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Clinical Research Article

Malignancies in Prader-Willi Syndrome: Results From a Large International Cohort and Literature Review

Karlijn Pellikaan,[1,2,3,4] Naomi Q. C. Nguyen,[1] Anna G. W. Rosenberg,[1,2,3,4] Muriel Coupaye,[5,6] Anthony P. Goldstone,[6,7,8] Charlotte Høybye,[6,9,10] Tania Markovic,[6,11,12] Graziano Grugni,[6,9,13] Antonino Crinò,[6,14] Assumpta Caixàs,[6,15] Christine Poitou,[5,6,9] Raquel Corripio,[16] Rosa M. Nieuwenhuize,[17] Aart J. van der Lely,[1,9] and Laura C. G. de Graaff[1,2,3,4,6,9,*]

[1]Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, University Medical Centre Rotterdam, 3015 GD Rotterdam, The Netherlands
[2]Center for Adults with Rare Genetic Syndromes, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[3]Dutch Center of Reference for Prader–Willi Syndrome, 3015 GD Rotterdam, The Netherlands
[4]Academic Center for Growth Disorders, Erasmus Medical Center, University Medical Centre Rotterdam, 3015 GD Rotterdam, The Netherlands
[5]Assistance Publique-Hôpitaux de Paris, Rare Diseases Center of Reference 'Prader-Willi Syndrome and Obesity with Eating Disorders' (PRADORT), Nutrition Department, Institute of Cardiometabolism and Nutrition, ICAN, Pitié-Salpêtrière Hospital, Sorbonne Université, INSERM, Nutriomics, F75013 Paris, France
[6]International Network for Research, Management & Education on adults with Prader-Willi Syndrome (INfoRMEd-PWS)
[7]PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Faculty of Medicine, Imperial College London, London SW7 2AZ, UK
[8]Imperial Centre for Endocrinology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0NN, UK
[9]ENDO-ERN (European Reference Network)
[10]Department of Molecular Medicine and Surgery and Department of Endocrinology, Karolinska Institute and Karolinska University Hospital, 17176 Stockholm, Sweden
[11]Metabolism & Obesity Services, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[12]Boden Initiative, Charles Perkins Centre, University of Sydney, Camperdown, NSW 2006, Australia
[13]Division of Auxology, Istituto Auxologico Italiano, IRCCS, 20095 Piancavallo VB, Italy
[14]Reference Center for Prader-Willi syndrome, Bambino Gesù Hospital, Research Institute, 00165 Palidoro (Rome), Italy
[15]Department of Endocrinology and Nutrition, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí (I3PT) and Department of Medicine, Universitat Autònoma de Barcelona, 08208 Sabadell, Spain
[16]Department of Pediatric Endocrinology, Parc Taulí Hospital Universitari, Research and Innovation Institute Parc Taulí I3PT, Autonomous University of Barcelona, 08208 Sabadell, Spain
[17]Department of Medical Oncology, Erasmus MC, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands

Correspondence: Laura de Graaff, MD, PhD, Department of Internal Medicine, Erasmus MC, University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Email: l.degraaff@erasmusmc.nl.

Abstract

Context: Prader-Willi syndrome (PWS) is a complex disorder combining hypothalamic dysfunction, neurodevelopmental delay, hypotonia, and hyperphagia with risk of obesity and its complications. PWS is caused by the loss of expression of the PWS critical region, a cluster of paternally expressed genes on chromosome 15q11.2-q13. As life expectancy of patients with PWS increases, age-related diseases like malignancies might pose a new threat to health.

Objective: To investigate the prevalence and risk factors of malignancies in patients with PWS and to provide clinical recommendations for cancer screening.

Methods: We included 706 patients with PWS (160 children, 546 adults). We retrospectively collected data from medical records on past or current malignancies, the type of malignancy, and risk factors for malignancy. Additionally, we searched the literature for information about the relationship between genes on chromosome 15q11.2-q13 and malignancies.

Results: Seven adults (age range, 18-55 years) had been diagnosed with a malignancy (acute lymphoblastic leukemia, intracranial hemangiopericytoma, melanoma, stomach adenocarcinoma, biliary cancer, parotid adenocarcinoma, and colon cancer). All patients with a malignancy had a paternal 15q11-13 deletion. The literature review showed that several genes on chromosome 15q11.2-q13 are related to malignancies.

Conclusion: Malignancies are rare in patients with PWS. Therefore, screening for malignancies is only indicated when clinically relevant symptoms are present, such as unexplained weight loss, loss of appetite, symptoms suggestive of paraneoplastic syndrome, or localizing symptoms. Given the increased cancer risk associated with obesity, which is common in PWS, participation in national screening programs should be encouraged.

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Key Words: Prader-Willi syndrome, neoplasms, hypothalamo-hypophyseal system, comorbidity

Abbreviations: BMI, body mass index; GH, growth hormone; ICD, imprinting center defect; mUPD, maternal uniparental disomy 15; PWS, Prader-Willi syndrome.

Prader-Willi syndrome (PWS) is a rare genetic, multisystem disorder characterized by hypothalamic dysfunction, developmental delay, hypotonia, increased pain threshold, and typical dysmorphic features. Hypothalamic dysfunction may lead to several clinical features, including hyperphagia and pituitary hormone deficiencies (1–3). Hyperphagia in combination with a decreased basal metabolic rate and reduced physical activity results in a high prevalence of obesity (1, 4, 5).

PWS is caused by the absence of expression of a cluster of paternally expressed, maternally imprinted genes on chromosome 15q11.2-q13, also called the "PWS critical region." In 65% to 75% of the patients, the underlying genotype is a type I (40%) or type II (60%) paternal deletion. Maternal uniparental disomy 15 (mUPD) occurs in 20% to 30% and 1% to 3% have an imprinting center defect (ICD). Balanced translocations (0.1%) and individual gene mutations (<0.1%) are rare (6).

As a result of earlier diagnosis, multidisciplinary care, and better weight management, the life expectancy of patients with PWS has substantially increased (7, 8). As patients with PWS become older, the development of age-related diseases is increasingly relevant. Additionally, adults with PWS have shorter leukocyte telomere lengths, premature symptoms of aging, an early functional decline, and higher brain age, all suggesting accelerated aging (9, 10). This highlights the importance of knowledge about the occurrence of age-related diseases, such as malignancies, in adults with PWS.

Previous studies investigating malignancies in PWS are limited by low numbers, lack of older patients, and results that were based on questionnaires only. Questionnaire studies could underestimate the occurrence of malignancies, as underdiagnosis of diseases in general is a common problem in patients with PWS (11). Underdiagnosis is common for several reasons, including their high pain threshold, specific behavioral phenotype, and the high prevalence of intellectual disability (1, 12).

In vitro studies, animal studies, and studies in non-PWS participants suggest that multiple genes in the 15q11.2-q13 chromosomal region may be involved in the development of malignancies (13–19). However, the relationship between genetic subtype and the development of malignancies has, to our knowledge, never been investigated.

To investigate the need to screen for malignancies in patients with PWS, we assessed the prevalence of malignancies in a large international cohort of adults and children with PWS. To understand the pathogenesis of malignancies in patients with PWS, we provide a literature overview of the relationship between the genes on chromosome 15q11.2-q13 and different types of malignancies.

Methods

All participating centers obtained approval from ethics committees and/or individual patients to retrospectively collect data on patients with PWS.

We collected data from patient records of 706 individuals (160 children and 546 adults) with PWS that were visiting or had previously been under the care of one of the centers participating in the INfoRMEd-PWS network in: Netherlands (115), United Kingdom (45), France (92), Spain (94), Italy (290), or Australia (70). The local investigators collected data from patients on: 1) past or current malignancies, and if applicable, which type; 2) growth hormone (GH) treatment during childhood and adulthood; 3) treatment with testosterone or estrogen replacement therapy; 4) for males, history of cryptorchidism and 5) measurements of prostate specific antigen (PSA); 6) type 2 diabetes mellitus; 7) family history of malignancy; 8) alcohol use; 9) smoking; 10) other substance abuse; and 11) baseline characteristics, including anthropometric measurements, current age, gender, genotype, and whether patients were still alive at the time of data collection. Data on height and weight was used to calculate body mass index (BMI). As measurements of fat mass were not available for all patients, obesity was defined as a BMI >30 kg/m^2 for adults and a BMI > +2 standard deviation score (SDS) for children.

Literature Review

In collaboration with the Medical Library of the Erasmus University Medical Center, we performed a literature search on Embase, Medline, the Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar. The search was last updated in September 2022. We reviewed studies that reported on the relationship between the expression of genes on chromosome 15q11.2-q13 and malignancies. Inclusion criteria were clinical trials, basic or translational research, and case reports or case series that researched the expression or methylation of one or more genes on chromosome 15q11.2-q13 in malignancies compared to normal cells/tissue. Exclusion criteria were meeting reports, workshop summaries, reviews, conference abstracts, guidelines, articles that were not available online, and articles that were not available in English. Articles that only reported on the relationship between gene expression and the prognosis or survival of patients with malignancies were also excluded. The full search strategy is included in Table S1 (20). As most genes were associated with both up- and downregulation, we concluded that a gene was mainly upregulated, when it was upregulated in ≥ 80% of studies and mainly downregulated, when it was downregulated in ≥ 80% of studies.

Data Analysis

Descriptive statistics for continuous variables are reported as median (interquartile range [IQR]). For dichotomous variables, the number and the percentage of people, n (%), are displayed. To investigate the relationship between malignancies and nominal variables, the Fisher exact test was used. To investigate the relationship between malignancies and genotype, genotype was dichotomized into deletion or no deletion. For the relationship between malignancies and continuous variables, the Wilcoxon rank sum test was used. The relationship between malignancies and anthropometric measurements (height, weight, and BMI) was investigated in adults only.

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Results

Baseline characteristics are shown in Table 1. We included 160 children and 546 adults. The median age was 25 years (IQR, 18-33 years). Thirty-seven patients were 50 years old or older. Of the patients included, 326 (46%) were males. Obesity was prevalent (53%), with a median BMI of 32 kg/m^2 (IQR 25-42 kg/m^2). Deletion was the most common genotype (58%). Patients from 6 countries were included in this study. Most patients had received GH treatment at some point in their life (65%) and 227 (32%) received GH treatment at the time of data collection.

Of 706 patients, 7 adults (4 male and 3 female), had been diagnosed with a malignancy, as seen in Table 2. Patients with a malignancy were significantly older, with a median age of 39 years (IQR, 22-46 years) compared to 24 years (IQR, 18-34 years) in the control group. All patients with a malignancy had a paternal deletion, compared with 58% in patients without a malignancy ($P = .045$). There was no relation between malignancies and gender, country, GH treatment, anthropometric measurements, use of alcohol or tobacco, sex hormone replacement, cryptorchidism, family history, or type 2 diabetes (T2DM).

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Four patients with malignancies had died, of whom 3 had died as a result of their malignancy and 1 from an infection 2 years after being diagnosed with acute lymphoblastic leukemia. Table 3 shows the prevalence of malignancies for different age groups, demonstrating that the prevalence increased with age: 0-9 years 0.0%; 10-19 years 0.8%; 20-29 years 0.4%; 30-39 years 1.6%; 40-49 years 2.6%; and 50-74 years 2.7%. All patients had different types of malignancies, namely acute lymphoblastic leukemia, intracranial hemangiopericytoma, melanoma, adenocarcinoma of the stomach, biliary cancer, adenocarcinoma of the parotid gland, and colon cancer. One patient with a malignancy had a family history of malignancies.

Literature Review

Table S2 (20) shows a literature-based overview of the genes on chromosome 15q11.2-q13 and their relation to malignancies. Genes that were (mainly) upregulated in malignant tumors were: *NIPA1, C15orf2, SNORD107, SNORD64, SNORD109A, SNORD116, UBE3A, ATP10A,* and *GABRA5*. Conversely, *CYFIP1, MAGEL2, NDN, GABRG3, OCA2,* and *HERC2* were downregulated in malignant tumors. *MKRN3, SNURF-SNRPN, SNORD115,* and *GABRB3* were associated with both up- and downregulation in malignant cells. These data are graphically summarized in Fig. 1.

Discussion

Malignancies were rare in our cohort of 706 patients with PWS. Our cohort included 546 adults, of whom 37 were aged over 50 years. Only 7 adults had a malignancy. The malignancies that occurred were all of different origin. This suggests a multifactorial etiology of the malignancies. Therefore, we do not recommend to screen routinely for a particular type of cancer.

Although scarce, there are some studies that have previously investigated the occurrence of cancer in PWS. Patja et al reported 3 malignancies (acute lymphatic leukemia, testicular tumor, and breast cancer), in a cohort of 56 children and adults with PWS, while the expected number was 1.5 patients. They concluded that there is "a possibility of increased risk of malignancies among persons with PWS" (22). A questionnaire-based study performed in the United States in patients with PWS aged 0 to 63 years (with only 2 being older than 50 years) found that 3 children and 5 adults had a malignancy, while 4.8 cases were expected based on the prevalence in the general USA population (difference not significant). Three patients had leukemia, which was significantly more than expected based on the general population (0.075 cases expected) (23). Several case reports describe patients with PWS and cancer, including acute lymphoblastic leukemia (24), acute and chronic myeloid leukemia (25), hepatoblastoma (26), medulloblastoma (27), pulmonary carcinoid tumor (28), Wilms tumor (29), intratubular germ cell neoplasia (30) and testicular seminoma (31–33). In 1 male patient with PWS and testicular seminoma, loss of methylation of the Prader-Willi syndrome imprinting center (PWS-IC) was found during histological examination, suggesting involvement of genes in the PWS critical region (31).

All 7 patients with malignancies had a deletion of the paternal copy of the PWS region, which was also the most common genotype. No malignancies were found in patients with the genotypes mUPD or ICD. We performed a literature review to explain this finding.

Literature Review

Our literature review revealed that various genes on chromosome 15q11.2-13 are up- or downregulated in different types of cancer. However, this relationship appears to be complex, with several genes being both up- and downregulated in different types of malignancies.

The proximal non-imprinted region contains *TUBGCP5*, *CYFIP1*, *NIPA2,* and *NIPA1*. They are expressed from both the maternal and the paternal allele. While this region is not affected in patients with a type 2 deletion or a mUPD, one copy of these genes is deleted in patients with a type 1 deletion, leading to a decreased expression (34). *CYFIP1* shows reduced expression in various types of human cancers as it acts as an invasion suppressor (15). Therefore, patients with a type 1 deletion might have an increased risk of malignancies. However, as the type of deletion was unknown for most patients, we were unable to investigate whether this was true in our cohort. Of the other genes in the proximal non-imprinted region, *NIPA1* is upregulated in acute myeloid leukemia. We did not find any studies relating *TUBGCP5* or *NIPA2* to malignancies.

Apart from the proximal non-imprinted region, we also studied literature about the genes on the PWS critical region itself. The genes in this region are not expressed in patients with PWS. In patients with a deletion, the paternal allele is absent, and the maternal allele is present but not expressed. In patients with an mUPD or ICD, there are 2 maternal alleles,

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Table 1. Baseline characteristics of 706 children and adults participating in this study

	Number of observations	Total N = 706	Children N = 160	Adults N = 546
Age[a]				
Median [IQR]	706	25 [18-33]	9 [5-14]	28 [22-38]
Range		0.4-73	0.4-18	18-73
Male gender	706	326 (46%)	75 (47%)	251 (46%)
Anthropometric measurements				
Height, cm, median [IQR]	690	153 [144-163]	135 [105-151]	156 [149-164]
Height, SDS, median [IQR]	120		−1.0 [−1.9; 0.16]	
Weight, kg, median [IQR]	690	78 [60-98]	38 [18-59]	83 [68-102]
Weight, SDS, median [IQR]	28		−0.5 [−1.3-1.6]	
BMI, kg/m^2, median [IQR]	690	32 [25-42]	21 [17-27]	34 [27-44]
BMI, SDS, median [IQR]	96		1.2 [0.01-1.9]	
BMI, range	690	13-80	13-80	17-73
Obesity	642	376 (53%)	22 (23%)	354 (65%)
Genotype				
Deletion	706	410 (58%)	78 (49%)	332 (61%)
mUPD		236 (33%)	74 (46%)	162 (30%)
ICD		13 (2%)	4 (3%)	9 (2%)
mUPD or ICD		20 (3%)	0 (0%)	20 (4%)
Translocation		1 (0%)	1 (1%)	0 (0%)
Other		8 (1%)	0 (0%)	8 (2%)
Unknown		18 (3%)	3 (2%)	15 (3%)
Country				
Netherlands	706	115 (16%)	0 (0%)	115 (21%)
United Kingdom		45 (6%)	1 (1%)	44 (8%)
France		92 (13%)	4 (3%)	88 (16%)
Spain		94 (13%)	54 (34%)	40 (7%)
Italy		290 (41%)	96 (60%)	194 (36%)
Australia		70 (10%)	5 (3%)	65 (12%)
GH treatment				
During childhood	706	420 (60%)	145 (91%)	275 (50%)
During adulthood	704	156 (22%)	NA	156 (29%)
Childhood and/or adulthood	706	462 (65%)	145 (91%)	317 (58%)
Current	693	227 (32%)	110 (69%)	117 (21%)
Duration, median [IQR]	396	8 [4-12]	7 [3-10]	8 [4-13]

Data are displayed as n (%).
Abbreviations: ICD, imprinting center defect; IQR, interquartile range; mUPD, maternal uniparental disomy; SDS, standard deviation score.
[a]Current age or, for deceased patients, age of death.

which are not expressed. According to our literature review, several genes in the PWS region have been associated with malignancies:

MKRN3 inactivation leads to proliferation and progression of non-small cell lung cancers (35). However, upregulation of *MKRN3* has been found in osteosarcoma and squamous cell carcinoma of the head and neck (36, 37).

NDN, also known as *necdin*, is a tumor suppressor gene that represses cell-cycle-promoting proteins, interacts with p53 and inhibits cell growth (38–41). *NDN* is downregulated in many types of cancer. Lack of expression of this tumor suppressor gene in PWS might therefore, in theory, lead to an increased risk of cancer.

Little is known about the relation between *MAGEL2* and *C15orf2* and malignancies. *MAGEL2* has been associated with down regulation in hepatocellular carcinoma (42) and *C15orf2* was upregulated in acute myeloid leukemia in one study (43), but other types of malignancies have not been investigated.

SNURF-SNRPN, due to its relation with the PWS imprinting center (44), has been extensively investigated in order to understand the relationship between epigenetic imprinting and cancer development. Both up- and downregulation of *SNURF-SNRPN* have been reported in different types of malignancies. *SNRPN* might affect cancer development through regulation of the cell cycle, tumor proliferation, and apoptosis (45, 46).

Small nucleolar RNAs (snoRNAs) are a class of non-coding RNAs (ncRNAs). Some snoRNAs demonstrate the capability to affect tumorigenesis and metastasis (47). Although evidence is scarce, studies suggest a role of the snoRNAs located on the PWS region in the tumorigenesis of different types of cancer. Most studies report the upregulation of these

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Table 2. Patient characteristics according to history of malignancies

	Number of observations	Malignancy absent N = 699	Malignancy present N = 7	*P* value
Age				
Median [IQR]	706	24 [18-34]	39 [22-46]	.04
Range		0.4-73	18-55	
Male gender	706	322 (46%)	4 (57%)	.7
Genotype				
Deletion	706	403 (58%)	7 (100%)	.045[a]
mUPD		236 (34%)	0 (0%)	
ICD		13 (2%)	0 (0%)	
mUPD or ICD		20 (3%)	0 (0%)	
Other		8 (1%)	0 (0%)	
Unknown		18 (3%)	0 (0%)	
Country				
The Netherlands	706	115 (17%)	0 (0%)	
United Kingdom		45 (6%)	0 (0%)	
France		91 (13%)	1 (14%)	
Spain		93 (13%)	1 (14%)	
Italy		287 (41%)	3 (43%)	
Australia		68 (10%)	2 (29%)	.5
GH treatment				
During childhood	706	418 (60%)	2 (29%)	.1
During adulthood	704	155 (22%)	2 (29%)	1
Childhood and/or adulthood	706	458 (66%)	4 (57%)	.7
Current	693	226 (32%)	1 (14%)	1
Duration, median [IQR]	396	8 [4-12]	1 [0.6-10]	
Anthropometric measurements				
Height, cm, median [IQR]	16	153 [144-163]	155 [152-162]	.8[b]
Weight, kg, median [IQR]	16	78 [60-98]	100 [69-127]	.5[b]
BMI, kg/m^2, median [IQR]	16	32 [25-42]	36 [28-55]	.4[b]
Obesity	16	374 (55%)	5 (71%)	.7[b]
Intoxications				
Alcohol	593	12 (2%)	1 (14%)[c]	.1
Glasses per week, median [IQR][d]	13	2 [1-4]	1[c]	
Smoking	598	36 (5%)	2 (29%)[c]	.07
Cigarettes per week, median	38	70 [42-113]	35 and 49[c]	
[IQR][d]	592		0 (0%)	
Drugs		0 (0%)		
Sex hormone replacement therapy				
Males, n (% of males)	313	149 (48%)	3 (75%)	.4
Median age at start [IQR]	313	18 [16-25]	23, 30, & 30[c]	
Females, n (% of females)	366	186 (51%)	1 (33%)[c]	.6
Median age at start [IQR]	355	17 [15-20]	13[c]	
Cryptorchidism, n (% of males)	310	250 (81%)	2 (67%)	.5
Surgery for cryptorchidism, n (% of cryptorchidism)	252	232 (93%)	2 (100%)	
Known family history of malignancy in first degree relatives	567	88 (16%)	1 (20%)	.6
Mortality	706	25 (4%)	4 (57%)	<.001
Age of death	706	33 [26-49]	39 [24-46]	
Type 2 diabetes mellitus (T2DM)	648	111 (17%)	2 (29%)	.4
Only non-insulin antidiabetics, n (%		59 (60%)	0 (0%)	
of T2DM)[e]	100	3 (3%)	0 (0%)	
Only insulin, n (% of T2DM)		35 (35%)	1 (100%)	

(*continued*)

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Table 2. Continued

	Number of observations	Malignancy absent N = 699	Malignancy present N = 7	*P* value
Both, n (% of T2DM)		2 (2%)	0 (0%)	
None, n (% of T2DM)				

Data are displayed as n (%).
Abbreviations: BMI, body mass index; ICD, imprinting center defect; IQR, interquartile range; mUPD, maternal uniparental disomy; T2DM, type 2 diabetes mellitus.
[a]*P* value calculated for deletion vs non-deletion.
[b]For adults only.
[c]Individual patient data as there were three or less patients in this category.
[d]In patients that smoke/drink alcohol only.
[e]Either oral antidiabetics or GLP-1 analogues.

Table 3. Prevalence of malignancies for different age groups

Age	Patients with malignancies/total (%)	Age at diagnosis	Current age	Type of malignancy	Genotype	Family history of malignancy in first degree relatives	WHO 1-year cancer prevalence[a]
0-9 years	0/85 (0%)						.014%
10-19 years	1/131 (0.8%)	18	[b]	Acute lymphoblastic leukemia	Deletion, unspecified	None	0.015%
20-29 years	1/247 (0.4%)	22	22	Intracranial hemangiopericytoma	Deletion, unspecified	None	0.040%
30-39 years	2/129 (1.6%)	39	39	Melanoma in neck	Type 1 deletion	None	0.093%
		33	[b]	Adenocarcinoma of stomach	Type 2 deletion	None	
40-49 years	2/77 (2.6%)	44	[b]	Biliary cancer	Deletion, unspecified	None	0.22%
		46	[b]	Adenocarcinoma parotid gland (metastasized)	Deletion, unspecified	None	
50-74 years	1/37 (2.7%)	*55*	*55*	Colon cancer (metastasized)	Type 1 deletion	Pancreatic cancer (father)	0.87%

[a]The WHO 1-year cancer prevalence for Europe for both sexes in 2020 (21). It should be noted that these numbers are not directly comparable to our results, as we do not report a 1-year prevalence.
[b]Deceased.

snoRNAs, in particular *SNORD116* and *SNORD115*, in malignancies. As these genes are not expressed in PWS, this might protect against cancer.

Downstream of the PWS region lies the Angelman syndrome region. This region contains *UBE3A* and *ATP10A*. Patients with an mUPD have increased expression of these genes compared to patients with a deletion or healthy controls (34).

UBE3A encodes E3 ligase E6-associated protein (E6AP), which is involved in viral oncogenesis (ie, human papillomavirus, hepatitis C virus, and Epstein-Bar virus-associated malignancies). *UBE3A* is also involved in the nonviral oncogenesis of multiple types of cancer by degradation of the tumor suppressor promyelocytic leukemia protein (PML) and $p27^{Kip1}$. Thus, upregulation of *UBE3A* is likely related to tumorigenesis (48). This might indicate that patients with an mUPD could have an increased risk of malignancies, which was not confirmed in our cohort. Little is known about the relationship between *ATP10A* and malignancies.

Next to the Angelman region lies the distal non-imprinted region. The genes in the distal non-imprinted region are deleted on one allele in patients with a paternal deletion, but not affected in patients with an mUPD or ICD.

GABRB3, GABRA5, and *GABRG3* all encode one of the 19 $GABA_A$ receptor subunits (49). The GABA pathway is involved in embryonic stem cell and peripheral neural crest cell proliferation, blunting rapid proliferation, resulting in a more tempered proliferation. This enhances genome integrity (50–52). Multiple studies reported loss of expression or decreased expression of *GABRB3* in malignancies, while some reported increased expression. *GABRA5* was upregulated in several malignancies and *GABRG3* was downregulated in colon adenocarcinoma.

OCA2 is involved in pigmentation and eye color. Therefore, alterations in the *OCA2* gene have been associated with melanoma (53–55). Mutations in *OCA2* result in oculocutaneous albinism (56), which is associated with an increased risk of skin cancer (51, 57). Additionally, it is downregulated in thyroid carcinoma.

HERC2 is a member of the HERC family. HERCs play a role in replication stress and DNA damage, cell proliferation, and migration and immune response (58). *HERC2* is associated with eye color and pigmentation. Genetic variants in this gene have been associated with an increased risk of melanoma (54, 59). Additionally, depletion of *HERC2* leads to inhibition of the tumor suppressor p53 (60). Mutations in and

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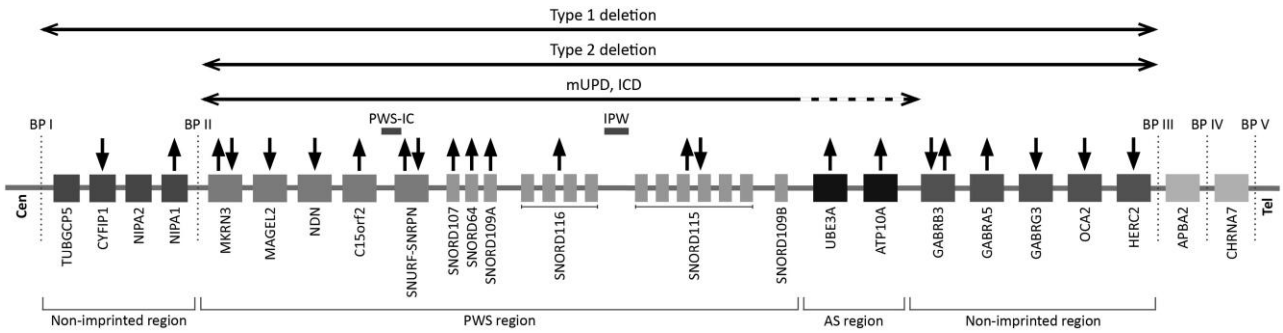


Figure 1. Genes on chromosome 15q11.2-q13 in relation to malignancies. Abbreviations: AS, Angelman syndrome; BP, breakpoint; Cen, centromere; IC, imprinting center; PWS, Prader–Willi syndrome; Tel, telomere. Figure based on Cheon et al (6). Chromosome 15q11.2-q13 can be divided into different regions: a proximal non-imprinted region, the Prader-Willi syndrome (PWS) region that is maternally imprinted, the paternally imprinted region that is also known as the Angelman syndrome region, and a distal non-imprinted region. Legends: Horizontal arrows indicate regions of chromosome 15q11.2-q13 affected by the different genotypes of PWS. Solid horizontal arrows indicate diminished or loss of expression, dotted arrows indicate increased expression. ↑: the gene is upregulated in one or multiple different malignancies in ≥ 80% of studies, ↓: the gene is downregulated in one or multiple different malignancies in ≥ 80% of studies, ↑↓: the gene is more often upregulated than downregulated in one or multiple different malignancies, ↓↑: the gene is more often downregulated than upregulated in one or multiple different malignancies, no symbol: we did not find any information about the relationship between this gene and the development of malignancies.

downregulation of *HERC2* have been associated with multiple types of malignancies (58). As patients with a deletion have only one copy of *HERC2*, this might lead to an increased risk of malignancies.

Hypopigmentation, which is common in patients with PWS with a deletion (61), is a risk factor for the development of skin cancers (51, 57). We report one patient with melanoma, who had a type 1 deletion.

We found several relatively rare types of malignancies in our population such as hemangiopericytoma, parotid gland cancer, and biliary cancer. Research regarding the relationship between these rare types of malignancy and the genes on chromosome 15q11.2-13 was scarce and therefore we could not explain this finding.

Besides the direct effects of altered gene expression, various clinical features of PWS may increase or decrease the risk of malignancies, including GH and sex hormone treatment, obesity, and use of alcohol and tobacco.

Growth Hormone Treatment

Nowadays, most children with PWS are treated with growth hormone (GH). Multiple observational studies in non-PWS populations did not indicate an increased risk of malignancies later in life after treatment with GH during childhood (62, 63). However, the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGHe) study showed increased incidence and mortality risks for several cancer sites, largely related to second primary malignancies in patients who received GH treatment after cancer treatment. Only the incidence of bone and bladder cancer was also significantly increased in patients without previous cancer who received GH therapy. Additionally, there was a significant increase in incidence of Hodgkin lymphoma with longer follow-up, also in patients without previous malignancies (64). However, these outcomes might reflect the effect of the underlying condition leading to GH treatment, rather than the effect of GH treatment itself. Therefore, GH treatment is still considered safe with regard to risk of malignancies.

Sex Hormone Replacement Therapy

Many patients with PWS have hypogonadism and are treated with estrogen or testosterone replacement therapy (65–67). In our cohort, 49% of males and 51% of females were receiving sex steroid replacement. In the general population, estrogen replacement therapy is associated with an increased risk of malignancies, especially breast cancer (68, 69). However, little is known about the risk of estrogen replacement therapy in patients with congenital hypogonadism.

The relationship between testosterone replacement therapy and prostate cancer remains complex. However, testosterone replacement therapy seems to be safe and might even be used to help control prostate cancer through normalization of testosterone concentrations (70). We recommend yearly measurement of prostate specific antigen in males with PWS who receive testosterone replacement therapy, according to the guidelines for the general population (71).

Obesity

Obesity was prevalent in our cohort (55%), especially among adults (65%). However, our definition of obesity was based on BMI only, which might lead to an underestimation of adiposity, due to abnormal body composition with low fat free mass compared to fat mass in patients with PWS (4). There is a clear correlation between obesity and many types of malignancies, with relative risks (RR) ranging from 1 to 3 per 10 kg/m^2 increase in BMI (72). However, obese patients with PWS have reduced visceral adiposity (73) and are more insulin sensitive (73–75) compared to non-PWS obese adults. This may partly protect adults with PWS from the increased risk of malignancies caused by obesity (76).

In obese individuals with PWS, serum leptin concentrations are increased, as is expected in obesity (75, 77). Leptin is associated with a higher risk of malignancies, ie, breast cancer (78), colorectal cancer (79), thyroid cancer (80), and endometrial cancer (81), also after adjustment for obesity. However, while obesity usually suppresses plasma ghrelin, plasma ghrelin concentrations are increased in PWS (82–85). The relation between circulating ghrelin and the risk of malignancies is still controversial (86). Furthermore, obesity is also associated with chronic low-grade systemic inflammation and oxidative stress (87, 88), which plays a role in the development of malignancies (89, 90). However, there are contradictory reports as to whether peripheral inflammatory

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markers and adipocytokines are lower, appropriate, or raised for their obesity in patients with PWS (74, 91–93).

Use of Tobacco and Alcohol

Adults with PWS smoke and drink alcohol less often than non-PWS adults. In the general population, tobacco use is associated with lung, laryngeal, pharyngeal, upper digestive tract, and oral cancers (94). Alcohol use leads to an increased risk of cancers of the oral cavity, pharynx, esophagus, colon, rectum, liver, larynx, and breast (95). While 25% of the general European population are cigarette smokers (96), only 5% of our PWS cohort were cigarette smokers. While almost three-quarters of the European population drinks alcohol, only 2% of our PWS cohort drank alcohol (97). Based on these numbers, tobacco and alcohol-associated malignancies are expected to be less prevalent in patients with PWS.

Population Screening for Malignancies

Studies have reported a lower participation in population screening programs for breast, cervical, and colorectal cancer in adults with an intellectual disability (ID) compared to the general population (98–102). Additionally, the consumption of cancer-related healthcare is also lower in adults with an ID (101), while the prevalence of cancer seems to be higher than in the non-ID population (102, 103). This could be due to underdiagnosis and undertreatment in this patient population (101, 102). In our clinical experience, participation in cancer screening programs is also low for patients with PWS, especially for the cervical cancer screening. It is often assumed that cervical cancer screening is not indicated in patients with an ID as they are not sexually active. However, assumption is not always correct, as these patients can be sexually active as well (67). On the other hand, cervical cancer screening could be traumatic for some patients, depending on their sexual history. Therefore, the decision to screen for cervical cancer should be carefully made for each individual patient. We do recommend participation in national screening programs for breast and colon cancer for all PWS adults, due to the increased cancer risk associated with obesity.

Cancer Treatment and Intellectual Disability

The diagnosis and treatment of malignancies is especially complicated in patients with PWS and ID (104). First, their inability to express their physical complaints could lead to underdiagnosis (102). Second, when a malignancy is diagnosed, it is more difficult to convey this information in an effective way to the patient. Information material designed for patients with ID is often unavailable (105). Physicians for IDs, who are experts in communication with and management of patients with ID, are often unfamiliar with the details of cancer diagnosis and cancer treatment. On the other hand, oncologists often lack the specific background and education needed for communication with individuals with ID. Therefore, it is important that these specialists work together, to make sure that both effective communication and accurate information is provided to both patients and their parents/caregivers.

Strengths and Limitations

Strengths of this study include that we report on malignancies in a large international cohort of patients with PWS, that clinical assessments of patients with PWS were performed by experienced physicians and that we report an elaborate literature review. One limitation is the relatively young age of the participants. Although we were able to collect data on a very large cohort of patients with this rare disease, only 37 subjects were older than 50 years, while most malignancies often occur later in life. This lack of older adults with PWS is related to their limited life expectancy (7). The second limitation is the possibility of underdiagnoses. All patients were subject to a yearly follow-up including medical interview, physical examination, and blood measurements. This reduces the risk of underdiagnosis compared to questionnaire studies that only assess self-reported malignancies. However, underdiagnosis cannot be completely ruled out as we did not perform any specific screening for malignancies. Furthermore, national screening programs for malignancies (eg, cervical, breast, colon) vary between countries and data on participation in these screening programs was largely unavailable. The third limitation is the risk of survival bias. We collected data on patients that visited or had visited the PWS reference centers in the past. However, it is possible that patients had already died as a result of cancer before visiting one of the PWS reference centers. The fourth limitation is the lack of a control population. We performed a cross-sectional study where we reported whether patients had a past or current diagnosis of a malignancy. We did not have access to similar data in a control population. However, even without comparing our findings to a control population, we believe that it is unlikely that the risk of a certain type of malignancy is increased, as all types of cancer only occurred once. Lastly, our literature review addresses the potential effect of the genes on chromosome 15q11.1-13 on cancer risk. However, most of the literature did not provide insight into the causal relation between the up- or downregulation of these genes and the development of malignancies. Therefore, a causal relationship cannot be proven.

In conclusion, cancer is rare in our cohort of 706 patients with PWS. The 7 patients with malignancies all had different types of cancer, which suggests a multifactorial etiology. All patients with a malignancy had a paternal deletion. However, the relationship between the PWS genes and cancer risk is complex. Due to the increased cancer risk associated with obesity, we recommend participation in national screening programs for breast and colon cancer for all adults with PWS. The decision to screen for cervical cancer should be carefully made for each individual patient, depending on sexual history and degree of intellectual disability. In males who receive testosterone replacement therapy, we recommend measurement of prostate specific antigen (PSA) according to the general guidelines for testosterone therapy (71). Additional screening for malignancies is only indicated in case of a clinical suspicion based on unexplained weight loss, loss of appetite, paraneoplastic symptoms, or localizing symptoms.

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Disclosures

K.P., N.N., A.R., M.C., A.G., C.H., T.M., G.G., An.C., As.C., C.P., R.C., R.N., A.v.d.L., and L.d.G. have nothing to declare.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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