

HDAC8 FAQ Sheet

In July 2012, the fourth “CdLS gene”—*HDAC8*—was announced. Many parents and professionals have questions about this latest finding and what it means.

HDAC8 is an X-linked gene, meaning it is located on the X chromosome. The X and Y chromosomes are the sex chromosomes that determine whether an individual will be a boy or girl. Typically, a female has two Xs (XX) and a male has an X and Y (XY).

Individuals with CdLS who have the gene change in *HDAC8* make up just a small portion of all people with CdLS.

Sara Noon, a genetic counselor at the Children’s Hospital of Philadelphia (CHOP) answers some common questions below.

Q: Does the child have to be tested for the previous genes first before being tested for this gene?

A: The University of Chicago offers clinical testing for the genes *NIPBL* and *SMC1A*. Approximately 50% of individuals with CdLS have a change (or mutation) in *NIPBL* and about 5% in *SMC1A*. Most recently, The University of Chicago began offering clinical genetic testing for *SMC3*, as well as the two new genes recently identified for CdLS, *RAD21* and *HDAC8*. Together, approximately 4% of individuals with CdLS have a change in either *SMC3*, *RAD21*, or *HDAC8*. Research enrollment in a study conducted by Dr. Ian Krantz at the Children’s Hospital of Philadelphia is offered to individuals with CdLS or a CdLS-like phenotype who have had clinical testing of *NIPBL*, *SMC1A* and no mutations were identified. While it is preferred that *SMC3*, *RAD21*, and *HDAC8* testing be completed prior to enrollment, this testing is currently not required to enroll. Submission of relevant clinical information, photographs, and consent forms are required.

Q: Should mothers be tested?

A: If a child has an identified mutation in the *HDAC8* gene, the mutation could have occurred as a new (*de novo*) event in that individual or it could have been inherited from a parent. Since women have two copies of the X chromosome, mothers can be carriers for an *HDAC8* mutation.

When a mother is a carrier for an *HDAC8* mutation, one copy of her X chromosome has the *HDAC8* mutation and the other copy does not. Unaffected mothers who are carriers typically do not show any signs or symptoms because the copy of the X chromosome without the mutation can compensate for the copy with the mutation. Once an *HDAC8* mutation is identified in a child, it is helpful to test the mother to determine her carrier status. Determining the carrier status of the mother can help identify whether the mutation in the child was a new mutation or inherited. It can also provide useful information about risk to siblings and future pregnancies.

Q: If the mother is carrying the mutation, what are the chances it will be passed to another child?

A: Most cases are *de novo*; however, if the mother is a carrier for the mutation overall she has a 50% chance of transmitting the mutation in each pregnancy. Males who inherit the mutation will be affected and females who inherit the mutation will be carriers and are usually not affected*. Therefore, when a mother is a carrier she has a 25% chance to have a son who is affected, a 25% chance to have a son who





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is not affected, a 25% chance to have a daughter who is a carrier, and a 25% chance to have a daughter who is neither a carrier nor affected. Note: In the absence of identifying a mutation in the mother, the possibility of germline mosaicism cannot be excluded. Germline mosaicism refers to when the mutation is present in some of the parents' egg or sperm cells. Recurrence risk to unaffected parents is therefore estimated to be approximately 1.5%.

**It is possible for female carriers of an HDAC8 mutation to be affected and present with either mild features or a more classically defined CdLS presentation. This is due to an effect called skewed x-inactivation.*

Q: What is the cost for testing for each of the genes? Is the Children's Hospital of Philadelphia the only place that tests for this new gene?

A: Clinical testing for *NIPBL*, *SMC1A*, *SMC3*, *RAD21* and *HDAC8* is offered at the University of Chicago. Costs and turnaround time are as follows:

- NIPBL sequencing (6 - 8 weeks) \$2,650
- NIPBL deletion/duplication testing (4 weeks) \$500
- SMC1A sequencing (4 - 6 weeks) \$2,025
- SMC1A deletion/duplication testing (4 - 6 weeks) \$1,000
- SMC3 sequencing (4 - 6 weeks) \$2,900
- RAD21 sequencing (4 - 6 weeks) \$2,900
- HDAC8 sequencing (4 - 6 weeks) \$2,900

For those interested in enrolling in the research study, CHOP does not charge a fee for individuals to be a part of the study. Since it is a research lab and not a clinical lab, there is no guarantee of a turnaround time for results. It could take up to one year for results to be returned.

Q: Will insurance cover testing?

A: Some insurance companies will cover the cost of genetic testing; however, how much is covered depends on each individual's insurance provider and particular plan.

For more information about testing:

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