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# Phenotype and Genotype in 17 Patients with Goltz-Gorlin Syndrome

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Goltz-Gorlin syndrome or focal dermal hypoplasia is a highly variable, X-linked dominant syndrome with abnormalities of ectodermal and mesodermal origin. In 2007 mutations in the *PORCN* gene were found to be causative in Goltz-Gorlin syndrome.

Here we report on a series of 17 Goltz-Gorlin patients, and describe their phenotype and genotype. In 14 patients, 13 females and one male, a *PORCN* mutation was found. Mutations included nonsense (n=5), frameshift (n=2), aberrant splicing (n=2), and missense (n=5) mutations. No genotype-phenotype correlation could be found. All patients with the classical features of the syndrome had a detectable mutation. In three females with atypical signs no mutation could be found. The male patient had classical features and showed a mosaicism for a *PORCN* nonsense mutation in fibroblasts. Two affected sisters had a mutation not detectable in their parents, supporting germline mosaicism. Their father had undergone radiation for testicular cancer in the past. Two classically affected females had three severely affected female fetuses which all had midline thoracic and abdominal wall defects, resembling the pentalogy of Cantrell and the limb-body wall complex. Thoracic and abdominal wall defects were also present in two surviving patients. Possibly, *PORCN* mutations can cause pentalogy of Cantrell and limb-body wall complexes as well, and particularly in cases with limb defects it seems useful to search for these.

We conclude that *PORCN* mutations can be found in all classically affected cases with Goltz-Gorlin syndrome, including males. Somatic and germline mosaicism occur. There is no evident genotype-phenotype correlation.

## Introduction

Goltz and Gorlin in 1962 and Gorlin and Goltz in 1963 defined a syndrome with widespread features including asymmetry of face, trunk and extremities: focal dermal hypoplasia and hyperpigmentations, often following Blaschko lines; localized subepidermal deposits of subcutaneous fat; multiple papillomas of mucous membranes and skin surrounding body orifices; and extremely variable skeletal anomalies which particularly involve the extremities.<sup>1,2</sup> Additional features include short stature, sparse hair, coloboma of the iris and retina, prominent and thin ears, cleft lip and palate, hypodontia and abnormally shaped teeth, infrequently internal anomalies of heart and kidneys, and developmental delay in 15% of affected individuals.<sup>3</sup> Approximately 95% of cases have been sporadic. Through pedigree analyses it was thought likely to be an X-linked dominant disorder, and about 90% of affected individuals were female. The few familial examples have been mostly mother-daughter reports.<sup>4</sup> Transmission from mildly affected fathers to severely affected daughters was postulated to be explainable by somatic mosaicism for the putative mutation.<sup>5-9</sup>

In 2007 two groups independently reported mutations in the *PORCN* gene at Xp11.23 in patients with Goltz-Gorlin syndrome.<sup>10,11</sup> The gene encodes an O-acyltransferase that catalyses cysteine N-palmitoylation and serine O-acylation in the endoplasmic reticulum, which allows membrane targeting and secretion of several Wnt proteins that have key roles in embryonic tissue development.<sup>12</sup> To date 71 disease-causing mutations in *PORCN* associated with Goltz-Gorlin syndrome have been identified.<sup>10-11, 13-18</sup> Here we report on our joint experience of a series of 17 Goltz-Gorlin patients, including an affected male, two vertical transmissions, and one pair of affected sibs without affected parents, and describe both their phenotype and genotype.

## Material and methods

### Patients

The laboratory in the Academic Medical Center in Amsterdam started to offer *PORCN* mutation analysis on 01.01.2008. Physicians who forwarded samples between 01.01.2008 and 01.07.2008 of patients in whom the diagnosis was felt to be firmly established, were contacted to ask for participation, and all agreed.

### Mutation analysis

Genomic DNA was extracted from peripheral leukocytes according to standard protocols. In one patient (Table II, patient 3) DNA was also obtained from cultured fibroblasts. All coding exons (2-15) of the *PORCN* gene were amplified using intronic primers, as described.<sup>10</sup> Polymerase chain reactions (PCRs) were carried out in a 25 µl volume containing 50-100 ng of genomic DNA, 2.5 µl of 10x PCR buffer (Solis Biodyne), 2.5 mM MgCl<sub>2</sub>, 0.2 mM of each dNTPs, 10 pmol of each primer and 0.2 U of HotFire Polymerase (Solis Biodyne). The PCR products were analysed by direct sequencing of both strands on an automated ABI Prism 3100 Genetic Analyser (Applied biosystems). All sequence files were compared to the reference genomic sequence (Ref.Seq. NM\_203475.1, variant D) and analysed with the aid of the Codon Code Aligner software (CodonCode Corporation, MA, USA). The presence of all identified variants was confirmed by resequencing of an independent sample. Analysis and interpretation of the mutations was conducted with the Alamut mutation interpretation software (V1.4).

Copy number of coding *PORCN* exons in mutation-negative patients was determined by Multiplex Ligation-dependent Probe Amplification (MLPA). Synthetic probes (Biologio), targeting all coding exons of *PORCN* were designed as described before.<sup>19</sup> MLPA reactions were performed essentially as previously described using MLPA kit reagents (MRC-Holland).<sup>20</sup> Probe sequences are available on request. Quantitative analysis of the methylation pattern at the *AR* locus was performed as described earlier.<sup>21</sup>

## Results

### Phenotype

We gathered data on 17 Goltz-Gorlin patients (age 0-64yr; mean 29yr). Mean parental age of parents was not increased (mean age of fathers 31.0 yr; mean age of mothers 28.6yr). There were 7 familial and 10 sporadic patients. One was an adult male; the other 16 were females of whom 13 survived infancy. One prematurely born girl was severely retarded; all other surviving patients had normal cognitive development. In five patients however, the parents considered the level of cognitive functioning of the child to be slightly lower than was felt to be common in the family. The cognition of the patients has not been tested formally. The major clinical features of Goltz-Gorlin syndrome in the present patients are tabulated in Table I and illustrated in Fig. 1. Only unusual additional features, and familial variability are described in more detail here.

**Table I. Tabulation of major physical features in 17 patients with Goltz-Gorlin syndrome**

Height <P3-P10	11/17
OFC <P3-P10	9/17
Thin, sparse scalp hair	13/17
Thin, protruding ears	13/16
Microphthalmia	7/17Unilateral / 3/17Bilateral
Coloboma	6/17Unilateral / 5/17Bilateral
Significantly decreased vision	5/17Unilateral / 5/17Bilateral
Tear duct obstruction	3/10Unilateral / 1/10Bilateral
Cleft lip/ palate	2/17Lip-Palate / 2/17Palate
Oligodontia	4/14
Enamel hypoplasia	6/12
Mamma hypoplasia in adults	4/10

Nipple hypoplasia in adults	3/10
Caudal appendage	2/17
Acral abnormalities	4/17 1 limb, 5/17 2 limbs, 5/17 3 limbs, 1/17 4 limbs
Oligodactyly	13/17
Polydactyly	1/17
Syndactyly	11/17
Nail hypoplasia	14/17
Hypohidrosis	3/9
Skin hypoplasia	17/17
Papilloma periorally	6/17
Papilloma elsewhere	3/16

Two unrelated female fetuses born to classically affected mothers had ectopia cordis, diaphragmatic hernia and abdominal wall defect. Another female fetus had an abdominal body wall defect (Fig. 2). An adult female had an inward displacement of a lateral part of her thorax, with normal skin covering of the lesion. The adult male had several areas of aplasia cutis at birth (Fig. 3). These were all located in the midline, either of the occipital region of the scalp, the anterior thoracic wall or overlying the spine in the lower thoracic region. Some had to be closed surgically in the first year of life as they did not heal spontaneously.

In one adolescent girl papillomas were present on the palate and vocal cords. She also had papillomas around the orifices. Another female patient had unilateral polythelia, and yet another adult female developed lymphedema of the lower legs at the end of puberty that did not react well to adjunctive therapy but remained static. Internal organ abnormalities included mild hydronephrosis in two females, bilateral renal agenesis in one of the female affected fetuses, anal atresia in one and an anteriorly placed anus in another female, and a ventricular septal defect in two and bicuspid aortic valve in one female. Unusual skeletal manifestations were scoliosis in two females, unilateral symphalangism of the thumb, unilateral hypermobility of the thumb, unilateral complete lower limb aplasia below the knee, unilateral and bilateral fibular aplasia, unilateral clavicular agenesis, and a seemingly

spontaneous fracture of the lower leg, each in one female. Other findings were preauricular tags in two females, dislocated lenses in two females, and in single affected females a preauricular pit, unilateral and bilateral moderate hearing loss, and a supracerebellar cyst.

One patient developed unilateral breast cancer at 50 years of age, another female patient developed a large tumour of the skin of her scalp at 64 years of age (possibly a trichilemmal tumor). No histology is available at present.

The familial cases were: an affected mother and female fetus; an affected mother and two affected female fetuses; and two affected sisters. In the latter family both parents were clinically unaffected on careful evaluation and the *PORCN* mutation, present in the sisters, was not found in either parent. It may be of importance that the father had testicular cancer in early adulthood, which had been treated by irradiation. In the two other familial cases the mothers were classically affected. All three fetuses were more severely affected than the mothers. These two mothers had experienced no miscarriages, and together they had two healthy daughters and one healthy son.

## Genotype

17 patients were analysed for point mutations by direct sequence analysis of the coding exons of the *PORCN* gene. In 14 patients (13 females, 1 male) sequence analysis revealed mutations, heterozygous and hemizygous respectively. No DNA was available in the three affected fetuses, but as their mothers had a detectable mutation it seems very likely that they had the same mutation. No mutation was found in three females. Protein alteration and location throughout *PORCN* are summarized in Table II and Fig. 4.

**Table II. Tabulation of the genotype in 14 patients with Goltz-Gorlin syndrome.**

Patient	Sex*	Nucleotide change	Protein alteration	<i>de novo</i>	Reference
1	F	c.283C>T	p.Arg95X	+	Bornholdt et al. <sup>13</sup>
2	F	c.509G>A	p.Trp170X	n.a.^	Harmsen et al. <sup>14</sup>
3	M	c.571C>T	p.Gln191X	n.a.	Novel
4	F	c.1331G>A	p.Trp444X	n.a.	Novel



5	F	c.1344G>A	p.Trp448X	n.a.	Novel
6	F	c.637delT	p.Tyr213ThrfsX27	+	Novel
7	F	c.1353dup	p.Gly452TrpfsX19	n.a.	Novel
8	F	c.947-2A>C		n.a.	Novel
9	F	c.1284+1G>A		+	Novel
10	F	c.502G>A	p.Gly168Arg	+	Bornholdt et al. <sup>13</sup>
11+12	F+F	c.890C>T	p.Ser297Leu	+	Novel
13	F	c.1094G>A	p.Arg365Gln	n.a.	Leoyklang et al. <sup>18</sup> Bornholdt et al. <sup>13</sup>
14	F	c.1120G>C	p.Ala374Pro	n.a.	Novel

\* F: female; M: male

^ n.a.: parental DNA not available

Mutations were premature nonsense (n=5), frameshifts (n=2), aberrant splicing (n=2) and missense mutations (n=5). All sequence alterations detected are likely to be pathogenic as the transcription products are predicted to result in prematurely truncated proteins, potentially targeted for nonsense mediated decay, or in dysfunctional proteins. All changes are predicted to result in prematurely truncated or dysfunctional proteins. Three changes (p.Trp444X, p.Trp448X and p.Gly452TrpfsX19) occur in exon 15 and affect the C-terminus of the PORCN protein, a region that is not included in the MBOAT (Membrane Bound O-Acyl Transferase) - functional domain, spanning aminoacids 115 to 402. However exon 15 is present in all *PORCN* alternatively spliced transcript variants and its amino acid sequence is strongly conserved throughout species, suggesting that integrity of the C-terminal part of the protein is essential for proper functional activity. Furthermore, four different missense mutations were identified in five patients, including the same mutation in female sibs. The sisters had the p.Ser297Leu substitution, where the hydrophobic amino acid Leucine replaces the hydrophilic Serine. This variant was not found in the parents, which suggests a germline mutation, possibly related to the testicular irradiation in father. Serine at 297 is a fully conserved residue, located within the MBOAT-domain of PORCN. The other three missense mutations (Fig. 4) also affect highly conserved residues within the MBOAT-domain. The p.Gly168Arg and p.Arg365Gln substitutions have been previously reported.<sup>13,18</sup> None of

the missense mutations was detected in 180 control X chromosomes and no other variants were found in the coding region of *PORCN*.

No mutation was found in three females. A skin biopsy taken from an affected area in one of them failed to show a mutation. No consent was obtained to study other tissues in the other females without mutation. In these mutation-negative females MLPA analysis was applied to search for small deletions or duplications within the *PORCN* gene: no variations in copy number of *PORCN* exons was found (data not shown). Analysis of exons 2, 5 and 12 was not informative, however, due to signal intensity below detection level.

In the two classically affected females who had three severely affected female fetuses (Table II; patients 5 and 8) an extremely skewed X-inactivation pattern was observed (98/2 and 95/5, respectively).

No mutation was initially detected in lymphocytes in the adult male, who was classically affected, except for relatively mild limb anomalies. Sequence analysis on DNA isolated from fibroblast cultured from two skin biopsies taken from affected and unaffected areas revealed a pathogenic mutation (p.Gln191X) in both skin biopsies. The mutant sequence was found superimposed on the wild-type sequence, with a lower signal intensity at the mutation site in non-affected fibroblasts (Fig. 5), suggesting somatic mosaicism. Chromosome analysis showed him to have a normal male karyotype (46, XY).

## Discussion

In this article we describe the clinical and molecular features of 17 patients with Goltz-Gorlin syndrome. In 14 (13 females, 1 male) of the 17 patients a mutation in the *PORCN* gene was found. All 13 females are classically affected with typical features of Goltz-Gorlin syndrome.<sup>4</sup> Statistical analysis failed to show a significant correlation between the nature and localisation of the mutation, and the phenotype (eye; skin; limbs) (data not shown). This is in agreement with earlier reports.<sup>13,14</sup>

In three mildly affected females no point mutations, small deletions or duplications were found. As MLPA analysis for 3 non contiguous exons of the *PORCN* gene failed, we cannot rule out the possibility that deletions or duplications of one of these exons might have occurred in these patients. Until now only larger microdeletions, encompassing the entire *PORCN* gene and sometimes also neighbouring genes, have been reported, however.<sup>10,11,13</sup> These patients were not classically affected: features were limited to focal dermal hypoplasia and hyperpigmentation following Blaschko lines; no papillomas, eye, limb or other abnormalities were present. These cases were each evaluated by the late Professor Robert J. Gorlin in 1995 who confirmed the diagnosis. One may speculate whether the diagnosis Goltz-Gorlin syndrome remains applicable in them. We conclude that a mutation has been found in all classically affected patients but in none of the atypical patients.

The mother of the two girls with abdominal wall defects (one with ectopia cordis with diaphragmatic hernia and abdominal wall defect, the other with only an abdominal body wall defect) had a premature nonsense mutation. She has classical features of the syndrome. The mother of the other severely affected fetus has classical features of the disorder too, and a missense mutation. In neither of the mothers was there evidence for mosaicism based on sequencing of lymphocyte DNA (no other tissues were available). Both showed extreme skewing by X-chromosome inactivation analysis, making a difference in X-inactivation a less

likely explanation for the difference in severity between mothers and fetuses. The data suggests that other factors (environmental; epigenetic; modifying genes) are of importance in determining the phenotype in individuals with *PORCN* mutations. Others were of the same opinion.<sup>10,14,15</sup>

The affected fetuses demonstrated a phenotype that resembles either the limb-body wall complex (including ectopia cordis) or the pentalogy of Cantrell (midline abdominal wall defects; sternum defects; anterior diaphragmatic defects; pericardial defects; congenital heart defects).<sup>22-25</sup> Particularly in the limb-body wall complex there have been case reports of limb defects, including ectrodactyly.<sup>26-28</sup> These have been explained as resulting from amniotic bands. The thoracic wall defect in one of the present affected females and the areas of aplasia cutis in the midline of the anterior and posterior thorax of the present affected male may be related defects. We suggest that some cases diagnosed with limb-body wall complex or pentalogy of Cantrell may in fact be severely affected fetuses with Goltz-Gorlin syndrome, and *PORCN* mutation analysis may be indicated in such patients, particularly if limb defects are present.

Although rare, male cases have occurred and some father-to-daughter transmissions have been reported. Fathers exhibit mild signs of the disease such as skin lesions on only one part of the body; the left thigh in one case and involving only one arm and one knee in another. These cases are thought to be mosaic.<sup>5-9</sup> In the presently reported affected male the mutation was detectable only in fibroblasts and not in lymphocytes. The imbalance in signal intensities at the mutation site in fibroblasts from affected skin and normal skin indicated under-representation of the mutant allele and suggests mosaicism for this mutation. This finding is similarly to the results in recently reported affected males in whom signal intensity was also reported to weaker.<sup>13</sup> The finding of a larger percentage of mutated cells in the biopsy from affected skin compared to unaffected skin in our patient is in agreement with this. If present in previously described affected fathers of classically affected daughters it would explain why fathers are usually only mildly affected. Sequencing of genomic DNA from peripheral blood lymphocytes in females with relatively mild phenotype also show the amount

of mutant DNA to be less than 50% of the wild type allele which supports somatic mosaicism.

10 14 17

The observation of two affected sisters with a mutation without detectable mutation in the parents is suggestive of germline mosaicism. The radiation the father received in early adulthood because of testicular cancer may explain this. Exposure of mouse germ cells to radiation results in various adverse effects including abortion, malformation, and cancer in the offspring depending on the dose though these findings have not been proven in human studies.<sup>29</sup>

## **Conclusion**

In 14 of 17 patients with Goltz-Gorlin syndrome a mutation in the *PORCN* gene was found. All of these individuals had classical features of the syndrome. All three girls born to affected mothers were severely affected. Both somatic and germline mosaicism occur. Some cases diagnosed with limb-body wall complex or pentalogy of Cantrell may in fact be severely affected fetuses with Goltz-Gorlin syndrome and *PORCN* mutation analysis may be indicated in such patients.

## **Acknowledgement**

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## Legends

**Fig. 1.** Selection of characteristic findings in females with Goltz-Gorlin syndrome including the general facial phenotype, irregular vermillion of the upper and lower lip, fat herniations in the elbow, streaky pigmentations following Blaschko lines, asymmetrical mildly affected hands, severely affected lower limb, and caudal appendage.

**Fig. 2.** Two severely affected female fetuses born to women with classical Goltz-Gorlin syndrome. Note the thoracic-abdominal body wall defect (**A**) and ectopia cordis (**B**).

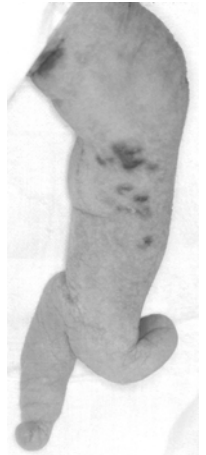
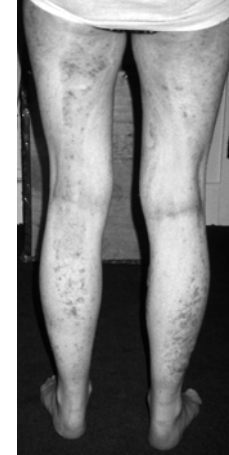
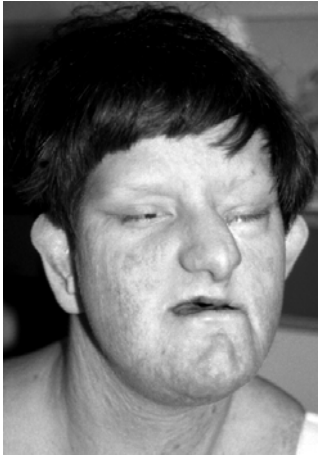
**Fig. 3.** Adult male with molecularly confirmed Goltz-Gorlin syndrome. Note skin lesions following Blaschko lines (**A**) and areas of aplasia cutis overlying the mid thoracic spine (arrows) (**B**).

**Fig. 4.** Overview of *PORCN* mutations identified in 17 patients with Goltz-Gorlin syndrome. Exon - intron organisation of *PORCN*: coding regions are in light blue and non-coding regions in dark blue. *PORCN* protein structure and amino acid (a.a.) numbering is given according to reference sequence NM\_203475.1, variant D. The arrows indicate approximate positions of the mutations. Splicing mutations are marked in italics.

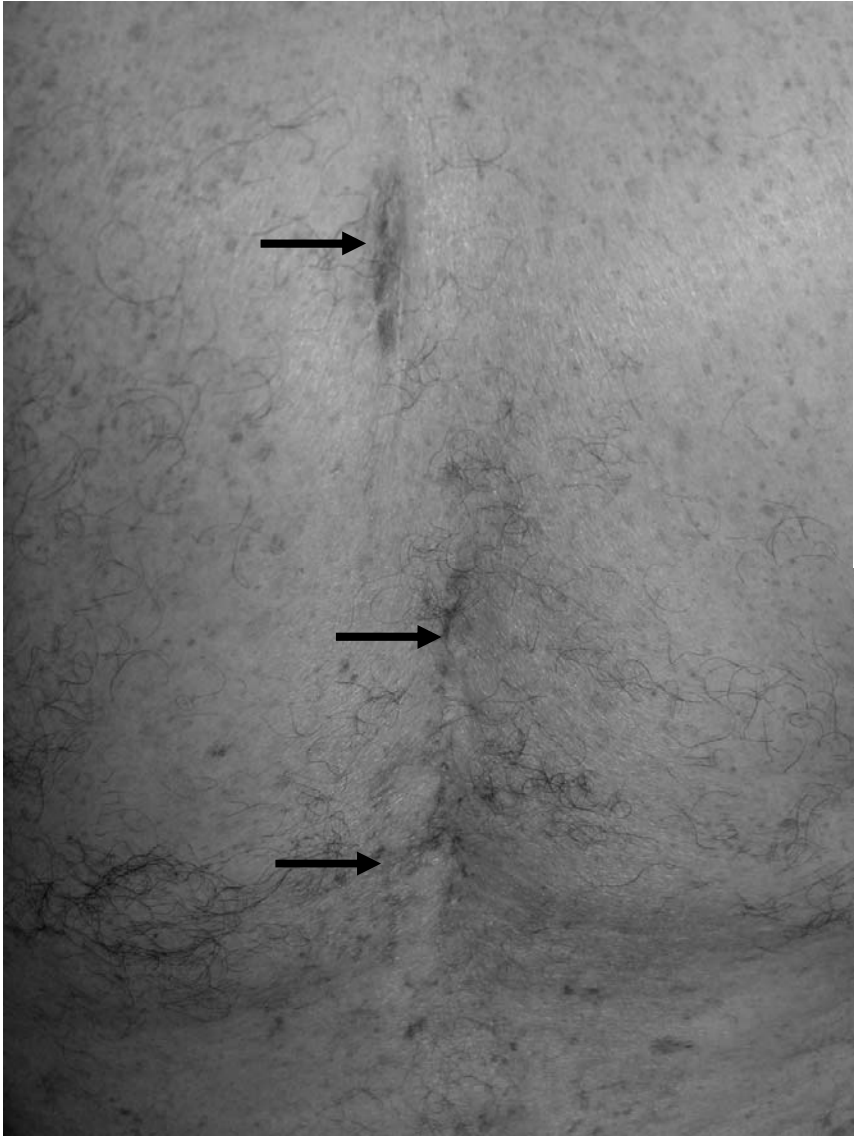
**Fig. 5.** Mosaicism for the c.571C>T *PORCN* mutation (p.Gln191X) in a male with Goltz-Gorlin syndrome. **Upper row.** sequence from non-affected fibroblasts of patient 3; **Middle row.** sequence from affected fibroblasts of patient 3; **Lower row.** sequence from a control individual.

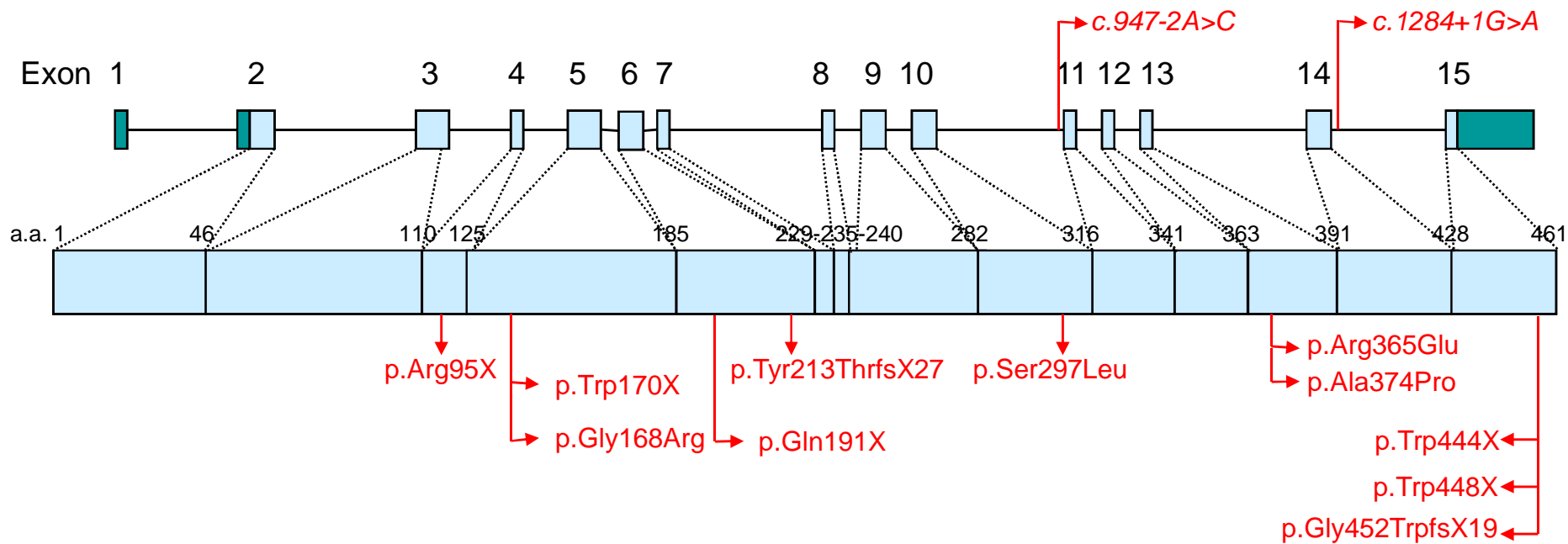
## **Statement**

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