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Mutation Update for the PORCN Gene

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Human Mutation: Mutation Update

Mutation Update for the *PORCN* Gene

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3 **Mutations in the *PORCN* gene were first identified in Goltz-Gorlin syndrome**
4 **patients in 2007. Since then several reports have been published describing a**
5 **large variety of genetic defects resulting in the Goltz-Gorlin syndrome, and**
6 **mutations or deletions were also reported in angioma serpiginosum, the**
7 **pentalogy of Cantrell and Limb-Body Wall Complex.**

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10 **Here we present a review of the published mutations in the *PORCN* gene to**
11 **date and report on 7 new mutations together with the corresponding clinical**
12 **data. Based on the review we have created a web-based locus specific**
13 **database which lists all identified variants and allows the inclusion of future**
14 **reports. The database is based on the Leiden Open (source) Variation Database**
15 **(LOVD) software and is accessible online at <http://www.lovd.nl/porcn>.**

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18 **At present the database contains 106 variants, representing 68 different**
19 **mutations, scattered along the whole coding sequence of the *PORCN* gene,**
20 **and 12 large gene rearrangements, which brings up to 80 the number of unique**
21 **mutations identified in Goltz-Gorlin syndrome patients.**
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Introduction

Goltz-Gorlin Syndrome (GGS) or Focal dermal hypoplasia (MIM 305600) is an X-linked dominant disorder characterized by a combination of malformations and dysplasias, mainly affecting the skin (linear hypoplastic areas; linear hyperpigmented and hypopigmented areas, fat herniation through skin; papillomas around body orifices), skeleton (oligodactyly; ectrodactyly; syndactyly; polydactyly; caudal appendage; extreme variability) and eyes (microphthalmia; coloboma; cataract; corneal opacities) [Goltz et al., 1963; Gorlin et al., 1963]. A wide variety of other manifestations has been reported. Goltz-Gorlin syndrome is an infrequently reported disorder: about 250 cases are reported in literature [Hennekam et al., 2010]. Estimates of the prevalence are not available.

In 2007 two groups independently described for the first time mutations in *PORCN* as being responsible for GGS [Grzeschik et al., 2007; Wang et al., 2007]. Subsequently it was found that *PORCN* mutations can also be found in the pentalogy of Cantrell and the limb-body wall complex [Maas et al., 2009] and deletions can cause angioma serpiginosum [Houge et al., 2008]. *PORCN* (isoform D NM_203475.1), located at Xp11.23, encodes a 52 kDa protein of 461 amino acids. PORC proteins are predicted to be putative O-acyltransferases involved in palmitoylation of Wnt signaling proteins, which have key roles in embryonic tissue development [Paller, 2009; Clements, 2010]. Similar to many other proteins in the PORC family *PORCN* has multiple transmembrane domains, predicted to traverse the membrane of the endoplasmic reticulum, and one large membrane bound O-acyltransferase domain (aa 115-402) [Hoffmann K, 2000; <http://www.uniprot.org/uniprot/Q9H237>].

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3 Here, we present a review of all 73 *PORCN* mutations published so far, and
4 report 7 new mutations, including 6 intragenic mutations and one microdeletion. In
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8 addition we announce a web-based locus specific database that has been created to
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10 list all identified variants and which allows the inclusion of future reports. The
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12 database is based on the Leiden Open (source) Variation Database (LOVD) software
13 [Fokkema et al., 2005]. In the *PORCN*-LOVD database emphasis is given to clinical
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15 data of each individual patient. Comparisons within the database should enable
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17 colleagues world-wide to study genotype-phenotype correlations in detail.
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27 ***PORCN* database construction**

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31 We performed a PubMed search using as search terms *PORCN*, Goltz-Gorlin
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33 syndrome, Focal Dermal Hypoplasia, Angioma Serpiginosum and pentalogy of
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35 Cantrell. The reference lists of all papers retrieved this way were hand searched for
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37 additional publications. Furthermore, we have been offering *PORCN* mutation
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39 analysis on a diagnostic basis from 2007 on and added all *PORCN* mutations
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41 detected ourselves since then. Part of our results has been published elsewhere
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44 [Maas et al., 2009].
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48 All information gathered on mutations and mutation carriers were initially
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50 stored in individual fields in an offline Microsoft Excel worksheet (Microsoft,
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52 Redmond, WA) and subsequently converted into a Web accessible *PORCN* gene
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54 variant database within the Leiden Open Variation Database (LOVD) platform
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56 [Fokkema et al., 2005]. This database has also been included in the Human
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58 Genome Variation Society (HGVS) list of LSDBs. In the database information are
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3 organised in Variant Data and Patient Data. The 'variant data' section contains the
4 following variant-specific fields : exon / intron location, DNA / RNA/protein change, X
5 chromosome **inactivation pattern**, database ID, variant origin, variant remarks,
6 reference, template / technique used for detection and frequency. In the 'patient data'
7 section the presence or absence of all major clinical manifestations of Goltz-Gorlin
8 syndrome is reported in addition to gender, geographic / ethnic origin, times reported
9 and patient remarks. Additional information on the pathogenicity of each variant, in
10 the format 'reported/concluded', are given in a separate field, which can be visualized
11 by using the 'View all contents' feature of the database.
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24 The database can be consulted at www.lovd.nl/PORCN and will be updated
25 with data from literature as well as with the unpublished variants identified in our
26 diagnostic unit. Furthermore, all scientists/clinicians are invited to submit their
27 unpublished data to the database using an online submission form. Submissions will
28 be checked by the curators (M.P.L.; R.C.H.) and completed if necessary. The
29 unpublished status will be clearly indicated, as well as the identity of the submitter.
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43 **Mutations in the *PORCN* gene**

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48 To date (September 2010), 106 GGS patients with an identified *PORCN* mutation are
49 registered in the PORCN-LOVD database. Ten are males having point mutations
50 identified in a mosaic status. All mosaic mutations were detected in fibroblasts and
51 not in peripheral blood leucocytes, except in one patient (database
52 ID_PORCN_00080; Vreeburg et al., 2010). In total 80 unique mutations have been
53 reported. Mutations are named according to HGVS nomenclature guidelines
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3 (www.HGVS.org) and numbered with respect to the *PORCN* gene reference
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5 sequence (NG_009278.1 covering *PORCN* transcript NM_203475.1). Previously
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7 reported mutations have been renamed accordingly but the original nomenclature is
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9 also included in the corresponding entry to allow cross-reference. All mutations listed
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11 in the database are predicted to be pathogenic either based on the nature of the
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13 mutation or on the location in a functional domain.
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17 Sixty-eight unique point mutations or small insertions/deletions have been
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19 detected so far (Table 1). Six mutations, p.Met1?, p.His252Tyr, p.Trp305X and the
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21 splicing mutations c.845+1G>C, c.947-1G>C and c.1024-2A>G, are reported here
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23 for the first time. The major clinical findings associated with these mutations, are
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25 provided in Table 2 as presented in the LOVD database in the 'Patient data' section,
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27 and compared to the data of the other patients in the database.
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31 **In Table 2 the available major clinical findings of all patients with an identified**
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33 ***PORCN* mutations are summarized, based on the mutation type.**
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37 The distribution of all mutations in *PORCN* is indicated in Figure 1. Mutations
38
39 are scattered along the coding sequence, with the exception of exons 6 and 7, where
40
41 no mutation have been found to date. Also the type of mutations is variable:
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43 nonsense mutations are the most represented (n=20), followed by missense (n=18)
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45 mutations. In addition there were 16 frameshift, 10 splicing and 4 in frame
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47 insertions/deletions. The majority of all *PORCN* mutations (46/68) are predicted to
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49 lead to protein truncation and loss of function. There are 11 recurrent mutations
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51 which are mostly transitions at CpG sites. Three mutations, p.Arg124X, p.Arg365Gln
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53 and p.Arg243X are particularly common and occurred in 5 (p.Arg124X, p.Arg365Gln)
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55 and 4 (p.Arg243X) patients, respectively. These mutations occurred also in patients
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57 with various ethnic backgrounds, suggesting that they may represent mutational
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3 hotspots in *PORCN*. In general however, the information available on the ethnic
4
5 background and/or country of origin of patients is limited and analysis of geographical
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7 distribution of mutations or of their incidence in the various ethnic groups is not
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9 possible at present.

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12 In 12 patients large deletions have been identified by array-CGH or MAPH
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14 analysis: 11 patients have deletions of the whole gene, in most cases encompassing
15
16 the neighbouring genes, and in a single patient a partial gene deletion encompassing
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18 exon 1 to exon 4 was present (Table 3, Figure 2). As the exact location of the
19
20 breakpoints of some deletions has not been determined, it remains uncertain whether
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22 some of these represent recurrent events. X-inactivation data were available for all
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24 patients except one and showed extreme skewing in all available patients.
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32 **Clinical and Diagnostic Relevance**

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34 The identification of mutations in *PORCN* confirms the clinical diagnosis in patients
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36 suspected of having GGS. In addition a molecular diagnosis allows for reliable
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38 genetic counselling and prenatal diagnosis if desired. Germ-line mosaicism for
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40 *PORCN* mutations has been described [Maas et al., 2009]. Our lab has been offering
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42 molecular genetic testing for *PORCN* mutations since 2007 with a combined
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44 approach based on direct sequencing and MLPA analysis. We analysed 40 index
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46 patients and found mutations in 25 patients (62.5%), including one deletion of the
47
48 entire *PORCN* gene. The lack of mutations in some patients is in part explainable as
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50 several samples were submitted 'to exclude GGS'. In all patients evaluated by the
51
52 present senior author as being classically affected a mutation has been found [Maas
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54 et al., 2009]. Still, the existence of phenocopies can not be excluded. Thus far no
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56 defects in other genes have been potentially correlated to the GGS phenotype,
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3 whereas mutations in *PORCN* have been found associated with additional
4 phenotypes: angioma serpiginosum [Houge et al., 2008], limb-body wall complex,
5 and pentalogy of Cantrell [Maas et al., 2009] (Table 1).
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10 The phenotypic variability, the small number of patients known so far which
11 are fully clinically characterised, and the lack of information on their clinical
12 presentation might have caused misdiagnoses.
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17 One of the major goals of the establishment of the *PORCN*_database is to
18 collect detailed information on the clinical findings in Goltz-Gorlin patients and to
19 harmonize the clinical criteria for diagnosis. At present, a description of the positively
20 present clinical features is available for most but not all patients. However we scored
21 features as present only if stated in the text of published cases or clearly visible in
22 figures. Therefore there will be a bias towards the number of positive manifestations
23 in patients in the database hampering reliable genotype-phenotype correlations.
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One characteristic that is consistently found in all patients with a *PORCN* mutation is the presence of linear skin lesions / skin hypoplasia reported in 91 out of 92 patients with documented clinical findings. Other features that appear to be prevalent upon documentation are skeletal defects (a limb anomaly was present in 83 patients) and the thin and protruding ears.

Data on X-inactivation were available for all patients except one with large rearrangements. Large deletions were associated in all available patients with an extremely skewed X-inactivation pattern. Three of the 11 patients of whom data were available showed a mild phenotype. This confirms the observation made by Houge et

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3 al. on the variability of the phenotype depending on the efficacy of the protective
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5 effect exerted by X-inactivation [Houge et al., 2008].
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8 Otherwise genotype-phenotype correlations have been elusive so far.
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10 Classically affected Goltz-Gorlin patients have been reported with additional defects
11 (midline thoracic and abdominal wall) [Maas et al., 2009] which are also found in the
12 pentalogy of Cantrell and the limb-body wall complex [Van Allen et al., 1987; Cantrell
13 et al., 1958; Smigiel et al., in the press]. Comparison of patients with similar
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15 characteristics might help clarify whether these defects might be part of the clinical
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17 presentation of Goltz-Gorlin syndrome.
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24 We believe that the availability of the extended clinical findings in *PORCN*
25 mutation carriers, as in the open *PORCN*-LOVD, allows for a better understanding of
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27 the disease, for a reappraisal of clinical criteria in case of unclear presentations and
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29 ultimately will provide more insights into genotype-phenotype correlations.
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43 **Acknowledgment**

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46
47 Community's Seventh Framework Programme (FP7/2007-2013) under grant
48
49 agreement n° 200754 - the GEN2PHEN project (www.gen2phen.org)
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3 **Legend to Figure 1:**
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5 Figure 1. Gene map of distribution of point mutations in the *PORCN* gene. The boxes
6 represent the exons (not to scale). The shaded areas in ex 2 and 15 are the
7 untranslated region. Mutations below the genogram represent intronic mutations
8 affecting the splicesites and are displayed as changes at DNA level (c.). Mutations
9 above the genogram represent exonic mutations and are displayed as changes at
10 protein level (p.). An * indicates mutations reported in this paper; # indicates recurrent
11 mutations; § indicates different nucleotide changes, leading to the same effect on
12 protein. —● point to missense mutations (below ●●●); —◆ point to nonsense and
13 frameshift mutations (above ●●●).
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32 **Legend to figure 2:**
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34 Figure 2. Graphic representation of distribution and extent of deletions (—) of
35 *PORCN* and neighbouring genes (—) in Xp11.23, listed in *PORCN*_LSDB. The
36 dotted lines indicates that the breakpoints of the deletion have not been confirmed
37 (· · ·) or that it extends beyond the area represented (· · ·).
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43 Xp11.23 is drawn as in

44 www.ensembl.org/Homo_sapiens/Location/Overview?db=core;g=ENSG0000010231
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Table 1. Variants listed on the PORCN Database

Database_ID	Gender	Exon	Mutation	Protein Change	Type	References	Disease
PORCN_00001	F	02	c.1A>G	p.Met1? [¶]	change of translation	this report[#]	GGs
PORCN_00002	F	02	c.3G>A	p.Met1Ile ^{*±¶}	initiation codon	Bornholdt et al, 2009	GGs
PORCN_00003	F	02	c.49dupT	p.Cys17LeufsX11	frameshift	Harmsen et al, 2009	GGs
PORCN_00004	F	02	c.53dupT	p.Leu18LysfsX10 [*]	frameshift	Wang et al, 2007	GGs
PORCN_00005	F	02	c.74delG	p.Gly25AlafsX27	frameshift	Clements et al, 2009	GGs
PORCN_00006	F	03	c.166_167dupAC	p.Val57ProfsX60	frameshift	Harmsen et al, 2009	GGs
PORCN_00007	F	03	c.178G>A	p.Gly60Arg	missense	Wang et al, 2007	GGs
PORCN_00008	F	03	c.221G>A	p.Trp74X	nonsense	Harmsen et al, 2009	GGs
PORCN_00009	F	03	c.222G>A	p.Trp74X	nonsense	Grzeschik et al, 2007	GGs
PORCN_00010	F	03	c.268C>T	p.Arg90X	nonsense	Wang et al, 2007	GGs
	F					Bornholdt et al, 2009	
	F					Harmsen et al, 2009	
PORCN_00011	F	03	c.283C>T	p.Arg95X	nonsense	Bornholdt et al, 2009	GGs
	F					Maas et al, 2009	
PORCN_00012	M	04	c.370C>T	p.Arg124X	nonsense	Wang et al, 2007	GGs
	F					Bornholdt et al, 2009	
	F					Grzeschik et al, 2007	
	F					this report[§]	
PORCN_00013	F	04i	c.373+1G>A	-	splicing	Leoyklang et al, 2009	GGs
PORCN_00014	F	04i	c.374-1G>A	-	splicing	Bornholdt et al, 2009	GGs
PORCN_00015	F	04i	c.374-15T>A	-	splicing	Schaffer et al, 2009	GGs
PORCN_00016	F	04i	c.374-46T>A	-	splicing	Harmsen et al, 2009	GGs
PORCN_00017	F	05	c.407C>T	p.Ser136Phe	missense	Bornholdt et al, 2009	GGs
PORCN_00018	F	05	c.479dupA	p.Tyr160X	nonsense	Wang et al, 2007	GGs
PORCN_00019	M	05	c.502G>A	p.Gly168Arg	missense	Bornholdt et al, 2009	GGs
	F					Maas et al, 2009	
PORCN_00020	F	05	c.509G>A	p.Trp170X	nonsense	Harmsen et al, 2009	GGs

1		F						Maas et al, 2009	
2	PORCN_00021	M	06	c.571C>T	p.Gln191X	nonsense		Maas et al, 2009	GGG
3									
4	PORCN_00022	F	06	c.576delG*	p.Val193TrpfsX47	frameshift		Wang et al, 2007	GGG
5	PORCN_00023	F	06	c.637delT	p.Tyr213ThrfsX27	frameshift		Maas et al, 2009	GGG
6									
7	PORCN_00024	F	06	c.682C>T	p.Arg228Cys	missense		Leoyklang et al, 2009	GGG
8	PORCN_00025	F	08i	c.720-2A>T	-	splicing		Grzeschik et al, 2007	GGG
9									
10	PORCN_00026	F	09	c.727C>T	p.Arg243X	nonsense		Grzeschik et al, 2007	
11		F						Harmsen et al, 2009	GGG
12		F						Smigiel et al, 2011	GGG/PC
13									
14									
15	PORCN_00028	F	09	c.737_738insA	p.Ser247GlufsX315*	frameshift		Leoyklang et al, 2009	GGG
16	PORCN_00027	F	09	c.754C>T	p.His252Tyr	missense		this report[#]	GGG
17									
18	PORCN_00029	F	09	c.773T>A	p.Val258Glu	missense		Bornholdt et al, 2009	GGG
19	PORCN_00030	F	09	c.787_792dup	p.Glu262_Ala263dup*	insertion		Wang et al, 2007	GGG
20									
21	PORCN_00031	F	09	c.816_817insGC*	p.Phe273fsX284*	frameshift		Grzeschik et al, 2007	GGG
22	PORCN_00077	F	09i	c.845+1G>C	-	splicing		this report[#]	GGG/LBWC
23									
24	PORCN_00032	F	10	c.846G>A	p.Trp282X	nonsense/ splicing		Clements et al, 2009	GGG
25									
26	PORCN_00033	F		c.846_879del34	p.Trp282fsX302*	frameshift		Bornholdt et al, 2009	GGG
27	PORCN_00080	M	10	c.886delC	p.Arg296GlyfsX18	frameshift		Vreeburg et al, 2010	GGG
28									
29	PORCN_00034	F	10	c.890C>T	p.Ser297Leu	missense		Maas et al, 2009	GGG
30	PORCN_00035	F	10	c.898G>T	p.Glu300X	nonsense		Clements et al, 2008	GGG
31									
32	PORCN_00036	F	10	c.914G>A	p.Trp305X	nonsense		this report[#]	GGG
33	PORCN_00037	F	10	c.924delC	p.308fsX313*	frameshift		Grzeschik et al, 2007	GGG
34	PORCN_00038	F	10	c.935G>A	p.Trp312X	nonsense		Bornholdt et al, 2009	GGG
35									
36	PORCN_00039	F	10i	c.947-2A>C	-	splicing		Maas et al, 2009	GGG/PC/LBWC
37	PORCN_00040	F	10i	c.947-1G>C	-	splicing		this report[#]	GGG
38									
39	PORCN_00041	F	11	c.992T>G	p.Leu331Arg	missense		Froyen et al, 2009	GGG
40	PORCN_00042	F	11	c.1022A>T	p.His341Leu	missense		Bornholdt et al, 2009	GGG
41									
42	PORCN_00076	F	11i	c.1024-2A>G	-	splicing		this report[#]	GGG
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1	PORCN_00043	F	12	c.1045_1065del21	p.Ala349_Ala355del	in frame deletion	Wang et al, 2007	GGG
2								
3	PORCN_00044	M	12	c.1059_1071dup13	p.Thr358ProfsX65	frameshift	Wang et al, 2007	GGG
4	PORCN_00074	F	12	c.1061_1062insAGGACCCT	p.Leu354fsX401*	frameshift	Grzeschik et al, 2007	GGG
5								
6	PORCN_00045	M	12	c.1064_1081del18	p.Ala355_Val360del6	in frame deletion	Wang et al, 2007	GGG
7								
8	PORCN_00046	F	12	c.1077C>A	p.Tyr359X	nonsense	Bornholdt et al, 2009	GGG
9								
10	PORCN_00079	F	12	c.1077C>G	p.Tyr359X	nonsense	Dias et al, 2010	GGG
11	PORCN_00047	F	12	c.1082A>T	p.Glu361Val	missense	Harmsen et al, 2009	GGG
12								
13	PORCN_00048	M	13	c.1093C>G	p.Arg365Gly	missense	Wang et al, 2007	GGG
14	PORCN_00049	F	13	c.1094G>A	p.Arg365Gln	missense	Bornholdt et al, 2009	
15		F					Maas et al, 2009	
16		F					Leoyklang et al, 2009	GGG
17		F					Froyen et al, 2009	
18		F					this report ^s	
19								
20	PORCN_00050	M	13	c.1110delG	p.Arg370fsX398*	frameshift	Bornholdt et al, 2009	GGG
21	PORCN_00052	F	13	c.1120G>C	p.Ala374Pro	missense	Maas et al, 2009	GGG
22								
23	PORCN_00053	F	13	c.1153T>C	p.Cys385Arg	missense	Bornholdt et al, 2009	GGG
24	PORCN_00054	F	13	c.1154G>A	p.Cys385Tyr	missense	Harmsen et al, 2009	GGG
25								
26	PORCN_00055	M	14	c.1186C>T	p.Arg396X	nonsense	Bornholdt et al, 2009	GGG
27		F					Harmsen et al, 2009	
28	PORCN_00051	F	14	c.1214_1215insAGA	p.Leu405_Ala406insGlu	in frame insertion	Wang et al, 2007	GGG
29								
30	PORCN_00056	F	14i	c.1284+1G>A	-	splicing	Maas et al, 2009	GGG
31								
32	PORCN_00057	F	15	c.1285_1297del13	p.Gly429fsX456*	frameshift	Bornholdt et al, 2009	GGG
33								
34	PORCN_00058	F	15	c.1290C>A	p.Tyr430X	nonsense	Bornholdt et al, 2009	GGG
35							Harmsen et al, 2009	
36	PORCN_00059	M	15	c.1315T>C	p.Trp439Arg	missense	Bornholdt et al, 2009	GGG
37								
38	PORCN_00060	F	15	c.1317G>A	p.Trp439X	nonsense	Harmsen et al, 2009	GGG
39	PORCN_00061	F	15	c.1331G>A	p.Trp444X	nonsense	Maas et al, 2009	GGG
40	PORCN_00062	F	15	c.1344G>A	p.Trp448X	nonsense	Maas et al, 2009	GGG/PC/LBWC
41								
42	PORCN_00063	F	15	c.1353dup	p.Gly452TrpfsX19	frameshift	Maas et al, 2009	GGG
43								

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2 * Nomenclature as in the original description; ± HGVS Nomenclature p.Met1?; ¶ ? indicates that the effect on protein is not predictable: either no protein is
3 produced or the translation initiation site moves up- or downstream; # the novel mutations in this paper are shaded; § previously described variant identified in an
4 additional patent
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7 GGS = Goltz-Gorlin syndrome; PC = Pentalogy of Cantrell; LBWC = limb-body wall complex
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For Peer Review

Table 2: Clinical findings in Goltz-Gorlin patients with newly identified mutations compared to all other patients in database

DB_ID	Gender	Skin			Skeleton			Face			Eyes		Brain	Trunc ^d	
		hypoplasia	papilloma ^a	nail hypoplasia	ectro dactyly	oligo- dactyly	syn- dactyly	cleft lip/ palate	oligo- dontia	protruding thin ears	micro- coloboma	ophthalmia	microcephaly	MR ^b	
PORCN_00001	F	+	-	-	-	-	+	-	-	+	-	-	+	-	
PORCN_00027	F	+	-	+	-	-	+	-	nd ^c	-	+	-	+	-	
PORCN_00077	F	-	-	-	+	+	+	-	+	+	+	-	+	-	
PORCN_00036	F	+	+	+	-	-	-	-	-	-	-	-	-	-	
PORCN_00040	F	+	+	+	+	+	+	-	+	+	+	+	+	-	
PORCN_00076	F	+	+	-	-	-	+	-	-	-	-	-	-	-	
PORCN_00078	F	+	-	+	-	-	-	-	-	+	-	-	-	-	
DB total ^e		101/102	25/47	56/67	23/89	28/89	62/89	14/46	36/58	31/37	39/60	35/60	28/38	15/32	4/106
DB missense/ deletions/ insertions		24/24	6/10	16/17	7/19	9/19	15/19	3/10	10/14	8/9	16/18	11/16	8/8	5/10	0/24
DB nonsense/splicing/ frameshifts		59/60	15/23	31/40	12/57	16/57	36/57	10/32	21/35	21/24	19/35	22/37	18/25	10/16	4/64
DB large rearrangements		8/8	3/4	6/7	1/4	3/4	3/4	0/1	2/4	0/1	1/4	0/4	0/2	0/3	0/8
DB males		10/10	1/10	3/3	3/9	0/9	8/9	1/5	3/5	2/3	3/3	2/3	2/3	0/3	0/10

^a either periorally or elsewhere; ^b MR = mental retardation; ^c nd= non documented ^d anomalies fitting Pentalogy of Cantrell or Limb-body wall complex ^e number of patients in database with documented finding

Table 3: Large deletions listed in the *PORCN* database

DB_ID_Gender	Patient_ID	DNA change	Effect on protein	Other genes deleted	Phenotype	Origin	X-inactivation	Detection method	Reference
PORCN_00064_F	GG26	8766 bp (ex1-4)	del PORCN	no	classical	sporadic	83/17	arrayCGH/MAPH	Bornholdt et al, 2009
PORCN_00075_F	case report	112 kb deletion	del PORCN,	<i>SLC38A5, FTSJ1, EBP, OATL1</i> [§]	mild (angioma serpiginosum)	familial	100/0	array CGH	Houge et al, 2008
PORCN_00065_F	GG25	~ 20 kb (min.) [¶]	del PORCN	several including <i>EBP</i>	classical	sporadic	98/2	arrayCGH/MAPH	Bornholdt et al, 2009
PORCN_00066_F	GG36	~ 20 kb (min.) [¶]	del PORCN	several including <i>EBP</i>	classical	sporadic	100/0	MAPH	Bornholdt et al, 2009
PORCN_00067_F	GG37	~ 20 kb (min.) [¶]	del PORCN	several including <i>EBP</i>	classical	familial	100/0	MAPH	Bornholdt et al, 2009
PORCN_00068_F	GG1	137.4 kb deletion	del PORCN	<i>SLC38A5, FTSJ1, EBP, TBC1D25</i>	mild	familial	95/5	arrayCGH/MAPH	Grzeschik et al, 2007*
PORCN_00073_F	FIN2	150 kb deletion (max.)	del PORCN	<i>SLC38A5, FTSJ1, EBP, TBC1D25, RBM3, WDR13</i> *	classical	de novo	non informative	qPCR/arrayCGH	Froyen et al, 2009
PORCN_00072_F	G17	219 kb deletion	del PORCN	<i>SLC38A5, FTSJ1, EBP, OATL1, RBM3, WDR13</i>	classical	de novo	100/0	qPCR/arrayCGH/	Wang et al, 2007
PORCN_00071_F	G43	~219kb deletion	del PORCN	<i>SLC38A5, FTSJ1, EBP, OATL1, RBM3, WDR13</i>	non documented	not available	100/0	qPCR/arrayCGH/ FISH	Wang et al, 2007
PORCN_00069_F	GG2	364.8 kb deletion	del PORCN	<i>SSX1, SSX9, SSX3, SSX4, SSX4B, SLC38A5, FTSJ1, EBP</i>	classical	familial	99/1	arrayCGH/MAPH	Grzeschik et al, 2007*
PORCN_00070_F	GG11	377.5 kb deletion	del PORCN	<i>SSX9, SSX3, SS4, SSX4B, SLC38A5, FTSJ1, EBP, TBC1D25, RBM3</i>	classical	familial	97/3	arrayCGH/MAPH	Grzeschik et al, 2007*
PORCN_00078_F	AMC_11	502 kb deletion	del PORCN	several	mild	familial	99/0	arrayCGH	this report [#]

(§) OATL1 and TBC1D25 are synonymous ; (¶) minimal size of a deletion including *PORCN* and *EBP*; (*) to be confirmed
 (*) deletions breakpoints characterized in Bornholdt et al, 2009; (#) the novel mutations in this paper are shaded

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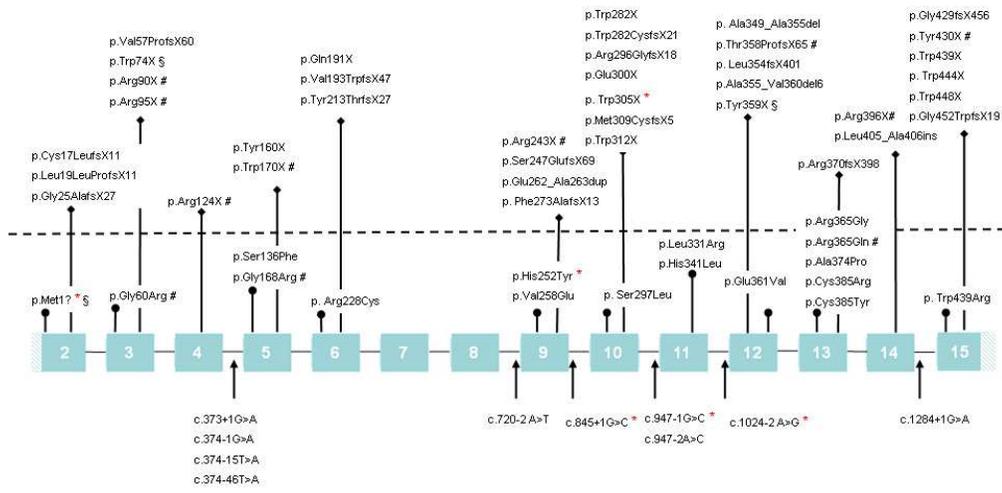


Figure 1
254x190mm (96 x 96 DPI)

Review

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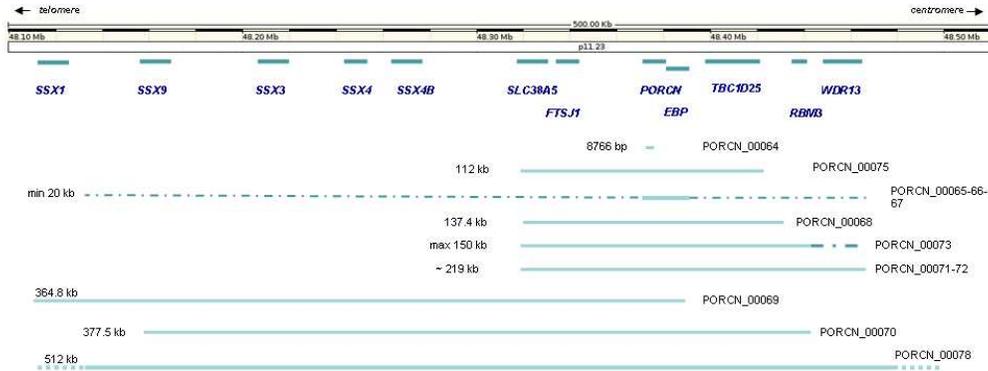


Figure 2
254x190mm (96 x 96 DPI)

Review