NEWS AND COMMENTARIES

Cancer Genetics

TSC1, TSC2, TSC3? or mosaicism?

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The largest mutation analysis series yet reported for tuberous sclerosis (TSC), on page 731 of this issue, provides insights into the number of genes that underlie this syndrome and sheds light onto several other important questions.¹

How many genes cause TSC, a tumor suppressor gene syndrome in which benign hamartomas develop in multiple organs? Positional cloning studies in the 1990s led to the identification of two genes, *TSC1* and *TSC2*. The failure of mutation identification efforts to yield 100% of mutations in TSC patients have led some to wonder whether or not a third or fourth TSC gene exists.

In this new study, the Halley-van den Ouweland lab report on mutation analysis of 490 samples from definite or suspect TSC cases summarizing several years of work from their clinical diagnostic laboratory. A combination of detection techniques were used, with a mutation detection rate of 74% overall, and 85% (235 of 276) in patients with definite TSC. This level of mutation detection is strikingly similar to two previous comprehensive studies on somewhat smaller numbers of patients.^{2,3} So, does this mean that 15% of TSC patients have mutations in a gene other than *TSC1* or *TSC2*?

Analysis of the 15% of TSC patients without a defined mutation provides some insight into this question. Ozgur Sancak and colleagues determined the presence or absence of 17 clinical features of TSC in their patients, and found that patients with defined mutations had a higher frequency of 15 of 17 features ($P=0.002$) in comparison to patients without a defined mutation. Considering

individual TSC findings, those identified with mutations were significantly more likely to have mental retardation, seizures, and three different cutaneous manifestations than those without. Our laboratory previously made similar observations.³ So, patients without defined mutations tend to have milder clinical symptoms (but still meet accepted diagnostic criteria) of TSC than patients in whom mutations are found. How should this be interpreted?

As in other tumor suppressor gene syndromes, mosaicism is well-documented in TSC, with rates as high as 26% (seven of 27) of all founding cases in one series in which highly sensitive detection techniques were employed in patients with large deletion mutations.⁴ In addition, documented mosaicism for a TSC mutation in the absence of diagnostic signs of TSC has not been reported to date.⁵ Sancak and colleagues found mosaicism in <1% patients in this series. So, it seems very likely that a proportion of those TSC patients in which a mutation could not be identified are mosaic for a causative mutation, explaining both why mutation detection failed and why these patients have milder symptoms and signs than those with defined mutations.

In addition, the authors found another 14 sequence variants (seen in 1/3 of patients without definite mutations) that might have been mutations but could not be proven. There is no doubt that other factors contributed to mutation detection failure in this series, including human error, failure of mutation detection methods, medium size (10–100 bp) deletion mutations missed both by PCR-based and macroscopic (eg Southern blot) screening techniques, and unscreened mutations

within promoter/enhancer or intronic regions that have critical functional effects. However, RT-PCR-based methods, including the protein truncation test and those permitting allele-specific identification, indicate that this latter category of mutations are rare,⁶ and do not explain most TSC cases in which mutation detection fails (Roberts and Kwiatkowski, unpublished observations).

So, available evidence suggests that all TSC cases are due to mutations in either *TSC1* or *TSC2*, and there is no good evidence for a third gene. There is, however, obvious room for improvement in our ability to quickly and reliably detect new mutations in these genes, particularly in the presence of mosaicism.

Sancak and colleagues also observed that patients with *de novo* *TSC1* mutations had on average milder disease in comparison to those with *de novo* *TSC2* mutations,¹ which tallies with previous observations.^{2,3} *TSC1* mutations were also found to be twice as frequent in familial cases of TSC (32%) as in *de novo* cases (16%), which is consistent with the milder clinical phenotype of familial cases.¹ Why is *TSC1* disease milder than *TSC2* disease? Although *TSC1*- or *TSC2*-specific functions are possible, it seems that the predominant biochemical activity of these proteins is exerted by an equimolar complex, which regulates the state of GTP-loading of the *rheb* GTPase, and thereby regulates mTOR activation in the cell.⁷ As most hamartomas in TSC develop through a two hit inactivation mechanisms, it appears likely that somatic mutations in *TSC1* are less common than those in *TSC2*, just as the rate of germline mutation in *TSC1* is much lower than that in *TSC2*. Thus, fewer and/or less severe clinical manifestations would be seen in *TSC1* patients ■

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Twin Research

Exploring female sexuality

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Two recent twin studies provide some fascinating insights into just how much of a role genes play in determining variation in female sexual behavior and debunk the common assumption that such behaviors are not heritable.

Twin researchers have always shown a keen interest in exploring the causes of variation in a broad range of human traits and disorders. Two papers in the December 2004 and February 2005 issues of *Twin Research & Human Genetics* that might attract some attention from a wider audience focus on the heritability of infidelity in a large sample of female twins from the UK, and on orgasm in Australian women.

Both papers go some way beyond the simple estimation of heritability. Specifically they include multivariate measures of the behavior under study and try to come up with evolutionary explanations for their findings. Moreover the UK paper reports on a genome-wide linkage scan, and examines the association of infidelity with a candidate gene suggested by animal studies.

In the UK study, Cherkas *et al*¹ surveyed over 1600 pairs of female twins about episodes of infidelity, lifetime number of sexual partners and their attitudes towards infidelity. The average age of the

women was 50 years and a quarter of these were divorced. Around 40% of the variation in the number of sexual partners and infidelity was due to genetic factors. The genetic correlation between the two traits was estimated at 0.47. Interestingly, genes influenced the variation in actual behavior, but genetic factors did not appear to influence women's attitudes to infidelity. Women who had been faithful had about four sexual partners, compared to eight in the infidelity group. This number is quite large compared to a previous study's estimate of the number of lifetime partners that women desire.² For a time interval of the next 30 years, women worldwide averaged a desire for 2.5 partners (by contrast men expressed a desire for an average of 13 partners).

Based on research in pair-bonding animals, the authors tested for association with a single tandem repeat marker in one of the exons of the argentine vasopressin 1A receptor gene in 149 dizygotic pairs. No significant results were found. However, given that there are 18 alleles at this marker the power of these tests might be limited so the lack of significant associations might not be so surprising. The linkage scan (in 515 dizygotic twin pairs) showed a maximum LOD score of 2.46 to chromosome 7 for number of sexual

partners and a LOD of 1.93 at chromosome 20 for infidel behavior.

Dawood *et al*³ surveyed an even larger sample of twins from the Australian twin register. In a truly anonymous study (twins from the same pair had to agree together on a 10-digit number that served as an identifier) 3080 women responded to three questions about the frequency with which they reached orgasm during sexual intercourse, during other activities with their partner and during masturbation. Significant twin correlations were found for all three variables with correlations in monozygotic twins higher than in dizygotic twins. Broad-sense heritabilities were between 29% (orgasm during intercourse) and 40% (masturbation). Correlations among the three phenotypes were not very high, and neither were genetic correlations, which may be derived from the path diagrams that summarize the multivariate analyses.

Both sets of authors discussed their findings in the context of sexual behavior as a fitness trait and addressed the common assumption that such traits should show zero heritabilities. Previous papers from the Australian twin register have already demonstrated that this is not necessarily true.⁴ However, it is surprising that neither paper tried to relate their phenotype to fitness indicators such as number of offspring.

Remarkably, after the demonstration of significant heritability in females, neither paper in its discussion, speculates on the possible expression of these genes in males. It is unlikely that the UK study has collected data in males, as the UK twin register consists almost entirely of female twins, but the Australian study might have collected data in male twins, including twins from opposite-sex pairs. Nonetheless, as the first studies to show significant