

## High Prevalence of Diabetes and Pre-Diabetes in Adults With Williams Syndrome

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**Abstract**

A standard oral glucose tolerance test (OGTT) was administered to 28 adults with Williams syndrome (WS). Three quarters of the WS subjects showed abnormal glucose curves, meeting diagnostic criteria for either diabetes or the pre-diabetic state of impaired glucose tolerance. Fasting mean glucose and median insulin levels did not differ significantly in the total WS cohort versus age–gender–BMI matched controls, though the glucose area under the curve was greater in the WS subjects. HbA1c levels were not as reliable as the OGTT in diagnosing the presence of diabetes. Given the high prevalence of impaired glucose regulation, adults with WS should be screened for diabetes, and when present should be treated in accordance with standard medical practice. Hemizygoty for a gene mapping to the Williams syndrome chromosome region (WSCR) is likely the major factor responsible for the high frequency of diabetes in WS. Syntaxin-1A is a prime candidate gene based on its location in the WSCR, its role in insulin release, and the presence of abnormal glucose metabolism in mouse models with aberrantly expressed *Stx-1a*.

**Keywords**

diabetes mellitus; impaired glucose tolerance; Williams syndrome chromosome region (WSCR); syntaxin-1A (STX-1A); oral glucose tolerance test

**INTRODUCTION**

Williams syndrome (WS, OMIM # 194050), originally described as a syndrome with “peculiar” facies, a distinctive cardiovascular lesion, and “mental retardation” [Williams et al., 1961; Beuren et al., 1962], is now known to be a multi-system disorder with potential impact on virtually all organ systems [Morris et al., 1988, 2001; Cherniske et al., 2004]. The features and complications of WS are caused by deletion of 26–28 genes contained in an approximate 1.5–1.8 million basepair Williams–Beuren syndrome chromosome region (WSCR) on chromosome 7q11.23 [Osborne, 1999; Peoples et al., 2000; Antonell et al., 2005]. Intense efforts to draw genotype–phenotype correlations are ongoing [Morris et al., 2003; Tassabehji et al., 2005].

One of the genes mapping to the WSCR is syntaxin-1A (STX-1A) encoding for a protein of the same name [Osborne et al., 1997]. STX-1A plays a role in membrane vesicle fusion and pancreatic beta-cell exocytosis of insulin granules [Bennett et al., 1992]. An overproducing syntaxin-1A transgenic mouse model shows hyperglycemia and reduced insulin secretion following intraperitoneal glucose challenge [Lam et al., 2005]. Findings from this and other

models of altered syntaxin-1A stoichiometry [Chan et al., 1999; Nagamatsu et al., 1999], combined with a few clinical reports of diabetes mellitus (DM) in patients with WS, prompted us to study glucose metabolism in WS. We report that 75% of adults with WS show either pre-diabetes (e.g., impaired glucose tolerance) or DM after an oral glucose tolerance challenge. This represents one of the highest frequencies of glucose dysregulation observed in any human population.

## METHODS

We recruited 28 adults with WS over the age of 20 for this study. All subjects were examined by one of the authors (BRP), and were offered participation in this research as part of a comprehensive study of adults with WS [Cherniske et al., 2004], or as part of their attendance in genetics clinic. Subjects with either an established diagnosis of DM or a prior history of elevated glucose levels were excluded. Information on past medical history and current pharmacotherapy was collected.

Subjects were studied in the Yale Center for Clinical Investigation—Hospital Research Unit (HRI) at the Yale University School of Medicine. A standard 2-hr oral glucose tolerance test (OGTT) was administered following an overnight fast. Details on the OGTT and biochemical determinations of glucose and insulin levels are provided elsewhere [Sinha et al., 2002]. Each subject's 2-hr glucose level following ingestion of a 75 g glucose load was used to classify them as having normal glucose tolerance (NGT, glucose at 120 min <140 mg/dl), the pre-diabetic state of impaired glucose tolerance (IGT, glucose at 120 min >140, but <200 mg/dl), or previously unrecognized DM (glucose at 120 min >200 mg/dl) [American Diabetes Association, 2004]. Two WS subjects did not receive an oral glucose load because their fasting glucose levels exceeded 150 mg/dl, thereby categorizing them as having DM. Body mass index (BMI) was calculated as weight in kilograms/[height in meters]<sup>2</sup>.

Data points are presented either as means  $\pm$  SD or as medians accompanied by interquartile range (25th centile–75th centile). Matched comparisons were made using McNemar's test for binary outcomes, and paired *t*-tests for comparison of means or Wilcoxon Signed Rank tests for comparison of medians. All data were analyzed using SAS version 9.1 (Cary, NC). Insulin sensitivity was measured with whole body insulin sensitivity index (WBISI) using the Matsuda Index [Matsuda and DeFronzo, 1999; Yeckel et al., 2004] and the HOMA-IR [Wallace and Matthews, 2002]. The insulinogenic index (IGI) was calculated as the ratio of the increment in plasma insulin level to that in plasma glucose level during the first 30 min after glucose ingestion [Phillips et al., 1994].

Age–gender–BMI matched controls were selected from a cohort of adults neither with known medical problems nor a family history of diabetes. Matching was successfully accomplished for 17 of the 18 WS subjects diagnosed with NGT or IGT; we were unable to identify a matched control for one 44-year-old WS male with a BMI = 20. Matching was *not* performed for the WS subjects diagnosed with DM.

The Yale University School of Medicine Human Investigation Committee approved this study on an annual basis. Adults with WS gave their assent to participate; consent was simultaneously obtained from a parent or legal-guardian.

## RESULTS

### Cohort of WS Subjects

Twenty-eight adults, 10 males and 18 females with a mean age of almost 35 years, participated in this study (Table I). The clinical diagnosis of WS was established in all cases by one of the co-authors (BRP), and confirmed in 25 subjects by FISH or microsatellite marker analysis. The majority of WS subjects were taking at least one medication at the time of OGTT administration; the most common medications were selective serotonin re-uptake inhibitors (SSRIs) and beta-blockers, taken by 50% and 25%, respectively. Additionally, one subject was taking the antipsychotic Olanzapine (Zyprexa), and three subjects were taking thyroid hormone supplementation.

Remarkably, 21 of the 28 WS subjects (75%) had either pre-diabetes with IGT or previously unrecognized DM (Table I). IGT and DM were present in all BMI categories, occurring in 60% of those with BMI's <25 and in 80% of those with BMI's >25.

Mean hemoglobin A1c for the entire cohort was normal (5.38%, 4.0–5.9%), but was greater than the upper limit of normal among half the DM group, ranging up to 6.7%.

### Comparison of Age–Gender–BMI Matched WS and Control Subjects

After excluding the 10 WS subjects whose OGTT results met criteria for DM, we successfully matched 17 of the remaining 18 subjects to healthy controls (Table II). All controls had NGT, while only 7 of 17 WS subjects demonstrated NGT ( $P=0.02$ ). The fasting glucose mean and fasting insulin median did not differ between WS and controls, though levels in the WS cohort encompassed a broader range. Insulin area under the curve (AUC) was comparable between WS subjects and controls. However, the glucose AUC was 24% greater in subjects with WS than their matched controls.

Further analyses were performed to consider the effect of BMI on average glucose and insulin levels (Fig. 1 and Table III). Both the lean and obese WS subjects showed more variability in glucose and insulin levels than did their matched controls.

Among the lean subjects, the mean fasting glucose levels were comparable between WS cases and the controls; though not statistically significant, all subsequent glucose means were higher in the lean WS subjects than in controls. Median insulin levels, including fasting insulin and 30-min insulin (reflective of 1st phase insulin release), were similar between lean WS and their matched controls.

Among overweight subjects, the WS cases and controls had comparable fasting mean glucose, but not median insulin, levels; the latter averaged higher in the WS cases. Both the absolute glucose and insulin levels trended higher at 60, 90, and 120 min in overweight WS subjects compared to either the matched controls or the lean WS subjects.

## DISCUSSION

The medical literature includes mention of overt DM in a few patients with WS [Morris et al., 1988; Lopez-Rangel et al., 1992; Plissart et al., 1994; Imashuku et al., 2000; Nakaji et al., 2001; Cherniske et al., 2004] However, systematic studies of glucose metabolism in this population have *not* been performed to date. We demonstrate that 21 of 28 (75%) of adults with WS have abnormal glucose tolerance in response to a 2-hr oral glucose challenge. Among WS study participants 34 years of age or older all, except one, have DM (8/17) or IGT (8/17). This extraordinarily high prevalence of glucose dysregulation is similar to that seen in the Pima Indians of Arizona, who are described as having “the highest frequency of type 2 DM of any population in the world” [Prately, 1998]. Comparison of the WS cohort to an age–gender–BMI matched healthy cohort, however, does not demonstrate insulin resistance; that is, individuals with WS do not collectively show elevated fasting insulin levels or an abnormal HOMA-IR.

WS is caused by an ~1.55–1.8 million basepair deletion resulting in the loss of between 26 and 28 genes, depending on the exact point of homologous recombination [Bayes et al., 2003]. We hypothesize that hemizyosity for one or more of these genes contributes to the high frequency of abnormal glucose tolerance seen in our cohort. Additional suggestive evidence comes from OGTT data (not shown) collected in seven 10-to 17-year old WS children and adolescents (mean age = 13.3 years; BMI <20 in four, 20–25 in two, and >30 in one). Even at this young age the pre-diabetic IGT state was found in four subjects, three of whom had a BMI <25. This early onset of pre-diabetes precedes risk factors, such as obesity, medication, and limited physical activity, and points to a genetic pre-disposition to abnormal glucose metabolism.

Hemizyosity for syntaxin-1A (STX-1A), a gene located in the WSCR could be the initiating diabetogenic “hit” in a cascade of events that ultimately result in glucose dysregulation. STX-1A encodes for a protein of the same name, a soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE). This protein contributes to a membrane complex responsible for vesicle docking and fusion, leading to the release of the stored insulin granules that constitute the 1st phase insulin response [Daniel et al., 1999]. Pancreatic beta cells from *Stx1a* knock-out mice were recently shown to exhibit impaired 1st phase but not 2nd phase insulin secretion [Ohara-Imaizumi et al., 2007]. Rat models of DM, such as Zucker *fa/fa* and Goto-Kakizaki (GK), demonstrate decreased level of SNARE proteins, including STX-1A [Chan et al., 1999; Nagamatsu et al., 1999]. Transduction of the STX-1A gene into GK pancreatic islets corrected hyperglycemia, though similar manipulation using islets from normal rats resulted in STX-1A over-expression with *decreased* insulin release [Gaisano et al., 2002]. A transgenic mouse model engineered to modestly over-express STX-1A (35% increase in protein levels) demonstrated fasting hyperglycemia and elevated glucose levels in response to a glucose load [Lam et al., 2005]. Pancreatic beta-cells isolated from these mice also showed reduced Ca<sup>2+</sup> ion channel currents and abnormal insulin tolerance.

It appears from these observations that even small fluctuations of STX-1A levels are sufficient to induce profound changes on the function of the components controlling

secretion [Lam et al., 2005]. Thus, either excess or deficient STX-1A protein levels can impair insulin release, presumably by disrupting the tightly regulated SNARE complex required for normal vesicle fusion and exocytosis. In WS, one STX-1A allele is deleted, a finding confirmed in 14 of our study subjects (data not shown); this reduction in gene dosage is likely to result in reduced protein levels, though this prediction remains to be experimentally verified. STX-1A has previously been implicated in the etiology or progression of diabetes in two human association studies. Tsunoda and coworkers reported that a single nucleotide polymorphism was associated with earlier age of onset and higher daily insulin requirement in individuals with type 2 diabetes of Asian descent, while a polymorphism in the STX1-A promoter was associated with impaired glucose regulation in overweight Italian subjects [Tsunoda et al., 2001; Romeo et al., 2008].

Hemizyosity for another gene located in the Williams–Beuren syndrome critical region, *MLXIPL* (formerly *WSCR14*), which encodes for a basic-helix-loop-helix leucine zipper protein, has also been implicated in abnormal glucose metabolism [Merla et al., 2004]. *MLXIPL* was recently identified as a locus affecting triglyceride levels in humans [Kathiresan et al., 2008; Kooner et al., 2008; Willer et al., 2008] and a knock-out mouse model showed that *MLXIPL* is required both for basal and carbohydrate-induced expression of several liver enzymes essential for the coordinated control of glucose metabolism and the synthesis of fatty acids and triglycerides [Iizuka et al., 2004]. Although heterozygous mice were not studied, mice lacking this protein showed somewhat elevated plasma glucose and insulin levels, combined with significant reductions in fatty acid synthesis and fat deposition. The tendency for abnormal fat accumulation seen in some patients with WS [Cherniske et al., 2004] would argue against a similar effect of hemizyosity for *MLXIPL*, but confirmation awaits a careful analysis of the heterozygous mouse model.

Although we predict that the genetic basis of WS is the major risk for developing diabetes, we cannot exclude other factors. For instance, the increased risk of DM could be non-specific due to gain or loss of genetic material, or a higher prevalence of diabetogenic lifestyle risk factors, rather than caused by deletion of a gene or genes in the WSCR. However, the glucose intolerance of WS seems to be distinct compared to that found in other genetic syndromes, such as Prader–Willi, Turner, and Down syndromes. In these latter disorders, the frequency of abnormal glucose tolerance is lower than that reported in our series. Furthermore, patients with Prader–Willi syndrome primarily have a blunted insulin response, those with Down syndrome typically manifest immune-mediated type I diabetes, while those with Turner syndrome demonstrate a mixed picture of diminished insulin release combined with impaired peripheral glucose utilization [Caprio et al., 1991; Schuster et al., 1996; Anwar et al., 1998; Bakalov et al., 2004; Talebizadeh and Butler, 2004].

There are several limitations of the current study. Our WS sample is small and possibly affected by selection bias. However, we suggest the WS cohort is representative of the general WS population, as study participants were *not* recruited specifically for an assessment of glucose metabolism [Cherniske et al., 2004]. Despite matching WS subjects to healthy controls of comparable age, gender, and BMI, the two populations differ in several important respects. The majority of WS subjects took one or more prescription medications, while the controls took none. Seven WS patients received beta-blockers for hypertension,



and six additional subjects had hypertension; both factors are modest but independent risk factors for diabetes type II [Taylor et al., 2006]. One subject with WS, diagnosed with IGT, was taking the atypical antipsychotic olanzapine (Zyprexa) which has been associated with an excess risk of type II diabetes [American Diabetes Association, 2004; Lamberta et al., 2006]. Finally, many adults with WS engage in limited physical activity. Although we did not administer an objective assessment of this, parents reported activity level in 14 members of our cohort as: not active in 4; moderately active in 8; and very active in 2. We suspect these additional risk factors contribute to the development of diabetes, but are acting in concert with the primary risk factor, deletion of a gene such as STX-1A within the WSCR.

Dissection of the underlying mechanism responsible for abnormal glucose dysregulation will require further studies on more individuals with WS. For the present, WS care-providers should vigilantly monitor for the development of diabetes given the high frequency observed in this cohort. The OGTT should remain the diagnostic standard in WS, since sole reliance on HbA1c levels would have missed the diagnosis of diabetes in half the WS subjects. And finally, we believe it is appropriate to institute lifestyle changes and pharmacotherapy in WS individuals diagnosed with diabetes.

## CONCLUSIONS

We report that the majority of individuals with WS over 20 years of age have pre-diabetes/IGT or previously unrecognized DM as defined by a standard oral glucose challenge. We suggest that deletion of a gene in the Williams–Beuren syndrome critical region is the greatest risk factor conferring abnormal glucose metabolism. Future studies will be required to elucidate the gene(s) and mechanism(s) underlying this phenomenon in WS, and whether mutations or polymorphisms in these same genes could contribute to abnormal glucose metabolism in persons in the general population.

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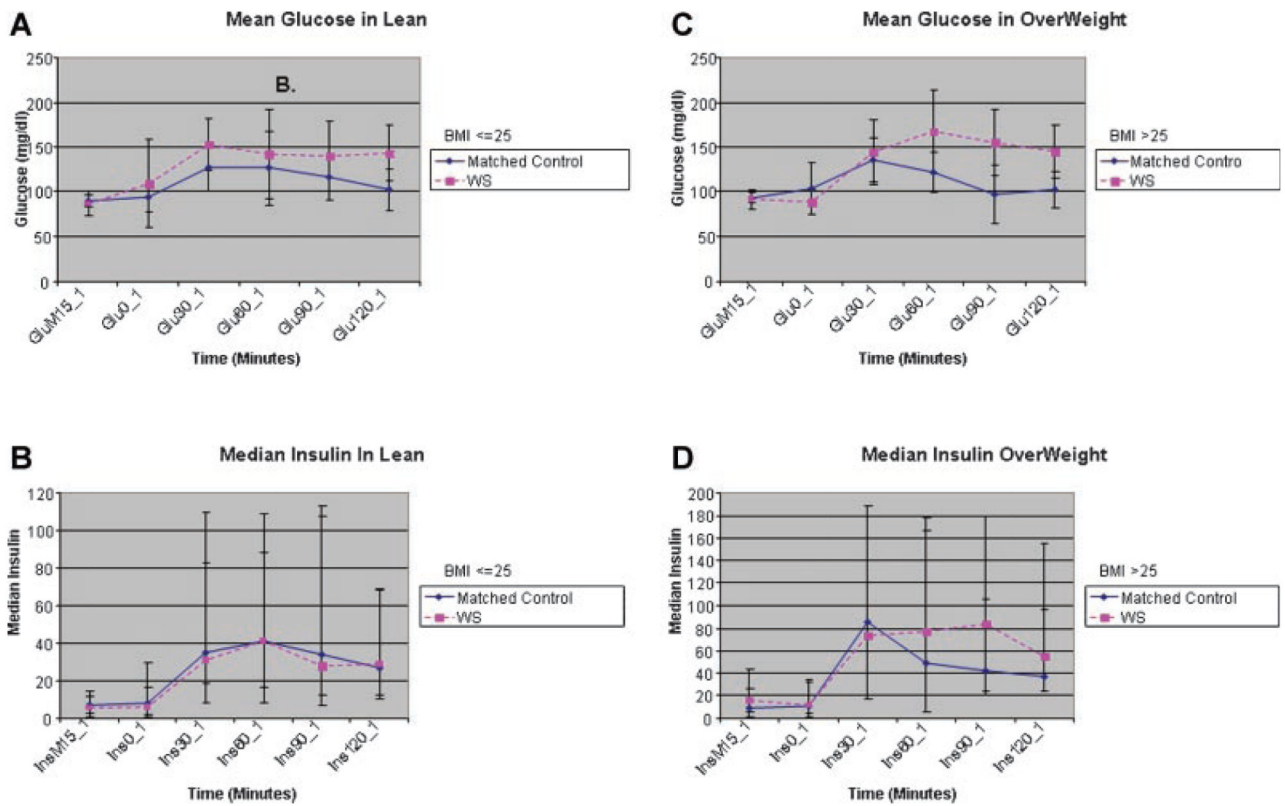
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**Figure 1.** Mean ( $\pm$ SD) plasma concentrations of glucose (panel A) and median ( $\pm$ IQR) concentrations of plasma insulin concentrations (panel B) before and during an oral glucose tolerance tests in 8 lean (BMI <25 mg/kg/m<sup>2</sup>) patients with Williams syndrome and controls. Mean ( $\pm$ SD) plasma concentrations of glucose (panel C) and median ( $\pm$ IQR) concentrations of plasma insulin concentrations (panel D) before and during an oral glucose tolerance tests in 9 overweight (BMI >25 mg/kg/m<sup>2</sup>) patients with Williams syndrome and controls. IQR, interquartile range; SD, standard deviation.

TABLE I

## Characterization of Williams Syndrome (WS) Cohort

Adults with Williams syndrome (n = 28)	
Age (y) <sup>a</sup>	34.9 (9.7)
Sex	
M	10
F	18
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	26.19 (5.86)
Dist. of BMI	
<20	6
20–25	4
25–30	13
>30	5
Glucose tolerance status <sup>b</sup>	
Normal glucose tolerance	7 (25)
Impaired glucose tolerance	11 (39)
Previously unrecognized diabetes	10 (36)
1st degree relative with diabetes mellitus <sup>b,c</sup>	
Yes	3 (12)
No	23 (88)
Medications <sup>b,d</sup>	
Any medications	21 (75)
Beta-blockers	7 (25)
Other anti-HTN	5 (18)
Psychiatric medications	14 <sup>e</sup> (50)
% Total body fat <sup>a</sup> (16 missing)	29.67 (11.74)
Mean HbA1c (%) <sup>a</sup>	5.38 (0.56)

HTN, hypertension; HbA1c, hemoglobin A1C.

<sup>a</sup>Mean (SD).

<sup>b</sup>Frequency (%).

<sup>c</sup>Two patients adopted.

<sup>d</sup>Several patients were taking multiple medications.

<sup>e</sup>The most common medications used to treat psychiatric symptoms were SSRIs; one male patient, taking olanzapine (Zyprexa), was classified as having IGT.

TABLE II

## Non-Diabetic Williams Syndrome Patients Versus Matched Controls

	WS (n = 17)	Matched control (n = 17)	P-value
Age (y) <sup>a</sup>	32.1 (9.1)	32.9 (9.2)	0.54
Sex			
M	7	7	1.00
F	10	10	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	24.8 (5.5)	25.7 (4.3)	0.34
Hypertension <sup>b</sup>			
Yes	8 (47)	0 (0)	0.01
No	9 (53)	17 (100)	
Glucose tolerance status <sup>b,c</sup>			
Normal glucose tolerance	7 (41)	17 (100)	0.02
Impaired glucose tolerance	10 (59)	0 (0)	
Fasting glucose (mg/dl) <sup>a</sup>	89.8 (11.7)	91.4 (6.1)	0.69
Fasting insulin (median/IQR)	10 (6–18)	9 (7–9)	0.09
HOMA-IR (median/IQR)	2.23 (1.4–5.4)	1.89 (1.5–2.4)	0.74
WBISI (median/IQR)	4.46 (2.8–7.3)	5.21 (4.2–6.1)	0.67
Insulinogenic index (median/IQR)	0.96 (0.4–1.1)	1.05 (.6–1.4)	0.32
AUC glucose <sup>a</sup>	144 (31)	116 (20)	0.004
AUC insulin (median/IQR)	46.4 (31.2–77.2)	41.0 (31.3–51.4)	0.62

AUC, area under curve; BMI, body mass index; F, female; HOMA-IR, homeostasis model assessment–insulin resistance; IQR, interquartile range; M, male; WBISI, whole body insulin sensitivity index; WS, Williams syndrome; y, year.

<sup>a</sup>Mean (SD).

<sup>b</sup>Frequency (%).

<sup>c</sup>WS cases with previously unrecognized diabetes were *not* matched to healthy controls.

**TABLE III**

Lean WS Patients Versus Matched Controls, and Overweight/Obese WS Patients Versus Matched Controls

	Lean			Overweight/obese		
	WS, N = 8	Control, N = 8	P-value	WS, N = 9	Control, N = 9	P-value
Age <sup>a</sup>	29.9 (8.2)	32.0 (9.1)	0.29	34.1 (10.0)	33.7 (9.8)	0.79
BMI <sup>a</sup>	20.1 (2.8)	21.6 (1.8)	0.03	29.0 (3.5)	28.6 (2.8)	0.63
Glucose tolerance status <sup>b,c</sup>						
Normal glucose tolerance	4	8	0.13	3	9	0.04
Impaired glucose tolerance	4	0		6	0	
Fasting glucose <sup>a</sup>	90.9 (17.6)	90.6 (6.1)	0.97	88.8 (13.8)	91.8 (5.7)	0.42
Fasting insulin (median/IQR)	5.5 (4.0–18.0)	7.5 (6.0–8.0)	0.89	14.0 (10.0–22.0)	9.0 (7.5–10.0)	0.04
HOMA-IR (median/IQR)	1.26 (0.71–4.86)	1.83 (1.36–1.90)	0.81	2.40 (2.09–5.96)	2.33 (1.57–2.84)	0.43
WBISI (median/IQR)	7.62 (4.01–9.10)	5.24 (5.08–7.43)	0.69	4.29 (2.03–4.50)	4.90 (4.53–5.37)	0.07
Insulinogetic index (median/IQR)	0.61 (0.07–1.19)	0.83 (0.32–1.13)	0.58	1.00 (0.94–1.08)	1.13 (1.00–1.69)	0.43
AUC glucose <sup>a</sup>	141.6 (31.4)	119.5 (23.5)	0.20	145.9 (32.6)	113.1 (16.1)	0.006
AUC insulin (median/IQR)	31.9 (25.1–45.5)	36.1 (30.7–47.8)	0.47	67.0 (47.4–77.5)	43.3 (33.9–59.0)	0.24

AUC, area under curve; BMI, body mass index; HOMA-IR, homeostasis model assessment–insulin resistance; IGT, impaired glucose tolerance; IQR, interquartile range; NGT, normal glucose tolerance; WBISI, whole body insulin sensitivity index; WS, Williams syndrome; y, year.

<sup>a</sup>Mean (SD).

<sup>b</sup>Frequency (%).

<sup>c</sup>WS cases with previously unrecognized diabetes were *not* matched to healthy controls.