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Beyond Li Fraumeni Syndrome: Clinical Characteristics of Families With *p53* Germline Mutations

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ABSTRACT

Purpose

A clinical testing cohort was used to gain a broader understanding of the spectrum of tumors associated with germline *p53* mutations to aid clinicians in identifying high-risk families.

Patients and Methods

Full sequencing of the coding exons (2 to 11) and associated splice junctions of the *p53* gene was performed on 525 consecutive patients whose blood samples were submitted for diagnostic testing. Clinical features of *p53* germline carriers in this cohort were characterized, clinical referral schemes based on reported *p53*-associated family phenotypes were evaluated, and practical mutation prevalence tables were generated.

Results

Mutations were identified in 91 (17%) of 525 patients submitted for testing. All families with a *p53* mutation had at least one family member with a sarcoma, breast, brain, or adrenocortical carcinoma (ACC). Every individual with a choroid plexus tumor (eight of eight) and 14 of 21 individuals with a childhood ACC had a mutation regardless of family history. Based on reported personal and family history, 95% of patients (71 of 75) with a mutation met either classic Li Fraumeni syndrome (LFS) or Chompret criteria. A simplified prevalence table provides a concise summary of individual and family characteristics associated with *p53* mutations.

Conclusion

This is, to our knowledge, the largest single report of diagnostic testing for germline *p53* mutations, yielding practical mutation prevalence tables and suggesting clinical utility of classic LFS and Chompret criteria for identifying a subset of cancer-prone families with *p53* germline mutations, with important implications for diagnosis and management.

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INTRODUCTION

Li Fraumeni syndrome (LFS; OMIM #151623) is an autosomal dominant highly penetrant cancer predisposition syndrome characterized by a variety of early onset tumors. The syndrome, described in 1969 by Li and Fraumeni based on a retrospective analysis of families with childhood rhabdomyosarcoma,[1] was characterized by the presence of five cancers: sarcoma, adrenocortical carcinoma (ACC), breast cancer, leukemia, and brain tumors.[2,3] LFS is associated with germline mutations in the *p53* gene, which codes for a transcription factor implicated in cell proliferation, apoptosis, and genomic stability.[4-6] The penetrance of *p53*-mediated cancer is high and is more pronounced in women than in men (lifetime risk, 93% and 68%, respectively), primarily due to female breast cancer.[7] Females also have an earlier average age of onset (29 years of age in women *v* 40 years of age in men).[8]

Several criteria have been developed to identify families at risk for a germline *p53* mutation (Table 1). Classic LFS was based on 24 families.[2] More inclusive clinical classification schemes were described by Birch[9] and Eeles in 1995 to 1996, which characterized Li Fraumeni–like syndrome (LFL) as having "features of the Li Fraumeni syndrome" but that did not "fulfill the strict definition."[9,10] The classic LFS, Birch, and Eeles criteria are generally used in clinical practice. More recently, Chompret at al[11,12] developed alternative criteria for identifying patients with *p53* germline mutations. The Chompret criteria are more restrictive on the cancer types and ages of onset for the proband, but allow for the possibility of a negative family history (Table 1).

Table 1. Description of the Established Clinical Classification Schemes for LFS

Classification Scheme	Description
Classic LFS[2]	Proband diagnosed with sarcoma before 45 years of age, and
	A first-degree relative with cancer before 45 years of age, and
	Another first- or second-degree relative with any cancer diagnosed under 45 years of age or with sarcoma at any age
Chompret[11,12]	Proband with sarcoma, brain tumor, breast cancer, or adrenocortical carcinoma before age 36 years, and at least one first- or second-degree relative with cancer (other than breast cancer if the proband has breast cancer) under the age of 46 years or a relative with multiple primaries at any age, or a proband with multiple primary tumors, two of which are sarcoma, brain tumor, breast cancer, and/or adrenocortical carcinoma, with the initial cancer occuring before the age of 36 years, regardless of the family history
	Or, a proband with adrenocortical carcinoma at any age of onset, regardless of the family history
Birch[9]	Among families that do not conform to classic LFS:
	Proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed under 45 years of age, and
	A first- or second-degree relative with a typical LFS-related cancer (sarcoma, breast cancer, brain tumor, leukemia, or adrenocortical carcinoma) diagnosed at any age, and
	A first- or second-degree relative in the same genetic lineage with any cancer diagnosed under the age of 60 years
Eeles[10]	Among families that do not conform to classic LFS:
	Two different tumors that are part of extended LFS in first- or second-degree relatives at any age (sarcoma, breast cancer, brain tumor, leukemia, adrenocortical tumor, melanoma, prostate cancer, and pancreatic cancer)

Abbreviation: LFS, Li Fraumeni syndrome.

Although *p53* mutations have been characterized in single institution studies or research cohorts,[3,13-18] the performance of the classification criteria or the prevalence of *p53* mutations in a clinical testing cohort is unknown. Using family histories and genetic analysis of *p53* from the largest cohort evaluated at a single reference laboratory (Clinical Molecular Diagnostic Laboratory [CMDL] at City of Hope Medical Center, Duarte, CA), we present a detailed analysis of the utility of existing clinical classification schemes and provide mutation prevalence tables to aid in the diagnosis of patients with germline *p53* mutations.

PATIENTS AND METHODS

Genotyping p53

DNA from 525 patient samples, sent to the CMDL at City of Hope, was analyzed for *p53* mutations extracted from peripheral blood samples and, in rare cases, from processed DNA. All coding exons (2 to 11) and junctions of the *p53* gene were analyzed in both directions by direct DNA sequencing using an automated fluorescent sequencer.

Interpretation of p53 Sequence Changes

Truncating mutations were scored as deleterious while missense mutations were scored as deleterious based on previous reports in the International Agency for Research in Cancer germline and somatic databases,[19] evolutionary conservation, and available functional data. CMDL uses the epidiomics approach to molecular diagnosis, in that all cases are interpreted in the context of molecular epidemiology and bioinformatics in order to guide the physician in the age of personalized predictive and preventive medicine.

Clinical Data

Personal and family cancer histories were collected from test request forms supplied with the biospecimens. The data collected included tumor type and age of onset for the patients and their family members. Information for affected family members included sex, tumor type, age of onset, number of primary cancers, and relationship to patient tested. Details of germline mutations were provided by the diagnostic laboratory.

Classification of Patients Sent for p53 Testing

In total, 341 of 525 patient samples (75 *p53* positive and 266 *p53* negative) were accompanied by sufficient family history (at least a three generation pedigree including types of cancer and ages of onset) to be classified according to the following classification schema: classic LFS, Birch, Eeles, and/or Chompret (Table 1). Standard classification criteria were used (International Agency for Research in Cancer; www-*p53*.iarc.fr), as in previous studies.[4,9,14,15,19,20] As necessary to conform to the various schema, proband was designated as either the patient tested or a first- or second-degree relative (based on the type and age of the cancer).

Data Analysis

Sensitivity and specificity were estimated as the respective fractions of all classified *p53*-positive or *p53*-negative patients for each of the four classification schema: classic LFS, Chompret, Birch, and Eeles. An analysis of the cumulative yield of these schema was also derived in the same order without overlap. Because the data are consecutive referrals to a clinical laboratory, the empirical estimates of the prevalence of *p53* mutations in clinical samples were regarded as estimates of the predictive value of the classification schema. The clinical prevalence of *p53* mutations was also determined based on types of cancer and ages of onset in the patient and their family members. Fisher's exact tests and rank-sum tests were computed using StatXact (CYTEL Software Corp, Cambridge, MA).

RESULTS

Patient Characteristics

Characteristics of patients tested are described in Table 2. Mutations were identified in 91 (17%) of 525 patients tested. The number of patients meeting a given classification scheme is indicated. Many patients met more than one classification scheme. The majority met Chompret and/or Eeles classification (57% and 60%, respectively); 13% of patients did not meet the criteria for any classification scheme. Breast cancer was the most common cancer among patients tested, accounting for 35% of all primary tumors while multiple primary cancers were also found in 35% of patients.

Performance of Current Classification Schema

Among the 341 classified patients, the *p53* mutation detection rate for patients meeting classic LFS was 56%, with a sensitivity of 40% and a specificity of 91% (Table 3). The Chompret classification detection rate was 36%. The LFL classification (Birch and Eeles), which by definition excludes patients meeting classic LFS, showed detection

Table 2. Patients' Clinical Characteristics		
	Patients Sent for *p53* Germline Testing	
Characteristic	No.	%
Patients with deleterious mutations	91/525	17
No. of families clinically categorized		
Classic Li Fraumeni syndrome[2]	54/341	16
Chompret[11,12]	195/341	57
Birch[9]	101/341	30
Eeles[10]	205/341	60
Patient's family does not meet any clinical classification	45/341	13
Average age of onset of first primary cancer	29.7*	
Cancer type (all primary cancers)		
Breast cancer	209/596†	35
Sarcoma	153/596†	26
Brain	37/596†	6
Adrenocortical carcinoma	21/596†	4
Other	176/596†	30
Average number of primary cancers		
≤ 1 primary tumor‡	252/390§	65
≥ 2 primary tumors	138/390§	35

*Age of onset was provided for a total of 379 patients.
†Cancer type was known for a total of 380 patients; there was a total of 596 tumors in these 380 patients.
‡Ten patients sent for testing had no primary cancers.
§Total of 390 patients (380 with cancer and 10 without cancer).

only). Of the four reported ovarian cancers, one was a germ cell cancer, one a teratoma, while the other two did not specify pathologic subtype. The four core cancers (breast cancer, sarcoma, brain cancer, ACC) accounted for 77% of all associated cancers. The median and average ages of onset of cancer varied with cancer type: ACC and choroid plexus carcinoma were among the earliest while melanoma and prostate cancer were among the latest ages of onset (data not shown).

Four Core Cancers Help Define "p53-opathy"

All *p53*-positive patients had at least one member of the family with sarcoma, brain tumor, breast cancer, or ACC. No *p53* mutations (zero of 21) were detected in families where no members have a core cancer under the age of 50 (Table 5). Sarcoma, brain tumor, breast cancer, and ACC were therefore referred to as germline *p53* core cancers.

Choroid Plexus Tumor Is Strongly Associated With Germline p53 Mutations

Eight patients with choroid plexus tumor (CPC) were referred for sequencing of the *p53* gene. These patients all had a negative family history among ancestors and very young ages of onset. An additional individual with four primary cancers who had a grandson with CPC was sent for testing. Among these nine patients, clinical classification was determined only for seven as insufficient family history information was provided for two patients. Three of seven classified patients met the Chompret classification alone, two met both Chompret and Eeles classifications, one met Chompret and classic LFS, and one patient did not meet any classification. All nine patients (100%) had identifiable mutations. Two patients, both meeting only the Chompret classification, had de novo mutations as determined by of absence of the *p53* mutation in both biologic parents (data not shown).

ACC Is a Strong Indicator of a p53 Germline Mutation

Of the 21 patients with ACC that were sent for *p53* testing, 14 had a *p53* mutation (67%). All patients with ACC at any age of onset, regardless of family history, meet the Chompret criteria (Table 1). Among the 14 positive patients, seven met Chompret alone; two also met classic LFS, and four also met Eeles. One patient could not be classified due to insufficient family history. None of the patients with ACC met Birch. Three of seven patients, diagnosed with ACC at ages

rates of 16% and 14%, respectively. Classic LFS and Chompret criteria together conferred a testing sensitivity of 95% and a specificity of 52%. When examining clinical classification based on a hierarchy, only one additional case was identified by each of the LFL criteria (Birch and Eeles).

p53 Is Associated With a Wide Spectrum of Cancers

Some cancer types not typically associated with LFS (eg, cancers of the ovary, pancreas, and prostate) were observed in patients with germline *p53* mutations (Table 4). This wide spectrum of cancers was also observed among pediatric cancers (Appendix Table A1, online

Table 3. Likelihood of Detecting a Mutation Based on Current Clinical Classification Schemes								
	Families Meeting Individual Criteria			Cumulative (including all families meeting criteria in previous rows)*				
		With *p53* Mutations			With *p53* Mutations			
Criteria	No. of Families	No.	%	No. of Families	No.	%	Sensitivity† (%)	Specificity‡ (%)
Classic LFS[2]	54	30	56	54	30	56	40	91
Chompret[11,12]	195	69	35	199	71	36	95	52
Birch[9]	101§	16	16	238	72	30	96	38
Eeles[10]	205§	29	14	296	73	25	97	16
Families meeting no criteria	45	2	4	341	75	22	100	0

Abbreviation: LFS, Li Fraumeni syndrome.
*Each category includes patients from the criteria within that row in addition to all patients from the criteria in the previous rows.
†Sensitivity: No. of positive patients meeting criteria/75 total positive patients (× 100).
‡Specificity: 1 − (No. of negative patients meeting criteria/266 total negative patients [× 100]).
§Does not include families that meet classic LFS.

Table 4. Spectrum of Cancers in Patients With Germline *p53* Mutations Submitted for Testing

Cancer in Patients With *p53* Mutations*	All Primary Tumors		Female			Male		
	No.	%	No. of Cases	Average Age (years)	Age Range (years)	No. of Cases	Average Age (years)	Age Range (years)
Breast	44	31.2	44	31.9	18-51	0		
Sarcoma	38	27.0	25	26.6	2-59	13	20.8	0.8-46
Adrenocortical carcinoma	14	9.9	11	11.5	0.5-38	3	3	2-3.5
Choroid plexus tumor	8	5.7	4	1.9	0.3-3	4	15.3	3-40
Brain (excluding choroid plexus)	5	3.5	4	19.8	3-29	1	14	
Colon	4	2.8	4	38.5	15-58	0		
Leukemia	4	2.8	3	36	12-69	1	17	
Lung	4	2.8	4	46.8	41-53	0		
Skin (excluding melanoma)	4	2.8	2	41	40-42	2	39.5	35-44
Ovary†	4	2.8	4	32.3	11-53			
Breast (phyllodes)	2	1.4	2	18.5	15-22	0		
Adrenal	2	1.4	2	4.5	3-6	0		
Lymphoma	2	1.4	2	12	10-14	0		
Thyroid	2	1.4	2	37.5	37-38	0		
Bone	1	0.7	1	29		0		
Melanoma	1	0.7	1	50		0		
Pancreas	1	0.7	0			1	60	
Prostate	1	0.7				1	44	
Total‡	141		115	27.5	0.3-69	26	21.3	0.8-60
Total excluding sex-specific cancers§	90		65	24.5	0.3-69	25	20.4	0.8-60

*Other cancer types in family members under the age of 50 years. Include cancers of the liver, adrenal gland, cervix, esophagus, stomach, abdomen, bone, heart, schwannoma, testis, thymus, and uterus.
†One of the ovarian cancers is a germ cell tumor, one a teratoma; the other two are of unknown type.
‡Total of 141 tumors in 82 patients tested (cancer type only known for 82 of 91 positive patients).
§Sex-specific cancers: prostate, ovarian, and breast (male breast cancer has never been reported in Li Fraumeni syndrome).

0.5, 1.33, and 2 years, were confirmed de novo mutation carriers as determined by the absence of the *p53* mutation in both biologic parents (data not shown). Of patients with ACC younger than 18 years old, 80% had a *p53* mutation (12 of 15), regardless of family history.

Breast Cancer Prevalence

Family history plays a major role in whether or not a breast cancer patient has a *p53* mutation. A patient with invasive breast cancer between ages 30 and 49 years and a family history with no

Table 5. Prevalence of *p53* Mutations

	Cancer in First- and Second-Degree Relatives Younger Than 50 Years of Age							
	No Core* Cancer in Any Family Members		Only One Family Member With at Least One Core Cancer; No Cancer in Any Other Relatives		Only One Family Member With at Least One Core Cancer and One or More Family Members With a Non-Core Cancer		Two or More Family Members With Core Cancers	
Patient Tested	No.	%	No.	%	No.	%	No.	%
No core cancer at any age	0/21	0	1/8	13	1/10	10	2/15	13
Only one core cancer, occurring at age > 40 years	1/18	6	0/12	0	0/9	0	5/24	21
Only one core cancer, occurring at age ≥ 18 and ≤ 40 years	2/43	5	1/15	7	2/21	10	16/28	57
At least one childhood core cancer, occurring at age < 18 years†	16/49	33	5/10	50	5/5	100	3/8	38
Two or more core cancers, both occurring at age > 40 years	0/7	0	0/3	0	2/3	67	0/2	0
Two or more core cancers, at least one occurring at age ≤ 40 years	3/14	21	2/6	33	1/2	50	7/8	88

*Core cancers are adrenocortical carcinoma, breast cancer, brain cancer, and sarcoma.
†Patients with childhood cancers as well as adult cancers fall into this category.

core cancers had a 0% (zero of 15) chance of having a *p53* mutation (Appendix Table A2, online only). In contrast, a patient with breast cancer under age 30 and family history of one or more core cancers in a first- or second-degree relative (one of the core cancers being something other than breast) had a 100% chance (five of five) of having a *p53* mutation. Testing of the *p53* gene was negative in two patients with bilateral breast cancer and no cancer in first- or second-degree relatives. However, patients with unilateral breast cancer younger than age 30 and no cancer in first- or second-degree relatives had a 7% chance (one of 14) of having a *p53* mutation.

p53 *Mutations in Patients With Leukemia*

Among the 341 classified patients, 18 patients had leukemia. Only two of these 18 patients (11%) had a *p53* mutation. However, these two patients also had other typical LFS cancers. One patient had breast cancer at age 25 and leukemia at age 27, while the second patient had sarcoma at ages 9 months and 15 years and leukemia at age 17.

Mutation Prevalence Tables for p53

Mutation prevalence Tables were compiled based on the extensive clinical data obtained from patient family histories (Tables 5 and A2). The highest mutation frequency (100%) was among patients with childhood cancers with only one family member with at least one core cancer as well as one or more family member with a non-core cancer. Another high mutation prevalence (88%) was among patients with two or more core cancers, at least one at or under the age of 40 and two or more family members with core cancers.

Germline p53 *Mutations Cause Multiple Primary Cancers and Early Onset of Cancer*

Patients submitted for testing who did not have mutations generally had a less dramatic family phenotype. Fifty percent of *p53*-positive patients had more than one primary cancer compared to 32% of *p53*-negative patients. Patients with two or more primary cancers were significantly more likely to have a mutation ($P < .005$). The average age of onset of the first cancer among patients with a *p53* mutation was 21.9 years of age, versus an average of 31.6 years in patients without a *p53* mutation. Among the 75 classified *p53*-positve patients, the median age of onset of the first cancer was 25 years, significantly younger (35 years, $P < .005$) than the 266 classified *p53*-negative patients. The range of onset in the *p53*-positive patients was 4 months to 49 years.

Distribution of First Cancer Type and Age of Onset by Sex

Excluding sex-specific cancers, there was no significant difference in the average age of onset of the first cancer in males versus females in patients with *p53* mutations (Table 4). Likewise, excluding sex-specific cancers, the sex ratio of tumors overall was not significantly different. The data suggest that the excess of tumors in females derives overwhelmingly from their predisposition to breast cancer (online-only Appendix, Supplementary Results). Among specific tumor types, ACC was seen more commonly in females (3.7:1, females: males, respectively), a ratio that was significantly different from that found in the general population (approximately 1.4:1, females: males, $P = .0375$).[21]

DISCUSSION

Identifying families with *p53* mutations is a daunting task given the wide variety of cancer types associated with LFS. This study is, to our knowledge, the largest reported cohort (525 families) analyzed to date and includes comprehensive personal and family history data on 75 of 91 *p53*-positive and 266 of 434 *p53*-negative families. Our data suggests that although classic LFS remains the indicator with the highest predictive value for mutation status, Chompret's classification dramatically improved sensitivity. This report provides mutation prevalence Tables as clinical tools to facilitate the identification of families with *p53* germline mutations.

Because all *p53*-positive families had at least one member of the family with sarcoma, brain tumor, breast cancer, or ACC younger than the age of 50, these four cancers were confirmed as core cancers. While previous studies indicated that these four cancers were strongly associated with LFS and *p53* mutations,[3] this study is the first to suggest that families without at least one member with a core cancer are highly unlikely to have a *p53* mutation. One important caveat is the ascertainment bias inherent in the analysis of patients referred for genetic testing. Given the published classification schema, most patients sent for testing had a core cancer or at least one family member with a core cancer.

Previous studies and reviews have reported that approximately 70% to 80% of families meeting classic LFS have *p53* mutations.[7,22-25] Herein, the detection rate for families meeting classic LFS was somewhat lower (56%). However, we found a higher than anticipated detection rate for the Chompret classification (35% *v* approximately 20% reported in Chompret et al[11]). Varley et al[22] found that 40% (12 of 30) of patients meeting LFL classification had an identifiable *p53* germline mutation. A review on *p53* showed about an 8% mutation frequency for Eeles classification and 22% to 40% for Birch.[7] In the initial description of the Birch classification, a *p53* mutation was detected in 11% of patients.[9] The same group indicated in a subsequent analysis that less than 25% of patients meeting the Birch classification had a *p53* mutation.[26] In the description of patients meeting Eeles classification, approximately 7% of patients had a mutation, based on analysis of 61 patients.[10] Evans et al,[27] citing their cumulative survey of LFL families to date, have suggested that the LFL classification has a much higher positive predictive value (up to 40% to 50%) than the Chompret criteria. In this study of a series of patients sent for *p53* germline testing in a clinical diagnostic laboratory, the positive predictive value of the Chompret criteria (35%) was slightly higher than the combined positive predictive values of the Birch (16%) and Eeles (14%) classifications for LFL. In addition, the cumulative sensitivity of the Chompret plus classic LFS identified 95% of the *p53*-positive patients, missing only four additional *p53*-positive patients (one each meeting Birch and Eeles and two meeting no criteria). While the LFL classification, Birch, and Eeles, showed detection rates of 16% and 14%, when examining clinical classification based on a hierarchy, the utility of these classifications diminish as the detection rates drop to 3% and 2%, respectively. Generally, the Chompret classification performs better because it identifies probands with ACC or multiple primary tumors but no family history, which would have been excluded by the other classification schema.

Among the 75 individuals with *p53* mutations, only two had leukemia (2.7%) and both had multiple primary cancers (one patient was first diagnosed with breast cancer; the other was first diagnosed with two primary sarcomas at 9 months and 15 years). Therefore, the leukemia diagnosis was not necessary to prompt *p53* testing for these two patients. Leukemia was initially considered one of the main components of LFS based on an analysis of the first 24 kindreds identified with LFS. These included 52 primary cancers, four of which were leukemia (7.7%).[3] The second primary cancer was not considered in the analysis which may introduce a bias given that, as the results herein show, approximately 50% of patients with *p53* germline mutations have more than one primary cancer. The contribution of leukemia to LFS was questioned by Birch[18] who noted the disease in just seven of 28 families in their cohort. It is unclear from the analysis whether these seven individuals had other primary cancers. Our data show that just 14 leukemias (8.4%) among 167 cancers are in family members of patients with *p53* mutations. These data are consistent with the notion of a weak association, although different sampling designs would be necessary to estimate the risk of leukemia associated with *p53* mutations.

There is a strong link between individuals with CPC or ACC, especially those occurring in childhood, and germline *p53* mutations. We recommend genetic testing of *p53* if an individual meets one of the following criteria: a patient with a CPC or an ACC, or a family meeting classic LFS or Chompret criteria. If the Chompret criteria are modified to include any patient with CPC, regardless of family history, all but one of the positive patients in our series meet classic LFS or Chompret criteria (99%). Given the relatively high detection rate of *p53* mutations in this study, *p53* germline mutations may be more common than previously appreciated. We estimate that the frequency of *p53* germline mutations may be as high as 1 in 20,000 (Appendix Table A3, online only).

In summary, this study is the first large series of *p53* testing for LFS reflective of clinical practice and not biased by specific selection criteria. We did not select patients on the basis of family history or particular types of tumors. The range of patients submitted for testing varied widely. One limitation of this study is that the data for pathology of the patient's tumor and the family history data were provided by the clinician ordering the genetic testing and, therefore, were not confirmed by the study investigators. This study highlights the potential benefits of critical analysis of diagnostic laboratory testing outcomes, and the importance of adequate clinical information supplied by the healthcare provider. The *p53* mutation prevalence tables should prove to be useful tools for clinicians considering the diagnosis of LFS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Glossary Terms

Transcription factor: A DNA-binding protein that functions to initiate, enhance, inhibit, or reduce the transcription of a gene. They act by promoting the formation of the pre-initiation complex (PIC), which recruits and activates RNA polymerase.

Penetrance: The likelihood that a given gene mutation will produce disease. This likelihood is calculated by examining the proportion of people with the particular genetic mutation that show symptoms of disease.

Missense mutation: A change (mutation) in one nucleotide that results in the coding of a different amino acid.

Germline mutation: An inherited variation in the lineage of germ cells. Germline mutations can be passed on to offspring.

Truncating mutation: Any mutation which causes premature truncation of the normal protein product. Examples of mutations that can cause truncation are nonsense mutations and out-of-frame deletions, insertions, or indels.

Apoptosis: Also called programmed cell death, it is a signaling pathway that leads to cellular suicide in an organized manner. Several factors and receptors are specific to the apoptotic pathway. The net result is that cells shrink, develop blebs on their surface, and their DNA undergoes fragmentation.

Autosomal: Any chromosome not related to the sex chromosomes (X or Y). The autosomes are chromosomes 1-22.

Dominant: A dominant gene refers to the allele that causes a phenotype that is seen in a heterozygous genotype.