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Polygenic Threshold Model with Sex Dimorphism in Adolescent Idiopathic Scoliosis: The Carter Effect

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Background: Adolescent idiopathic scoliosis occurs between two and ten times more frequently in females than in males. The exact cause of this sex discrepancy is unknown, but it may represent a difference in susceptibility to the deformity. If this difference is attributable to genetic factors, then males with adolescent idiopathic scoliosis would need to inherit a greater number of susceptibility genes compared with females to develop the deformity. Males would also be more likely to transmit the disease to their children and to have siblings with adolescent idiopathic scoliosis. Such a phenomenon is known as the Carter effect, and the presence of such an effect would support a multifactorial threshold model of inheritance.

Methods: One hundred and forty multiplex families in which more than one individual was affected with adolescent idiopathic scoliosis were studied. These families contained 1616 individuals, including 474 individuals with adolescent idiopathic scoliosis and 1142 unaffected relatives. The rates of transmission from the 122 affected mothers and from the twenty-eight affected fathers were calculated, and the prevalence among siblings was determined in the nuclear families of affected individuals.

Results: The prevalence of adolescent idiopathic scoliosis in these multiplex families was lowest in sons of affected mothers (36%, thirty-eight of 105) and highest in daughters of affected fathers (85%, twenty-two of twenty-six). Affected fathers transmitted adolescent idiopathic scoliosis to 80% (thirty-seven) of forty-six children, whereas affected mothers transmitted it to 56% (133) of 239 children ($p < 0.001$). Siblings of affected males also had a significantly higher prevalence of adolescent idiopathic scoliosis (55%, sixty-one of 110) compared with siblings of affected females (45%, 206 of 462) ($p = 0.04$).

Conclusions: This study demonstrates the presence of the Carter effect in adolescent idiopathic scoliosis. This pattern can be explained by polygenic inheritance of adolescent idiopathic scoliosis, with a greater genetic load required for males to be affected.

Adolescent idiopathic scoliosis (AIS) is a structural curvature of the spine with an onset between the age of ten years and skeletal maturity; its prevalence is 0.2% to 3%[1]. Scoliosis may be neuromuscular, congenital, degenerative, or part of a known syndrome. Neuromuscular, hormonal, growth, and biomechanical abnormalities as well as environmental factors have been studied in patients with AIS, but none has been established as causal. Although the etiology of AIS is unknown, genetic factors are thought to contribute to the development of scoliosis.

Evidence for a genetic etiology is provided by the elevated prevalence of 6% to 11% in first-degree relatives of individuals

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A commentary by William Cole, MBBS, MSc, PhD, FRACS, FRCSC, is linked to the online version of this article at jbjs.org.

with AIS[2,3]. A meta-analysis of studies of twins revealed that 73% of monozygotic twins but only 36% of dizygotic twins were concordant for scoliosis[4]. However, a more recent population-based survey of twins revealed only 13% concordance in monozygotic twins and no concordance in dizygotic twins[5]. Studies of the inheritance pattern of AIS are also conflicting; some show evidence of multigenic or multifactorial inheritance[3,6,7], whereas others suggest autosomal dominant transmission[2,8,9], or X-linked susceptibility[10].

Genetic studies of AIS have shown linkage to many different loci throughout the genome, depending on the ethnic population studied. Wise et al. found weak evidence of linkage to three loci on chromosomes 6p and 18q and the distal portion of 10q in several Caucasian families[11], whereas others have demonstrated linkage to chromosome 17p in a large Italian family[12] and to chromosome 19p in an extended Chinese family[13]. Linkage to the chromosomal region 19p was also replicated in a separate Caucasian family[14]. Additional reported linkage peaks for AIS include regions on chromosomes 6, 9, 16, and 17[15], as well as 18q in a single family with both pectus excavatum and AIS[16]. In addition to identifying areas of linkage, several studies have provided support for different candidate genes[17] including melatonin-related receptors[18] and estrogen receptors[19,20]. The results of recently reported genome-wide association studies also suggest that AIS is weakly to modestly associated with dozens if not hundreds of common polymorphisms across the genome[21,22]. Despite numerous linkage studies, association studies, and evaluations of candidate genes, no single gene has been established to cause AIS.

No explanation has been established for the greater prevalence of AIS in females. The female-to-male ratio is approximately 2:1 for minor curves and increases progressively with increasing degree of curvature, approaching 10:1 in curves of >30°[23,24]. No ethnic population appears to be resistant to AIS[25].

The inability to identify a specific disease-causing gene as well as the sex discrepancy without sex-linked inheritance suggest a polygenic or multifactorial inheritance model with a dimorphic sex threshold for the affected phenotype. This model requires males to inherit a greater number of susceptibility genes or risk factors to develop scoliosis, and they therefore have a higher rate of transmission of the affected phenotype to their children. This is known as the Carter effect, which involves a multifactorial threshold model with sex dimorphism of inheritance[26]. Carter originally described this effect in pyloric stenosis[27], and it has also been demonstrated in clubfoot[28], multiple sclerosis[29], familial malignant melanoma[30], and atopy[31]. We hypothesized that adolescent idiopathic scoliosis is a disease with multigenic, multifactorial inheritance in which males require a higher genetic and environmental load to be affected. The existence of the Carter effect would be demonstrated by a higher rate of AIS in children and siblings of affected males compared with children and siblings of affected females.

Materials and Methods

This prognostic study was performed after approval from the Washington University Human Studies Committee, and all participants signed an approved informed-consent form. Pedigrees were constructed prospectively for probands treated at St. Louis Children's Hospital and Shriners Hospitals for Children-St. Louis between 2001 and 2009. Both patients making an initial visit and patients making follow-up visits were included. Family history was queried at all subsequent visits to capture new diagnoses and to decrease recall bias. The inclusion criteria and population description are shown in Figure 1.

Probands were considered affected if a structural curve of >20° was demonstrated on radiographs and the onset of the scoliosis was on or after the age of ten years. All patients were evaluated by one of four orthopaedic spinal deformity surgeons at Washington University. Family members were judged to be affected only if at least one of the following criteria was satisfied: radiographic evidence of a >20° curve, a history of spinal fusion surgery or bracing, evidence of a scoliometer reading of >7°, or a verbal report of deformity. The latter criterion, in which a verbal report alone was used to designate an individual as affected, was used only for individuals who were deceased or otherwise unable to be examined in person, and only thirty-four of the 474 individuals affected with AIS were designated as affected on this basis. Offspring under the age of fourteen years were excluded because their affected status could not be determined. All ethnicities were included. Individuals were excluded if they had a diagnosis known to be associated with scoliosis (e.g., Marfan syndrome), developmental delay, multiple congenital abnormalities, or known or suspected neurological abnormalities.

Multiplex families were divided into nuclear families (parents and children), and data were entered into a spreadsheet containing information about the sex and affected status of each individual's parents, siblings, and children. This spreadsheet was used to calculate transmission rates. Utilizing nuclear families allowed individuals to be represented as both a parent and a child while preventing double-counting of individuals.

Statistical Methods

A p value of <0.05 was considered significant unless otherwise noted. Sex ratios were compared with use of the Pearson chi-square test. Kruskal-Wallis one-way analysis of variance was used to determine whether affected status influenced the number of offspring. The Pearson chi-square test was used to determine whether the sex or affected status of the parents influenced the sex or affected status of their children. Transmission of scoliosis was calculated as a percentage with an associated 95% confidence interval; transmission rates were compared by calculating odds ratios with 95% confidence intervals, and the significance of differences was assessed with use of the Pearson chi-square test. All statistical analyses were performed with use of Microsoft Excel (Redmond, Washington).

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TABLE I Sex Ratios in the Study Population

Population	Female:Male Ratio	P Value*
All affected individuals	3.31:1 (364:110)	—
Affected children with unaffected parents	3.92:1 (200:51)	0.38
Affected parents	4.36:1 (122:28)	0.21
Affected children with an affected parent	2.31:1 (113:49)	0.06

*Compared with the ratio in all affected individuals.

Results

We evaluated the pedigrees of 140 families in which more than one individual was affected with adolescent idiopathic

Paradigm of selection and description of data: UA=unaffected; AF = affected with adolescent idiopathic scoliosis AIS = adolescent Idiopathic Scoliosis.

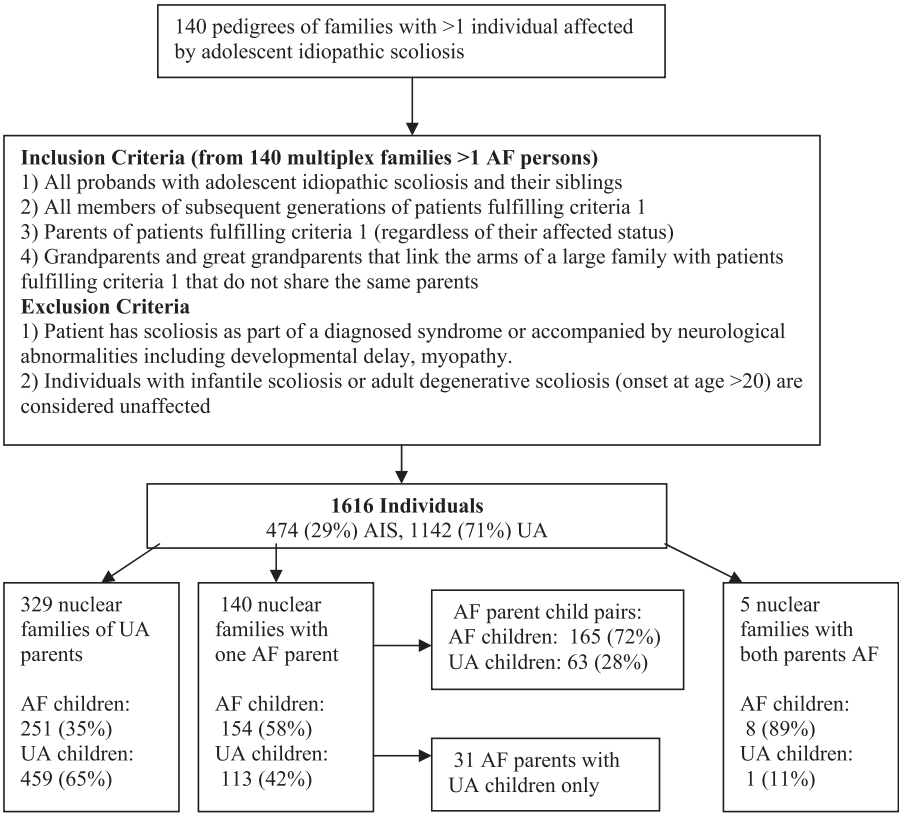

Fig. 1

Identification and description of the study population. AIS = adolescent idiopathic scoliosis, AF = affected with AIS, and UA = unaffected with AIS.

scoliosis. A total of 1616 individuals met the inclusion criteria; 474 (29%) were affected with AIS and 1142 (71%) were unaffected (Fig. 1). The mean pedigree size (and standard deviation) was 12 ± 9 individuals (range, three to forty-nine). The frequency distribution of the number of affected individuals per pedigree is shown in Figure 2. In the 149 nuclear families with one affected parent, 154 (58%) of the children were affected and 113 (42%) were unaffected. In the 329 nuclear

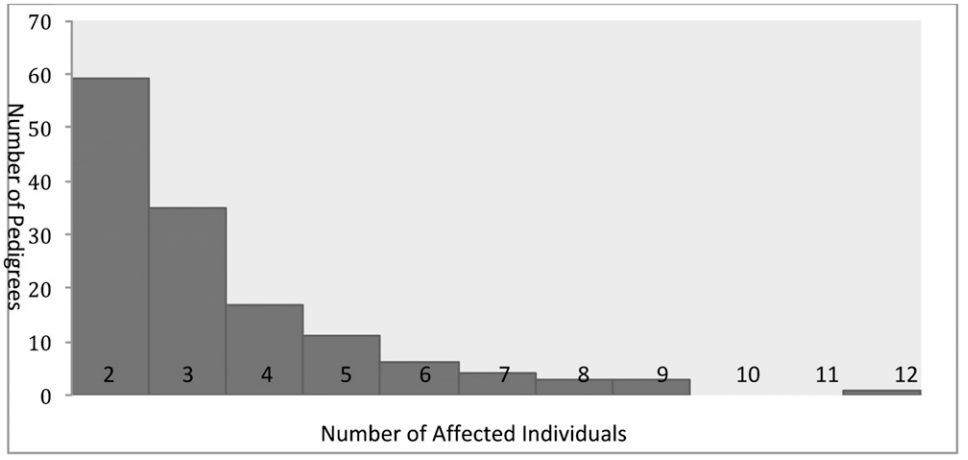

Fig. 2

Histogram of the number of affected individuals per multiplex pedigree.

TABLE II Number of Children According to the Sex and Affected Status of the Parent*

Parent	No. with 1 Child	No. with 2 Children	No. with >2 Children	Total No. of Children	No. of Children per Parent†
Unaffected					
Father	178 (40%)	154 (35%)	114 (26%)	940	2.1 ± 1.2
Mother	127 (37%)	123 (36%)	93 (27%)	747	2.2 ± 1.3
Affected					
Father	13 (46%)	10 (36%)	5 (18%)	46	1.7 ± 0.8
Mother	56 (46%)	38 (31%)	28 (23%)	232	1.9 ± 1.1

*Kruskal-Wallis one-way analysis of variance revealed no difference in the number of children according to parental type ($p = 0.90$). †The values are given as the mean and the standard deviation.

families with neither parent affected, 251 (35%) of the children were affected and 459 (65%) were unaffected. In the five nuclear families with both parents affected, eight (89%) of the nine children were affected.

The ratio of affected females to affected males was analyzed according to the affected status of their parents. None of the ratios in the subgroups differed significantly from the 3.31:1 ratio in affected individuals in the overall study population ($p > 0.05$) (Table I). The ratio of unaffected females to unaffected males was 0.80:1 (506:636). The total number of children per nuclear family did not depend on the affected status of the parents (Table II). The sex and affected status of the parent did not significantly alter the approximately 1:1 female-to-male ratio in unaffected children overall or the 3.3:1 ratio in all affected individuals in this population ($p = 0.38$ for offspring with unaffected parents and $p = 0.06$ for offspring with affected parents) (Table I).

The affected status of offspring was analyzed according to the sex and affected status of the parents to determine whether affected parents were more likely to have affected children. Affected fathers and affected mothers were both more likely than unaffected mothers and fathers to have affected male and affected female children ($p < 0.01$ for all) (Table III).

Transmission rates from affected parents to their offspring were calculated to determine the presence of the Carter effect (Table IV). Overall, affected fathers transmitted AIS to 80.4% (95% confidence interval [CI], 79.8% to 81.1%) of their children, whereas affected mothers transmitted AIS to 55.6% (95% CI, 55.4% to 55.9%; $p < 0.001$). Thus, assessed on the basis of the odds ratio, an affected father was 3.28 times (95% CI, 1.51 to 7.09 times) more likely than an affected mother to have an affected child. When female children were analyzed separately, 84.6% (95% CI, 83.7% to 85.6%) of those with affected fathers were affected compared with 70.9% (95% CI, 70.6% to 71.2%) of those with affected mothers. This increase in the risk of transmission to daughters from affected fathers compared with affected mothers did not reach significance ($p = 0.15$). However, when males were analyzed separately, 75.0% (95% CI, 73.3% to 76.8%) of those with affected fathers were affected compared with 36.2% (95% CI, 35.8% to 36.6%) of those with affected mothers. This represents a 5.29-fold (95% CI, 1.78 to 15.7-fold) increased risk of transmission of AIS to males from affected fathers compared with affected mothers.

The prevalence of AIS in siblings of affected individuals was also determined (Table V). Overall, 55.5% (95% CI, 55.0% to 56.0%) of siblings with an affected brother were affected compared with 44.6% (95% CI, 44.5% to 44.7%) of siblings with an affected sister. This represents a 1.55-fold increased risk of AIS in siblings of an affected male compared with an affected female ($p = 0.04$). When this result was analyzed according to sex, 77.1% (95% CI, 76.3% to 77.7%) of sisters of affected males

TABLE III Relationship Between Sex and Affected Status of the Parents and Children

	Father (N = 474)			Mother (N = 465)		
	Affected (N = 28)	Unaffected (N = 446)	P Value	Affected (N = 122)	Unaffected (N = 343)	P Value
Female children			<0.001			<0.001
No. affected	22/26 (85%)	291/558 (52%)		95/134 (71%)	218/450 (48%)	
No. unaffected	4	267		39	232	
Male children			<0.001			<0.01
No. affected	15/20 (75%)	85/382 (22%)		38/105 (36%)	62/297 (21%)	
No. unaffected	5	297		67	235	

TABLE IV Transmission from Affected Parents to Children

	No. to Whom Scoliosis Transmitted	No. to Whom Scoliosis Not Transmitted	P Value	Male:Female Odds Ratio of Transmission	95% Confidence Interval
All children			<0.001	3.28	1.51 to 7.09
Father affected	37/46 (80%)	9			79.8% to 81.1%
Mother affected	133/239 (56%)	106			54.5% to 57.1%
Female children			0.15	2.26	0.73 to 6.98
Father affected	22/26 (85%)	4			83.7% to 85.6%
Mother affected	95/134 (71%)	39			70.6% to 71.2%
Male children			<0.001	5.29	1.78 to 15.69
Father affected	15/20 (75%)	5			73.3% to 76.8%
Mother affected	38/105 (36%)	67			35.8% to 36.6%

TABLE V Affected Status According to Status of Siblings

	No. of Siblings Affected	No. of Siblings Unaffected	P Value	Male:Female Odds Ratio	95% Confidence Interval
All siblings			0.04	1.55	1.02 to 2.35
Brother affected	61/110 (55.5%)	49			55.0% to 55.9%
Sister affected	206/462 (44.6%)	256			44.5% to 44.7%
Female siblings			0.01	2.26	1.10 to 4.60
Brother affected	37/48 (77.1%)	11			76.3% to 77.7%
Sister affected	170/284 (60.0%)	114			59.8% to 60.2%
Male siblings			0.002	2.49	1.43 to 4.36
Brother affected	24/62 (38.7%)	38			38.0% to 39.4%
Sister affected	36/178 (20.2%)	142			20.0% to 20.4%

had AIS compared with 60.0% (95% CI, 59.8% to 60.2%) of sisters of affected females. This represents a 2.26-fold increased risk of AIS in sisters with an affected brother compared with sisters with an affected sister ($p = 0.01$). Finally, 38.7% (95% CI, 38.0% to 39.4%) of males with an affected brother and 20.2% (95% CI, 20.0% to 20.4%) of males with an affected sister were affected, representing a 2.49-fold increased risk of AIS in brothers of affected males compared with brothers of affected females ($p = 0.002$).

Discussion

Much effort has been put forth to determine the inheritance of AIS, including research to identify a specific causative gene. No single gene has been found, and genome-wide association studies and other linkage analyses have shown evidence for the involvement of numerous different areas in the human genome in the etiology of AIS. This suggests a multifactorial threshold model of inheritance. Our data support the existence of the Carter effect in AIS since males, who are less commonly affected with AIS, appeared to require a greater genetic load to become affected and were therefore more likely to transmit the disorder to their offspring[27]. Specifically, males with AIS were 3.28 times more likely than females with AIS to transmit AIS to their children ($p < 0.001$).

Ward et al. demonstrated evidence for a polygenic model of inheritance of AIS that was independent of curve type and severity, as well as evidence for over-transmission from males, consistent with the Carter effect[7]. Further evidence for polygenic inheritance can be extracted from a study by Riseborough and Wynne-Davies; 15.8% of the first-degree relatives of individuals with scoliosis were affected compared with 2.4% of second-degree relatives and 1.4% of third-degree relatives[3]. Since individuals who are more closely related are expected to inherit genes that are more similar, they will have a higher prevalence of a polygenic inherited trait compared with more distantly related individuals who share fewer genes.

The Carter effect assumes that there is a greater threshold for disease expression in the less affected sex, but the mechanism of this greater threshold is not specified. The difference in threshold in AIS could be due to multiple environmental or genetic factors.

The hormonal factors that are present, especially the changing hormonal environment during adolescence, may contribute to the differential threshold between males and females for AIS development. Several studies have indicated an association between estrogen receptor polymorphisms and scoliosis[19,20], and another study indicated that girls with scoliosis had a tendency toward later menarche compared with girls who did not develop

scoliosis[32]. Lower bone mineral density and disturbances in bone metabolism have also been related to AIS[33-37]; the structural differences between males and females could contribute to the sex dimorphism of scoliosis. One study indicated that decreased differentiation ability of mesenchymal stem cells may contribute to osteopenia in individuals with AIS[38]. Environmental factors such as diet, calcium intake, vitamin-D level, and exercise have been related to AIS[39,40]. A greater threshold for disease expression in males may also explain why AIS appears to skip generations in some families, particularly when passed through unaffected males.

One limitation of this study is the absence of direct radiographic confirmation of the scoliosis diagnosis and severity for a small number of affected distant relatives in certain of the pedigrees. In these cases, the diagnosis was made on the basis of either a physical examination or a review of medical and radiographic reports, which may be less reliable. However, since our data are consistent with previously reported sex ratios in affected individuals, we believe that the probability of this limitation altering our results is low[23,24]. In addition, the lack of curve measurements for some of the family members prevented us from determining whether severity correlated with heritability. In the study by Ward et al., heritability of severity and of the type of curve occurred separately[7].

Our results are consistent with the Carter effect, as transmission of AIS was lowest in sons of affected mothers (36%) and greatest in daughters of affected fathers (85%). Additionally, sisters of affected males were much more likely to be affected (77%) compared with brothers of affected females (20%). This information is useful in monitoring children and siblings of affected individuals and in advising families regarding the risk of their other children developing AIS. It should be noted, however, that our data apply only to multiplex families since simplex families (families in which only a single individual was affected with AIS) were excluded from our study; our data would therefore appear to inflate the overall risk to siblings and children of individuals with AIS. Additional parameters, including curve severity and family history, likely need to be considered in individual families to more precisely predict the risk of developing AIS. Ideally, a genetic profile consisting of both common risk polymorphisms and rare gene mutations will eventually be used to predict AIS risk and severity, although the role of environmental factors in determining the outcome remains uncertain. In addition to identifying the genes responsible for AIS susceptibility, future studies will need to evaluate the synergistic effect of genetics and environment on the development of AIS. ■

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