

copy number alteration at *TAF7L*. However, unsupervised clustering of *TAF7L* DNA methylation indicated a strong association with gene expression ($P = 1.3 \times 10^{-11}$). Because no component normal testicular tissue was available in the TCGA data, we also evaluated DNA methylation of the *TAF7L* gene in 90 pairs of patient-matched specimens of primary breast tumor and adjacent normal breast tissue from TCGA. Among 3 promoter-associated CpGs (cg08704539, cg16723800, and cg01786967) located within the *TAF7L* CpG island, methylation was consistently higher in tumors when compared with matched normal breast tissue (Fig 1). Because the role of *TAF7L* within breast tissue may be necessarily reflect activity within testicular tissue, we next evaluated RNA-sequencing gene expression of *TAF7L* in a Gene Expression Omnibus data set with both testicular cancer cases and healthy controls. Although only 7 matched pairs of normal testis and testicular germ cell tumor were available in this data set, *TAF7L* gene expression was consistently elevated in normal-adjacent tissues compared with patient-matched tumors ($n = 7$; $P = .09$, 2-sided t test). Taken together, these findings support a putative role of *TAF7L* in tumor suppression.

The contiguous gene syndrome in our patient raises several considerations. Although this contiguous gene syndrome has been previously described,^{1,9} this is the first report of a primary testicular cancer and subsequent metachronous contralateral testicular cancer occurring with this syndrome. The association questions what role *TAF7L* may play as a tumor suppressor gene in the testis and possibly other tissues. The precursor lesion of almost all postpubertal testicular germ cell tumors is intratubular germ cell neoplasia unclassified, defined as malignant germ cells confined to the seminiferous tubules (in situ carcinoma). We speculate that the promoter CpG island hypermethylation events in *TAF7L* may play a role in intratubular germ cell neoplasia unclassified development regardless of further histologic differentiation and absence of *TAF7L* gene expression may explain the development of seminomatous and nonseminomatous testicular cancers in this patient. Further investigation comparing *TAF7L* expression in normal fresh testicular tissue with expression in testicular cancers may provide important insight into this association.

Although most *BTK* mutations are missense, nonsense, splice site, and small deletional events, large deletions still account for approximately 3.5% of XLA cases.⁹ This report highlights the need to consider the MTS-XLA contiguous gene syndrome in patients who present with XLA and sensorineural hearing loss and the possible

role of careful and prolonged testicular cancer surveillance in patients with *TAF7L* alteration.

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Penicillin skin testing without minor determinate mixture and amoxicillin challenge in the Appalachian region



Approximately 10% of the population self-reports a history of penicillin allergy, but when formally evaluated for penicillin allergy, 90% or more of these individuals are found to not be allergic and are able to tolerate penicillin.^{1–3} Skin testing to rule out penicillin allergy is performed with penicillin G, benzylpenicilloyl-poly-L-lysine, and minor determinant mixture (MDM). MDM is not commercially available and used in academic centers. This study aimed to determine the safety of penicillin G and benzylpenicilloyl-poly-L-lysine without MDM to rule out penicillin allergy.

We performed a retrospective medical record review of all patients undergoing β -lactam allergy evaluation at our outpatient

allergy clinic from July 2015 to June 2016. All patients underwent immediate hypersensitivity skin testing⁴ with penicillin G, 10,000 IU, and benzylpenicilloyl-poly-L-lysine, 6.0×10^{-5} M, followed by an oral provocation dose with 1/10 of amoxicillin (25 mg) with observation for 30 minutes, followed by a full dose of amoxicillin (250 mg) with observation for 60 minutes.⁵ This protocol has been recommended by the American College of Allergy, Asthma, and Immunology in the form of the penicillin tool kit.⁵ Fifty-two patients were included in the study. Most were female (75.0%) and white (94.2%). Mean (SD) age at evaluation was 61.0 (16.86) years. Most patients reported a type I immediate hypersensitivity reaction (76.7%), almost half reported an allergy to a non- β -lactam antibiotic (48.1%), and approximately one-third of patients were atopic (36.5%). The most common reported sign or symptom was urticaria (55.3%), followed by angioedema (26.3%).

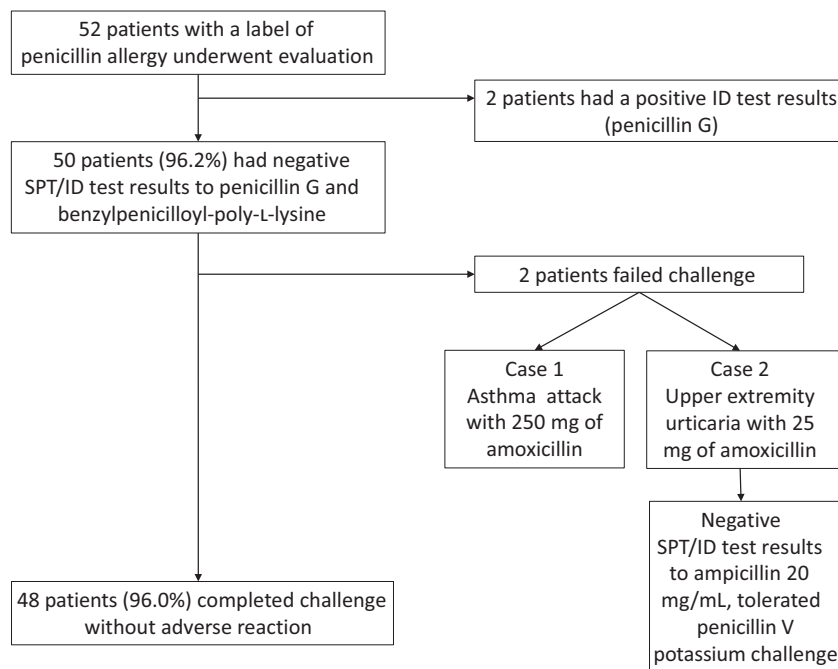


Figure 1. Cases of penicillin allergy. ID, intradermal; SPT, skin prick test.

Figure 1 summarizes skin test and provocation test results of all cases. Of the 52 patients, 50 (96.2%) had negative skin test results. The 2 patients with positive skin test results were classified as truly allergic to penicillin. Of the 50 patients with negative skin test results, 48 (96.0%) tolerated the oral provocation test without adverse reactions. The oral provocation test failed in 2 patients (Fig 1). Patient 1 had an asthma attack approximately 40 minutes after receiving the second dose of amoxicillin (250 mg). The patient required an epinephrine injection and emergency department visit. The patient's symptoms resolved within 2 to 3 hours. Patient 2 had an episode of right upper extremity urticaria within 10 minutes of receiving the first dose of amoxicillin. The urticaria resolved within 1 hour after receiving a single 180-mg dose of fexofenadine. The patient underwent further skin testing with 20 mg/mL of ampicillin 20 mg/mL, the results of which were negative, and tolerated an open oral challenge to penicillin V potassium without adverse reactions.

We performed a retrospective analysis of 52 patients with penicillin allergy undergoing skin testing with penicillin G and benzylpenicilloyl-poly-L-lysine without MDM, followed by a 2-step amoxicillin provocation test.⁵ Of the 52 patients undergoing penicillin allergy evaluation, 2 (3.8%) had a positive skin test result. Of the 50 patients with negative skin test results, 2 (4.0%) had an objective reaction to the challenge. The negative predictive value was 96.0%. This is consistent with previous reports.^{6,7}

Recent studies⁸ have found a combined 2.2% benign positive objective response to oral challenges. However, contrary to previous reports,⁸ one of our patients (patient 1) had anaphylaxis that required an emergency department visit and epinephrine injection. Clinical manifestations and the rate of atopy in the series were consistent with previous studies.

Penicillin skin testing is greatly underused in the United States; one of the reasons is the commercial unavailability of MDM and ampicillin skin test reagents.^{6,9} In the past, MDM was commonly synthesized by some academic centers and made available to the regional community allergist. The legal implication of using compounded MDM has led to the elimination of this practice.

A recent study¹⁰ using only a 250-mg amoxicillin challenge in recruits previously thought to have penicillin allergy found that only 1.5% had an objective mild reaction to the challenge. The study concluded that only challenge with amoxicillin might be appropriate in low-risk populations. New reactions may occur between 3% and 4.5% of patients who had negative skin test results and were exposed again to penicillin.⁶

Limitations of our study include small sample size and patients not followed up to confirm whether they received a complete course of β -lactams without adverse reactions.

In conclusion, we conducted a retrospective analysis of 52 patients evaluated for penicillin allergy at our outpatient clinic in the Appalachian region during a 2-year period. We found that 96% of patients were able to tolerate amoxicillin challenge without adverse reactions. However, from the 4 truly penicillin allergic patients, only 2 were identified by skin testing (sensitivity of 50%). Oral provocation testing with amoxicillin should always be performed before eliminating the description of penicillin allergy in patients with negative skin test results using benzylpenicilloyl-poly-L-lysine and penicillin G.

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Suspected asthma status and time spent in physical activity across multiple childhood age groups



Asthma is the most common chronic condition in children worldwide; however, rates of overdiagnosis are high, particularly when the case definition is not confirmed by spirometric assessment.¹ However, it is important to encourage physical activity (PA) in children and adolescents across age groups regardless of asthma status because a physically active lifestyle is associated with many beneficial health outcomes.²

Several studies have investigated whether PA is reduced in children with asthma, but the results of these studies have been inconsistent. Some found that children with asthma ranging between the ages of 5 and 12 years were less active than their peers,^{3,4} whereas others, including one study that confirmed asthma diagnosis through spirometric testing,⁵ concluded there was no difference between children with and without asthma within the age range of 5 to 18 years.^{5–7} Our objective was to compare the amount of time spent in moderate to vigorous PA (MVPA) between children and adolescents with and without suspected asthma at 5 different ages that span the important transitory phases of childhood and adolescence.

We used data collected from the Growing Up in Australia: Longitudinal Study of Australian Children (LSAC), whose sampling and recruitment methods have previously been described.⁸ Briefly, the cohort has been followed up biennially since the initial wave of data collection in 2004 at the ages of 6, 8, 10, 12, and 14 years (waves 2, 3, 4, 5, and 6, respectively). We defined current suspected asthma status at each age as follows: (1) parental report of physician's diagnosis of asthma and (2) current wheeze and/or (3) use of asthma medications in the previous 12 months. PA was measured through the completion of a single time use diary (TUD), which indicated what the study child was doing and with whom for every 15-minute interval of a 24-hour period.⁸ For this analysis, the activities within the TUDs were graded as MVPA based on the Compendium of Energy Expenditure for Youth categorizations.⁹

Time spent in MVPA was the dependent variable, which was log transformed for linear regression analyses because of its right-skewed distribution. Univariate and multivariate analyses were undertaken, with the covariates of socioeconomic status (SES) z score, sex, and categorical body mass index (BMI) added to the models in the multivariate analyses. Interactions between sex and suspected asthma, SES z score and suspected asthma, and BMI and suspected asthma were investigated by fitting an interaction term into the adjusted linear regression model where appropriate. To accommodate for attrition from wave 1, each model was weighted using the cross-sectional sampling weights provided for the cohort.

Results of the regression model were back transformed and are presented as geometric means and 95% confidence intervals (CIs).

Of the 4,983 children initially recruited, 4464, 4332, 4169, 3956, and 3537 children participated at ages 6, 8, 10, 12, and 14 years, respectively. Female participants made up 49% of the study sample at each wave. The prevalence of suspected asthma was 16% at each follow-up between the ages of 6 and 12 years and decreased to 14% at age 14 years (Table 1). Multiple regression found no evidence of a difference in time spent in MVPA at any age between children with and without suspected asthma, after adjusting for categorical BMI, SES z score, and sex. Adjusted linear regression coefficients were 1.01 (95% CI, 0.93–1.09) at 6 years of age, 0.98 (95% CI, 0.89–1.07) at 8 years of age, 0.94 (95% CI, 0.86–1.03) at 10 years of age, 1.01 (95% CI, 0.91–1.12) at 12 years of age, and 1.04 (95% CI, 0.91–1.18) at 14 years of age. There was no evidence of effect modification by sex, BMI, or SES z score at any wave.

This large study compares PA levels across many ages for children with and without suspected asthma. Overall, we found that asthma status was not associated with time spent in MVPA at any age. These results concur with the findings of previous Brazilian and US studies in which no difference was found between children with and without asthma in the time spent in PA.^{6,7} The fact that children with suspected asthma were not less active than those without suspected asthma in our study may be related to an inaccurate asthma diagnosis, disease severity, and/or symptom control. Well-controlled suspected asthma may enable individuals to be more physically active. Hence, the lack of difference observed between children with and without suspected asthma in our analysis may be attributable to a good level of suspected asthma control within this study population or a high level of asthma overdiagnosis.

This study had several strengths, including use of the LSAC population, whose large sample size improved the statistical power of the analysis. In addition, the collection of multiple waves of data enabled us to observe the trends and changes that occur during the important transitional phase between childhood and adolescence. Conversely, this analysis had several limitations, the greatest being the lack of confirmation of the asthma diagnosis by documenting reversible airflow obstruction or methacholine hyperreactivity. Other limitations were the lack of data on asthma severity and control and loss to follow-up. To account for loss to follow-up from the initial recruitment, this analysis included a weighting variable at each wave. Another limitation is that the TUD collection of a single 24-hour TUD is limiting and may not accurately represent a child's habitual PA. However, the TUD is a validated and accepted technique that gives an indication of the amount of time spent in various activities.¹⁰