

# Genetic Counseling in Angelman Syndrome: The Challenges of Multiple Causes

Heather J. Stalker\* and Charles A. Williams

Division of Pediatric Genetics and R.C. Philips Unit, Department of Pediatrics, University of Florida, Gainesville, Florida

The causal heterogeneity of Angelman syndrome (AS) makes providing information regarding recurrence risk both important and challenging, and may have a dramatic impact on reproductive decision-making for the nuclear and extended family. Most cases of AS result from typical large de novo deletions of 15q11–q13, and are expected to have a low (<1%) risk of recurrence. AS due to paternal uniparental disomy (UPD), which occurs in the absence of a parental translocation, is likewise expected to have a <1% risk of recurrence. Parental transmission of a structurally or functionally unbalanced chromosome complement can lead to 15q11–q13 deletions or to UPD and will result in case-specific recurrence risks. In instances where there is no identifiable large deletion or UPD, the risk for recurrence may be as high as 50% as the result of either a maternally inherited imprinting center (IC) mutation or a ubiquitin-protein ligase (*UBE3A*) gene mutation. Individuals with AS who have none of the above abnormalities comprise a significant proportion of cases, and some may be at a 50% recurrence risk. Misdiagnoses, as well, can be represented in this group. In light of the many conditions which are clinically similar to AS, it is essential to address the possibility of diagnostic uncertainty and potential misdiagnosis prior to the provision of genetic counseling. Summaries of the different causal classes of AS as an algorithm for determination of recurrence risks are presented. *Am. J. Med. Genet.* 77:54–59, 1998. © 1988 Wiley-Liss, Inc.

**KEY WORDS:** Angelman syndrome; genetic counseling; imprinting center;

methylation; 15q11–q13 deletion; uniparental disomy; *UBE3A*; recurrence risk

## INTRODUCTION

Angelman syndrome is a neurobehavioral condition which is characterized by developmental delay, progressive microcephaly, ataxic gait, absence of speech, seizures, and spontaneous bouts of laughter [Angelman, 1965]. The incidence is estimated to be between 1 in 15,000 and 1 in 20,000 live births [Clayton-Smith and Pembrey, 1992]. Angelman syndrome (AS) and its counterpart Prader-Willi syndrome (PWS) are recognized as classical examples of genomic imprinting; PWS results from deletions in the paternally derived chromosome and AS results from similar deletions in the maternally derived chromosome [Knoll et al., 1989]. The presence of maternally and paternally imprinted gene(s) in this region is further evidenced by the occurrence of maternal uniparental disomy (UPD) in many individuals with PWS and the discovery of paternal UPD in some individuals with Angelman syndrome [Knoll et al., 1991].

In addition to the impressively different phenotypes of AS and PWS, the risk of recurrence in future pregnancies is also quite different. Whereas familial recurrence of PWS has rarely been observed, there are many reports in the literature of familial AS [Baraitser et al., 1987]. It has been hypothesized that the difference in familial representation between AS and PWS is due to the presence of only 1 critical gene for AS within the region, and the presence of 2 or more critical genes for PWS [Ozcelik et al., 1992] such that AS could result from a single gene mutation; whereas, PWS would require alteration of multiple genes. Recently, a putative AS gene encoding a ubiquitin-protein ligase (*UBE3A*) was identified [Matsuura et al., 1997; Kishino et al., 1997].

The heterogeneity of AS makes it essential and difficult to determine recurrence risk in future pregnancies. It is known that both the numerical risk and the perceived risk have an impact on reproductive decision-making [Somer et al., 1988; Sorenson et al., 1981]. Accordingly, genetic counseling must provide families with the most accurate information available regarding their risk in subsequent pregnancies. Although

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\*Correspondence to: Heather J. Stalker, Division of Pediatric Genetics, Box 100296 UFHSC, Gainesville, FL 32610.

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though families at high risk for recurrence of AS are undoubtedly a small group, it is important to be able to identify them, and to provide accurate information regarding their potential 50% recurrence risk; conversely, appropriate information needs also to be provided to families with a low risk.

### GENETIC CLASSES OF ANGELMAN SYNDROME

There are currently 6 classes of AS:

1. Those with a typical, large deletion of the maternal 15q11–q13 region;
2. Those with less typical chromosomal anomalies which involve the 15q11–q13 region;
3. Those with paternal UPD of chromosome 15;
4. Those with imprinting control center mutations identified by abnormal methylation pattern;
5. Those with mutations in the *UBE3A* gene;
6. Those who have normal genetic study results (i.e., normal methylation and FISH studies and no apparent mutation in the *UBE3A* gene), but who still have classical AS.

Each of these subcategories, summarized in Figure 1, will be discussed with respect to incidence, mechanism, diagnostic studies, risk of recurrence, and availability of prenatal diagnosis.

#### Maternal 15q11–q13 Deletions

Approximately 70% of individuals with Angelman syndrome have either cytogenetically or molecularly identifiable deletions in the q11–q13 region of their maternally derived chromosome 15 [Williams et al., 1995; Chan et al., 1993]. The typical deletion encompasses approximately 4 megabases (Fig. 1), and has rather consistent deletion breakpoints which commonly delete the *P* gene distally. Deletion of the *P* gene is responsible for the hypopigmentation seen in many AS deletion patients.

To date, there has been no evidence that AS families in which there has a typical large deletion have an increased risk of recurrence. Connerton-Moyer et al. [1997] report on 2 families in which there is recurrence of Angelman syndrome (1 in second cousins, and 1 in first cousins once-removed). However, further molecular and cytogenetic evaluation in these families showed that the children did not have deletion of the same ancestral chromosome 15. The authors conclude that these families are most likely the result of independent events.

In families where AS is shown to be the result of a de novo large deletion, the risk of recurrence is expected to be less than 1%, and genetic counseling can reflect that risk. This figure is an estimation derived from our experience [Hendrickson et al., 1991], plus the cumulative data of many large surveys of AS cases where the typical, large deletion was not associated with recurrence within the family. Although the risk is expected to be quite low in future pregnancies, prenatal diagnosis by either FISH cytogenetic techniques or by molecular studies is available.

#### Other Cytogenetic Abnormalities

The 15q11–13 region is considered to have an increased liability toward rearrangement, especially recombination with telomeric and subtelomeric regions of other autosomes. This may be related to the presence of repeat elements (palindromes) flanking 15q12 that share homology with telomeric regions [Reeve et al., 1993].

The incidence of complex structural chromosome abnormalities (translocations, inversions, etc.) resulting in AS are relatively infrequent, accounting for less than 1–2% of cases in 1 large study [Chan et al., 1993]. Complex structural chromosome abnormalities in PWS have been more extensively studied than in AS, and they underpin our understanding of observed or anticipated chromosome abnormalities in AS. Less than 4% of cases of PWS are caused by a complex structural abnormality of chromosome 15 [Ledbetter et al., 1987; Butler, 1990], the most common involving a parental

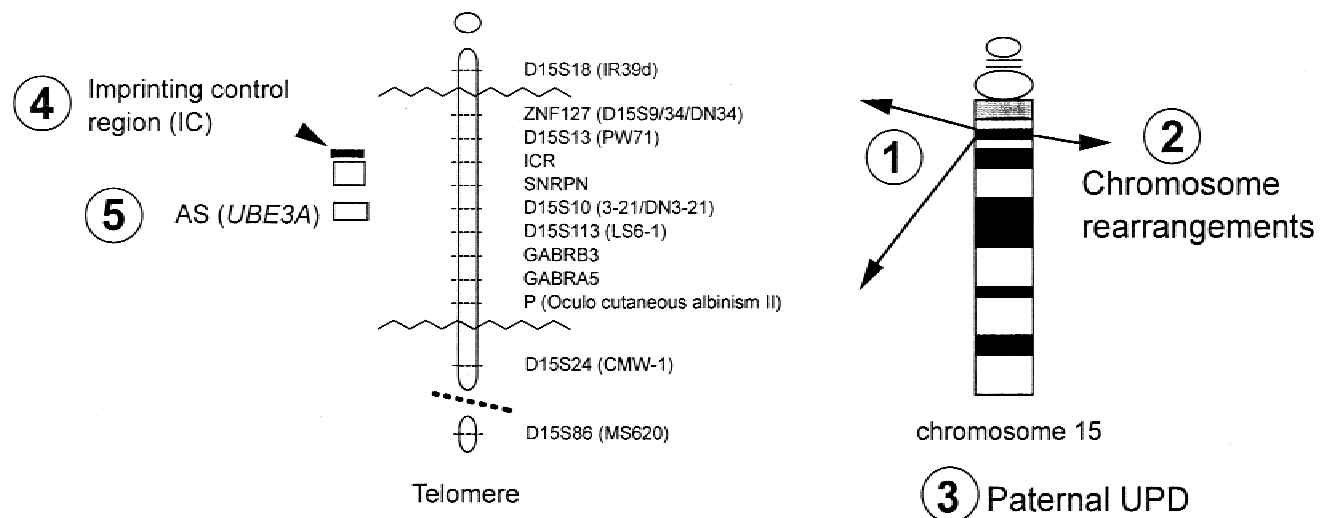


Fig. 1. Genetic classes of AS resulting from identifiable cause. 1. Large common deletions; 2. Other chromosome abnormalities; 3. Paternal uniparental disomy; 4. Imprinting center deletion; 5. *UBE3A* mutation/deletion.

translocation of the 15q13-qter arm to the telomere of another autosome. PWS then occurs via either paternally derived deletions or maternally derived uniparental disomy, each the result of abnormal meiotic segregation. A review by Rivera et al. [1990] reported that only 1 of 19 informative cases with a complex abnormality of chromosome 15 was inherited, so it appears that most structural abnormalities in PWS result from de novo event during gametogenesis. The recurrence risk is thus expected to be very low.

We have reviewed 9 published cases of AS resulting from complex chromosome abnormalities [Smeets et al., 1992; Webb et al., 1992; Chan et al., 1993; Freeman et al., 1993; Smith et al., 1994; Jauch et al., 1995; Burke et al., 1996; Greger et al., 1997; Wenger et al., 1997]. The cytogenetic abnormalities included paracentric and pericentric inversions, isochromosome formation, cryptic translocations involving the centromeric region, and more obvious 15q11-13/telomeric translocations. The resultant abnormalities involved 3 cases of paternal UPD, 5 with deletions in the critical maternally derived 15q11-13 AS region, and 1 with an interruption of the *UBE3A* gene. However, 6 of 9 cases were inherited, suggesting that the frequency of inherited chromosome rearrangements in AS may be greater than that observed in PWS.

Of particular relevance is the recent observation, in 2 different families, of a PWS child in whom an apparent de novo 15q11-13 deletion occurred on an otherwise normal chromosome 15. The deleted 15 in each was apparently derived by abnormal crossing over with a balanced translocation chromosome carried by the father [Horsthemke et al., 1996]. This observation has important implications in AS and PWS. For example, when amniocentesis reveals normal chromosomes in the fetus of such a balanced translocation carrier, one cannot automatically exclude risk. In these rare situations, they advise further study of the fetal chromosomes 15 with FISH and microsatellite analyses. We are not aware of any instance of a typical deletion AS case being caused by this parental mechanism, but it seems theoretically possible.

When a complex structural abnormality of chromosome 15 has been identified in a given family, the approach to counseling is relative straightforward, based on whether it is inherited and based on either observed or theoretical risks associated with the given abnormality.

A counseling problem arises when attempting to provide recurrence risk estimation to a family with a deletion-positive child, when neither the chromosomes of the affected child nor mother have been adequately evaluated to exclude the aforementioned complex structural chromosome abnormalities. Many AS families have had only a limited study of their child's chromosomes 15, and further study should be encouraged so as to ensure that the chromosome containing the deletion is not the result of a familial chromosome abnormality. Complex aberrations are usually ruled out by methods that allow identification of the proximal segments of the deleted chromosome; e.g., use of centromeric probes or by distamycin-A/DAPI staining in combination with AS region FISH probes.

All AS cases, regardless of the presumed genetic defect, should have a complete karyotype performed. Additionally, given the observations related to PWS and paternal chromosome defects, chromosome analysis of the mother in AS deletion positive cases will add further certainty that a maternal abnormality is absent and that the deletion in the child is a true de novo event. Even if all of the above is normal, one is still left with the possibility of gonadal mosaicism for the deletion. This has not yet been described in AS to our knowledge, but it remains as a theoretical possibility. Empiric recurrence risks for cryptic mosaicism (including gonadal and somatogonadal) in cases of chromosome deletion are not easily derived. However, Gardner and Sutherland [1996] state that it is safe to assume that the risk is "less than 0.5%." There is no evidence to date that this risk is greater in the case of Angelman syndrome.

### Paternal Uniparental Disomy

Approximately 5% of individuals with AS have been shown to have paternal UPD for chromosome 15. Paternal UPD can either be demonstrated by the use of polymorphic probes or microsatellite analysis for chromosome 15. Unlike PWS, in which the origin of the UPD is almost always in maternal meiosis 1, in AS, UPD generally appears to arise from a postzygotic or second meiotic origin of the external paternal chromosome [Robinson et al., 1993; Rogan et al., 1993]. The possibility of trisomy rescue leading to AS must still be considered in instances in which CVS shows trisomy or mosaic trisomy 15, and subsequent amniocentesis demonstrates normal chromosomes. In families where AS is shown to be the result of paternal UPD in the absence of a familial Robertsonian translocation, the risk of recurrence is expected to be less than 1% in future pregnancies. This risk figure was selected based on the lack of recurrence among all known cases of UPD in AS, the experience with UPD in other disorders, and on theoretical consideration regarding the mechanism of UPD. Although the risk of recurrence is expected to be quite low in future pregnancies, prenatal diagnosis using PCR is available.

### Imprinting Center Mutations

Approximately 2% of individuals with Angelman syndrome show no evidence of a deletion, or of UPD 15, but demonstrate a DNA methylation pattern consistent with AS. These patients are thought to have mutations in the imprinting control center (IC), which controls imprinting and gene expression via methylation and demethylation throughout the 15q11-q13 region. IC mutations produce the clinical phenotype of AS or PWS by preventing the resetting of imprinting during gametogenesis in a parent or grandparent [Reis et al., 1994]. The identification of molecular deletions upstream of *SNRPN* by Buiting et al. [1995] in patients with both Angelman and Prader-Willi syndromes defined the location of the imprinting center.

More recent evaluation of the IC reveals that it contains 2 spatially distinct regions which control maternal (AS) and paternal (PWS) imprinting of chromosome

15, with the smallest region of overlap (SRO) for AS being approximately 2kb [Saitoh et al., 1997] and that for PWS being approximately 3kb (Nicholls, personal communication). Of the AS patients presently studied by sequence analysis within the SRO of the imprinting center, mutations have been identified in approximately 50%. Of those AS patients in which a mutation has been identified, all have been familial, with the unaffected mother also carrying the mutation. In 2 instances, the mother was shown to be mosaic for the mutation [Saitoh et al., 1997]. Of the 50% in which no mutation has been identified despite sequencing of the entire IC, no familial recurrence was noted to date, suggesting the possibility that these are de novo or stochastic events which do not imply the same recurrence risk as those with identified IC mutations (Nicholls, personal communication) [Saitoh et al., 1997]. However, the small numbers of patients involved in these studies to date make it impossible to exclude a higher risk of recurrence.

That IC mutations can be inherited from the mother is important to the recurrence risk for future pregnancies, and potentially increased the risk for even distant relatives since the mutation can theoretically be passed silently in the family by the phenomenon of imprinting inheritance (Fig. 2) [Driscoll, 1994]. Mothers who carry a known IC mutation will have a 50% risk of recurrence in future pregnancies (less than 50% if the mothers are mosaic), as may any female relatives who carry the mutation. Male relatives who carry the mutation would not be at risk to have affected children, but might be at risk to have affected grandchildren through daughters who inherit the mutation.

Although microdeletion analysis and sequencing of the IC is presently available only through research labs, this information may be critical in determination of risk to families with a putative imprinting center mutation. Prenatal diagnosis is theoretically possible by mutation analysis for families in which known IC mutations exist, but is not possible in this manner for families without a known mutation. The possibility of methylation analysis for these families to look for recurrence would theoretically be able to identify a subsequent affected fetus.

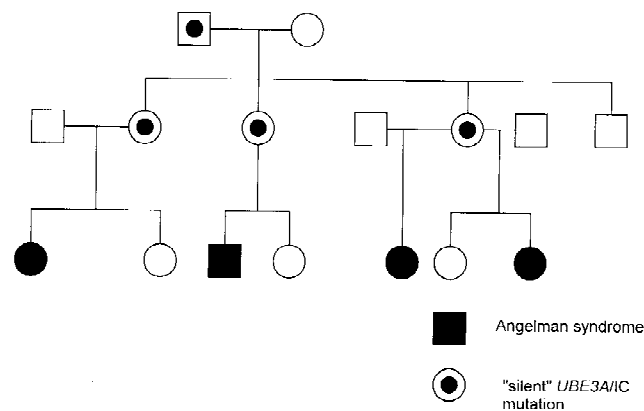


Fig. 2. Pedigree illustrating inheritance pattern of *UBE3A* or IC mutations in Angelman syndrome.

### *UBE3A* Mutation

A substantial group of individuals with clinical features of AS have no cytogenetic or molecular evidence of a deletion, and inheritance of the chromosomes 15 is clearly biparental. Estimated to make up approximately 20% of all individuals with AS, this group is one of the most difficult to deal with from a clinical and genetic counseling perspective because there has been no diagnostic study which confirms the AS diagnosis. It is suggested that many of these individuals have mutations (either de novo or inherited) in the *UBE3A* gene.

One documented case of an inherited molecular deletion which includes the *UBE3A* gene has been reported in Angelman syndrome: that of a molecular deletion transmitted from grandfather to mother, and on to 3 affected children [Saitoh et al., 1992]. In instances where there is a small inherited deletion such as this, the risk of recurrence would be 50% in subsequent pregnancies.

The identification of protein truncation mutations in *UBE3A* in 2 of 11 patients with AS by Matsuura et al. [1997] and in 1 isolated and 1 familial case of AS by Kishino et al. [1997] provided compelling evidence that absence of expression of *UBE3A* could be the causative factor in some individuals in the class of AS with biparental inheritance. More recent mutation analysis of all coding regions of the *UBE3A* gene show identifiable mutations in this gene in approximately 15–20% of clinically typical AS patients with negative cytogenetic, molecular, and methylation studies. A large percentage of these mutations are protein truncation defects. Family studies performed when a mutation is identified have shown that about 50% of AS mutations are maternally inherited (Fig. 2), and about 50% are de novo (Wagstaff, personal communication). The small number of families examined thus far means that these percentages could be subject to significant ascertainment bias, and the proportion of inherited and de novo mutations may change as further investigations continue. The recurrence risk in familial *UBE3A* mutations is expected to be 50%; and just as with IC mutations, other matrilineal relatives may be at risk to have affected children or grandchildren. *UBE3A* mutation analysis is still available on a research only basis, but such studies may be crucial for determination of recurrence risk and for prenatal diagnosis in families in which a mutation is identified.

Several areas of investigation will likely increase our understanding of this gene. The characterization of upstream exons and other regulatory elements may help our understanding of *UBE3A* function in the brain, as well as increase the identifiable mutation rate in *UBE3A*. Another issue which has yet to be determined is the mechanism by which mutations in *UBE3A* result in the AS phenotype. This gene was initially identified as coding for a cellular protein which, together with the E6 protein of certain human papillomaviruses, plays a role in the degradation of p53 [Huibregtse et al., 1991]. One can only hypothesize that a specific isoform of *UBE3A* could play a role in protein turnover in the brain, which may be crucial to normal neurological de-



velopment, and that disturbance of this role may result in the phenotype recognized as AS.

**Normal Genetic Results**

This group of individuals remains relatively large, and is estimated to be approximately 15%. Unfortunately, because of the nonspecific nature of many manifestations of AS, other conditions which involve ataxia, mental retardation, and lack of speech may be mistaken for AS. Therefore, for AS individuals with normal genetic studies, it is essential to be clinically certain of the diagnosis of AS; not only because of the wide range of recurrence risk which is presented to families, but also so that sporadic conditions or conditions with a known risk of recurrence are not missed. Williams et al. [1995] have published a consensus statement of diagnostic criteria for AS.

In children who have classical AS phenotype, careful 15q11–q13 haplotype analysis of the affected child and their normal sibs (if available) may provide evidence against a familial form of Angelman syndrome (if the affected and unaffected maternal haplotypes are the same); but until the cause for their manifestations is identified, it will be difficult to exclude a 50% risk. In families where the AS child is the only child, haplotype analysis is not possible. For these families, empiric risk data are not available, so the theoretical possibility of a 50% recurrence risk should be acknowledged in counseling. In instances in which AS is clearly familial, as

evidenced by the presence of affected siblings, haplotype analysis may be of assistance in determination of risk for more distant relatives. However, caution must be used in the provision of prenatal diagnostic information by the use of haplotype analysis, because the interpretation of this information is dependent upon the correct diagnosis of Angelman syndrome in the proband. If the diagnosis is incorrect, prenatal diagnosis in this manner would be meaningless.

**CONCLUSIONS**

Figure 3 presents an algorithm which can be used to determine the risk of recurrence for AS based on the diagnostic tests which have been performed and the abnormalities observed. There are several different approaches to the question of which diagnostic tests for AS and PWS should be performed first [Working group on Prader-Willi and Angelman syndromes, 1996], and this may differ depending on the degree of clinical suspicion, the availability of a particular test, and other factors. From the standpoint of genetic counseling, it is imperative that the diagnostic testing performed be sufficient to delineate the causal class of AS, since this will have a direct impact on the counseling provided, the recurrence risk given, and the identification of other at-risk relatives. As emphasized above, in the absence of any diagnostic test confirmation of AS, the clinical diagnosis should be certain in those families in

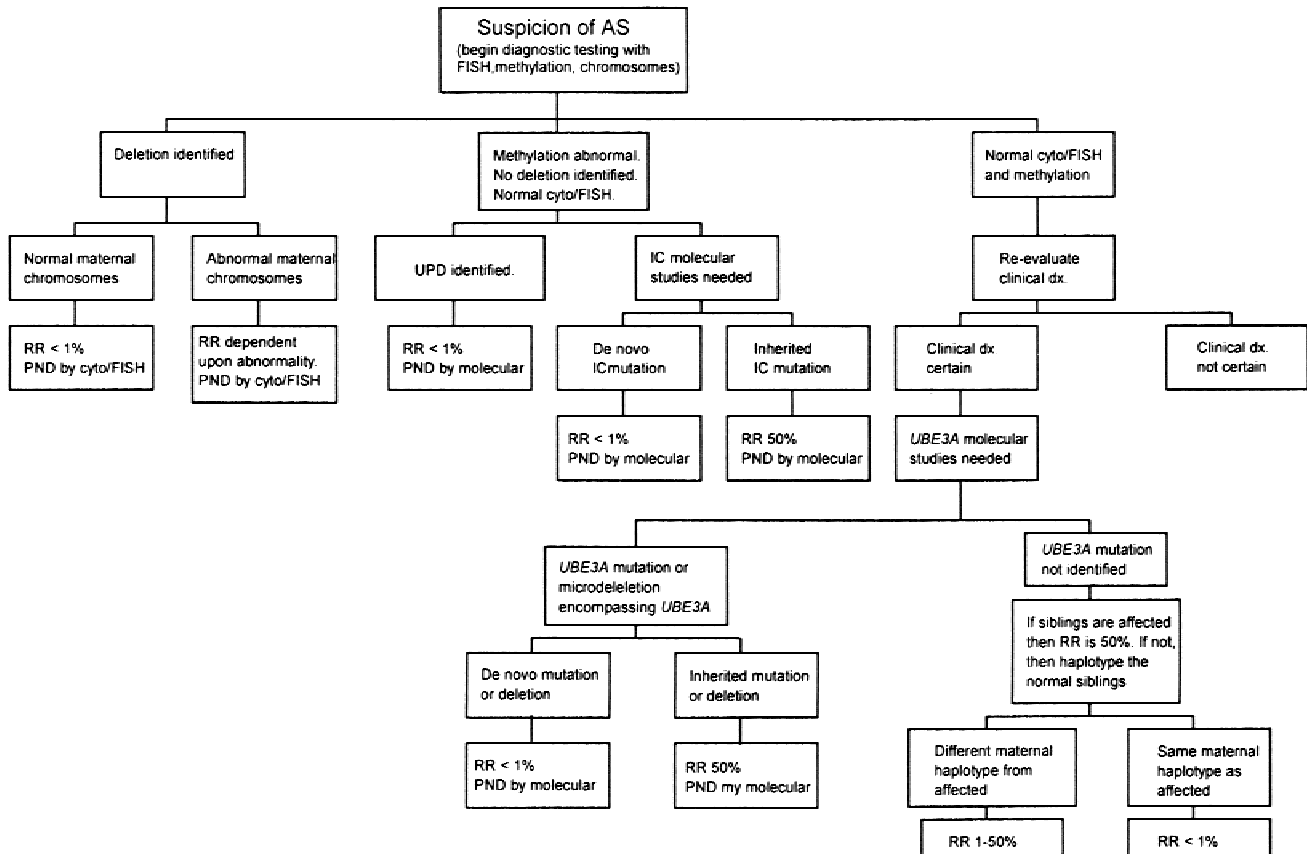


Fig. 3. Diagnostic approach and genetic counseling in AS.

which genetic counseling is provided since many other conditions involving developmental delay can appear similar to Angelman syndrome.

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