

[264] Evidence for an Environmental Influence Leading to the Development of *JAK2V617F*-Positive Polycythemia Vera: A Molecular Epidemiological Study. Session Type: Oral Session

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Polycythemia vera (PV) is a chronic myeloproliferative disorder (MPD) associated with an acquired mutation (*JAK2V617F*) in over 90% of patients. The incidence of PV in the US, based on national cancer registry data from 2001-03, is 0.9 persons/10⁵population/year. In Oct. 2006, the PA Dept. of Health requested the assistance of the Agency for Toxic Substances and Disease Registry (ATSDR) in confirming a suspected cluster of PV in the 3 counties (Carbon, Luzerne, & Schuylkill) surrounding the borough of Tamaqua, home to multiple Superfund and National Priorities Listing sites. These counties have a total population of ~527,000 individuals. The ATSDR investigation identified a total of 131 possible PV cases, including 97 state cancer registry and 34 self-reported cases, of which 72 agreed to be interviewed and 63 were tested for *JAK2V617F*. The PV diagnosis was confirmed in 38 of the interviewed participants (53%) based on a *JAK2V617F*⁺ assay with granulocytes (37 cases) or a *JAK2V617F*⁻ assay but satisfying WHO criteria for the diagnosis of PV (1 case). Of the 37 cases who met both clinical and molecular criteria (*JAK2V617F*⁺) for a diagnosis of PV, 18 (49%) had resided within a 13 mile radius of the McAdoo Associates Superfund Site (MASS) for >5 years during the period 1970-95. The MASS was the home of a hazardous waste recycling business from 1975-79 where large quantities of toxic chemicals were dumped directly into old mine shafts. The Environmental Protection Agency completed surface remediation in the early 90's, but was unable to determine the extent and fate of the chemicals poured into the mine. A spatial scan statistical analysis identified this area as a significant cluster and individuals living within this area had a 4.5 times greater risk of developing PV compared to individuals residing in the remainder of the 3 counties (p<0.001). 4 cases of *JAK2V617F*⁺ PV were identified within the described area along a 2-mile stretch of a single street containing 70 homes, including 2 individuals who lived in the same dwelling. No familial inheritance patterns of PV were documented, nor were any correlations noted with regards to type of employment or recreational/leisure activities. The lack of traditional epidemiological explanations and the high degree of statistical certainty for the geographical association of the cases strongly suggests that an external influence led to the development of PV. Since the PV rates are based on both self-identified and cancer registry cases, direct comparisons to state and national rates can't be made. However, it is likely that at least as many confirmed cases would have been found in the 61 "missing" registry cases as were found in the 20 "self-reporting" cases. Thus, the number of confirmed cases identified in this investigation should represent a conservative estimate of the total number of actual cases in the registry. The diagnosis of PV was confirmed in less than half of the registry participants, which highlights the utility of *JAK2V617F* analysis in epidemiological studies evaluating the incidence of MPD. Finally, the results of this investigation provide, for the first time, significant evidence for an association between an as yet uncharacterized external stimulus and the development of *JAK2V617F*⁺ PV.

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