNA change, exon, type of mutation, reported pathogenicity, technique used, and source of material, and phenotype information if available. The Sequence Variant Nomenclature of all mutations (new and published) is updated according to the latest guidelines of the Human Genome Variation Society (HGVS) version 15.11 and based on NCBI Reference Sequence NM_000264.3.
| Case identifier | Members affected | Gender | Age of diagnosis | Exon/Intron | DNA variant | Protein change | RNA change | Classification |
|-----------------|-----------------|--------|-----------------|-------------|-------------|----------------|------------|----------------|
| Nonsense mutations |
| BCNS1 | 1 | M | 67.7 | 2 | c.205A>T | p.(Lys69*) | r.(?) | 5 |
| BCNS2 | 1 | F | 24.4 | 2 | c.279C>G | p.(Tyr93*) | r.(?) | 5 |
| BCNS3 | 1 | F | 27.9 | 2 | c.294C>A | p.(Cys98*) | r.(?) | 5 |
| BCNS4 | 2 | M | 38.9 | 3 | c.403C>T | p.(Arg135*) | r.(?) | 5 |
| BCNS5 | 3 | F | 26.1 | 3 | c.403C>T | p.(Arg135*) | r.(?) | 5 |
| BCNS6 | 3 | M | 11.0 | 3 | c.466C>T | p.(Gln156*) | r.(?) | 5 |
| BCNS7 | 1 | M | 14.1 | 5 | c.707G>A | p.(Trp236*) | r.(?) | 5 |
| BCNS8 | 2 | M | 38.9 | 3 | c.403C>T | p.(Arg135*) | r.(?) | 5 |
| BCNS9 | 3 | M | 11.0 | 3 | c.466C>T | p.(Gln156*) | r.(?) | 5 |
| BCNS10 | 1 | M | 8.4 | 8 | c.1119C>G | p.(Tyr373*) | r.(?) | 5 |
| BCNS11 | 1 | F | 1.1 | 8 | c.1198C>T | p.(Gln400*) | r.(?) | 5 |
| BCNS12 | 1 | F | 8.3 | 10 | c.1379G>A | p.(Trp460*) | r.(?) | 5 |
| BCNS13 | 2 | M | 31.0 | 10 | c.1380G>A | p.(Trp460*) | r.(?) | 5 |
| BCNS14 | 1 | M | 0.0 | 12 | c.1691T>G | p.(Glu604*) | r.(?) | 5 |
| BCNS15 | 1 | M | 14.1 | 5 | c.707G>A | p.(Trp236*) | r.(?) | 5 |
| BCNS16 | 1 | F | 23.0 | 13 | c.1810G>T | p.(Glu604*) | r.(?) | 5 |
| Missense mutations |
| BCNS17 | 1 | F | 33.0 | 14 | c.1975C>T | p.(Gln59*) | r.(?) | 5 |
| BCNS18 | 2 | F | 24.4 | 14 | c.2098C>T | p.(Gln700*) | r.(?) | 5 |
| BCNS19 | 1 | F | 25.1 | 14 | c.2170G>T | p.(Glu724*) | r.(?) | 5 |
| BCNS20 | 2 | F | 56.7 | 15 | c.2308C>T | p.(Arg770*) | r.(?) | 5 |
| BCNS21 | 1 | M | 42.4 | 15 | c.2359G>T | p.(Gln816*) | r.(?) | 5 |
| BCNS22 | 1 | F | 22.4 | 15 | c.2446C>T | p.(Gln816*) | r.(?) | 5 |
| BCNS23 | 1 | M | 19.7 | 15 | c.2557C>T | p.(Gln853*) | r.(?) | 5 |
| BCNS24 | 1 | M | 4.3 | 16 | c.2619C>A | p.(Tyr873*) | r.(?) | 5 |
| BCNS25 | 1 | M | 25.8 | 16 | c.2619C>A | p.(Tyr873*) | r.(?) | 5 |
| BCNS26 | 1 | M | 14.1 | 16 | c.2619C>G | p.(Tyr873*) | r.(?) | 5 |
| BCNS27 | 1 | F | 6.2 | 18 | c.3027C>A | p.(Tyr1009*) | r.(?) | 5 |
| BCNS28 | 2 | F | 47.9 | 18 | c.3027C>G | p.(Tyr1009*) | r.(?) | 5 |
| BCNS29 | 1, de novo | F | 14.1 | 18 | c.3058C>T | p.(Gln1020*) | r.(?) | 5 |
| (Continues) |
| Case identifier | Members affected | Gender | Age of diagnosis | Exon/Intron | DNA variant | Protein change | RNA change | Classification |
|----------------|------------------|--------|-----------------|-------------|-------------|----------------|------------|----------------|
| BCNS40         | 1                | M      | 38.9            | 14          | c.2250G>C   | p.(Lys750Asn)  | r.spl?     | 4              |
| BCNS41         | 1                | M      | 46.7            | 15          | c.2414T>G   | p.(Ile805Arg)  | r.(?)      | 4              |
| BCNS42         | 1                | M      | 22.6            | 15          | c.2447A>G   | p.(Gln816Arg)  | r.(?)      | 4              |
| BCNS43         | 1                | F      | 52.1            | 18          | c.2917C>A   | p.(Gln973Lys)  | r.(?)      | 4              |
| Splice site mutations |
| BCNS44         | 1                | F      | 17.1            | 1i          | c.202-2A>G  | p.?           | r.spl?     | 4              |
| BCNS45         | 2                | F      | 23.5            | 2i          | c.394+1G>A  | p.?           | r.spl?     | 4              |
| BCNS46         | 2                | M      | 17.7            | 2i          | c.394+1G>C  | p.?           | r.spl?     | 4              |
| BCNS47         | 1                | F      | 13.6            | 4i          | c.566_584+8del | p.?           | r.spl?     | 4              |
| BCNS48         | 1                | M      | 12.3            | 4i          | c.655-1G>A  | p.?           | r.spl?     | 4              |
| BCNS49         | 1                | F      | 21.5            | 5i          | c.747-2A>G  | p.?           | r.spl?     | 4              |
| BCNS50         | 4                | M      | 2.6             | 6i          | c.946-1G>T  | p.?           | r.spl?     | 4              |
| BCNS51         | 2                | F      | 22.3            | 8i          | c.1216-2A>G | p.?           | r.spl?     | 4              |
| BCNS52         | 2                | F      | 33.1            | 9i          | c.1347+1G>A | p.?           | r.spl?     | 4              |
| BCNS53         | 2                | M      | 32.3            | 9i          | c.1348-1G>C | p.?           | r.spl?     | 4              |
| BCNS54         | 1                | M      | 24.0            | 10i         | c.1504-1G>C | p.?           | r.spl?     | 4              |
| BCNS55         | 1                | M      | 59.7            | 10i         | c.1504-2A>T | p.?           | r.spl?     | 4              |
| BCNS56         | 2                | M      | 27.1            | 12i         | c.1729-1G>C | p.?           | r.spl?     | 5              |
| BCNS57         | 1                | M      | 69.4            | 14i         | c.2250+1G>T | p.?           | r.spl?     | 4              |
| BCNS58         | 1                | F      | 28.2            | 14i         | c.2251-2A>G | p.?           | r.spl?     | 4              |
| BCNS59         | 1                | M      | 7.1             | 15i         | c.2561-2A>G | p.?           | r.spl?     | 4              |
| Small deletions or duplications |
| BCNS60         | 1              | M      | 5.4             | 1           | c.114del    | p.(Leu39Cysfs*41) | r.(?)     | 5              |
| BCNS61         | 2              | M      | 31.0            | 2           | c.254_255del | p.(Arg85Thrfs*4) | r.(?)     | 5              |
| BCNS62         | 1              | F      | 49.7            | 2           | c.258_259del | p.(Leu87Ilefs*2) | r.(?)     | 5              |
| BCNS63         | 1              | M      | 28.5            | 2           | c.258_259del | p.(Leu87Ilefs*2) | r.(?)     | 5              |
| BCNS64         | 1              | M      | 52.0            | 2           | c.262_266del | p.(Phe88Thrfs*50) | r.(?)     | 5              |
| BCNS65         | 1              | M      | 30.9            | 2           | c.385_386dup | p.(Trp129Cysfs*9) | r.(?)     | 5              |
| BCNS66         | 1              | M      | 14.7            | 3           | c.479_482del | p.(Gln160Profs*10) | r.(?)     | 5              |
| BCNS67         | 1              | M      | 10.7            | 3           | c.572_575dup | p.(Met192Ilefs*61) | r.(?)     | 5              |
| BCNS68         | 1              | F      | 63.8            | 5           | c.724del    | p.(Gln324Serfs*8) | r.(?)     | 5              |
| BCNS69         | 1              | F      | 25.8            | 6           | c.770_771delinsGGTTTGG | p.(Thr257Argfs*14) | r.(?)     | 5              |
| BCNS70         | 1              | F      | 43.8            | 6           | c.842del    | p.(Met281Lys*2) | r.(?)     | 5              |
| BCNS71         | 1              | F      | 11.4            | 7           | c.1040_1049del | p.(Val347Alafs*17) | r.(?)     | 5              |
| BCNS72         | 1              | F      | 35.1            | 8, 14       | c.[1114del;2183C>T] | p.(Met372Cysfs*60); p.(Thr728Met) | r.(?)     | 5:3            |
| BCNS73         | 1              | F      | 23.9            | 9           | c.1279del   | p.(Leu427Trpf*5) | r.(?)     | 5              |
| BCNS74         | 1              | M      | 35.1            | 10          | c.1348_1350del | p.(Leu450del)  | r.(?)     | 4              |
| BCNS75         | 1              | M      | 55.5            | 10          | c.1366dup   | p.(Thr456Asnf*41) | r.(?)     | 5              |
| BCNS76         | 2              | F      | 13.3            | 10          | c.1415_1429del | p.(Ala472_Leu476del) | r.(?)     | 4              |
| BCNS77         | 1              | M      | 47.9            | 11          | c.1508dup   | p.(Leu503fs*) | r.(?)     | 5              |
| BCNS78         | 1              | M      | 2.7             | 13          | c.1767_1769del | p.(Leu590del)  | r.(?)     | 4              |

(Continues)
| Case identifier | Members affected | Gender | Age of diagnosis | Exon/Intron DNA variant | Protein change | RNA change | Classification |
|-----------------|-----------------|--------|------------------|--------------------------|----------------|------------|----------------|
| BCNS79          | 1               | F      | 8.3              | c.1852del                | p.(Cys618Alafs*5) | r.(?)      | 5              |
| BCNS80          | 1               | M      | 43.0             | c.1925dup                | p.(Pro643Thrfs*11) | r.(?)      | 5              |
| BCNS81          | 1               | F      | 16.4             | c.2011dup                | p.(His671Profs*10) | r.(?)      | 5              |
| BCNS82          | 1               | M      | 15.5             | c.2178_2179insA          | p.(Cys727Metfs*11) | r.(?)      | 5              |
| BCNS83          | 1               | M      | 14.9             | c.2179del                | p.(Cys727Valfs*19) | r.(?)      | 5              |
| BCNS84          | 1               | M      | 42.2             | c.2612_2615del           | p.(Asn871Ilefs*31) | r.(?)      | 5              |
| BCNS85          | 1               | F      | 9.7              | c.2748del                | p.(Ser917Alafs*7) | r.(?)      | 5              |
| BCNS86          | 1               | F      | 1.2              | c.2793del                | p.(Val932Serfs*30) | r.(?)      | 5              |
| BCNS87          | 1               | F      | 14.5             | c.2833_2843del           | p.(Arg945Glyfs*10) | r.(?)      | 5              |
| BCNS88          | 1               | M      | 52.4             | c.3050del                | p.(Phe1017Serfs*32) | r.(?)      | 5              |
| BCNS89          | 2               | M      | 40.3             | c.3056_3059del           | p.(Glu1019Valfs*29) | r.(?)      | 5              |
| BCNS90          | 2               | F      | 21.0             | c.3107_3108del           | p.(Leu1036Cysfs*108) | r.(?)      | 5              |
| BCNS91          | 3               | F      | 0.6              | 18, 23                   | c.[3135del;4048C>T] | p.[Phe1046Serfs*3; (Arg1350Trp)] | r.(?) 5;3 |
| BCNS92          | 1               | M      | 15.8             | c.3139_3142del           | p.(Leu1047*) | r.(?)      | 5              |
| BCNS93          | 1               | M      | 13.8             | c.3139del                | p.(Leu1047fs*11) | r.(?)      | 5              |
| BCNS94          | 1               | F      | 23.1             | c.3150del                | p.(Trp1051fs*7) | r.(?)      | 5              |
| BCNS95          | 1               | M      | 33.2             | c.3233_3239del           | p.(Leu1078Profs*7) | r.(?)      | 5              |
| BCNS96          | 1               | U      | 9.3              | 19                       | c.3251_3272del | p.(Val1084Alafs*2) | r.(?) 5 |
| BCNS97          | 1               | M      | 44.7             | 20                       | c.3364_3365del | p.(Met1122Valfs*22) | r.(?) 5 |
| BCNS98          | 1               | M      | 10.9             | 20                       | c.3364_3365del | p.(Met1122Valfs*22) | r.(?) 5 |
| BCNS99          | 1               | F      | 54.4             | 20                       | c.3375del | p.(Val1126Serfs*13) | r.(?) 5 |
| BCNS100         | 1               | F      | 41.8             | 21                       | c.3497dup | p.(Asn1166Lysfs*18) | r.(?) 5 |
| BCNS101         | 1               | U      | 6.7              | 21                       | c.3525_3526del | p.(Leu1175Phefs*8) | r.(?) 5 |
|                 |                 |        |                  |                          |                |            | Large deletions or duplications |
| BCNS102         | 1               | F      | 48.5             | _1_24_                   | c.(?,-188),(*3411 ?)del | p.0? | r.0? | 5 |
| BCNS103         | 1               | M      | 47.2             | _1_24_                   | c.(?,-188),(*3411 ?)del | p.0? | r.0? | 5 |
| BCNS104         | 1               | F      | 44.2             | _1_24_                   | c.(?,-188),(*3411 ?)del | p.0? | r.0? | 5 |
| BCNS105         | 1               | M      | 36.6             | _1_2i                    | c.(?,-188),_1(394+1_395-1) | del | p.? | r.(?) 5 |
| BCNS106         | 1               | F      | 38.0             | 2i_12i                   | c.(394+1_395-1)_, (1728+1_1729-1)(2) | p.? | r.(?) 4 |
| BCNS107         | 1, de novo      | F      | 14.9             | 2i_16i                   | c.(394+1_395-1)_, (2703+1_2704-1)(2) | p.? | r.(?) 4 |
| BCNS108         | 1               | F      | 37.1             | 2i_24_                   | c.(394+1_395-1)_, (*3411 ?)del | p.? | r.(?) 5 |
| BCNS109         | 1               | F      | 19.9             | 14i_16i                  | c.(2250+1_2251-1), (2703+1_2704-1)del | p.? | r.(?) 5 |
| BCNS110         | 4               | M      | 35.0             | 16i_19i                  | c.(2703+1_2704-1), (3306+1_3307-1)del | p.? | r.(?) 5 |

**Probably nonpathogenic**

| Case identifier | Members affected | Gender | Age of diagnosis | Exon/Intron DNA variant | Protein change | RNA change | Classification |
|-----------------|-----------------|--------|------------------|--------------------------|----------------|------------|----------------|
| BCNS111         | 1               | F      | 27.3             | c.1067+5G>C             | p.?            | r.spl? 2  | 2              |
| BCNS112         | 1               | F      | 51.2             | c.1792A>T             | p.(Met598Leu) | r.(?) 2  | (Continues)    |
2 | ANALYSIS OF THE DATABASE

The database lists 331 previously published unique PTCH1 mutations (http://www.lovd.nl/PTCH1). In addition, we included 117 new PTCH1 variations (Table 2). These mutations were found in 141 patients who had a positive PTCH1 mutation analysis in either the VU University Medical Centre (VUMC) or Maastricht University Medical Centre (MUMC) between 1995 and 2015. Mutation analysis was performed using Sanger sequencing and Multiplex Ligation-dependent Probe Amplification. Polymorphisms and patients from the same family were excluded. Of the 117 different PTCH1 variations, 110 mutations are classified as pathogenic or probably pathogenic according to the guidelines of the Associations for Clinical Genetic Science, the Dutch Society of Clinical Genetic laboratory Specialists, and the American College of Medical Genetics and Genomics (ACMG) (Wallis et al., 2013; Richards et al., 2015). A number of 23 PTCH1 mutations are reported by previous studies and 79 are novel.

Of the 110 new mutations 38% (42/110) are frameshift (33 small deletions, eight small duplications, one small indel), 26% (29/110) nonsense, 13% (14/110) missense, and 15% (16/110) are splicing mutations. The remaining 8% (9/110) are large genomic PTCH1 deletions and duplications. The mutations were found in all coding exons (1–23) and no hotspot was found.

The majority of patients were from the Netherlands (68%, 76/110). The age of DNA test ranged from 0 to 70 years, with a mean age of 26.5 years. Motivations for genetic testing written on the application forms were: (1) clinical suspicion of BCNS (47.4%); (2) clinical diagnosis of BCNS (32.6%); (3) first-degree family member with BCNS (16.8%); and (4) family members with symptoms of BCNS (3.2%). In total, four individuals were prenatally screened for BCNS, because of a first-degree family member or a clinical suspicion based on ultrasonography.

DATABASE AVAILABILITY

The data are accessible to the public at http://www.lovd.nl/PTCH1. Contributors will have to register for a login and password.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Marie G. Reinders http://orcid.org/0000-0002-3612-2486

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