The frequency of incidental findings in expanded carrier screening

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Introduction

Expanded carrier screening (ECS) identifies couples at risk for transmitting a genetic condition to their offspring. Patients may be counseled during the informed consent process that carriers of recessive conditions usually do not experience symptoms. Yet, there are several conditions on ECS panels where carriers may have clinical health implications (CHI). We analyzed Counsyl's laboratory experience with over 346,790 ECS to examine this frequency.

Methods

Individuals were tested by Counsyl for carrier status in up to 108 genes by either targeted genotyping (TG) of up to 417 sites or next-generation sequencing (NGS) of the exons and selected introns of the chosen genes. Carrier frequencies for each condition were calculated as the higher of TG or NGS frequencies.[1]

Table 1

Five autosomal recessive diseases were identified for their associations with CHI.

Disease	Gene	Clinical Health Implications (CHI) for Carriers
Ataxia-telangiectasia	*ATM*	~Four fold increased cancer risk than that of the general population, primarily because of the increased risk of breast cancer.[2]
Pseudocholinesterase deficiency	*BCHE*	Risk for slightly prolonged period (5 minutes to an hour) of breathing paralysis after receiving choline ester drugs.[3]
Hereditary thymine-uraciluria	*DPYD*	Toxicity risk following 5-fluorouracil chemotherapy.[4]
Factor XI deficiency	*F11*	Elevated risk for bleeding problems.[5]
Nijmegen breakage syndrome	*NBN*	Increased risk of developing cancer.[6]

Carrier frequencies for each condition were computed from de-identified aggregate data, tabulated by ethnicity, weighted by US Census Data 2010, and summated to represent the ethnic distribution in USA. Test requisition forms required individuals to self-report their racial/ethnic background in 1 of 14 categories: African/African American (af); Ashkenazi Jewish (aj); Mixed or Other Caucasian (co); French Canadian or Cajun (cj); East Asian (ea); Finnish (fi); Hispanic (hi); Middle Eastern (me); Native American (na); Northern European (ne); Pacific Islander (pi); South Asian (sa); Southeast Asian (se); and Southern European (so).

Results

346,790 patients indicating "routine carrier testing" as the reason for testing were selected, where 308,668 (89%) received TG and 38,122 (11%) received NGS.

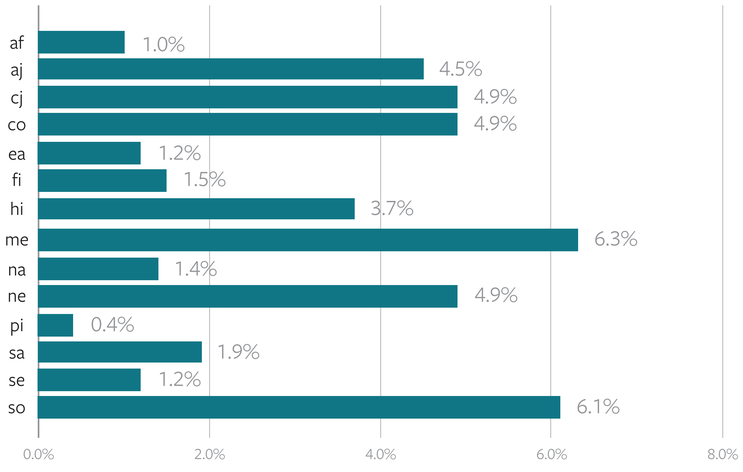
Table 2

Carrier frequency per disease, weighted by US ethnic distribution, that may have CHI

Disease	Gene	Carrier frequency weighted by US Census Data 2010
Ataxia-telangiectasia	*ATM*	0.36% (1/280)
Pseudocholinesterase deficiency	*BCHE*	4.2% (1/24)
Hereditary thymine-uraciluria	*DPYD*	0.92% (1/109)
Factor XI deficiency	*F11*	0.65% (1/150)
Nijmegen breakage syndrome	*NBN*	0.18% (1/560)
Total		6.3% (1/16)

Figure 1

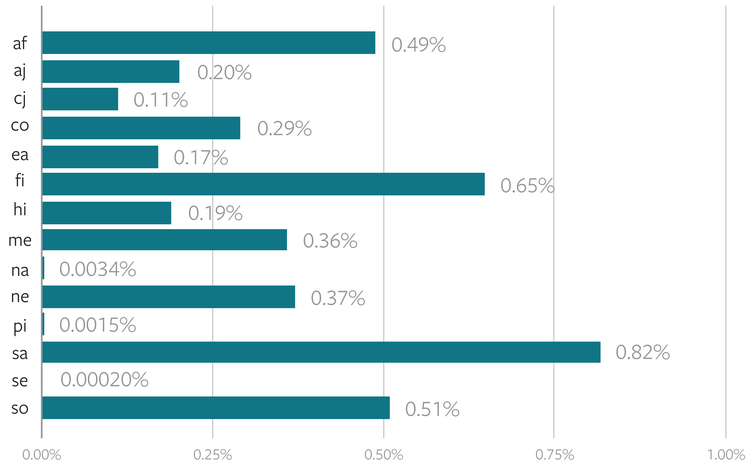
Carrier frequency for *BCHE* by ethnicity



BCHE accounted for 67% of the frequency of CHI and is more common in individuals of Ashkenazi Jewish (4.5%) and Other Caucasian (4.9%) than African/African American (1.0%) or East Asian/Southeast Asian descent (1.2%).

Figure 2

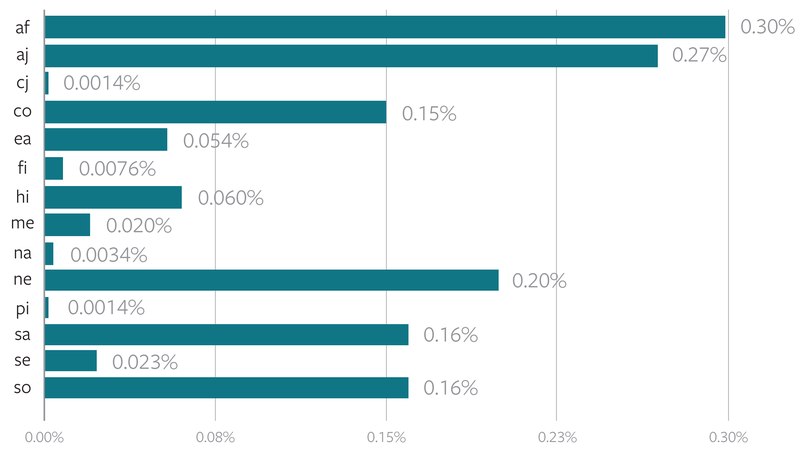
Carrier frequency for *ATM* by ethnicity



ATM accounted for 5.7% of the frequency of CHI and is more common in individuals of South Asian (0.82%) and South European (0.51%) than those of Southeast Asian (0.00020%) or Pacific Islander (0.0015%) descent.

Figure 3

Carrier frequency for *NBN* by ethnicity



NBN accounted for 2.9% of the frequency of CHI and is more common in individuals of African/African American (0.30%) and Ashkenazi Jewish (0.27%) than those of French Canadian/Cajun (0.0014%) or Pacific Islander (0.0014%).

Conclusion

6.3% of individuals (1/16) screened for these diseases will have an incidental finding—where carriers identified may experience CHI. Pre-test counseling, informed consent, reporting, and post-test counseling should educate patients and providers regarding this possibility.

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