

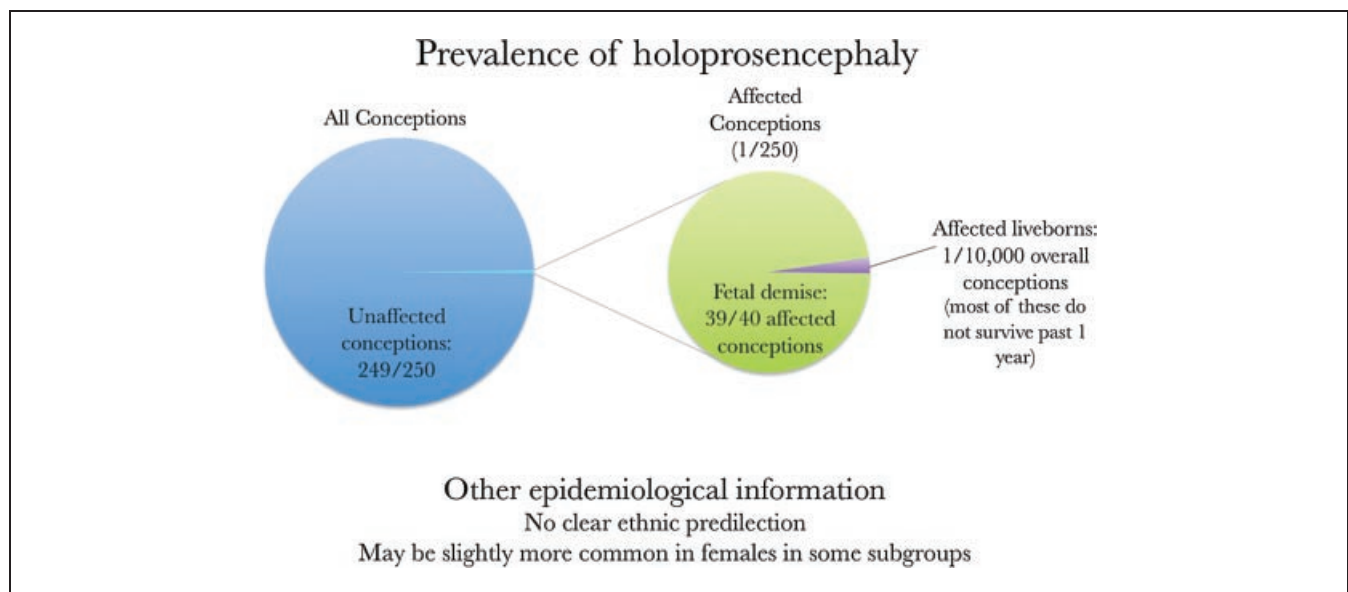
Holoprosencephaly Flashcards: A Summary for the Clinician

**BENJAMIN D. SOLOMON, DANIEL E. PINEDA-ALVAREZ, SANDRA MERCIER,
MANU S. RAAM, SYLVIE ODENT, AND MAXIMILIAN MUENKE***

This material contains general information regarding the approach to patients with holoprosencephaly. For more detailed discussion, please refer to specific articles in this issue. Published 2010 Wiley-Liss, Inc.†

KEY WORDS: holoprosencephaly; flashcards

How to cite this article: Solomon BD, Pineda-Alvarez DE, Mercier S, Raam MS, Odent S, Muenke M. 2010. Holoprosencephaly flashcards: A summary for the clinician. Am J Med Genet Part C Semin Med Genet 154C:3–7.



Benjamin D. Solomon, M.D. is a fellow in the Combined Pediatrics and Medical Genetics Residency Program, based at the National Human Genome Research Institute. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly.

Daniel E. Pineda-Alvarez, M.D. is a medical graduate trained in Colombia and is currently a Clinical Molecular Genetics fellow in the Medical Genetics Branch of the National Human Genome Research Institute. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly and attention deficit hyperactivity disorder.

Sandra Mercier, M.D. is a researcher in the holoprosencephaly group in the "Génétique des Pathologies Liées au Développement" branch of UMR 6061 CNRS, IGDR, at the University of Rennes 1, France. She is also a senior registrar in the Clinical Genetics Service at CHU Hôpital Sud in Rennes.

Manu S. Raam, B.S.E. is a trainee in the HHMI-NIH Research Scholars Program, which is a medical student training program jointly administered by the Howard Hughes Medical Institute and the National Institutes of Health. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly.

Sylvie Odent, M.D., Ph.D. is a professor of genetics and a member of the holoprosencephaly group in the "Génétique des Pathologies Liées au Développement" branch of UMR 6061 CNRS, IGDR, at the University of Rennes 1, France. She is the chief of the Clinical Genetics Service at CHU Hôpital Sud in Rennes and is a coordinator of a Center of Reference for Rare Diseases, focusing on developmental abnormalities and dysmorphism. Her clinical and research interests mainly concern holoprosencephaly and mental retardation.

Maximilian Muenke, M.D. is the chief of the Medical Genetics Branch at the Division of Intramural Research in the National Human Genome Research Institute. He has a longstanding interest in elucidating the genetics behind holoprosencephaly, craniofacial malformation syndromes, and attention deficit hyperactivity disorder, as well as an interest in improving knowledge about the formation of the central nervous system.

*Correspondence to: Maximilian Muenke, Building 35, 1B203, 35 Convent Drive, MSC 3717, Bethesda, MD 20892-3717, USA.

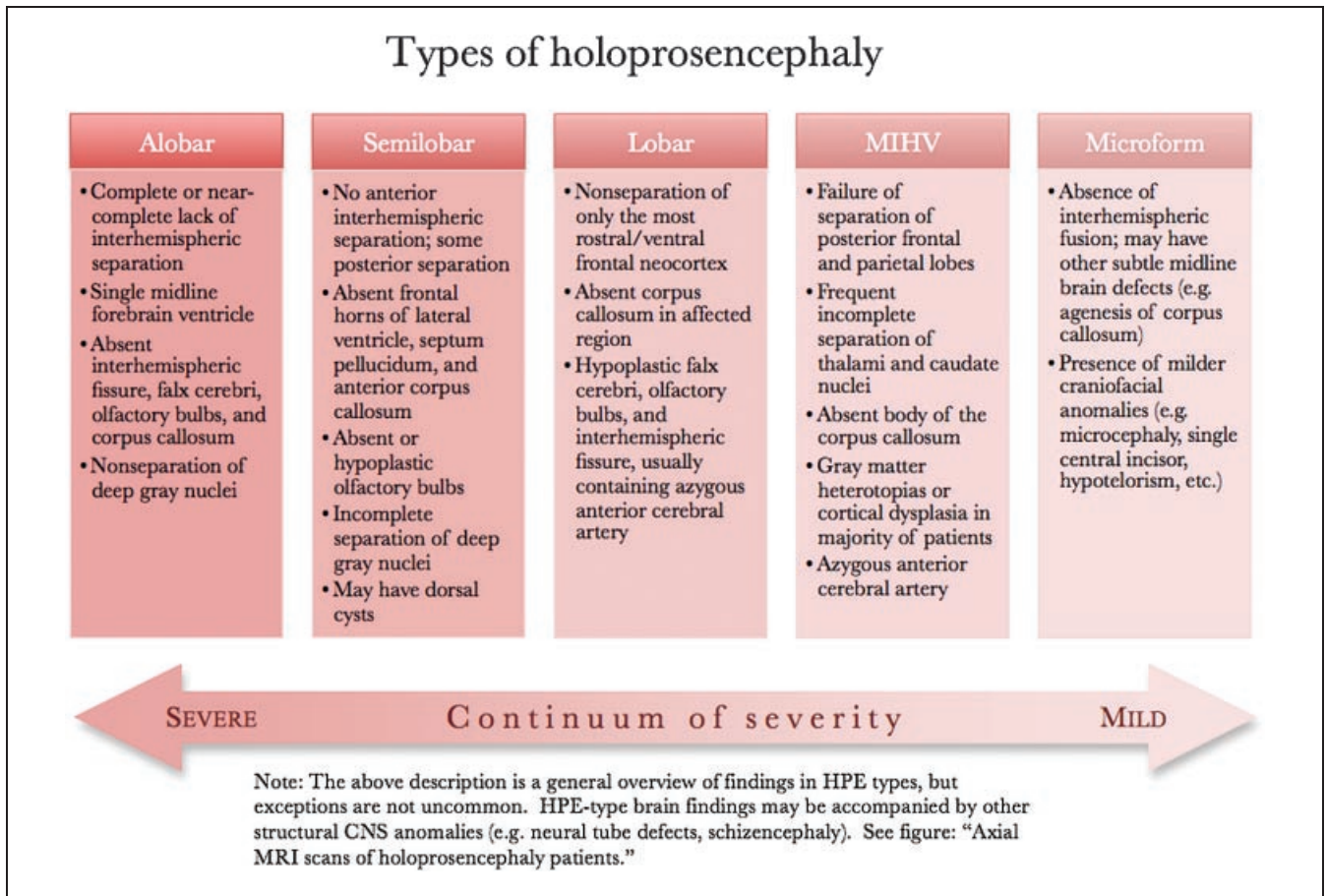
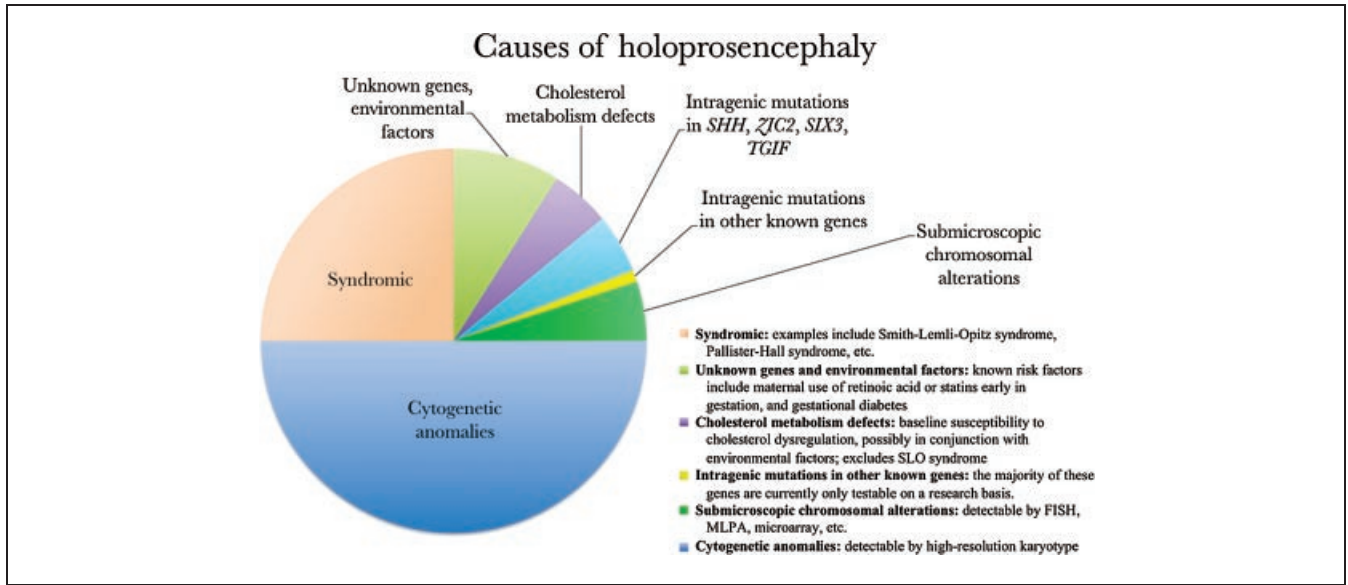
E-mail: muenke@nih.gov

DOI 10.1002/ajmg.c.30245

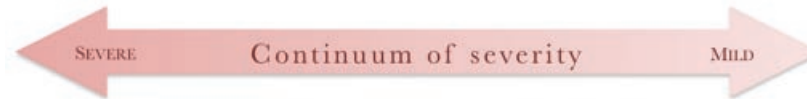
Published online 26 January 2010 in Wiley InterScience (www.interscience.wiley.com)

Published 2010 Wiley-Liss, Inc.

†This article is a US Government work and, as such, is in the public domain in the United States of America.



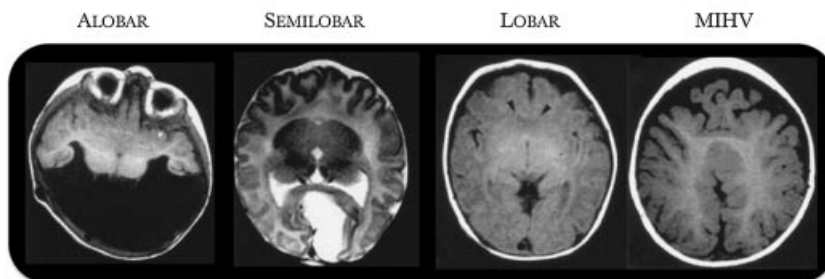
Craniofacial findings in patients with holoprosencephaly-spectrum disorders



From left to right: (A) synophthalmia (two fused eyes in one orbit) and a proboscis in a patient with alobar HPE; (B) severe hypotelorism, flat nasal bridge, bilateral colobomas, and midline cleft lip and palate in a patient with alobar HPE; (C) hypotelorism, flat nasal bridge, and closely spaced nostrils in a patient with lobar HPE; (D) hypotelorism, sharp nasal bridge, and single maxillary central incisor in an individual with a microform of HPE.

[Roessler *et al.*, 1996; Lachawan *et al.*, 2009]

Axial MRI scans of holoprosencephaly patients



[Hahn and Plawner, 2004]

Spectrum of physical examination features (patients with full HPE)

Facial features

- Microcephaly (can be extreme)
- Macrocephaly (in cases with hydrocephalus)
- Continuous spectrum of eye anomalies from cyclopia to hypotelorism
- Proboscis or nose with single nostril
- Flat nasal bridge
- Cleft lip/palate
- Single maxillary central incisor
- A subset of patients may also have relatively normal facial appearances or may have anomalies not typically associated with HPE
- See figure: "Craniofacial findings in patients with holoprosencephaly-spectrum disorders"

Extracranial features

- Signs of major organ malformations (e.g. cardiac, GI, GU defects)
- Limb anomalies
- Skeletal anomalies

Possible physical examination features (patients with microform HPE)

Facial features

- Microcephaly (typically less severe than in full HPE)
- Midface hypoplasia
- Hypotelorism
- Iris coloboma
- Flat or sharp nasal bridge
- Cleft lip/palate
- Single maxillary central incisor
- Relatively normal facial appearance in a subset of patients
- See figure: "Craniofacial findings in patients with holoprosencephaly-spectrum disorders"

Clinical approach to holoprosencephaly

Prenatal diagnosis

- Detailed radiologic examination, including fetal ultrasound and/or MRI
- Consultation with clinicians and geneticists familiar with HPE
- Discussion of testing options (e.g. amniocentesis, chorionic villus sampling, and including parental testing)

Postnatal diagnosis

- Detailed evaluation, including family history, by clinicians familiar with HPE
- Neuroimaging (MRI preferred)
- Discussion of testing options to identify underlying etiologies (see figure: "Causes of holoprosencephaly")

Management

- Thorough genetic counseling, including detailed family history
- Consultations that may include: neurology, endocrinology, rehabilitative medicine (speech therapy, physical therapy, occupational therapy, psychiatry), ophthalmology, development, genetics, complex care, surgery (e.g. general surgery, oromaxillofacial), orthopedics, adjunctive therapy
- Referral to family support groups (e.g. Families for HoPE)

Frequent complications of holoprosencephaly

Neurocognitive impairment	Seizure disorders	Diabetes insipidus (and associated electrolyte imbalances)
Autonomic instability	Cleft lip/palate	Other endocrine abnormalities
Recurrent infections (e.g. aspiration pneumonia)	Other major organ malformations (e.g. cardiac defects)	Feeding intolerance

List of resources for holoprosencephaly

The Carter Centers for Brain Research (USA)

Research center and source of information and support for affected families

<http://hpe.stanford.edu/>

National Institutes of Health (USA)

Research regarding clinical and genetic findings in patients with holoprosencephaly

<http://www.clinicaltrials.gov/>

Families for HoPE (USA)

Nonprofit family-run organization formed to address needs of children and families with HPE

<http://www.familiesforhope.org/>

Université de Rennes: CNRS Génétique et Développement UMR6061 (France)

Research analyzing developmental mechanisms and genetic findings in HPE patients

<http://umr6061.univ-rennes1.fr/english/equipes>

CHU de Rennes: Centre de Référence Maladies Rares (France)

Research into clinical findings in HPE patients

<http://www.feclad.org/ouest.html>

REFERENCES

All previously published images reprinted with permission. Reproduced from: [Hahn and Plawner, 2004 Evaluation and management of children with holoprosencephaly, 31:80, Copyright (2004), with permission from Elsevier;

[Roessler et al., 1996 Mutations in the human *Sonic Hedgehog* gene cause holoprosencephaly, 14:357, Copyright (1996), with permission from Nature Publishing Group; [Lacbawan et al., 2009 Clinical spectrum of *SIX3*-associated mutations in holoprosencephaly: correlation between genotype, pheno-

type and function, 46:390, copyright notice 2009, with permission from BMJ Publishing Group, Ltd.

REFERENCES (for images)

- Hahn JS, Plawner LL. 2004. Evaluation and management of children with holoprosencephaly. *Pediatr Neurol* 31:79–88.
- Lacbawan F, Solomon BD, Roessler E, El-Jaick K, Domené S, Vélez JI, Zhou N, Hadley D, Balog JZ, Long R, Fryer A, Smith W, Omar S, McLean SD, Clarkson K, Lichty A, Clegg NJ, Delgado MR, Levey E, Stashinko E, Potocki L, Vanallen MI, Clayton-Smith J, Donnai D, Bianchi DW, Juliusson PB, Njølstad PR, Brunner HG, Carey JC, Hehr U, Müsebeck J, Wieacker PF, Postra A, Hennekam RC, van den Boogaard MJ, van Haeringen A, Paulussen A, Herbergs J, Schrander-Stumpel CT, Janecke AR, Chitayat D, Hahn J, McDonald-McGinn DM, Zackai EH, Dobyns WB, Muenke M. 2009. Clinical spectrum of *SIX3*-associated mutations in holoprosencephaly: correlation between genotype, phenotype and function. *J Med Genet* 46:389–398.
- Roessler E, Belloni E, Gaudenz K, Jay P, Berta P, Scherer SW, Tsui LC, Muenke M. 1996. Mutations in the human *Sonic Hedgehog* gene cause holoprosencephaly. *Nat Genet* 14: 357–360.