

Familial Clustering of Hemangiomas

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Objectives: To assess the degree of relationship among individuals with hemangiomas and to evaluate the relative risk (RR) for family members of individuals with hemangiomas.

Design: Retrospective case-control study.

Setting: Utah Population Database.

Participants: Data sets of individuals of different ages with *International Classification of Diseases, Ninth Revision (ICD-9)* codes for hemangiomas were created from sources having medical records linked to the Utah Population Database. Controls were selected who matched cases for sex, birth year, and birthplace inside vs outside of Utah. Ten controls were selected per case, and sampling was performed without replacement. Kinship analysis tools were used to identify pedigrees having excess individuals with hemangiomas.

Main Outcome Measure: Using conditional logistic regression analysis, RR for hemangiomas among several kinship classes was determined.

Results: Identified were 2514 distinct cases 12 years or younger with ICD-9 code 228.01, and the RR for sibs in this group was significantly increased (RR, 2.52; $P < .001$). Seventy-three founder families had 5 or more affected descendants with cluster P values $\leq .01$; familial standardized incidence ratios ranged from 1.64 to 9.50. Family sizes ranged from 546 to 22 291 descendants.

Conclusions: Sibs have increased RR for infantile hemangiomas, suggesting a potential genetic contribution to this likely multifactorial disease. Identification of large families with distantly related individuals will be helpful for future shared segment identification analyses.

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INFANTILE HEMANGIOMA IS A BENIGN vascular tumor and is the most common head and neck tumor of infancy. Usually not present at birth, infantile hemangiomas grow rapidly in the first year of life and then typically regress, requiring no intervention. However, infantile hemangiomas in some instances can cause significant morbidity, including deformity, cardiac failure, functional impairment, and airway and alimentary obstruction.^{1,2} Reported risk factors include female sex, prematurity, white race, and chorionic villus sampling.³⁻⁷

The incidence of infantile hemangiomas among individuals of white race is between 9% and 13%.^{3,6} Most infantile hemangiomas are sporadic, although there are reports of families with multiple affected individuals.^{8,9} There may be a genetic contribution to the development of hemangiomas. To assess the degree of relationship among individuals with hemangiomas and to evaluate the relative risk (RR) for family members of individuals with hem-

angiomas, we used the Utah Population Database (UPDB), a unique computerized resource linking electronic medical records and pedigrees.

METHODS

UTAH POPULATION DATABASE

A central component of the UPDB is its extensive set of Utah family histories, in which family members are linked to demographic and medical information representing more than 6 million individuals. The UPDB includes genealogies of the founders of Utah and their Utah descendants, as well as statewide information from driver license records, the Utah cancer registry, Utah hospital inpatient records, and vital records (births, marriages, and deaths). Most Utah families are represented, and some have as many as 11 generations.¹⁰

Data sets were created using Utah hospital inpatient records and records from the University of Utah Health Sciences Center and Intermountain Healthcare Enterprise Data Warehouses. These data have been linked to the UPDB.¹¹ The use of 2 sources in addition to Utah

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Table 1. Individuals With Hemangiomas

Age, y	University of Utah Health Sciences Center	Intermountain Healthcare	Utah Hospital Inpatient Records	Total Cases	Distinct Cases
≤5 ^a	1328	681	1240	3249	2798
≤12 ^b	1156	596	1062	2814	2514
Years covered	1991-2008	1994-2009	1995-2008		

^aCases 5 years or younger at the first record of diagnosis for *International Classification of Diseases, Ninth Revision (ICD-9)* codes 228.0, 228.00, 228.01, and 228.09.

^bCases 12 years or younger at the first record of diagnosis for *ICD-9* code 228.01.

Table 2. Age Distribution of Distinct Cases With Hemangiomas

Age, y	Age ≤5 y ^a	Age ≤12 y ^b
0 to <1	972	842
1	1451	1112
2	145	113
3	92	69
4	83	57
5	55	38
6 to 12	Not applicable	283
Total	2798	2514

^aCases 5 years or younger at the first record of diagnosis for *International Classification of Diseases, Ninth Revision (ICD-9)* codes 228.0, 228.00, 228.01, and 228.09.

^bCases 12 years or younger at the first record of diagnosis for *ICD-9* code 228.01.

Table 3. Utah Population Database Logistic Regression Kinship Analysis

Relationship	Relative Risk (95% Confidence Interval)	P Value
	Age ≤5 y^a	
Sibs	2.28 (1.50-3.49)	<.001
First cousins	1.35 (0.98-1.84)	.06
	Age ≤12 y^b	
Sibs	2.52 (1.58-4.02)	<.001
First cousins	1.13 (0.78-1.64)	.53

^aCases 5 years or younger at the first record of diagnosis for *International Classification of Diseases, Ninth Revision (ICD-9)* codes 228.0, 228.00, 228.01, and 228.09.

^bCases 12 years or younger at the first record of diagnosis for *ICD-9* code 228.01.

hospital inpatient records is a particular strength of our study, likely capturing most of the Utah population. Individuals with records in multiple sources were counted only once to identify distinct cases. *International Classification of Diseases, Ninth Revision (ICD-9)* codes were used to identify individuals with hemangiomas. Attempts were made to select the most appropriate *ICD-9* codes that correlate with infantile hemangiomas, including the following: 228.0 (hemangioma of any site), 228.00 (hemangioma of unspecified site), 228.01 (hemangioma of skin and subcutaneous tissue), and 228.09 (hemangioma of other sites). Two analytic data sets were created from the sources. Given that infantile hemangiomas are typically not present at birth, birth certificates were not used to identify cases.

The first data set was created using individuals with *ICD-9* code 228.01 who were 12 years or younger at the first record of diagnosis. The rationale for creating a data set using only code 228.01 was based on the assumption that hemangiomas of the skin and subcutaneous tissues were most likely infantile hemangiomas compared with the other *ICD-9* codes that are less specific to location.

The second data set was created using individuals with *ICD-9* codes 228.0, 228.00, 228.01, and 228.09 who were 5 years or younger at the first record of diagnosis. The *ICD-9* codes with less specific information on location of the hemangiomas were included in this data set. To minimize potential misdiagnosis in a data set that included data with limited information on location of the hemangiomas, the second data set comprised only individuals who were 5 years or younger at the first record of diagnosis given that infantile hemangiomas are typically present in younger individuals.

This study was approved by the institutional review boards of the University of Utah and Intermountain Healthcare Utah Resource for Genetic and Epidemiologic Research, which oversees the use of the UPDB, also gave approval.

STATISTICAL ANALYSIS

Analytical tools for familial analysis were used as previously described.¹²⁻¹⁵ Controls were selected who matched cases on sex, birth year, and birthplace inside vs outside of Utah. Ten controls were selected per case, and sampling was performed without replacement. The set of cases and controls was used to compute RRs for several kinship classes by conditional logistic regression analysis as previously described.¹⁶

Pedigrees having excess individuals with hemangiomas were identified using kinship analysis tools as previously described, and statistics were computed (eg, *P* value, familial standardized incidence ratio, numbers of descendants among founder pedigrees, and observed and expected numbers of affected individuals).¹⁶ Families were required to contain at least 5 affected individuals in a pedigree with significant clustering ($P \leq .01$).

RESULTS

DATA SET 1 (ICD-9 CODE 228.01 AND ≤12 YEARS)

In the first data set, 2514 distinct cases were identified (**Table 1**). Most individuals had the first record of diagnosis at 1 year or younger (**Table 2**). Sixty-three percent ($n=1571$) of cases were female. The RR for hemangiomas was significantly increased among sibs (RR, 2.52; $P < .001$) (**Table 3**). There was a 13% increase in risk for hemangiomas among first cousins of probands with hemangiomas, but this did not reach statistical significance ($P = .53$).

Seventy-three founder families had 5 or more affected descendants with significant clustering ($P \leq .01$).

Familial standardized incidence ratios ranged from 1.64 to 9.50. Family sizes ranged from 546 to 22 291 descendants. The founder families are not necessarily unique and can have considerable overlap among descendants.

DATA SET 2 (ICD-9 CODES 228.0, 228.00, 228.01, AND 228.09 AND ≤5 YEARS)

In the second data set, 2798 distinct cases were identified (Table 1). Most individuals had the first record of diagnosis at 1 year or younger (Table 2). Girls (n=1782) outnumbered boys (n=1016). The RR for hemangiomas was significantly increased among sibs (RR, 2.28; $P < .001$) (Table 3). There was a 35% increase in risk for hemangiomas among first cousins of probands with hemangiomas, but this did not reach statistical significance ($P = .06$).

Eighty-eight founder families had 5 or more affected descendants with significant clustering ($P \leq .01$). Familial standardized incidence ratios ranged from 1.57 to 8.39. Family size ranges were the same as for the first data set. Examples of selected pedigrees from both data sets are shown in the **Figure**.

COMMENT

The origin of infantile hemangiomas is likely heterogeneous and multifactorial. Sibs of individuals with hemangiomas had a 2-fold increased risk for the development of hemangiomas. The familial clustering reported herein may represent genetic, epigenetic, or environmental factors. For example, prematurity has been associated with the development of hemangiomas, and women with medical reasons for recurrent premature deliveries may have an increased risk for hemangiomas among their nuclear family.^{3,7} A genetic contribution is independently supported by reports of several families with an apparent autosomal dominant inheritance pattern.^{8,9}

Alterations of genes within the germline likely predispose some individuals to the development of hemangiomas.^{8,17} In addition, somatic mutations or allelic loss of genes associated with vasculogenesis may be necessary for the development of hemangiomas.¹⁸⁻²⁰ Secondary somatic events are likely necessary for expression of the phenotype, which may explain the sporadic and non-mendelian pattern of expression in most cases.

A unique aspect of the UPDB is the ability to search for familial relatedness beyond the nuclear family. As evidenced by several pedigrees (Figure), large families with a common ancestor were identified in which individuals might not have been aware of their more distantly related relatives. Such families are a rich source for future whole-genome sequencing studies looking for areas of shared genomic segments.

One limitation is that our data are reliant on the accuracy of diagnostic codes. It is likely that some individuals in our data sets have vascular anomalies that are not infantile hemangiomas. We attempted to minimize misdiagnosis by restricting age at the first record of diagnosis within the respective data warehouses to younger individuals, as this correlates with the natural history of infantile hemangiomas. Furthermore, the incidence of in-

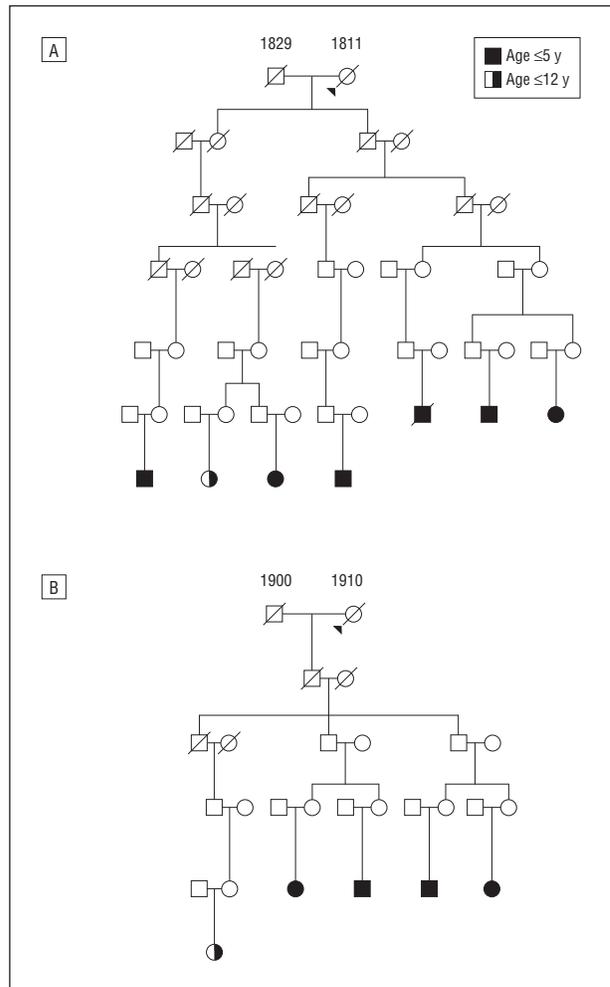


Figure. Two kindreds having multiple members with hemangiomas. Full-shaded symbols indicate individuals with hemangiomas who were 5 years or younger at the first record of diagnosis. Half-shaded symbols indicate individuals with hemangiomas who were 12 years or younger at the first record of diagnosis. Pedigrees have been trimmed for space. Squares indicate males; circles, females; slash, deceased; and arrowhead, proband. A, The actual number of descendants is 348 with founders dating back to 1829 and 1811. B, The actual number of descendants is 222 with founders dating back to 1900 and 1910.

fantile hemangiomas among individuals of white race is between 9% and 13%,^{3,6} as described earlier. Venous malformations and port-wine stains, 2 lesions commonly misdiagnosed as infantile hemangiomas, have a much lower incidence. For example, venous malformations occur in 1 of 5000 to 10 000 births, rendering the number of misdiagnosed venous malformations in our data sets likely small compared with actual infantile hemangiomas.²¹ Most other common capillary malformations, such as “stork bites” and “angel kisses,” would likely not have been excluded because these do not cause morbidity or require medical intervention prompting a physician to list a diagnostic code. However, based on this same reasoning, the inclusion of seemingly insignificant hemangiomas may also be limited, with a bias toward more severe cases.

The vast amount of genealogical information in the UPDB allows for the creation of large pedigrees. The clinical information of older individuals within pedigrees is unavailable given the restricted availability years of clini-

cal data from the various data warehouses (Table 1). Because we restricted cases to those 12 years or younger in the first data set and 5 years or younger in the second data set based on the natural history of presentation age and regression of infantile hemangiomas, older individuals who may have a history of infantile hemangioma would not have been identified as affected when drawing the pedigrees. However, this situation is similar in our statistical analysis for both the case and control groups.

In summary, there is a 2-fold increased RR for hemangiomas among sibs of an affected proband. Future studies to identify associated genes may provide pathogenetic insights that will be helpful for shared segment identification analyses and the development of specific interventions.

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