Title: Joubert Syndrome *GeneReview* — Risk to Family Members – X-Linked Inheritance (*OFD1*-Related)
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Risk to Family Members – X-Linked Inheritance (*OFD1*-Related)

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *OFD1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), or the affected male may have a *de novo OFD1* pathogenic variant, in which case the mother is not a carrier.

Sibs of a male proband

- The risk to sibs depends on the genetic status of the mother.
    - If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant are unlikely to be affected.
    - If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband

- No individuals with JS have been reported to have reproduced.
- Males with X-linked JS will pass the pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) and the aunts' offspring, depending on their gender, may be at risk of being heterozygotes (carriers) or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status for the extended family.